CHAPTER 22

Skin Infections

Howard T. Ricketts was born in Ohio in 1871. He studied medicine in Chicago, and then specialized in pathology, the study of the nature of disease and its causes. In 1902, he was appointed to the faculty of the University of Chicago, where his research interests turned to an often fatal and little understood disease characterized by a dramatic rash, Rocky Mountain spotted fever. The disease could be transmitted to laboratory animals by injecting them with blood from an infected person, and Ricketts noticed that people and laboratory animals with the disease had tiny bacilli in their blood. Ricketts was sure that these tiny bacteria were the cause of the disease, but he was never able to cultivate them on laboratory media. Based on observations of victims with the disease, Ricketts and others suspected that Rocky Mountain spotted fever was contracted from tick bites, and Ricketts went on to prove that certain species of ticks could transmit the disease from one animal to another. The infected ticks remained healthy but capable of transmitting the disease for long periods of time, and oftentimes the offspring of infected ticks were also infected. Ricketts was able to explain this by showing that the eggs of infected ticks often contained large numbers of the tiny bacilli, an example of transovarial, meaning via the eggs, passage of an infectious agent. Frustrated by his inability to cultivate the bacilli for further studies, Ricketts declined to give them a scientific name and went off to Mexico to study a very similar disease, louse-borne typhus (Rocky Mountain spotted fever is also known as tick-borne typhus). Unfortunately, Ricketts contracted the disease and died at the age of 39. Five years later a European scientist, Stanislaus Prowazek, studying the same disease in Serbia and Turkey, met the same fate at almost the same age. The martyrdom of the two young scientists struggling to understand infectious diseases is memorialized in the name of the louse-borne agent, Rickettsia prowazekii. Both the genus and species names of the Rocky Mountain spotted fever agent, Rickettsia rickettsii, recognize Howard Ricketts. We now know that these bacteria are obligate intracellular parasites, which explains why they could not be cultivated on ordinary laboratory media. Antibiotics, which could have saved these men, had not yet been discovered.

—A Glimpse of History

A dividing *Staphylococcus epidermidis* cell

A MAJOR PART OF THE BODY'S CONTACT WITH THE outside world occurs at the surface of the skin. As long as skin is intact, this tough, flexible outer covering is remarkably resistant to infection. Because of its exposed state, however, it is frequently subject to cuts, punctures, burns, chemical injury, hypersensitivity reactions, and insect or tick bites. These skin injuries provide a way for pathogens to enter and infect the skin and underlying tissues. Skin infections also occur when microorganisms or viruses are carried to the skin by the bloodstream after entering the body from another site, such as the respiratory or gastrointestinal systems.

22.1 Anatomy and Physiology

The skin is far more than an inert wrapping for the body. Control of body temperature and prevention of loss of fluid from body tissues are vitally important functions of the skin. It also plays an important role in the synthesis of vitamin D, which is needed for normal teeth and bones. Numerous sensory receptors of various types occur in the skin, providing the central nervous system with information about the environment. The skin also produces cytokines that aid the development and function of cell-mediated immunity, and collections of lymphocytes are closely associated with the skin. Because of its exposed location, the temperature of the skin is generally lower than that of the rest of

the body. ■ **cytokines, p. 379** ■ **cell-mediated immunity, p. 395** ■ **skin-associated lymphoid tissue, p. 397**

The **epidermis,** the surface layer of the skin **(figure 22.1),** is composed of layers of squamous epithelial cells and ranges from 0.007 to 0.12 mm thick. The outer portion is composed of scaly material made up of flat cells containing **keratin,** a durable protein also found in hair and nails. The cells on the skin surface are dead and, along with any resident organisms, continually peel off, replaced by cells from deeper in the epidermis. These cells, in turn, become flattened and die as keratin is formed within them. This process results in a complete regeneration of the skin about once a month. Dandruff represents excessive shedding of skin cells, but mostly the shedding process is unnoticed and represents one of the skin's defenses against infection.

The epidermis is supported by the **dermis,** a second, deeper layer of skin cells through which many tiny nerves, blood vessels, and lymphatic vessels penetrate. The dermis adheres in a very irregular fashion to the fat and other cells that make up the subcutaneous tissue (see figure 22.1).

Fine tubules of sweat glands and hair follicles traverse the dermis and epidermis (see figure 22.1). Since sweat is a salty solution, high concentrations of salt occur as it evaporates. Evaporation of sweat and regulation of the amount of blood flow through the skin's blood vessels are critically important in controlling body temperature. Sebaceous glands produce an oily secretion called **sebum** that feeds into the sides of the hair follicles. This secretion flows up through the follicles and spreads out over the skin surface, keeping the hair and skin soft, pliable, and water-repellent. The hair follicles provide passage for certain salt-tolerant bacteria to penetrate the skin and reach deeper tissues.

The secretions of the sweat and sebaceous glands are essential to the normal microbial population of the skin because they

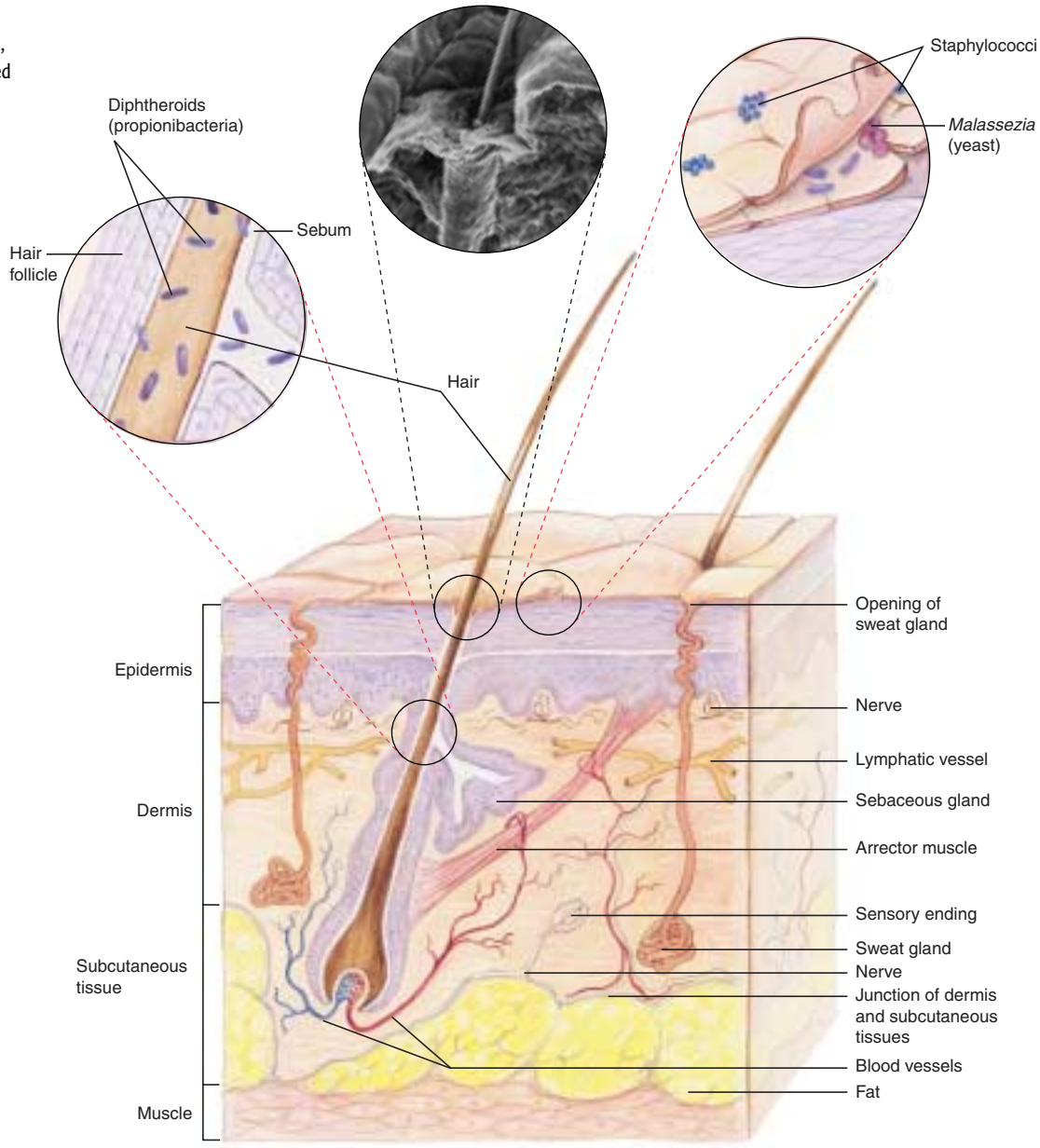


Figure 22.1 Microscopic Anatomy of the Skin Notice that the sebaceous unit, composed of the hair follicle and the attached sebaceous gland, almost reaches the subcutaneous tissue.

supply water, amino acids, and lipids, which serve as nutrients for microbial growth. The normal pH of skin ranges from 4.0 to 6.8. Breakdown of the lipids by the microbial residents of normal skin results in fatty-acid by-products that inhibit the growth of many potential disease-producers. In fact, the normal skin surface is an unfriendly habitat for most potential pathogens, being too dry, salty, unstable because of shedding, acidic, and toxic for their survival.

MICROCHECK 22.1

The skin is a large, complex organ that covers the external surface of the body. Properties of the skin cause it to resist colonization by most microbial pathogens, pose a physical barrier to infection, provide sensory input from the environment, and assist the body's regulation of temperature and fluid balance.

- Give three routes by which microorganisms invade the skin.
- Give four characteristics of skin that help it resist infection.
- Would a person living in the tropics or in the desert have larger numbers of bacteria living on the surface of their skin?

22.2 Normal Flora of the Skin

The skin represents a distinct ecological habitat, analogous to a cool desert, compared to the warm, moist tropical conditions that exist in other body systems. Large numbers of microorganisms live on and in the various components of the normal skin. For example, depending on the body location and amount of skin moisture, the number of bacteria on the skin surface may range from only about 1,000 organisms per square centimeter on the back to more than 10 million in the groin and armpit, where moisture is more plentiful. The numbers actually increase after a hot shower because of increased flow from the skin glands where many reside. Most of the microbial skin inhabitants can be categorized in three groups: diphtheroids, staphylococci, and yeasts (**table 22.1,** and see figure 22.1). Although generally harmless, skin organisms are opportunistic pathogens, meaning that they can only cause disease in people with impaired body defenses.

Table 22.1 Principal Members of the Normal Skin Flora

Name	Characteristics
Diphtheroids	Variably shaped non-motile, Gram-positive rods of the *Corynebacterium* and *Propionibacterium* genera
Staphylococci	Gram-positive cocci arranged in packets or clusters; coagulase negative; facultatively anaerobic
Fungi	Small yeasts of the genus *Malassezia* that require oily substances for growth

AIDS patients and others with impaired immunity are especially vulnerable. ■ normal flora, pp. 375, 461

Diphtheroids

Diphtheroids are a group of bacteria named for their resemblance to the diphtheria bacillus, *Corynebacterium diphtheriae.* Their distinctive characteristics are Gram-positive staining, variation in shape, and low virulence. Unlike *C. diphtheriae,* they do not produce exotoxin. Diphtheroids are responsible for body odor, caused by their breakdown of substances in sweat, which is odorless when it is first secreted. A diphtheroid found on the skin in large numbers is *Propionibacterium acnes,* which is present on virtually all humans. Surprisingly, most strains of *P. acnes* are anaerobic, although some strains are aerotolerant. This bacterium grows primarily within the hair follicles, where conditions are anaerobic. Growth of *P. acnes* is enhanced by the oily secretion of the sebaceous glands, and the organisms are usually present in large numbers only in areas of the skin where these glands are especially well developed—on the face, upper chest, and back. These are also the areas of the skin where acne most commonly develops, and the frequent association of *P. acnes* with acne inspired its name, even though most people who carry the organisms do not have acne. ■ aerotolerance, p. 89

Acne in its most common form begins at puberty in association with a rise in sex hormones, enlargement of the sebaceous glands, and enhanced secretion of sebum. The hair follicle epithelium thickens and sloughs off in cohesive clumps, causing increasing obstruction to the flow of sebum to the skin surface. Continued sebum production by the gland can force a plug of material to the surface, where it is visible as a blackhead. With complete obstruction the follicle becomes distended with sebum, which causes the epidermis to bulge outward, producing a whitish lesion called a whitehead. The *P. acnes* that normally reside in the gland multiply to enormous numbers in the trapped sebum. Lipases of the bacteria degrade the sebum, releasing fatty acids and glycerol, a growth requirement of the organisms. The metabolic products of the bacteria cause an inflammatory response, attracting leukocytes (white blood cells) whose enzymes damage the wall of the distended follicle. The inflammatory process can cause the follicle to rupture, releasing the follicle contents into the surrounding tissue. The result is an **abscess,** a collection of white blood cells, bacteria, and cellular debris, which eventually heals and leaves a scar. Squeezing acne lesions is ill-advised, because it promotes rupture of the inflamed follicles and therefore more acne scars. Usually acne can be controlled until it goes away by itself, by using medications such as antibiotics and benzoyl peroxide that inhibit the growth of *P. acnes,* or by those such as azelaic acid (Azelex) and isotretinoin (Accutane) that act primarily to reverse the hair follicle abnormalities. The latter medication is reserved for the most serious cases of acne because it has potentially serious side effects. ■ inflammation, p. 385 ■ leukocytes, p. 376

Staphylococci

The second group of microorganisms universally present on the normal skin is composed of members of the genus *Staphylococcus.* They are salt-tolerant organisms and grow well on the salty skin surface. As with the diphtheroids, most of these bacteria have little virulence, although they certainly can cause serious disease

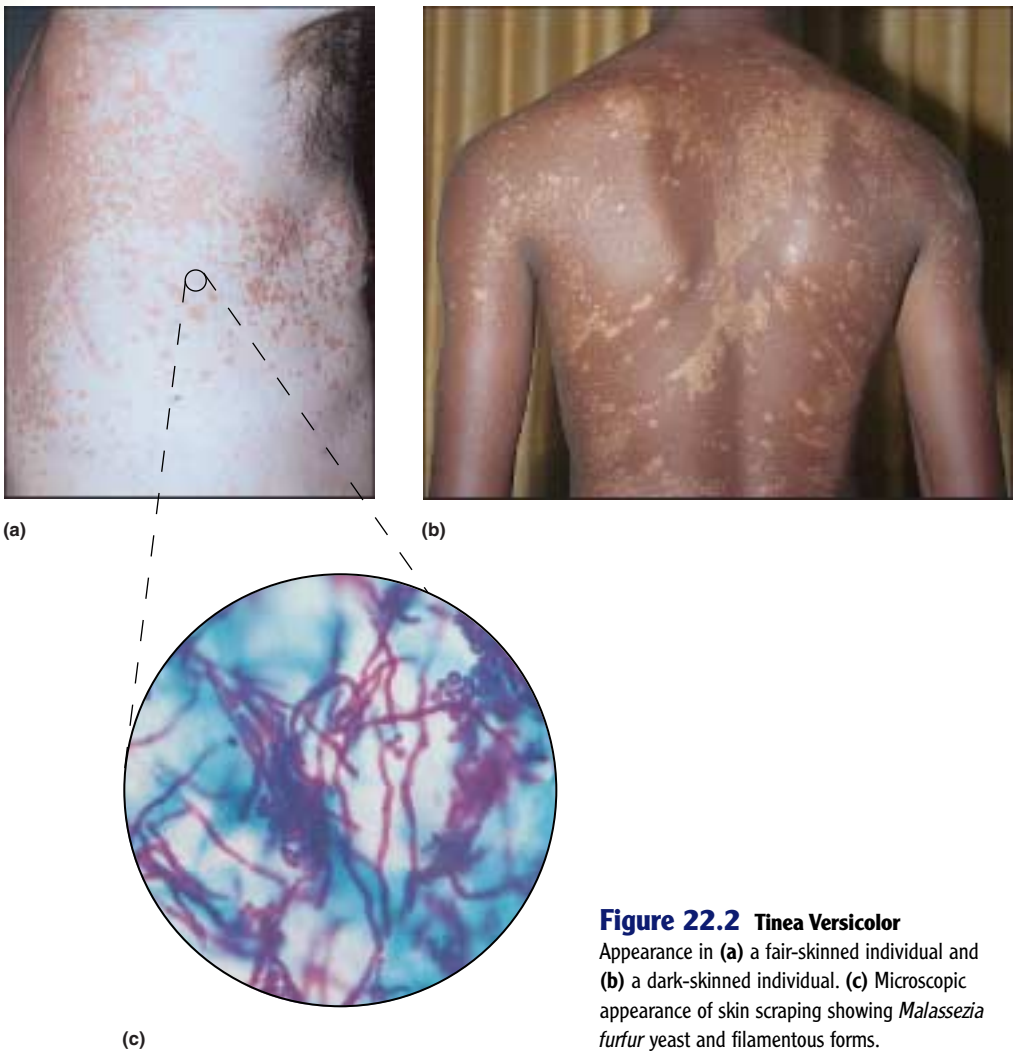


Figure 22.2 Tinea Versicolor
Appearance in **(a)** a fair-skinned individual and **(b)** a dark-skinned individual. **(c)** Microscopic appearance of skin scraping showing *Malassezia furfur* yeast and filamentous forms.

if host defenses are impaired. Generally, staphylococci are the most common of the skin bacteria able to grow aerobically. The principal species is *Staphylococcus epidermidis.* ■ **staphylococci, p. 290**

Important functions of the skin's staphylococci are to prevent colonization by pathogens and to maintain a balance among the microbial inhabitants of the skin ecosystem. These Gram-positive cocci compete for nutrients with other potential skin colonizers, and they also produce antimicrobial substances highly active against *P. acnes* and other Gram-positive bacteria.

Fungi

Tiny lipophilic, meaning oil-requiring, yeasts almost universally inhabit the normal human skin from late childhood onward. Their shape varies with different strains, being round, oval, or sometimes short, rods. These yeasts can be cultivated on laboratory media containing fatty substances such as olive oil. They belong to the genus *Malassezia,* formerly *Pityrosporum,* and are generally harmless. In some people, however, they cause skin conditions such as a scaly face rash, dandruff, or **tinea versicolor (figure 22.2).** The latter is a common skin disease that causes a patchy scaliness and increased pigment in light-skinned persons, or a decrease in pigment in dark-skinned people. Scrapings of the affected skin show large numbers of *Malassezia furfur* both in its yeast form and as short filaments called pseudohyphae. Unknown factors, probably relating to the host, are important in these diseases since most people carry *Malassezia* sp. on their skin without any disease. AIDS patients often have a severe rash with pus-filled pimples caused by *Malassezia* yeasts, and the organisms may even infect internal organs in patients receiving fat-containing intravenous feedings. ■ **yeasts, p. 309**

MICROCHECK 22.2

The normal skin flora are important because they help protect against colonization by pathogens. Occasionally, they cause disease when body defenses are impaired. They are responsible for body odor, and probably contribute to acne.

- Name and describe the three groups of organisms generally present on normal skin.
- Under what circumstances is *Malassezia furfur* most likely to be pathogenic?
- Would frequent showering tend to increase or decrease the numbers of *Staphylococcus* on the surface of the skin? Why?

22.3 Bacterial Skin Diseases

Only a few species of bacteria commonly invade the intact skin directly, which is not surprising in view of the anatomical and physiological features discussed earlier. Hair follicle infections exemplify direct invasion.

Hair Follicle Infections

Infections originating in hair follicles commonly clear up without treatment. In some instances, however, they progress into severe or even life-threatening disease.

Symptoms

Folliculitis, furuncles, and carbuncles represent different outcomes of hair follicle infections. In **folliculitis,** a small red bump, or pimple, develops at the site of the involved hair follicle. Often, the hair can be pulled from its follicle, accompanied by a small amount of pus, and then the infection goes away without further treatment. If, however, the infection extends from the follicle to adjacent tissues, causing localized redness, swelling, severe tenderness, and pain, the lesion is called a **furuncle** or boil. Pus may drain from the boil along with a plug of inflammatory cells and dead tissue. A **carbuncle** is a large area of redness, swelling, and

pain punctuated by several sites of draining pus. Carbuncles usually develop in areas of the body where the skin is thick, such as the back of the neck. Fever is often present, along with other signs of a serious infection.

Causative Agent

Most furuncles and carbuncles, as well as many cases of folliculitis, are caused by *Staphylococcus aureus*, a staphylococcus that produces coagulase and is therefore called "coagulase-positive." It is much more virulent than the staphylococci normally found on the skin. The name derives from *staphyle*, "a bunch of grapes," referring to the arrangement of the bacteria as seen on stained smears, and *aureus*, "golden," referring to the color of the *S. aureus* colonies. This bacterium is an extremely important pathogen and is mentioned frequently throughout this text as the cause of a number of medical conditions **(table 22.2).**

■ coagulase, p. 694

Table 22.2 Some Diseases Often Caused by *Staphylococcus aureus*

Disease	Page for More Information
Carbuncles	p. 536
Endocarditis	p. 718
Folliculitis	p. 536
Food poisoning	p. 812
Furuncles	p. 536
Impetigo	p. 540
Osteomyelitis (bone infection)	p. 538
Scalded skin syndrome	p. 538
Toxic shock syndrome	p. 641
Wound infections	p. 693

Pathogenesis

Infection begins when virulent staphylococci attach to the cells of a hair follicle, multiply, and spread downward to involve the follicle and sebaceous glands. The infection induces an inflammatory response with swelling and redness, followed by attraction and accumulation of polymorphonuclear leukocytes. If the infection continues, the follicle becomes a plug of inflammatory cells and necrotic tissue overlying a small abscess **(figure 22.3).** The infectious process spreads deeper, reaching the subcutaneous

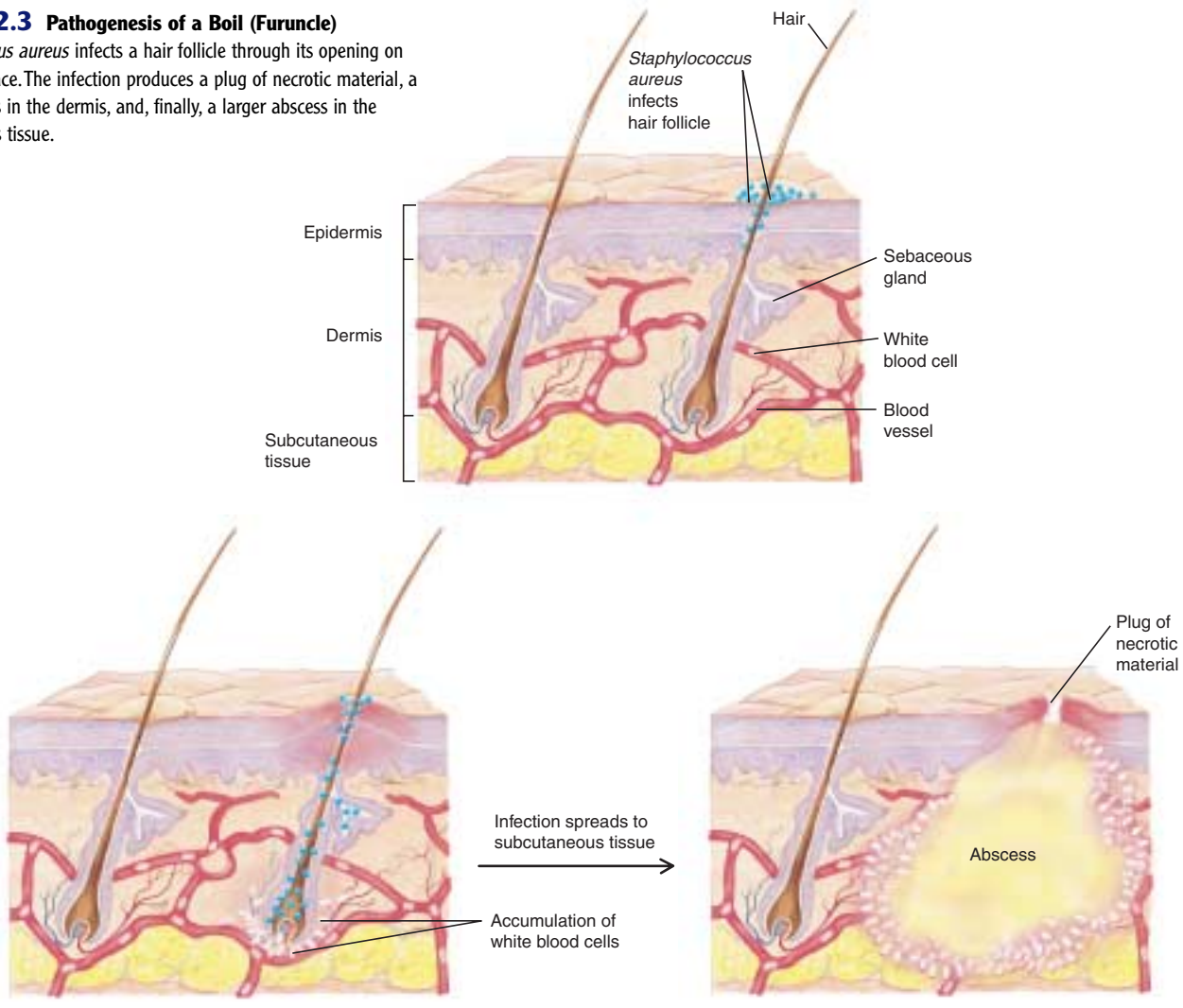


Figure 22.3 Pathogenesis of a Boil (Furuncle)
Staphylococcus aureus infects a hair follicle through its opening on the skin surface. The infection produces a plug of necrotic material, a small abscess in the dermis, and, finally, a larger abscess in the subcutaneous tissue.

Table 22.3 Virulence Factors of *Staphylococcus aureus*

Product	Effect
Capsule	Inhibits phagocytosis
Coagulase	May impede progress of leukocytes into infected area by producing clots in the surrounding capillaries
Exfoliatin	Separates layers of epidermis, causing scalded skin syndrome
Hyaluronidase	Breaks down hyaluronic acid component of tissue, thereby promoting extension of infection
Leukocidin	Kills white blood cells by producing holes in their cytoplasmic membrane
Lipase	Breaks down fats by hydrolyzing the bond between glycerol and fatty acids
Proteases	Degrade collagen and other tissue proteins
Protein A	Binds to Fc portion of antibody, inhibiting phagocytosis (blocks attachment to Fc receptors on white blood cells)
Toxic shock syndrome toxin	Causes rash, diarrhea, and shock

tissue where a large abscess forms. This subcutaneous abscess is responsible for the painful localized swelling that constitutes the boil. Without effective treatment, pressure within the abscess increases, causing it to expand to other hair follicles, causing a carbuncle. If organisms enter the bloodstream, the infection can spread to other parts of the body, such as the heart, bones, or brain. ■ **abscess, p. 692**

The properties of *S. aureus* that contribute to its virulence are shown in **table 22.3.** Virtually all strains possess an unusual cell wall component called **protein A.** This protein, some of which is released from the cell, prevents the antibody from attaching to Fc receptors on phagocytes. Thus, a major effect of protein A is to interfere with phagocytosis. Many strains of *S. aureus* growing in body tissues synthesize a polysaccharide capsule that also inhibits phagocytosis. The *S. aureus* genes responsible for capsule formation are activated following invasion of tissue. Besides producing these cellular components, *S. aureus* produces numerous extracellular products that might contribute to virulence. These products include **leukocidins,** which kill white blood cells; **hyaluronidase,** which degrades hyaluronic acid, a component of host tissue that helps hold the cells together; **proteases,** which degrade various host proteins including collagen, the white fibrous protein found in skin, tendons, and connective tissue; and **lipases,** which degrade lipids. Lipases may assist colonization of the oily hair follicles by strains of *S. aureus* that cause follicle infections. ■ **protein A, p. 470** ■ **Fc receptors, p. 470**

Epidemiology

Staphylococcus aureus inhabits the nostrils of virtually everyone at one time or another, each nostril containing as many as 10^8 bacteria. About 20% of healthy adults have continually positive nasal cultures for a year or more, while over 60% will be colonized at some time during a given year. The organisms are mainly disseminated to other parts of the body and to the environment by the hands. Although the nostrils seem to be the preferred habitat of *S. aureus,* moist areas of skin are also frequently colonized. People with boils and other staphylococcal infections shed large numbers of *S. aureus* and should not work with food, or near patients with surgical wounds or chronic illnesses. Staphylococci survive well in the environment, which favors their transmission from one host to another. Since *S. aureus* is so commonplace and there are many different strains in the population, epidemics of staphylococcal disease can generally be traced to their sources only by precise identification of the epidemic strain. Techniques for characterizing strains of *S. aureus* include the pattern of susceptibility to multiple antibiotics, bacteriophage typing, and plasmid identification. All of these techniques, however, have their limitations. A more reliable method is to compare the electrophoretic patterns of the DNA fragments produced by treatment with a restriction enzyme. ■ **bacteriophage typing, p. 257** ■ **restriction enzymes, pp. 219, 231**

Prevention and Treatment

Prevention of staphylococcal skin disease is very difficult. Attempts are made to eliminate the carrier state by applying an antistaphylococcal cream to the nostrils, and using soaps containing an antistaphylococcal agent such as hexachlorophene to bathe the skin. Effective treatment of boils and carbuncles often requires that the pus be surgically drained from the lesion and an antistaphylococcal medicine be given. Antibiotic treatment is complicated by the fact that about 90% of *S. aureus* strains produce the penicillin-destroying enzyme penicillinase, a β-lactamase, and so penicillin cannot routinely be used in treatment. Some strains are resistant to multiple antibiotics including β-lactamase-resistant penicillins, cephalosporins, and vancomycin.

■ **cephalosporins, p. 515**

Scalded Skin Syndrome

Staphylococcal scalded skin syndrome, SSSS, is a potentially fatal toxin-mediated disease that occurs mainly in infants but can also occur in children and adults.

Symptoms

As the name suggests, the skin appears to be scalded **(figure 22.4).** SSSS begins as a generalized redness of the skin affecting 20% to 100% of the body. Other symptoms, such as **malaise**—a vague feeling of discomfort and uneasiness—irritability, and fever are also present. The nose, mouth, and genitalia may be painful for one or more days before the typical features of the disease become apparent. Within 48 hours after the redness appears, the skin becomes wrinkled, and large blisters filled with clear fluid develop. The skin is tender to the touch and looks like sandpaper.

Causative Agent

Staphylococcal scalded skin syndrome is caused by toxins called **exfoliatins** produced by certain strains of *Staphylococcus aureus.*

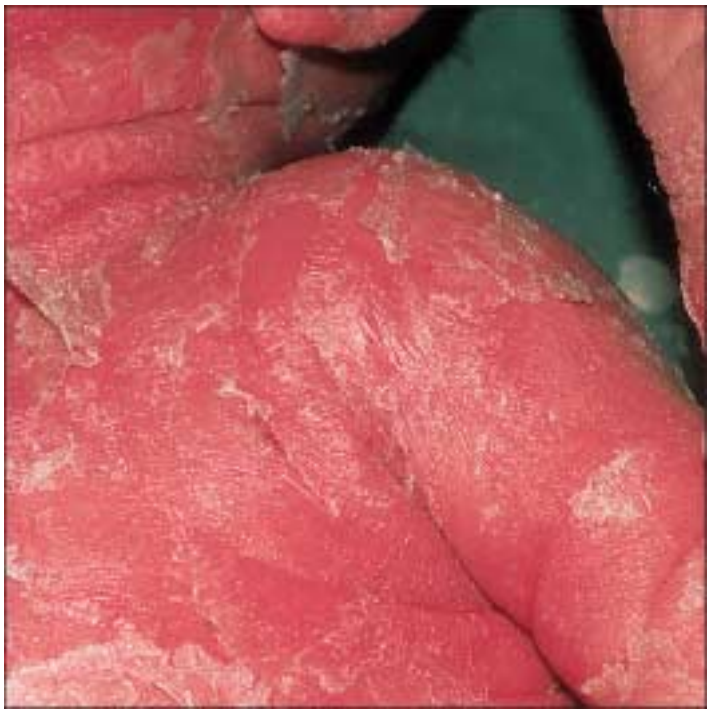


Figure 22.4 Staphylococcal Scalded Skin Syndrome (SSSS) A toxin called exfoliatin, produced by certain strains of *Staphylococcus aureus,* causes the outer layer of skin to separate.

These toxins destroy material that binds together the layers of skin. At least two kinds of exfoliatins exist: one is coded by a plasmid gene, and the other is chromosomal. ■ **plasmids, pp. 66, 209**

Pathogenesis

Exfoliatin, released by *S. aureus* at the site of infection, is absorbed and carried by the bloodstream to large areas of the skin. In the skin, it causes a split in the cellular layer of the epidermis just below the dead keratinized outer layer. *Staphylococcus aureus* is usually not present in the blister fluid. Because the outer layers of skin are lost as in a severe burn, there is marked loss of body fluid and danger of secondary infection with Gram-negative bacteria such as *Pseudomonas* sp., or with fungi such as *Candida albicans.* **Secondary infection** means invasion by a new organism of tissues damaged by an earlier infection. Mortality can range up to 40%, depending on how promptly the disease is diagnosed and treated, and the patient's age and general health. ■ ***Candida albicans*, p. 311**

Epidemiology

About 5% of *S. aureus* strains produce exfoliatins. The disease can appear in any age group but occurs most frequently in newborn infants, the elderly, and immunocompromised adults. Transmission is generally person-to-person. Staphylococcal scalded skin syndrome usually appears in isolated cases, although small epidemics in nurseries sometimes occur.

Prevention and Treatment

There are no preventive measures except to place patients suspected of having SSSS in protective isolation. These measures help to limit spread of the pathogen to others and help prevent secondary infection of the isolated patient. Initial therapy includes a bactericidal antistaphylococcal antibiotic such as methicillin, a penicillinase-resistant derivative of penicillin. All dead skin and other tissue are removed to help prevent secondary infection.

Table 22.4 describes the main features of this disease.

Table 22.4 Staphylococcal Scalded Skin Syndrome

Symptoms	Tender red rash with sandpaper texture, malaise, irritability, fever, large blisters, peeling of skin
Incubation period	Variable, usually days
Causative agent	Strains of *Staphylococcus aureus* that produce exfoliatin toxin
Pathogenesis	Exfoliatin toxin is produced by staphylococci at an infection site, usually of the skin, and carried by the bloodstream to the epidermis, where it causes a split in a cellular layer; loss of body fluid and secondary infections contribute to mortality
Epidemiology	Person-to-person transmission; seen mainly in newborns, but can occur at any age
Prevention and treatment	Isolation of the victim to protect from environmental potential pathogens; penicillinase-resistant penicillins; removal of dead tissue

Streptococcal Impetigo

A skin infection characterized by pus production is called **pyoderma.** Pyodermas can result from infection of an insect bite, burn, scrape, or other wound. Sometimes, the injury is so slight that it is not apparent. **Impetigo** is the most common type of pyoderma **(figure 22.5).**

Symptoms

Impetigo is a superficial skin infection, involving patches of epidermis just beneath the dead, scaly outer layer. Thin-walled

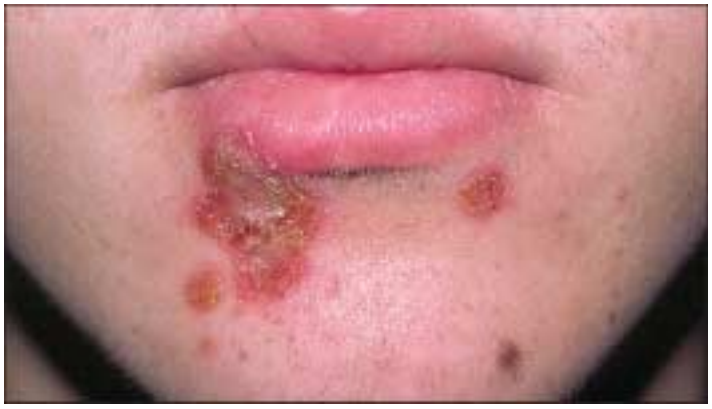


Figure 22.5 Impetigo This type of pyoderma is often caused by *Streptococcus pyogenes* and may result in glomerulonephritis.

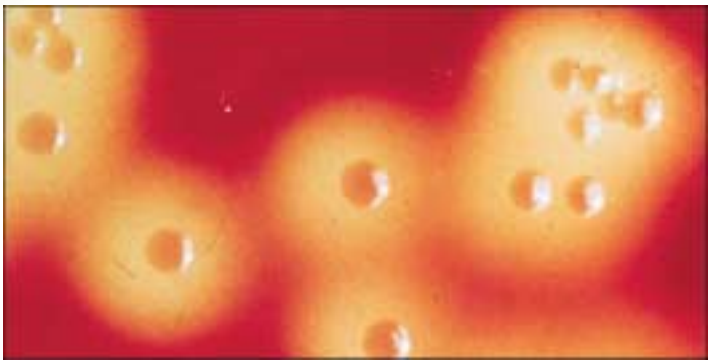


Figure 22.6 ***Streptococcus pyogenes*** **Growing on Blood Agar** The colonies are small and surrounded by a wide zone of β-hemolysis.

blisters first develop, then break, and are replaced by yellowish crusts that form from the drying of plasma that weeps through the skin. Usually, little fever or pain develop, but lymph nodes near the involved areas often enlarge, indicating that bacterial products have entered the lymphatic system and an immune response is occurring.

Causative Agent

Although *Staphylococcus aureus* often causes impetigo, many cases, even epidemics, are due to *Streptococcus pyogenes.* These Gram-positive, chain-forming cocci are β-hemolytic **(figure 22.6)** and are frequently referred to as β-hemolytic group A streptococci because their cell walls contain a polysaccharide called group A carbohydrate. A more detailed description of *S. pyogenes* is found in chapters 23 and 27. ■ **hemolysis, p. 94** ■ ***Streptococcus pyogenes*, p. 565**

Table 22.5 compares *Staphylococcus aureus* and *Streptococcus pyogenes.*

Pathogenesis

Many different strains of *Streptococcus pyogenes* exist, some of which can colonize the skin. Infection is probably established by scratches or other minor injuries that introduce the bacteria into the deeper layer of epidermis. In impetigo, even though the infection is limited to the epidermis, streptococcal products are absorbed into the circulation.

As with *Staphylococcus aureus,* a number of extracellular products may contribute to the virulence of *Streptococcus pyogenes.* These products include enzymes such as proteases that degrade protein, nucleases that degrade nucleic acids, and hyaluronidase, which degrades the hyaluronic acid component of host tissues. As with staphylococci, it is probable that such enzymes contribute to streptococcal pathogenicity. None of them appear to be essential, however, since antibody against them fails to protect experimental animals. On the other hand, the surface components of *S. pyogenes,* notably a hyaluronic acid capsule and a cell wall component known as the M protein, are very important in enabling this organism to cause disease because they interfere with phagocytosis. ■ **M protein, p. 470**

Acute glomerulonephritis is a serious complication of *S. pyogenes* pyoderma. This condition may appear abruptly during convalescence from untreated *S. pyogenes* infections, with fever, fluid retention, high blood pressure, and blood and protein in the urine. Acute glomerulonephritis is caused by inflammation of structures within the kidneys, the glomeruli (singular: glomerulus), small tufts of tiny blood vessels, and the nephrons, responsible for the formation and composition of urine **(figure 22.7).** Only a few of the many *S. pyogenes* strains cause the condition. Streptococci are absent from the urine and diseased kidney tissues. Indeed, the bacteria have generally been eliminated from the infection site in the skin by the immune response by the time symptoms of glomerulonephritis appear. Damage to the kidney is caused by immune complexes that are deposited in the glomeruli and provoke an inflammatory reaction. Both streptococcal skin and throat infections can sometimes cause acute glomerulonephritis, but rheumatic fever, a serious complication of strep throat, is not generally a complication of streptococcal pyoderma. ■ **immune complexes, p. 448** ■ **rheumatic fever, p. 567**

Epidemiology

Impetigo is most prevalent among poor children of the tropics or elsewhere during the hot, humid season. Children two to six years are mainly afflicted. Person-to-person contact spreads the disease, as do flies and other insects, and fomites—inanimate objects such as toys or towels. Impetigo patients often become throat and nasal carriers of *S. pyogenes.*

Table 22.5 ***Streptococcus pyogenes*** **vs.** ***Staphylococcus aureus***

	Streptococcus pyogenes	***Staphylococcus aureus***
Characteristics	Gram-positive cocci in chains; β-hemolytic colonies; cell wall contains group A polysaccharide and M protein	Gram-positive cocci in clusters; cream-colored colonies; cell wall contains protein A
Extracellular Products	Hemolysins: streptolysins O and S; streptokinase, DNase, hyaluronidase, and others	Hemolysins, leukocidin, hyaluronidase, nuclease, protease, penicillinase, and others
Disease Potential	Causes impetigo, strep throat, wound infections, scarlet fever, puerperal fever, toxic shock, and flesh-eating fasciitis. Complications: glomerulonephritis, rheumatic fever, and chorea	Causes boils, scalded skin syndrome, wound infections, abscesses, bone infections, impetigo, food poisoning, and toxic shock syndrome

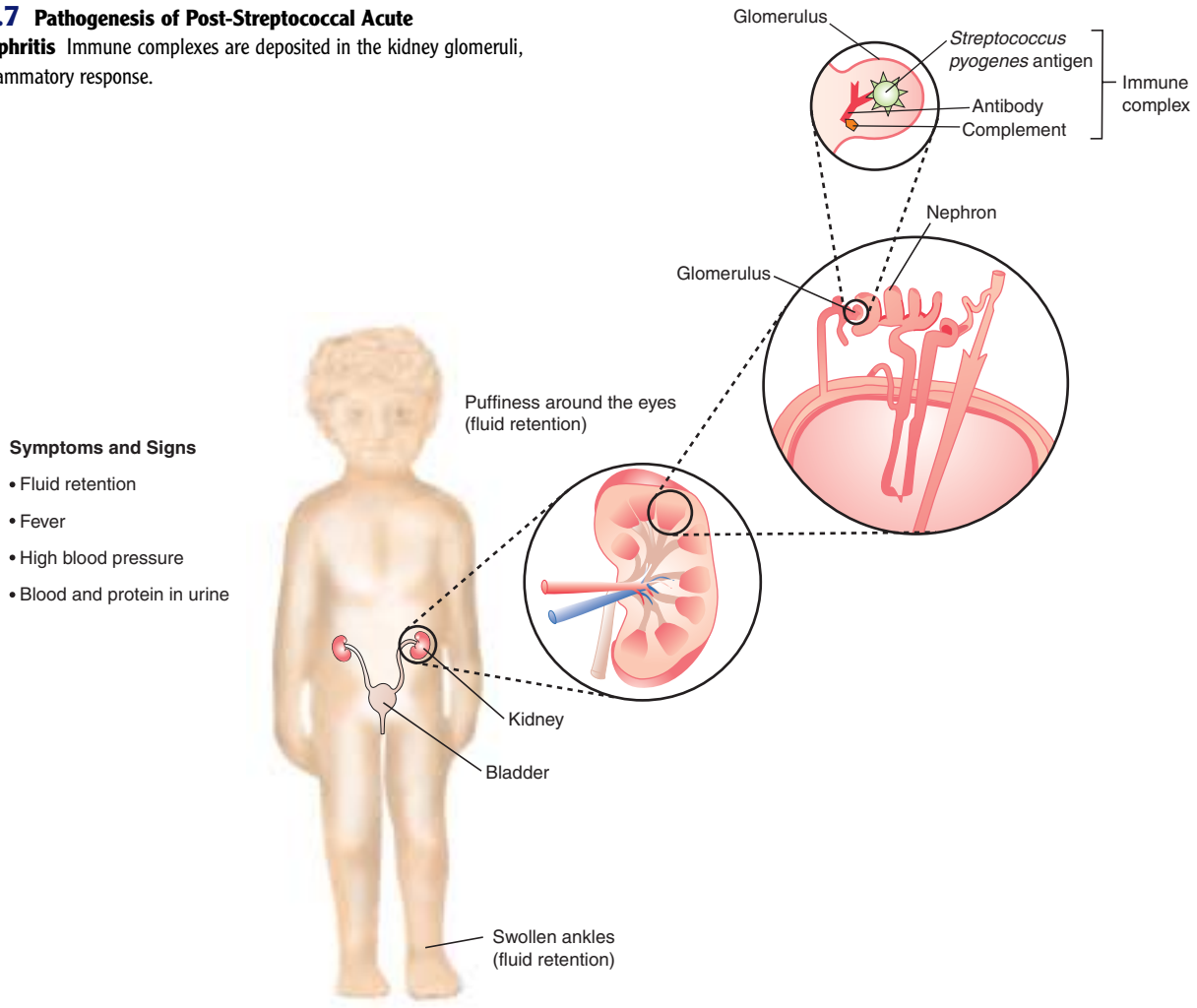


Figure 22.7 Pathogenesis of Post-Streptococcal Acute Glomerulonephritis Immune complexes are deposited in the kidney glomeruli, inciting an inflammatory response.

Prevention and Treatment

General cleanliness and avoiding people with impetigo help prevent the disease. Prompt cleansing of wounds and application of antiseptic probably also decrease the chance of infection. So far, *S. pyogenes* strains remain susceptible to penicillin. In patients allergic to penicillin, erythromycin can be substituted.

Table 22.6 summarizes the main features of impetigo.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever was first recognized in the Rocky Mountain area of the United States—thus its name. The disease is representative of a group of serious rickettsial diseases that occur worldwide and are transmitted by certain species of ticks, mites, or lice.

Symptoms

Rocky Mountain spotted fever generally begins suddenly with a headache, pains in the muscles and joints, and fever. Within a few days, a rash consisting of faint pink spots appears on the palms, wrists, ankles, and soles. This rash spreads up the arms and legs to the rest of the body and becomes raised and hemorrhagic **(figure 22.8),** meaning that it is due to blood leaking from damaged blood vessels. Bleeding may occur at various other sites, such as the mouth and nose. Involvement of the heart, kidneys, and other body tissues can result in shock and death unless treatment is given promptly.

Table 22.6 Impetigo

Symptoms	Blisters that break and "weep" plasma and pus; formation of golden-colored crusts; lymph node enlargement
Incubation period	2 to 5 days
Causative organisms	*Streptococcus pyogenes, Staphylococcus aureus*
Pathogenesis	Initiated by organisms entering the skin through minor breaks; certain strains of *S. pyogenes* are prone to cause impetigo; some *S. aureus* strains that make exfoliatin produce large blisters called bullae. Glomerulonephritis is a potential complication
Epidemiology	Spread by direct contact with carriers or patients with impetigo, insects, and fomites
Prevention and treatment	Cleanliness; care of skin injuries. Oral penicillin if cause is known to be *S. pyogenes;* otherwise, an anti-staphylococcal antibiotic orally or topically

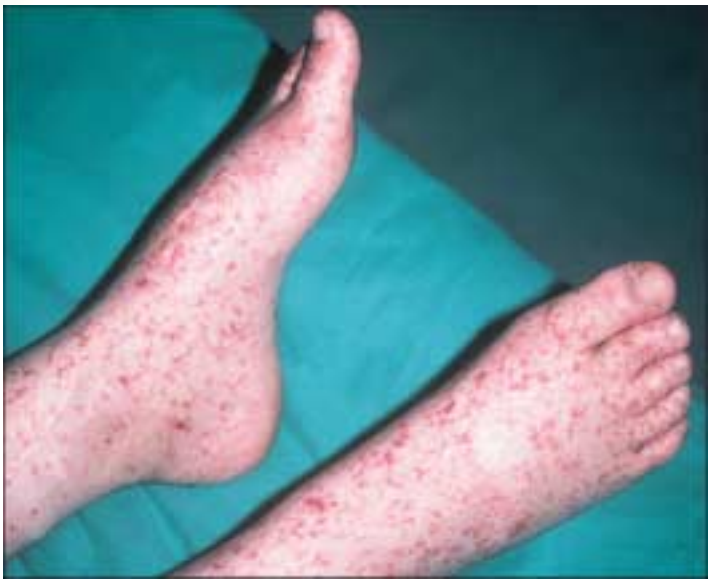


Figure 22.8 Rash Caused by Rocky Mountain Spotted Fever
Characteristically, the rash begins on the arms and legs, spreads centrally, and as shown in this photo, becomes hemorrhagic.

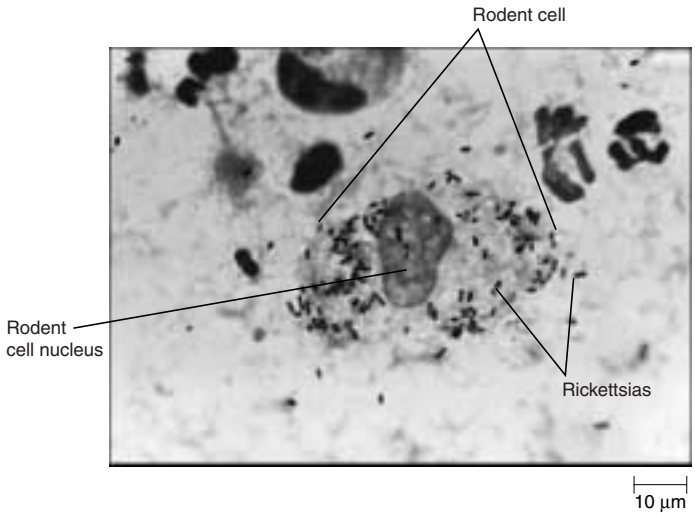


Figure 22.9 ***Rickettsia rickettsii*** **Growing Within a Rodent Cell**

Causative Agent

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii* **(figure 22.9),** an obligate intracellular bacterium. The organisms are tiny, Gram-negative, non-motile coccobacilli. *Rickettsia rickettsii* is difficult to see well in Gram-stained smears but can be seen using special stains such as Giemsa. *Rickettsia rickettsii* can sometimes be identified early in an infection by demonstrating the organisms in **biopsies**—bits of tissue removed surgically—of skin lesions. Also, their DNA can be magnified by the polymerase chain reaction (PCR) and identified with a probe. ■ **PCR, pp. 229, 239**

Pathogenesis

Rocky Mountain spotted fever is acquired from the bite of a tick infected with *R. rickettsii.* The bite is usually painless and unnoticed; the tick remains attached for hours while it feeds on capillary blood. Rickettsias are not immediately released into tick saliva from the tick's salivary glands. Therefore, the infection is not usually transmitted until the tick has fed for 4 to 10 hours. When the organisms are released into capillary blood with the tick saliva, they are taken up preferentially by the cells lining the small blood vessels. Following attachment to host cells, *R. rickettsii* is taken into the cells by endocytosis. Inside the cell, the bacteria leave their phagosome and multiply in both the cytoplasm and nucleus without being enclosed in vacuoles. Early in the infection the bacteria enter and then lyse fingerlike host cell cytoplasmic projections. Eventually, the cell membrane is so damaged by this process, the cell takes in water, lyses, and releases the remaining rickettsias. These seed the bloodstream, infecting even more cells. Infection can also extend into the walls of the small blood vessels, causing an inflammatory reaction, clotting of the blood vessels, and small areas of necrosis, or death of tissue. This process is readily apparent in the skin as a hemorrhagic rash but, more ominously, occurs throughout the body, resulting in damage to vital organs such as the kidneys and heart. Potentially even more serious is the release of endotoxin into the bloodstream from the rickettsial cell walls, causing shock and generalized bleeding because of **disseminated intravascular coagulation.** ■ **endotoxin, pp. 59, 475** ■ **disseminated intravascular coagulation, p. 720**

Epidemiology

Rocky Mountain spotted fever is an example of a **zoonosis,** a disease that exists primarily in animals other than humans. It occurs in a spotty distribution across the contiguous United States and extends into Canada, Mexico, and a few countries of South America. The involved areas change over time, but despite the name of the disease, in the United States the highest incidence has generally been in the south Atlantic and south-central states **(figure 22.10).** Rocky Mountain spotted fever is maintained in nature in various species of ticks and mammals. Generally, little or no illness develops in these natural hosts, but humans, being an accidental host, often develop severe disease. Several species of ticks transmit the disease to humans. The main vector in the western United States is the wood tick, *Dermacentor andersoni* **(figure 22.11),** while in the East it is the dog tick, *Dermacentor variabilis.* Once infected, ticks remain infected for life, transmitting *R. rickettsii* from one generation to the next through their eggs. Ticks are most active from April to September, and it is during this time period that most cases of Rocky Mountain spotted fever occur.

Prevention and Treatment

No vaccine against Rocky Mountain spotted fever is currently available to the public, although promising genetically engineered vaccines are under development. The disease can be prevented if people take the following precautions: (1) avoid tick-infested areas when possible; (2) use protective clothing; (3) use tick repellents such as dimethyltoluamide; (4) carefully inspect their bodies, especially the scalp, armpits, and groin, for ticks several times daily; and (5) remove attached ticks carefully

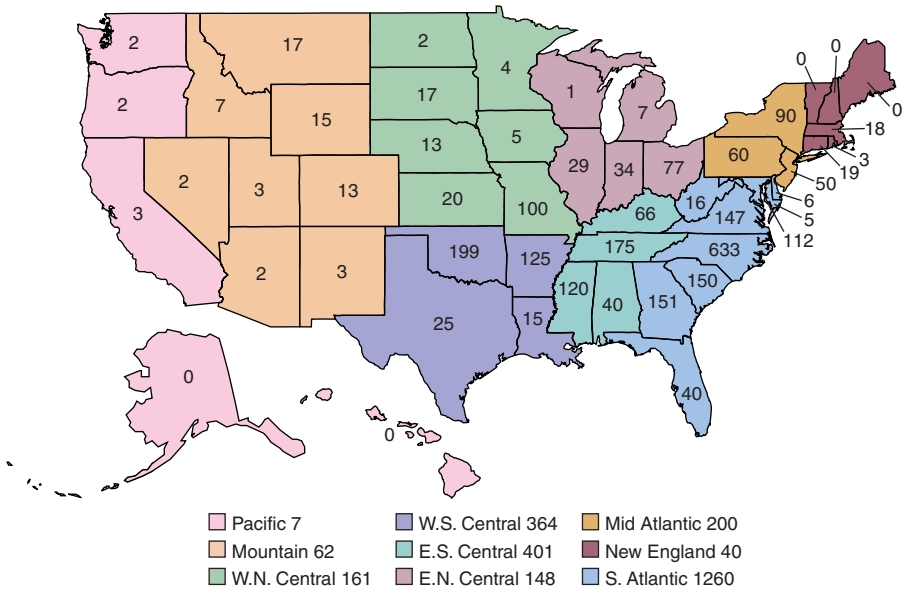


Figure 22.10 **Total Reported Cases of Rocky Mountain Spotted Fever by State and Region, 1994–1998**

to avoid crushing them and thereby contaminating the bite wound with their infected tissue fluids. Gentle traction with blunt tweezers applied at the mouthparts is the safest method of removal. Touching the tick with a hot object, gasoline, or whiskey is ineffectual. After removal of the tick, the site of the bite should be treated with an antiseptic.

The antibiotics tetracycline and chloramphenicol are highly effective in treating Rocky Mountain spotted fever if given early in the disease, before irreversible damage to vital organs has occurred. Without treatment, the overall mortality from the disease is about 20%, but it can be considerably higher in elderly patients. With early diagnosis and treatment, the mortality rate is less than 5%.

The main features of Rocky Mountain spotted fever are summarized in **table 22.7.**

Figure 22.11 ***Dermacentor andersoni*, the Wood Tick** The wood tick is the principal vector of Rocky Mountain spotted fever in the western United States.

Lyme Disease

In the mid-1970s, studies of a group of cases in Lyme, Connecticut, led to the recognition of Lyme disease as a distinct entity. It was not until 1982 that the cause was first identified, in ticks from New York State, by Dr. Willy Burgdorfer at the Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, in Hamilton, Montana. We now know that Lyme disease was present in many areas of the world long before its identification at Lyme. The ecology of the disease is complex and still incompletely understood, but we are beginning to get some answers as to why the disease has increased and extended its range.

Symptoms

Symptoms of Lyme disease can be divided roughly into three stages, although individual patients may lack symptoms in one or more of the three.

- The first stage typically begins a few days to several weeks after a bite by an infected tick. It is characterized by a skin rash called **erythema migrans (figure 22.12)** and enlargement of nearby lymph nodes. The rash begins as a red spot or bump at the site of the tick bite and slowly

Table 22.7 Rocky Mountain Spotted Fever

Symptoms	Headache, pains in muscles and joints, and fever, followed by a hemorrhagic rash that begins on the extremities
Incubation period	4 to 8 days
Causative organism	*Rickettsia rickettsii,* an obligate intracellular bacterium
Pathogenesis	Organisms multiply at site of tick bite; the bloodstream is invaded and endothelial cells of blood vessels are infected; vascular lesions and endotoxin account for pathologic changes
Epidemiology	A zoonosis transmitted by bite of infected tick, usually *Dermacentor* sp.
Prevention and treatment	Avoidance of tick-infested areas, use of tick repellent, removal of ticks within 4 hours of exposure. Treatment: tetracycline or chloramphenicol

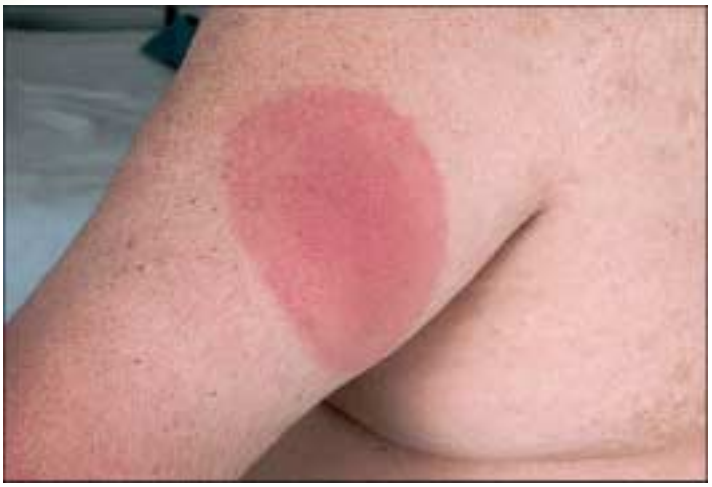


Figure 22.12 Erythema Migrans, the Characteristic Rash of Lyme Disease The rash usually has a targetlike or bull's-eye appearance. It generally causes little or no discomfort. While highly suggestive of Lyme disease, many victims of the disease fail to develop the rash.

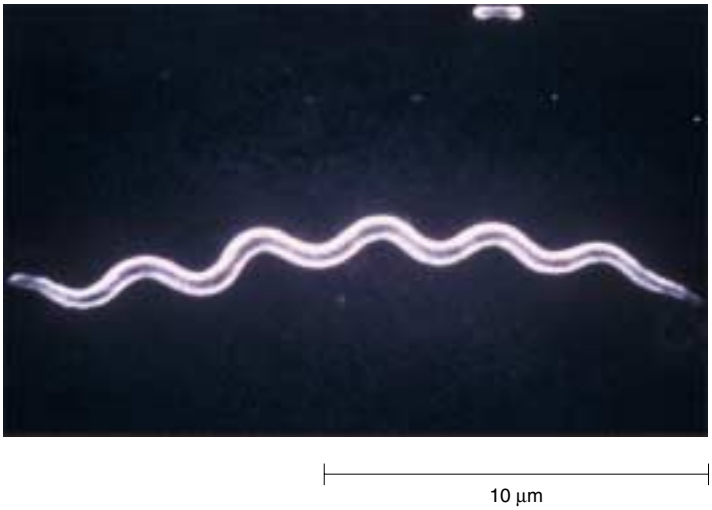


Figure 22.13 Scanning Electron Micrograph of *Borrelia burgdorferi*, the Cause of Lyme Disease

enlarges to a median diameter of 15 cm (about 6 inches). The advancing edge is bright red, while the redness of the central portion fades as the lesion enlarges. About half of these cases develop smaller satellite lesions that behave similarly. The characteristic rash is the hallmark of Lyme disease but is present in only two-thirds of the cases. Most of the other symptoms that occur during this stage are influenza-like—malaise, chills, fever, headache, stiff neck, joint and muscle pains, and backache.

- Symptoms of the second stage generally begin 2 to 8 weeks after the appearance of erythema migrans and involve the heart and the nervous system. Electrical conduction within the heart is impaired, leading to dizzy spells or fainting, and a temporary pacemaker is sometimes required to maintain a normal heartbeat. Involvement of the nervous system can cause one or more of the following symptoms: paralysis of the face, severe headache, pain when moving the eyes, difficulty concentrating, emotional instability, fatigue, and impairment of the nerves of the legs or arms.
- The symptoms of the third stage are characterized by arthritis, manifest as joint pain, swelling, and tenderness, usually of a large joint such as the knee. These symptoms develop in 60% of untreated cases, beginning on the average 6 months after the skin rash, and slowly disappear over subsequent years. Chronic nervous system impairments such as localized pain, paralysis, and depression can occur.

Causative Agent

Lyme disease is caused by *Borrelia burgdorferi*, a large microaerophilic spirochete **(figure 22.13),** 11 to 25 µm in length, with a number of axial filaments wrapped around its body and enclosed in the outer sheath of the cell wall. Surprisingly, the *Borrelia* genome is linear and present in multiple copies, completely unlike *E. coli* and most other prokaryotes, which have a single copy of a circular chromosome. The organism also contains plasmid-like elements, both circular and linear, peculiar in that they contain genes usually found on bacterial chromosomes. These findings may lead to an understanding of how *B. burgdorferi* can infect such widely differing species as mice, lizards, and ticks. ■ **spirochetes, p. 289** ■ **microaerophilic conditions, p. 94**

Pathogenesis

The spirochetes are introduced into the skin by an infected tick, multiply, and migrate outward in a radial fashion. The cell walls of the organisms cause an inflammatory reaction in the skin, which produces the expanding rash. The host's immune response is initially suppressed, allowing continued multiplication of the spirochete. The organisms then enter the bloodstream and become disseminated to all parts of the body but generally do not cross the placenta of pregnant women. Wide dissemination of the organisms accounts for the influenza-like symptoms of the first stage. After the first few weeks, an intense immune response occurs, and thereafter, it becomes very difficult to recover *B. burgdorferi* from blood or body tissues. The immune response against the bacterial antigens is probably responsible for the symptoms of the second stage. The third stage of Lyme disease is characterized by arthritis, and the affected joints have high concentrations of highly reactive immune cells and immune complexes. The joint and chronic nervous system symptoms of the third stage probably result from immune responses against persisting bacterial antigens, but evidence suggests a role for autoimmunity in some cases.

Epidemiology

Like Rocky Mountain spotted fever, Lyme disease is a zoonosis, and humans are accidental hosts. The disease is widespread

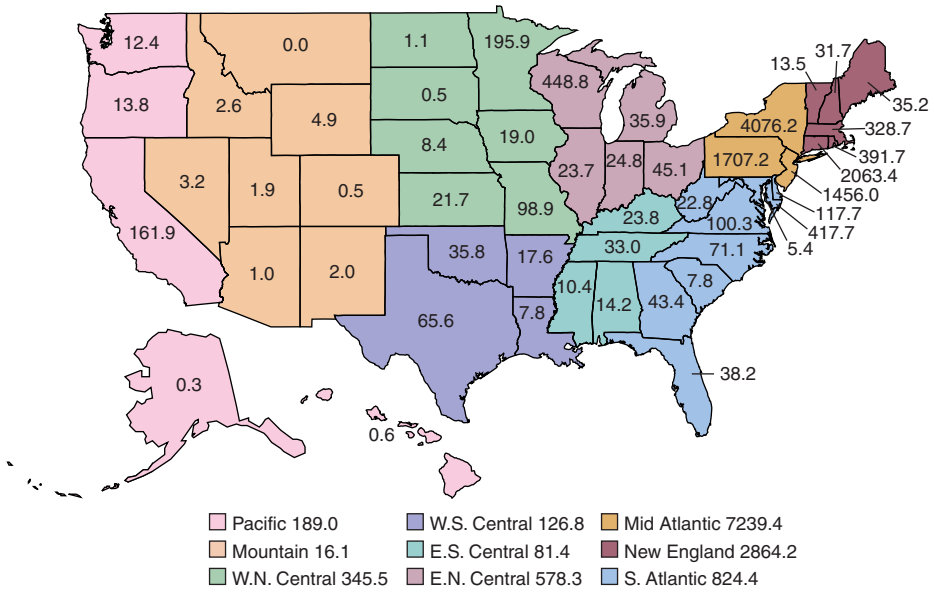


Figure 22.14 **Average Number of Reported Cases of Lyme Disease per Year 1990–1999**

in the United States **(figure 22.14),** and its incidence depends on complex factors that place humans and infected ticks in close proximity. Several species of ticks have been implicated as vectors, but the most important in the eastern United States is the black-legged tick, *Ixodes scapularis* **(figure 22.15).** In some areas of the East Coast, 80% of these ticks are infected with *Borrelia burgdorferi*. Because of their small size (1–2 mm before feeding; 3–5 mm when fully engorged with blood), these ticks often feed and drop off their host without being detected, so that two-thirds of Lyme disease patients are unable to recall a tick bite. The ticks mature during a 2-year cycle **(figure 22.16).** A six-legged larval form emerges from the egg. After growing, it molts, shedding its outer covering to become an eight-legged form called a nymph. After another molt as the tick grows in size, the nymph becomes the sexually mature adult form. The nymph avidly seeks blood meals and is therefore mainly responsible for transmitting Lyme disease. The preferred host of *I. scapularis* is the white-footed mouse, which acquires *Borrelia burgdorferi* from an infected tick and develops a sustained bacteremia (meaning the bacteria circulate in the mouse's bloodstream for long periods of time). The mouse thus becomes a source of infection for other ticks. Passage of the spirochete from adult tick to its offspring via its eggs rarely occurs. Infected ticks and mice constitute the main reservoir of *B. burgdorferi*, but deer, while not a significant reservoir, are important because they are the preferred host of the adult ticks and the site where mating occurs. Moreover, deer can quickly spread the disease over a wide area. Tick nymphs are the most active from May to September, corresponding to the peak occurrence of Lyme disease cases. Adult ticks sometimes bite humans late in the season and transmit the disease. Infectious ticks can be present in well-mowed lawns as well as in wooded areas. Expanding human populations continually intrude into the zoonotic life cycle.

■ **reservoirs, p. 486**

Prevention and Treatment

General preventive measures for Lyme disease are the same as those for Rocky Mountain spotted fever. A recombinant vaccine produced in *E. coli* is no longer marketed. Persons are advised to use every other means to avoid infection. Several antibiotics are effective in patients with early disease. In late disease, the response to treatment is less satisfactory, presumably because the spirochetes are not actively multiplying and antibacterial medications are usually ineffective against nongrowing bacteria. Nevertheless, prolonged treatment with intravenous ampicillin or ceftriaxone has been curative in many cases.

Figure 22.15 **The Black-Legged Tick, *Ixodes scapularis*, Adult and Nymph** This tick is the most important vector of Lyme disease in the eastern and north-central United States.

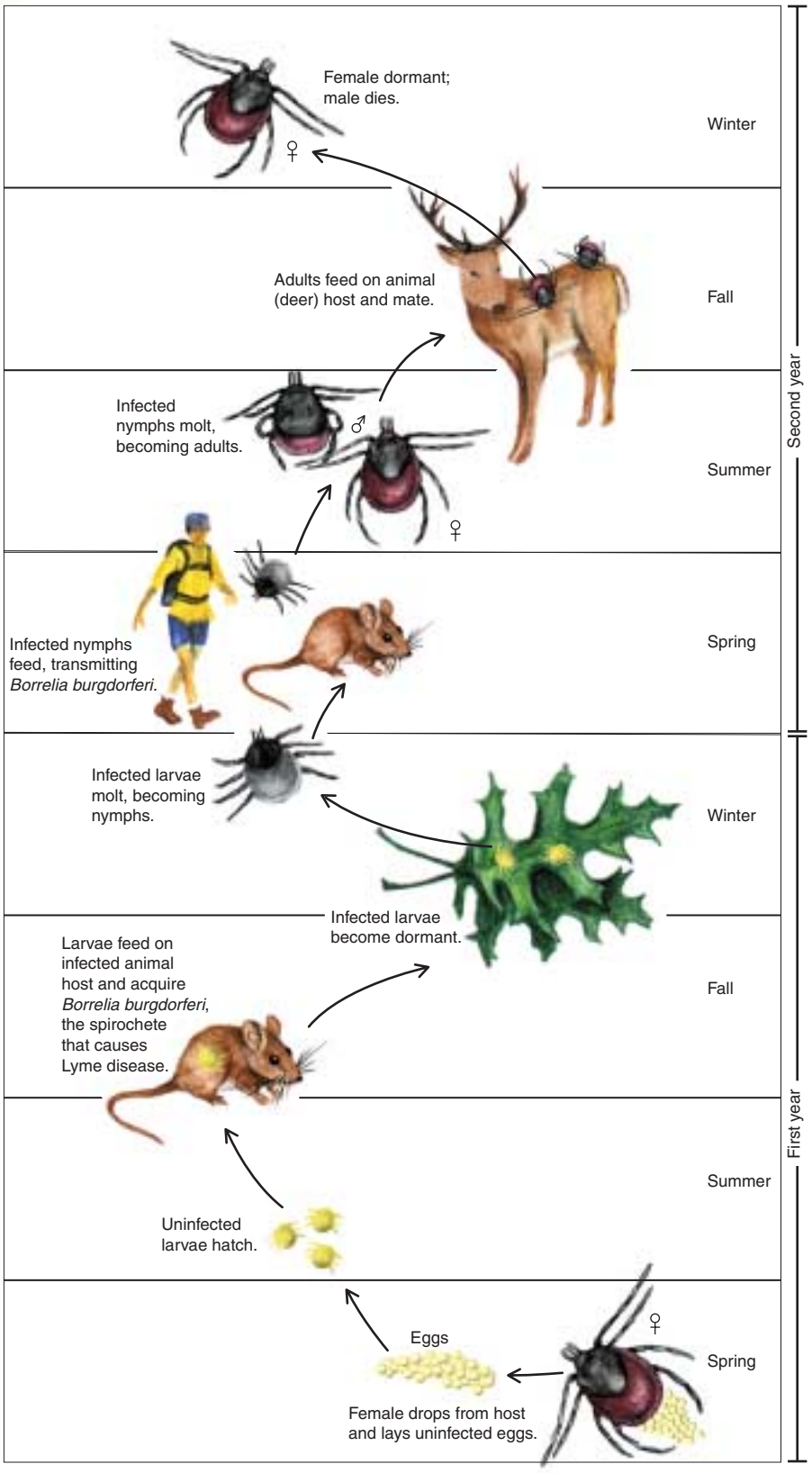


Figure 22.16 **Life Cycle of the Black-Legged Tick, *Ixodes scapularis*, the Principal Vector of *Borrelia burgdorferi*, Cause of Lyme Disease** Note that the life cycle covers 2 years, during which the tick obtains three blood meals. The males die soon after mating, the females after depositing their eggs in the following spring. Variations in the life cycle occur, probably dependent on climate and food availability.

Table 22.8 summarizes some features of Lyme disease.

MICROCHECK 22.3

Extensive skin damage can result from a toxin absorbed into the circulation from a localized infection. An immunological reaction to circulating microbial products can damage the kidneys. Changes in the skin in an infectious disease commonly reflect similar changes in other body tissues. Zoonoses involving ticks and small mammals pose a widespread danger to humans. Complex ecological factors can govern the incidence of infectious diseases.

- List four extracellular products of *Staphylococcus aureus* that contribute to its virulence.
- Describe the characteristic rash of Lyme disease.
- The existence of extensive scalded skin syndrome does not indicate that *Staphylococcus* is growing in all the affected areas. Why?

22.4 Skin Diseases Caused by Viruses

Several childhood diseases are characterized by distinctive skin rashes, **exanthems,** caused by viruses carried to the skin by the blood from sites of infection in the upper respiratory tract. This group of diseases is usually diagnosed by inspection of the rash and other clinical findings. When the disease is not typical, however, tests can be performed to identify specific antibody against the virus, and the virus can often be cultivated from skin lesions, upper respiratory secretions, or other material. Viruses, like obligate intracellular bacteria, can only reproduce in living cells, most conveniently in cultures of cells originally derived from human or other tissues and maintained in the laboratory.

Chickenpox (Varicella)

Chickenpox is the common name for **varicella,** the most common of the viral rashes of childhood. The causative virus is a member of the herpesvirus family and, like others in that group, produces a latent infection that can reactivate long after recovery from the initial illness. ■ **latent infections, p. 463**

Table 22.8 Lyme Disease

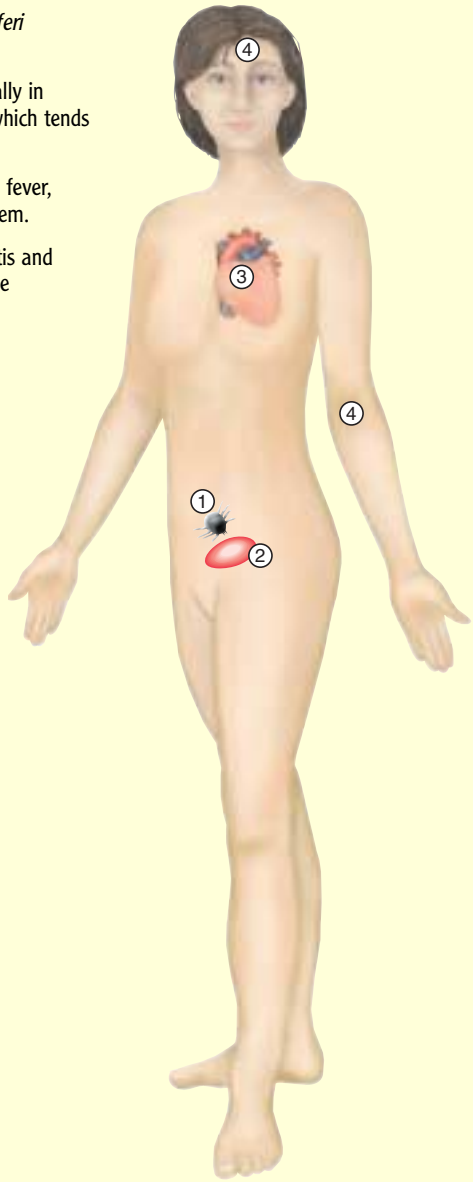
① Bite of tick infected with *Borrelia burgdorferi* introduces the bacteria into the skin.

② *B. burgdorferi* reproduce and spread radially in the skin, causing an expanding red rash which tends to clear centrally.

③ The bacteria enter the bloodstream, cause fever, acute injury to the heart and nervous system.

④ Chronic symptoms develop, such as arthritis and paralysis due to persisting bacteria and the immune response to them.

⑤ No person-to-person transmission.



Symptoms	*Stage I:* Enlarging, red rash at the site of the bite; fever, malaise, headache, general achiness, enlargement of lymph nodes near bite, joint pains. *Stage 2:* Acute involvement of heart and nervous system. *Stage 3:* Chronic arthritis and impairment of the nervous system.
Incubation period	Approximately 1 week
Causative agent	*Borrelia burgdorferi,* a spirochete
Pathogenesis	Spirochetes injected into the skin by an infected tick multiply and spread radially; the spirochetes enter the bloodstream and are carried throughout the body; the immune reaction to bacterial antigen causes tissue damage.
Epidemiology	Spread by the bite of ticks, *Ixodes* sp., usually found in association with animals such as white-footed mice and white-tailed deer living in wooded areas.
Prevention and treatment	Protective clothing; tick repellents. Early treatment with doxycycline and others; prolonged antibiotic therapy in chronic cases.

Symptoms

Most cases of chickenpox are mild, sometimes unnoticed, and recovery is usually uncomplicated. The typical case has a rash that is diagnostic. It begins as small, red spots called macules, little bumps called papules, and small blisters called vesicles, surrounded by a narrow zone of redness. The lesions can erupt anywhere on the body, although usually they first appear on the back of the head, then the face, mouth, main body, and arms and legs, ranging from only a few lesions to many hundreds. The lesions appear at different times, and within a day or so they go through a characteristic evolution from macule to papule to vesicle to pustule, a pus-filled blister. After the pustules break, leaking virus-laden fluid, a crust forms, and then healing takes place. At any time during the rash, lesions are at various stages of evolution **(figure 22.17).** The lesions are pruritic, meaning itchy, and scratching may lead to serious, even fatal, secondary infection by *Streptococcus pyogenes* or *Staphylococcus aureus.*

Symptoms of varicella tend to be more severe in older children and adults. In about 20% of adults, pneumonia develops, causing rapid breathing, cough, shortness of breath, and a dusky skin color. The pneumonia subsides with the rash, but respiratory symptoms often persist for weeks. Varicella is also a major threat to newborn babies if the mother develops the disease within 5 days before delivery to 2 days afterward. Mortality in these babies has been as high as 30%. Also, **congenital varicella syndrome** develops in a fraction of a percent of babies

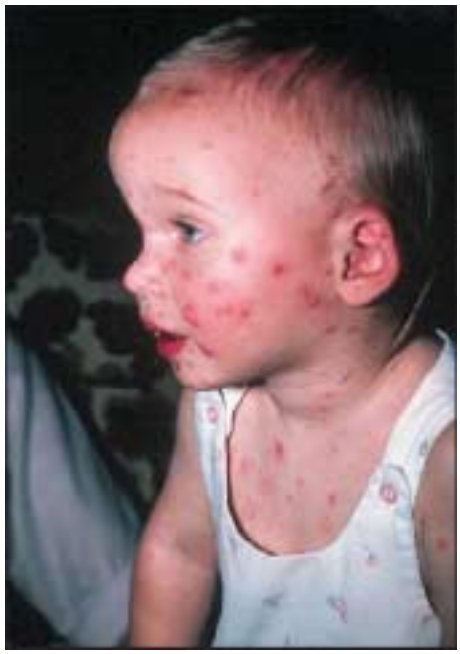


Figure 22.17 **A Child with Chickenpox (Varicella)** Characteristically, lesions in various stages of evolution—macules, papules, vesicles, and pustules—are present.

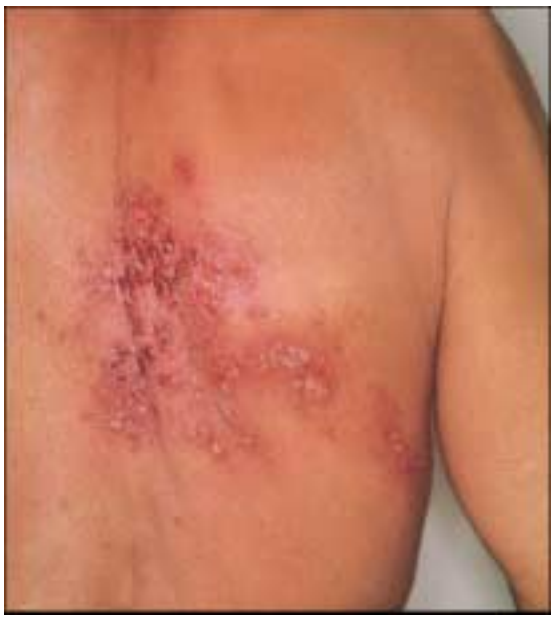


Figure 22.18 **Shingles (Herpes Zoster)** The rash mimics that of chickenpox, except that it is limited to a sensory nerve distribution on one side of the body.

whose mothers contract varicella earlier in pregnancy. These babies are born with such defects as underdeveloped head and limbs, and cataracts. In addition, the disease is a threat to immunocompromised patients of any age. The virus can damage the lungs, heart, liver, kidneys, and brain, resulting in death in about 20% of the cases.

Reactivation of chickenpox is called **shingles,** or **herpes zoster.** It can occur at any age but becomes increasingly common with advancing age. It begins with pain in the area supplied by a nerve of sensation, often on the chest or abdomen but sometimes on the face or an arm or leg. After a few days to 2 weeks, a rash characteristic of chickenpox appears, but unlike chickenpox the rash is usually restricted to an area supplied by the branches of the involved sensory nerve **(figure 22.18).** The rash generally subsides within a week, but pain may persist for weeks, months, or longer. In people with AIDS or other serious immunodeficiency, instead of being confined to one area the rash often spreads to involve the entire body, as in a severe case of chickenpox.

A curious affliction known as **Reye's syndrome** occasionally occurs in association with chickenpox, usually within 2 to 12 days of the onset of the infection. The patients begin vomiting and slip into a coma. The syndrome occurs predominantly in children between 5 and 15 years old and is characterized by liver and brain damage. It occurs uncommonly, with a general trend to declining incidence, but the death rate has been around 30%. Reye's syndrome is also seen in association with a number of other viral infections including influenza A and B. Epidemiologic evidence suggesting that aspirin therapy increases the risk of Reye's syndrome has led physicians to use this drug sparingly in children with fever.

Causative Agent

Chickenpox is caused by the **varicella-zoster virus,** a member of the herpesvirus family. It is an enveloped, medium-sized (150–200 nm), double-stranded DNA virus, indistinguishable from other herpesviruses in appearance **(figure 22.19).**

Pathogenesis

The virus enters the body by the respiratory route, establishes an infection, replicates, and disseminates to the skin via the bloodstream. After the living layers of skin cells are infected, the virus spreads directly to adjacent cells, and the characteristic skin lesions appear. Stained preparations of infected cells show **intranuclear inclusion bodies,** visible as pink staining bodies at the place in the nucleus where the virus reproduces. Some infected cells fuse together, forming multinucleated giant cells. The infected cells swell and ultimately lyse. The virus enters the sensory nerves, presumably when an area of skin infection advances to involve a sen-

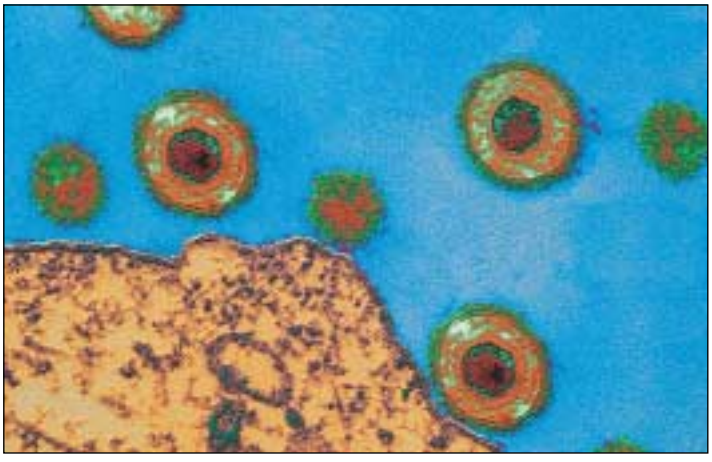


Figure 22.19 **Electron Micrograph of Varicella-Zoster Virus, Cause of Chickenpox and Shingles**

sory nerve ending. Conditions inside the nerve cell do not permit full expression of the viral genome; however, viral DNA is present in the ganglia (singular: ganglion) of the nerves and is fully capable of coding for mature infectious virus. Ganglia are small bulges in sensory nerves located near the spine; they contain the nuclei and cell bodies of the nerves. The mechanism of suppression of viral replication within the nerve cell is not known but is probably under the control of immune cells.

The occurrence of shingles correlates with a decline in cell-mediated immunity. With the decline, infectious varicella-zoster virus is presumably produced in the nucleus of the nerve cells and is carried to the skin by the normal circulation of cytoplasm within the nerve cell. With the appearance of the skin lesions, a prompt, intense anamnestic boost of both cellular and humoral immunity ensues. A marked inflammatory reaction occurs in the ganglion with an accumulation of immune cells, and shingles quickly disappears, although sometimes leaving scars and chronic pain. ■ secondary response, p. 405

Epidemiology

The annual incidence of chickenpox in the United States has been estimated at 3.7 million but is probably lower now that immunization is widespread. Reporting the disease is not required, so that most cases go unreported, and many are so mild that they go unnoticed. Both respiratory secretions and skin lesions are infectious; as with many diseases transmitted by the respiratory route, most cases occur in the winter and spring months. Humans are the only reservoir, and because the disease is highly contagious, about 90% of people are infected by the age of 15. The incubation period of the disease averages about 2 weeks, with a range of 10 to 21 days. Cases are infective from 1 to 2 days before the rash appears until all the lesions have crusted (usually 4 days after the onset).

The mechanism by which the varicella-zoster virus persists in the body allows it to survive indefinitely in small isolated populations. By contrast, when a virus such as measles is introduced into an isolated community, it spreads quickly and infects most of the susceptible individuals, who either become immune or die. If susceptible victims are unavailable, the measles virus will disappear from the community. On the other hand, varicella-zoster virus will reappear from cases of shingles whenever sufficient numbers of susceptible children have been born. Shingles occurs in about 1% of elderly people.

Prevention and Treatment

In 1995, an attenuated chickenpox vaccine was licensed in the United States. It has proven safe with use in millions people in various countries, since about 1984. The vaccine is recommended for all healthy persons age 12 months or older who do not have a history of chickenpox or who lack laboratory evidence of immunity to the disease. Immunization should be done sometime before one's 13th birthday because of the increased likelihood of serious complications from chickenpox in older children and adults. It is not given during pregnancy, and pregnancy should be avoided for 3 months after vaccination because of fear the vaccine might rarely result in congenital varicella syndrome. In general, the vaccine should not be administered to people with malignant or immunodeficiency diseases. Healthy, non-immune contacts of such people, however, should be vaccinated. By preventing chickenpox, the vaccine markedly decreases the chance of developing shingles. ■ attenuated vaccines, p. 422

Increasing numbers of individuals with impaired immunity are at risk of severe disseminated varicella-zoster virus infections. These include persons with cancer, AIDS, and organ transplants and newborn babies whose mothers contracted chickenpox near the time of delivery. They can be partially protected from severe disease if they are passively immunized by injecting them with zoster immune globulin (ZIG) derived from the blood of recovered herpes zoster patients. The antiviral medications acyclovir and famciclovir, among others, are helpful in preventing and treating varicella-zoster infections. ■ passive immunity, p. 420

The main features of chickenpox are summarized in **table 22.9.**

Measles (Rubeola)

Measles, "hard measles," and "red measles" are common names for **rubeola.** One of the great success stories of the last half of the twentieth century has been the dramatic reduction in measles cases by immunizing children with an attenuated vaccine against the disease. Now there is reason to hope that the disease can be entirely eliminated from the world.

Symptoms

Measles begins with fever, runny nose, cough, and swollen, red, weepy eyes. Within a few days, a fine red rash appears on the forehead and spreads outward over the rest of the body **(figure 22.20).** Unless complications occur, symptoms generally disappear in about 1 week.

Unfortunately, many cases are complicated by secondary infections caused by bacterial pathogens, mainly *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Haemophilus influenzae.* These pathogens readily invade the body because measles damages the normal body defenses. Secondary infections most commonly cause earaches and pneumonia.

Figure 22.20 A Child with Measles (Rubeola) The rash is usually accompanied by fever, runny nose, and a bad cough.

Table 22.9 Chickenpox (Varicella)

① Varicella-zoster virus is inhaled, infects nose and throat.

② The virus infects nearby lymph nodes, reproduces, and seeds the bloodstream.

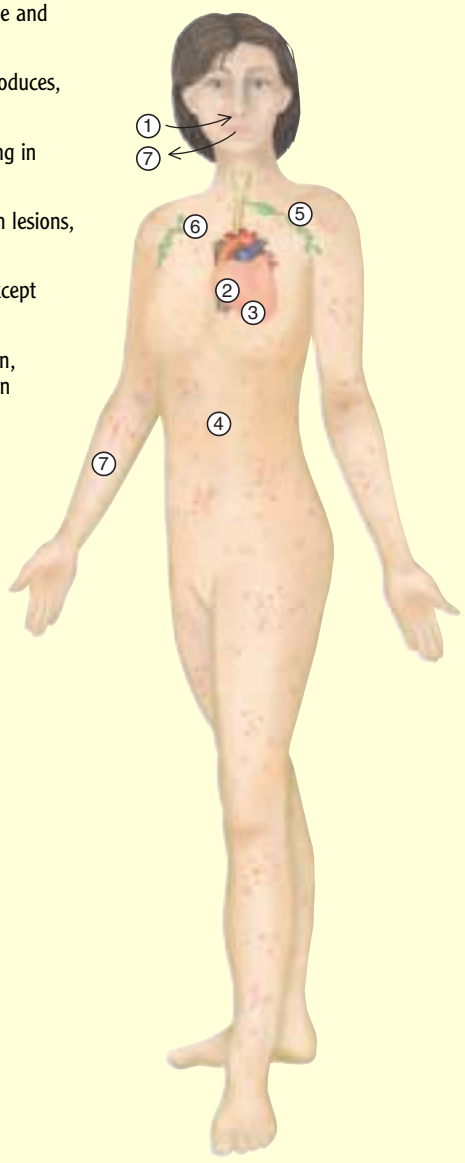
③ Infection of other body cells occurs, resulting in showers of virions into the bloodstream.

④ These virions cause successive crops of skin lesions, which evolve into blisters and crusts.

⑤ Immune system eliminates the infection except for some virions inside the nerve cells.

⑥ If immunity wanes with age or other reason, the virus persisting in the nerve ganglia can infect the skin, causing herpes zoster.

⑦ Transmission to others occurs from respiratory secretions and skin.



Symptoms	Itchy bumps and blisters in various stages of development, fever; latent infections can become manifest as shingles (herpes zoster) years later
Incubation period	10 to 21 days
Causative agent	Varicella-zoster virus; enveloped double-stranded DNA virus of the herpesvirus family
Pathogenesis	Upper respiratory virus multiplication followed by dissemination via bloodstream to the skin; cytopathic effect of virus includes the formation of giant cells
Epidemiology	Highly infectious. Acquired by the respiratory route; humans, both individuals with chickenpox and those with shingles, the only source; dissemination is from skin lesions and respiratory secretions
Prevention and treatment	Attenuated vaccine. Passive immunization with zoster immune globulin (ZIG) for immunocompromised individuals; acyclovir or similar antiviral medication for prevention and treatment

In about 5% of cases, the rubeola virus itself causes pneumonia, with rapid breathing, shortness of breath, and dusky skin color from lack of adequate oxygen exchange in the lungs. Encephalitis, inflammatory disease of the brain, is another serious complication, marked by fever, headache, confusion, and seizures. This complication occurs in about one out of every 1,000 cases of measles. Permanent brain damage, with mental retardation, deafness, and epilepsy, commonly results from measles encephalitis.

Very rarely, rubeola is followed 2 to 10 years later by a disease called **subacute sclerosing panencephalitis (SSPE),** which is marked by slowly progressive degeneration of the brain, generally resulting in death within 2 years. A defective measles virus can be detected in the brains of these patients, and high levels of measles antibody are present in their blood. This is an example of a "slow virus" disease. It has all but disappeared from the United States with widespread vaccination against measles. ■ **slow infections, p. 355**

Measles that occurs during pregnancy results in an increased risk of miscarriage, premature labor, and low birth weight. Birth defects, however, are generally not seen.

Causative Agent

Measles is caused by rubeola virus, a pleomorphic, medium-sized (120–200 nm diameter), single-stranded, negative-sense RNA virus of the paramyxovirus family. The viral envelope has two biologically active projections. One, H, is responsible for viral attachment to host cells, and the other, M, is responsible for fusion

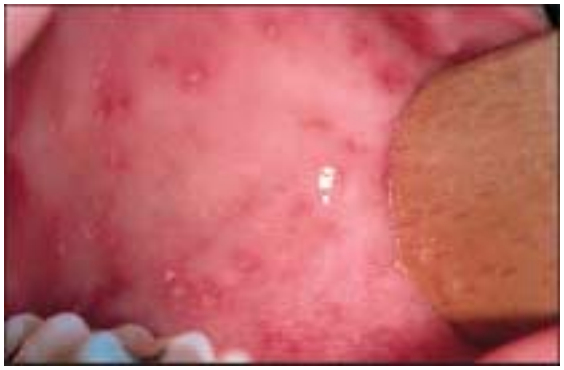


Figure 22.21 Koplik's Spots, Characteristic of Measles (Rubeola), Are Usually Transitory They resemble grains of salt on a red base.

of the viral outer membrane with the host cell. The M antigen also causes adjacent infected host cells to fuse together, producing multinucleated giant cells. ■ **positive- and negative-sense viruses, p. 351**

Pathogenesis

Rubeola virus is acquired by the respiratory route. It presumably replicates in the upper respiratory epithelium, spreads to lymphoid tissue, and following further replication, eventually spreads to all parts of the body. Mucous membrane involvement is responsible for an important diagnostic sign, **Koplik's spots (figure 22.21),** which are usually best seen opposite the molars, located in the back part of the mouth. Koplik's spots look like grains of salt lying on an oral mucosa that is red and rough, resembling red sandpaper. Damage to the respiratory mucous membranes partly explains the markedly increased susceptibility of measles patients to secondary bacterial infections, especially infection of the middle ear and lung. Involvement of the intestinal epithelium may explain the diarrhea that sometimes occurs in measles and contributes to high measles death rates in impoverished countries. In the United States, deaths from measles occur in about one to two of every 1,000 cases, mainly from pneumonia and encephalitis.

The skin rash of measles results from the effect of rubeola virus replication in skin cells and the cellular immune response against the viral antigen in the skin. The measles virus temporarily suppresses cellular immunity, causing cold sores to appear and latent tuberculosis to activate. ■ **cold sores, p. 606** ■ **tuberculosis, p. 580**

Epidemiology

Humans are the only natural host of rubeola virus. Spread is by the respiratory route. Before vaccination became widespread in the 1960s, probably less than 1% of the population escaped infection with this highly contagious virus. Continued use of measles vaccine resulted in a progressive decline in cases, so that endemic measles no longer occurs in the United States. Small outbreaks of the disease, however, continue to be seen as a result of introductions from other countries.

These outbreaks occur due to the presence of non-immune populations including (1) children too young to be vaccinated; (2) preschool children never vaccinated; (3) children and adults inadequately vaccinated; and (4) persons not vaccinated for religious or medical reasons. Worldwide, measles ranks among the leading causes of death and disability among the impoverished, where the mortality rate may reach 15% and secondary infections may reach 85%.

Prevention and Treatment

Measles can be prevented by injecting an attenuated rubeola virus vaccine. At the time of the introduction of the vaccine in the early 1960s, there were about 400,000 cases of the disease reported each year in the United States, probably representing one-tenth of the actual number of victims. At present, less than 100 are generally reported. In 1980 the worldwide incidence of rubeola was estimated to be 100 million with 5.8 million deaths. Globally, vaccination programs have lowered the number of cases dramatically since then. However, the decline in incidence has not been uniform among the different regions of the world **(figure 22.22),** largely due to wars and poverty, but substantial progress has been made, and complete elimination of measles is now a realistic goal.

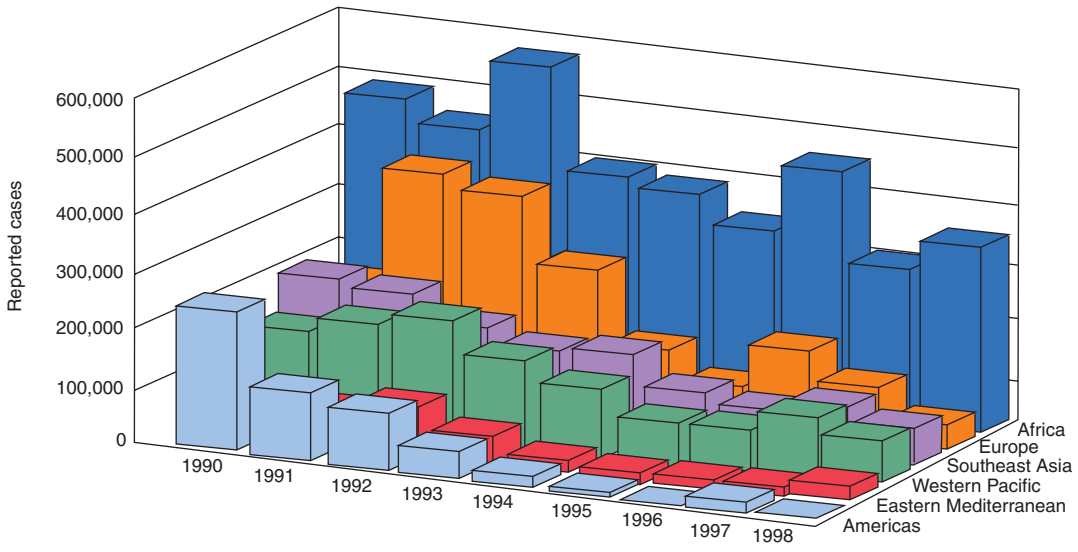


Figure 22.22 Reported Incidence of Measles in Different Regions of the World, 1990–1998 Reported cases represent only a small fraction of the total. The lack of progress in measles control in some regions reflects difficulties in delivering measles vaccine.

Table 22.10 Measles (Rubeola)

① Airborne rubeola virus infects eyes and upper respiratory tract, then the lymph nodes in the region.

② Virus enters the bloodstream and is carried to all parts of the body including the brain, lungs, and skin.

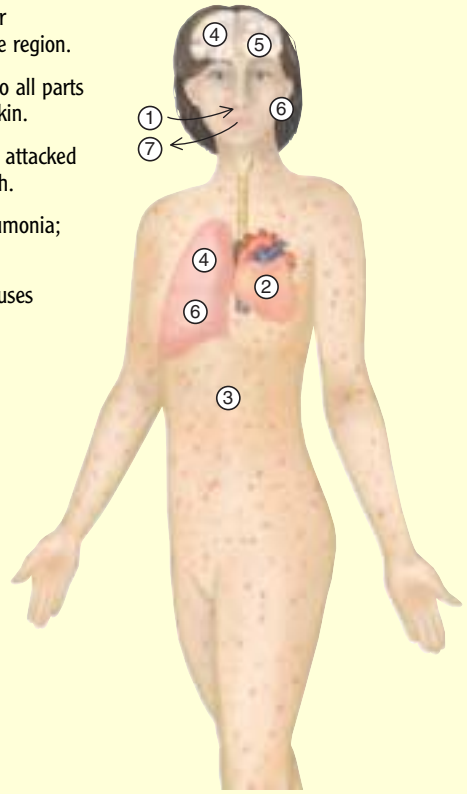
③ Skin cells infected with the rubeola virus are attacked by immune T cells, causing a generalized rash.

④ Virus replicating in the lungs can cause pneumonia; the brain can also be infected.

⑤ In rare cases, virus persisting in the brain causes subacute sclerosing panencephalitis, months or years after the acute infection.

⑥ Secondary infection of the ears and lungs is common.

⑦ Transmission is by respiratory secretions.



Symptoms	Rash, fever, weepy eyes, cough, and nasal discharge
Incubation period	10 to 12 days
Causative agent	Rubeola virus, a single-stranded, negative-sense RNA virus of the paramyxovirus family
Pathogenesis	Virus multiplies in respiratory tract; spreads to lymphoid tissue, then to all parts of body, notably skin, lungs, and brain; damage to respiratory tract epithelium leads to secondary infection of ears and lungs
Epidemiology	Acquired by respiratory route; highly contagious; humans only source
Prevention and treatment	Attenuated virus vaccine after age 12 months; second dose upon entering elementary school or at adolescence. No antiviral treatment available at present.

The measles vaccine is usually given together with mumps and rubella vaccines, MMR. The first injection of vaccine is given near an infant's first birthday. Since 1989, a second injection of vaccine is given at entry into elementary school. The two-dose regimen has resulted in at least 99% of the recipients becoming immune. In an epidemic, vaccine is given to babies as young as 6 months, who are then reimmunized before their second birthday. Students entering high school or college are advised to get a second dose of vaccine if they have not received one earlier. Those at special risk of acquiring rubeola, such as medical personnel, should be immunized regardless of age, unless they definitely have had measles or have laboratory proof of immunity.

No antiviral treatment exists for rubeola at present. Some features of rubeola are summarized in **table 22.10.**

German Measles (Rubella)

German measles and three-day measles are common names for **rubella.** The term *German measles* arose because the disease was first described in Germany. In contrast to varicella and rubeola, rubella is typically a mild, often unrecognized disease that is difficult to diagnose. Nevertheless, infection of pregnant women can have tragic consequences.

Symptoms

Characteristic symptoms of German measles are slight fever, mild cold symptoms, and enlarged lymph nodes behind the ears and on the back of the neck. After about a day, a faint rash consisting of innumerable pink spots appears over the face, chest, and abdomen **(figure 22.23).** Unlike rubeola, there are no diagnostic mouth lesions. Adults commonly develop painful joints, with pain generally lasting 3 weeks or less. Other symptoms generally last only a few days. The significance of rubella, however, lies not with these symptoms but rather with rubella's threat to the fetuses of pregnant women.

Causative Agent

German measles is caused by the rubella virus, a member of the togavirus family. It is a small, about 60 nm in diameter, enveloped, single-stranded, positive-sense RNA virus that can readily be cultivated in cell cultures. Surface glycoproteins give the virus *in vitro* hemagglutinating ability, which is inhibited by specific antibody, allowing serological identification of the virus.

Pathogenesis

The rubella virus enters the body via the respiratory route. It multiplies in the nasopharynx and enters the bloodstream, causing a

CASE PRESENTATION

The patient was a 20-year-old asymptomatic man who was immunized against measles as a requirement for starting college. He had received his first dose of measles vaccine at approximately 1 year of age.

Past medical history revealed that he was a hemophiliac and had contracted the human immunodeficiency virus from clotting factor (a blood product given to control bleeding) contaminated with the virus.

Laboratory tests showed that he had a very low $CD4^+$ lymphocyte count, indicating a severely damaged immune system.

About a month after his precollege immunization, he developed pneumocystosis, a lung infection characteristic of AIDS, was hospitalized, had a good response to treatment, and was discharged. Ten months later, he was again hospitalized for symptoms of a severe lung infection. He had no rash. Multiple laboratory tests to determine the cause of his infection were negative. Finally, a lung biopsy was performed and revealed "giant cells," very large cells with multiple nuclei. Cytoplasmic and intranuclear inclusion bodies were also present. This picture was highly suggestive of measles pneumonia, and measles virus subsequently was recovered from cell cultures of the biopsy material. Other studies showed it to be the measles vaccine virus. The patient received intravenous gamma globulin and an experimental antiviral medication, ribavirin, and improved. Subsequently, however, his condition deteriorated, and he died of presumed complications of AIDS.

1. Is measles immunization a good idea for people with immunodeficiency?
2. Is it surprising that the vaccine virus was still present in this patient 11 months after vaccination? Explain.
3. Despite the severe infection, there was no rash. Why?

Discussion

1. Measles is often disastrous for persons with AIDS or other immunodeficiencies. They should be immunized as soon as possible in their illness, before the immune system becomes so weakened it cannot respond effectively to the vaccine. Also, as this and other cases have shown, the vaccine virus can itself be pathogenic when immunodeficiency is severe. With the worldwide effort to eliminate measles, the risk of exposure to the wild-type measles virus, as opposed to the laboratory-derived vaccine virus, is declining, but outbreaks in colleges and other institutions still occur. A severely immunodeficient individual can be passively immunized against measles with gamma globulin if exposure to the wild-type virus occurs.
2. Measles is often given as an example of a persistent viral infection, meaning that following infection the virus can persist in the body for months or years in a slowly replicating form. It has been suggested but not proven that this explains the lifelong immunity conferred by measles infection in normal people. In rare presumably normal individuals and more commonly in malnourished or immunodeficient individuals, persistent infection leads to damage to the brain, lung, liver, and possibly, the intestine. Subacute sclerosing panencephalitis can follow measles vaccination, but at a much lower rate than after wild virus infection.
3. Following acute infection, the measles virus floods the bloodstream and is carried to various tissues of the body, including the skin. The rash of measles is caused by T lymphocytes attacking measles virus antigen lodged in the skin capillaries. In the absence of functional T lymphocytes, the rash does not occur.

sustained viremia (meaning viruses circulating in the bloodstream). The blood transports the virus to various body tissues, including the skin and joints. Humoral and cell-mediated immunity develop against the virus, and the resulting antibody-antigen complexes probably account for the rash and joint symptoms.

In pregnant women, the placenta becomes infected during the period of viremia. Early in pregnancy, the virus readily crosses the placenta and infects the fetus, but as the pregnancy progresses, fetal infection becomes increasingly less likely. Virtually all types of fetal cells are susceptible to infection; some cells are killed, while others develop a persistent infection in which cell division is impaired and chromosomes are damaged. The result is a characteristic pattern of fetal abnormalities that is referred to as the **congenital rubella syndrome.** The abnormalities include cataracts and other abnormalities of the eyes, brain damage, deafness, heart defects, and low birth weight despite normal gestation. Babies may be stillborn. Those that live continue to excrete rubella virus in throat secretions and urine for many months. The likelihood of the syndrome varies according to the age of the fetus when infection occurs. Infections occurring during the first 6 weeks of pregnancy result in almost 100% of the fetuses having a detectable injury, most commonly minor deafness. Even infants who are apparently normal, however, excrete rubella virus for extended periods and thus can infect others. ■ neutralizing antibody, p. 400

Epidemiology

Humans are the only natural host for rubella virus. The disease is highly contagious although less so than rubeola; it is estimated that in the prevaccine era, 10% to 15% of people reached adulthood without being infected. Complicating the epidemiology of rubella is the fact that over 40% of infected individuals fail to develop symptoms, but can spread the virus. People who develop typical rubella can be infectious for as much as 7 days before the rash appears until 7 days afterward. Before widespread use of the vaccine began in 1969, periodic major epidemics arose. One epidemic in 1964 resulted in about 30,000 cases of congenital rubella syndrome.

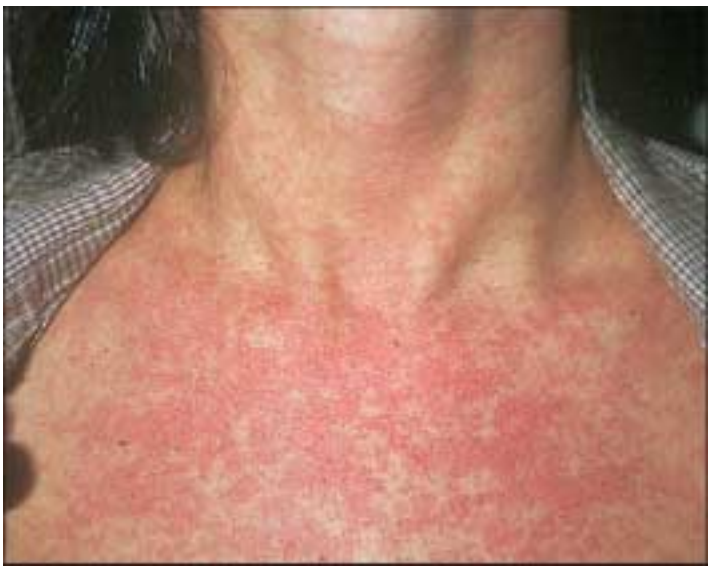


Figure 22.23 Adult with German Measles (Rubella) Symptoms are often very mild, but the effects on a fetus can be devastating.

PERSPECTIVE 22.1 The Ghost of Smallpox, An Evil Shade

Historically, smallpox epidemics have been devastating to the Americas. In the 1500s smallpox virus introduced into Central and South America caused horrendous loss of life and may have contributed to the downfall of the Inca and Aztec nations. An epidemic that swept the Massachusetts coast in the 1600s killed so many Native Americans that in some communities there were not enough survivors to bury the dead. Even in the latter 1700s, during the Revolutionary War, a smallpox epidemic raged through the American colonies. General George Washington suspected that the virus had been deliberately introduced by the British. So many of his men were ill after his defeat at Quebec in 1777 that he ordered the mass variolation of remaining troops. ■ **smallpox, pp. 497, 503,** ■ **variolation, p. 419**

Why does the ghost of smallpox concern us now, when the last case, acquired through a laboratory accident, occurred in 1978? The answer is that the smallpox virus still exists, locked in high-security laboratories in the United States and the Russian Federation, and perhaps held in secret locations by countries or individuals that could use it to harm others. A number of factors need to be considered in choosing the smallpox virus as an agent of bioterror.

Factors that might encourage its use:

- It spreads easily from person to person, mainly through close contact with respiratory secretions, but also by airborne virus from the respiratory tract, skin lesions, and contaminated bedding or other objects.
- It can be highly lethal, with mortality rates generally above 25%. After the virus establishes infection of the respiratory system, it enters the lymphatics and bloodstream, finally causing lesions of the skin and throughout the body.
- The virus is relatively stable, probably remaining infective for hours in the air of a building; viable smallpox has been demonstrated in dried crusts from skin lesions after storage for 10 years at room temperature in ordinary envelopes.
- Large numbers of people are highly susceptible to the virus. Routine vaccination against smallpox was discontinued in the United States several decades ago.
- The relatively large genome of the smallpox virus probably permits genetic modifications that could enhance its virulence.

Factors that discourage its use:

- Propagating the smallpox virus is dangerous and requires advanced knowledge and laboratory facilities.
- A proven highly effective vaccine (vaccinia virus) is available. A protective antibody response occurs rapidly and prevents fatalities for 10 years or more. Smallpox is prevented even when the vaccine is administered up to four days after exposure to the virus.
- Infected persons do not spread the disease during the long incubation period, generally 12 to 14 days; they only become infectious with the onset of fever.
- The disease can usually be diagnosed rapidly, by the characteristic appearance of skin lesions that predominate on the face and hands, and by laboratory examination of material from skin lesions.
- There is already widespread experience on how to watch for and contain the disease.

In a simulated attack on an American city in the summer of 2001, only 24 primary cases of smallpox grew in 2 months to 3 million, with 1 million deaths. This study probably greatly exaggerated the risk. Nevertheless, even though unlikely, the potential danger from a smallpox introduction has caused the United States to begin preparations for this possibility, including markedly expanding its stockpile of smallpox vaccine.

Prevention and Treatment

Prevention of German measles depends on subcutaneous injection of an attenuated rubella virus administered to babies at 12 to 16 months of age with a second dose at age 4 to 6 years. The vaccine produces long-lasting immunity in about 95% of recipients. The vaccine is not given to pregnant women for fear that it might result in congenital defects. As an added precaution, women are advised not to become pregnant for 28 days after receiving the vaccine.

Use of the vaccine has markedly reduced the incidence of rubella in the United States to generally less than 250 cases per year **(figure 22.24).** Nevertheless, outbreaks of the disease continue to occur because of the presence of underimmunized populations. No specific antiviral therapy is available.

Some features of German measles are summarized in **table 22.11.**

Other Viral Rashes of Childhood

The kinds of viruses that can cause childhood rashes probably number in the hundreds. One group alone, the enteroviruses, has about 50 members that have been associated with skin lesions. In the early 1900s the causes of the common childhood rashes were largely unknown, and it was common practice to number them 1 to 6 as follows: (1) rubeola, (2) scarlet fever, (3) rubella, (4) Duke's disease—a mild disease with fever and bright red generalized rash, now thought to have been due to an enterovirus, (5) erythema infectiosum, and (6) exanthem subitum. The causes of two common childhood rashes, erythema infectiosum and exanthem subitum, have only been established in recent years.

Fifth disease (erythema infectiosum) occurs in both children and young adults. The illness begins with fever, malaise, and

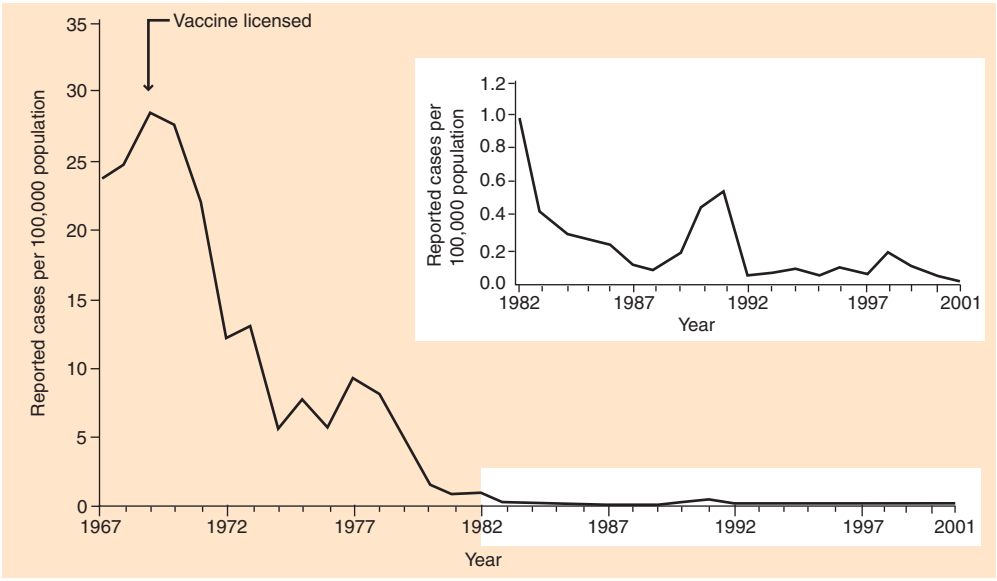


Figure 22.24 Reported Cases of German Measles (Rubella), United States, 1967–2001 Most rubella virus infections now occur in people more than 20 years old. Can you explain why?

Table 22.11 German Measles (Rubella)

① Airborne rubella virus infects nose and throat.

② Virus taken up by lymph nodes in the region.

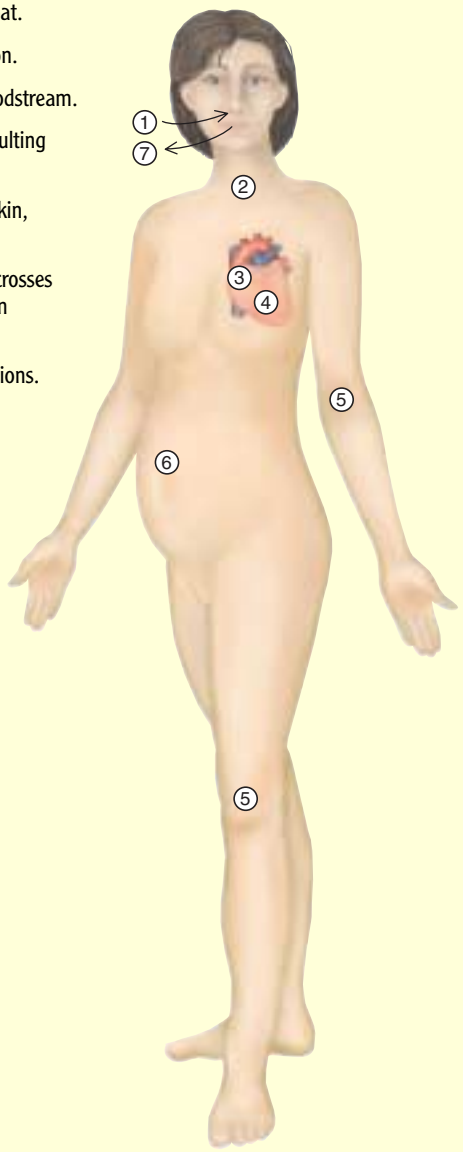
③ Rubella virus multiplies and enters the bloodstream.

④ Circulating virus reacts with antibodies, resulting in antibody-antigen complexes.

⑤ Antibody-antigen complexes lodge in the skin, causing a rash and pain in the joints.

⑥ In women during pregnancy, rubella virus crosses the placenta, infecting the fetus, resulting in congenital rubella syndrome.

⑦ Transmission to others by respiratory secretions.



Symptoms	Mild fever and cold symptoms, rash beginning on forehead and face, enlarged lymph nodes behind the ears
Incubation period	14 to 21 days
Causative agent	Rubella virus, an RNA virus of the togavirus family
Pathogenesis	Following replication in the upper respiratory tract, virus disseminates to all parts of the body and crosses the placenta; surviving fetuses often develop abnormally, and they excrete the virus for months after birth
Epidemiology	Virus possibly present in nose and throat from 1 week before rash to 1 week after; infection occurs via the respiratory route; humans are the only source
Prevention and treatment	Attenuated rubella virus vaccine administered to children at 12 to 16 months, repeated at 4 to 6 years of age. No specific antiviral treatment

head and muscle aches. A diffuse redness appears on the cheeks, giving the appearance of the face as if it were slapped. The rash commonly spreads in a lacy pattern to involve other parts of the body, especially the extremities. The rash may come and go for 2 weeks or more before recovery. Joint pains are a prominent feature of some adult infections. The disease is caused by parvovirus B-19, a small (18–28 nm), non-enveloped, single-stranded DNA virus of the parvovirus family. The virus preferentially infects certain bone marrow cells and is a major threat to persons with sickle cell and other anemias because the infected marrow sometimes stops producing blood cells, a condition known as **aplastic crisis.** Also, about 10% of women infected with the virus during pregnancy suffer spontaneous abortion.

Roseola (exanthem subitum, roseola infantum), is a common disease in infants six months to three years old. It causes a great deal of parental anxiety because it begins abruptly with fever that may reach 105°F and cause convulsions. The children generally do not appear ill, however. After several days, the fever vanishes and a transitory red rash appears, mainly on the chest and abdomen. The patient has no symptoms at this point, and the rash vanishes in a few hours to 2 days. This disease is caused by herpesvirus, type 6. There is no vaccine against the disease, and no treatment except to reduce the risk of seizures by sponging with lukewarm water and using medication to keep the temperature below 102°F.

Warts

Papillomaviruses, cause of warts, can infect the skin through minor abrasions. **Warts** are small tumors called papillomas that consist of multiple nipplelike protrusions of tissue covered by skin or mucous membrane. Warts rarely become cancers, although some sexually

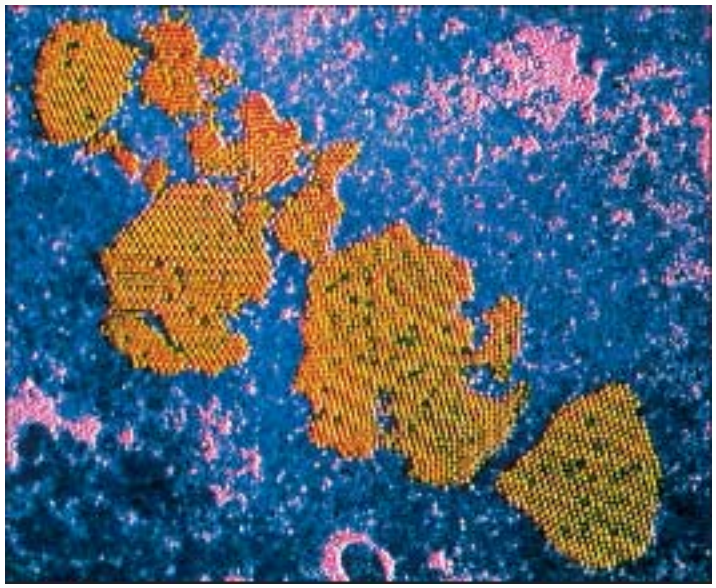


Figure 22.25 **Wart Virus** The virions appear yellow in this color-enhanced transmission electron micrograph.

transmitted papillomaviruses are strongly associated with cervical cancer. About 50% of the time, warts on the skin disappear within 2 years without any treatment. Papillomaviruses **(figure 22.25)** belong to the papovavirus family. They are small (about 50 nm diameter), non-enveloped, double-stranded DNA viruses. More than 50 different papillomaviruses are known to infect humans. Warts of other animals are generally not infectious for humans.

Papillomaviruses have been very difficult to study because they fail to grow in cell cultures or experimental animals. Wart viruses can survive on inanimate objects such as wrestling mats, towels, and shower floors, and infection can be acquired from such contaminated objects. The virus infects the deeper cells of the epidermis and reproduces in the nuclei. Some of the infected cells grow abnormally and produce the wart. The incubation period ranges from 2 to 18 months. Infectious virus is present in the wart and can contaminate fingers or objects that pick or rub the lesions. Like other tumors, warts can only be treated effectively by killing or removing all of the abnormal cells. This can usually be accomplished by freezing the wart with liquid nitrogen, by cauterization, meaning burning the tissue usually with an electrically heated needle, or by surgical removal. Virus generally remains in the adjacent normal-appearing skin, however, and may cause additional warts. Warts that grow on the soles of the feet are called **plantar warts** (often mistakenly called planter's warts; *plantar* is a word meaning "referring to the sole of the foot"). These warts are very difficult to get rid of because the pressure of standing on them causes them to grow wide and deep. ■ **cervical cancer, p. 754**

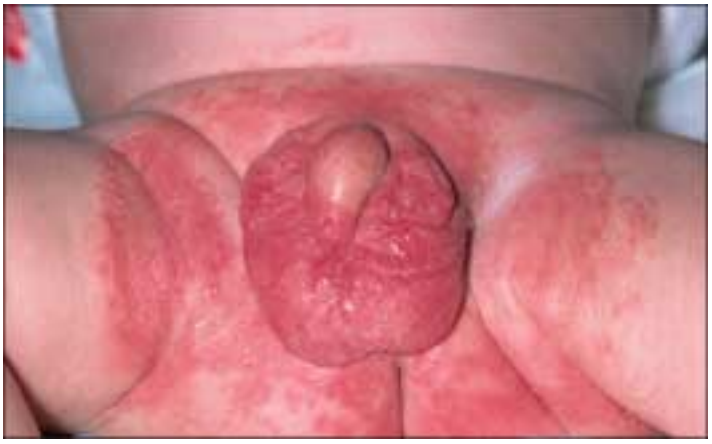
MICROCHECK 22.4

Chickenpox, measles, and rubella can be controlled by vaccines. Viral diseases that may only inconvenience a pregnant woman can be disastrous to her fetus. A viral infection acquired in childhood can remain latent for years only to reactivate in a different form. One group of viruses causes benign skin tumors.

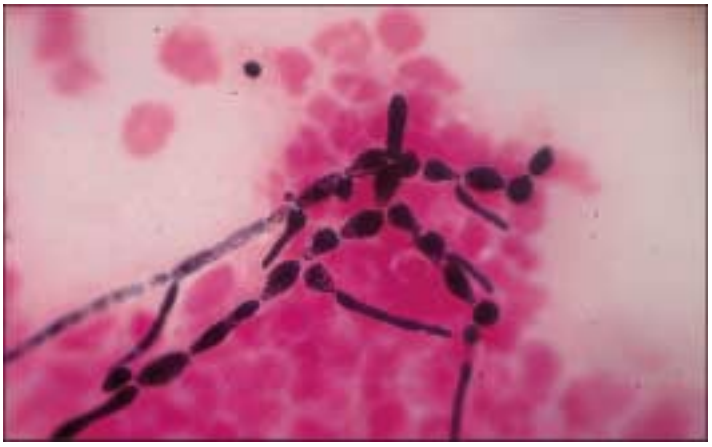
- What important diagnosis sign is often present in the mouth of measles (rubeola) victims?
- What is the epidemiological significance of shingles?
- Why is it a good idea to immunize little boys against rubella?

22.5 Skin Diseases Caused by Fungi

Diseases caused by fungi are called **mycoses.** Earlier in this chapter, we mentioned the role of normal flora yeast of the genus *Malassezia* in causing mild skin diseases, such as tinea versicolor. Other fungi are responsible for more serious infections of the skin, although even in these cases the condition of the host's defenses against infection is often crucial. The yeast *Candida albicans* **(figure 22.26)** may live harmlessly among the normal flora of the skin, but in some people it invades the deep layers of the skin and subcutaneous tissues. In many people with candidal skin infections, no precise cause for the invasion can be determined. Certain molds



(a)



(b)

Figure 22.26 ***Candida albicans*** **(a)** Causing a diaper rash; **(b)** Gram stain of pus showing *C. albicans* yeast forms and filamentous forms called pseudohyphae.

also cause cutaneous mycoses, but they are not as likely as *C. albicans* to invade the deep skin layers.

Superficial Cutaneous Mycoses

Certain species of molds can invade hair, nails, and the keratinized portion of the skin. The resulting mycoses have colorful names such as jock itch, athlete's foot, and ringworm, and more traditional latinized names that describe their location: tinea capitis—scalp, tinea barbae—beard, tinea axillaris—armpit, tinea corporis—body, tinea cruris—groin, and tinea pedis—feet, to list a few. Tinea just means "worm," which probably reflects early ideas about the cause.

Symptoms

Most people colonized by these molds have no symptoms at all. Others complain of itching, a bad odor, or a rash. In ringworm, a rash occurs at the site of the infection and consists of a scaly area surrounded by redness at the outer margin, producing irregular rings or a lacy pattern on the skin. On the scalp, patchy areas of hair loss can occur, with a fine stubble of short hair left behind. Involved nails become thickened and brittle and may separate from the nailbed. Sometimes, a rash consisting of fine papules and vesicles develops distant from the infected area. This rash is referred to as a dermatophytid, or "id" reaction, a reflection of allergy to products of the infecting fungus.

Causative Agents

The skin-invading molds belong mainly to the genera *Epidermophyton, Microsporum,* and *Trichophyton* and are collectively termed **dermatophytes (figure 22.27).** They can be cultivated on media especially designed for molds and are identified by their colonial and microscopic appearance, their nutritional requirements, and biochemical tests.

Pathogenesis

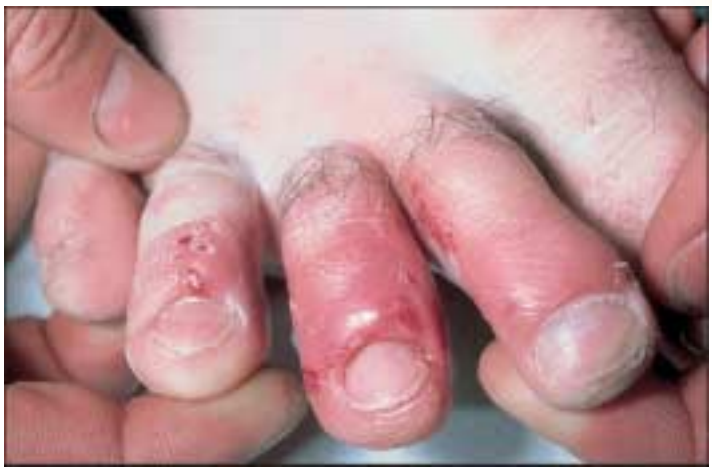
The normal skin is generally resistant to invasion by dermatophytes. Some species, however are relatively virulent and can even cause epidemic disease, especially in children. In conditions of excessive moisture, dermatophytes can invade keratinized structures, including the epidermis down to the level of the keratin-producing cells. A keratinase enables them to dissolve keratin and use it as a nutrient. Hair is invaded at the level of the hair follicle because the follicle is relatively moist. Fungal products diffuse into the dermis and provoke an immune reaction, which probably explains why adults tend to be more resistant to infection than children. It also explains why some people develop the allergic "id" reactions.

Epidemiology

As mentioned, age, virulence of the infecting strain of mold, and excessive moisture are important factors in causing infections. Common causes of excessive moisture are obesity causing folds of skin to lie together, tight clothing, and plastic or rubber footware. Potentially pathogenic molds may be present in soil and on pets such as young cats and dogs.

Prevention and Treatment

Attention to cleanliness and maintenance of normal dryness of the skin and nails effectively prevent most dermatophyte infections. Powders, open shoes, changing of socks, and application of alcohol after bathing may help prevent toenail infections. Numerous prescription and over-the-counter medications are promoted for treating dermatophytoses, and most are effective for treating superficial skin infections. Nail infections are often very difficult to cure, requiring taking medication by mouth for months, and sometimes surgical removal of the nail.



(a)

(b)

20 µm

Figure 22.27 Dermatophytosis **(a)** Tinea pedis, usually caused by species of *Trichophyton*. **(b)** Large boat-shaped spores of *Microsporum gypseum,* a cause of scalp ringworm in children.

MICROCHECK 22.5

Fungal causes of skin mycoses commonly colonize skin without causing symptoms. The best protection against fungal skin infections is to maintain normal skin dryness.

- What is a mycosis?
- What kinds of structures are invaded by dermatophytes?
- Would you be surprised if a child contracted ringworm from a pet that showed no signs of the disease? Why, or why not?

FUTURE CHALLENGES

The Ecology of Lyme Disease

Lyme disease is often referred to as one of the emerging diseases. Unrecognized in the United States before 1975, it is now the most commonly reported vector-borne disease. Because of the seeming explosion in the numbers of Lyme disease cases, and its apparent extension to new geographical areas, the ecology of Lyme disease is under intense study. In the northeastern United States, large increases in white-footed mouse populations occur in oak forests during years in which there is a heavy acorn crop, with a corresponding increase in Ixodes scapularis ticks. Both deer and mice feed on the acorns and subsequently spread the disease to adjacent areas. Variations in weather conditions, and their effect on food supply for these animals, might therefore be an important ecological factor, although it is not clear that weather cycles completely explain the emerging nature of the disease. The presence of animals other than white-footed mice for the ticks to feed on is another factor. Alternative tick hosts usually do not have a sustained Borrelia burgdorferi bacteremia following infection from a tick, and the blood of a common lizard host along the West Coast even kills the spirochetes. The role of snakes, foxes, and birds of prey that control mouse populations and that of birds, spiders, and wasps that feed on ticks are also under study. The challenge is to define more completely the ecology of Lyme and other tick-borne diseases in order to predict their emergence and find new ways for their prevention.

SUMMARY

22.1 Anatomy and Physiology (Figure 22.1)

1. The skin is a large complex organ with many functions, including temperature regulation, vitamin D synthesis, and aiding cell-mediated immunity.
2. The skin repels potential pathogens by shedding and being dry, acidic, and toxic.

22.2 Normal Flora of the Skin

1. Skin is inhabited by large numbers of bacteria of little virulence that help prevent colonization by more dangerous species (Table 22.1)

Diphtheroids

1. **Diphtheroids** are Gram-positive, pleomorphic, rod-shaped bacteria that play a role in acne and body odor. Fatty acids, produced from their metabolism of the oily secretion of sebaceous glands, keep the skin acidic.

Staphylococci

1. Staphylococci are Gram-positive cocci arranged in clusters. Universally present, they help prevent colonization by potential pathogens and maintain the balance among flora of the skin. The principal species, *Staphylococcus epidermidis,* can sometimes be pathogenic.

Fungi

1. *Malassezia* sp. are single-celled yeasts found universally on the skin. Usually harmless, they can cause tinea versicolor, probably some cases of dandruff, and serious skin disease in AIDS patients. (Figure 22.2)

22.3 Bacterial Skin Diseases

Hair Follicle Infections (Figure 22.3)

1. Boils and **carbuncles** are caused by *Staphylococcus aureus* (Table 22.3), which is coagulase-positive and often resists penicillin and other antibiotics. A carbuncle is more serious because the infection is more likely to be carried to the heart, brain, or bones.

Scalded Skin Syndrome (Figure 22.4, Table 22.4)

1. Staphylococcal scalded skin syndrome results from exotoxins produced by certain strains of *Staphylococcus aureus.*

Streptococcal Impetigo (Figure 22.5, Table 22.6)

1. Impetigo is a superficial skin infection caused by *Streptococcus pyogenes* and *Staphylococcus aureus.*
2. **Acute glomerulonephritis,** a kidney disease, caused by an antibody-antigen reaction, is an uncommon complication of *S. pyogenes* infections. (Figure 22.7)

Rocky Mountain Spotted Fever (Figures 22.8, 22.10 Table 22.7)

1. Rocky Mountain spotted fever, caused by the obligate intracellular bacterium *Rickettsia rickettsii,* is an often fatal disease transmitted to humans by the bite of an infected tick. (Figure 22.9, 22.11)

Lyme Disease (Figures 22.12, 22.14, Table 22.8)

1. Lyme disease can imitate many other diseases. It is caused by a spirochete, *Borrelia burgdorferi,* transmitted to humans by certain ticks. A target-shaped rash, present in most victims, is the hallmark of the disease. (Figures 22.12, 22.13, 22.15, 22.16)

22.4 Skin Diseases Caused by Viruses

Chickenpox (Varicella) (Figure 22.17, Table 22.9)

1. Chickenpox is a common disease of childhood caused by the varicella-zoster virus, a member of the herpesvirus family (Figure 22.19). **Shingles,** or **herpes zoster** (Figure 22.18), can occur months or years after chickenpox, a reactivation of the varicella-zoster virus infection in the distribution of a sensory nerve. Shingles cases can be sources of chickenpox epidemics.

Measles (Rubeola) (Figures 22.20, 22.21, Table 22.10)

1. Measles (**rubeola**) is a potentially dangerous viral disease that can can lead to serious secondary bacterial infections, and fatal lung or brain damage.
2. Measles can be controlled by immunizing young children and susceptible adults with an attenuated vaccine. (Figure 22.22)

German Measles (Rubella) (Figure 22.23, Table 22.11)

1. German measles (**rubella**), if contracted by a woman in the first 6 weeks of pregnancy, often results in birth defects making up the **congenital rubella syndrome.**
2. Immunization with an attenuated virus protects against this disease. (Figure 22.24)

Other Viral Rashes of Childhood

1. Numerous other viruses can cause rashes. **Fifth disease** (**erythema infectiosum**) is characterized by a "slapped cheek" rash. It is caused by parvovirus B-19. It can be fatal to people with certain anemias.
2. **Roseola** (**exanthem subitum**) is marked by several days of high fever and a transitory rash that appears as the temperature returns to normal. It occurs mainly in infants six months to three years old. The disease is caused by human herpesvirus, type 6.

Warts

1. Warts are skin tumors caused by a number of papillomaviruses (Figure 22.25). They are generally benign, but some sexually transmitted papillomaviruses are associated with cancer of the uterine cervix.

22.5 Skin Diseases Caused by Fungi

Superficial Cutaneous Mycoses

1. Invasive skin infections, such as diaper rashes, are sometimes caused by the yeast *Candida albicans.* (Figure 22.26)
2. Certain species of molds that feed on keratin cause athlete's foot, ringworm, and invasions of the hair and nails. (Figure 22.27)

REVIEW QUESTIONS

Short Answer

1. What is the difference between a furuncle and carbuncle?
2. In what age group is staphylococcal scalded skin syndrome most likely to occur?
3. Why is the blister fluid of staphylococcal scalded skin syndrome free of staphylococci?
4. Give three ways in which *Streptococcus pyogenes* resembles *Staphylococcus aureus,* and three ways in which it differs.
5. What is the epidemiological importance of passage through tick eggs by *Rickettsia rickettsii?*
6. Describe the causative agent of Lyme disease.
7. Outline the life cycle of the main vector of Lyme disease in the eastern and north-central United States.
8. What is characteristic about the rash of varicella?
9. What is the relationship between chickenpox (varicella) and shingles (herpes zoster)?
10. Why do so many people suffer permanent damage or die from measles?
11. What viral disease might be associated with an aplastic crisis? Describe its characteristic rash.
12. What is the significance of rubella viremia during pregnancy?
13. How does a person contract warts?
14. What is the allergic rash called that appears in response to ringworm and distant to it?

Multiple Choice

1. Which of the following conditions are important in the ecology of the skin?
   A. Temperature **B.** Salt concentration **C.** Lipids
   D. pH **E.** All of the above
2. *Staphylococcus aureus* can be responsible for which of these following conditions?
   A. Impetigo **B.** Food poisoning **C.** Toxic shock syndrome
   D. Scalded skin syndrome **E.** All of the above
3. The main effect of staphylococcal protein A is to
   A. interfere with phagocytosis.
   B. enhance the attachment of the Fc portion of antibody to phagocytes.
   C. coagulate plasma.
   D. kill white blood cells.
   E. degrade collagen.
4. Which of the following is essential for the virulence of *Streptococcus pyogenes?*
   A. Protease **B.** Hyaluronidase **C.** DNase
   D. All of the above **E.** None of the above
5. Which of the following statements is true of streptococcal acute glomerulonephritis?
   A. It is a streptococcal infection of the kidneys.
   B. It is caused by immune complexes containing streptococcal antigen.
   C. It is caused by most strains of β-hemolytic group A streptococci.
   D. It is the result of a streptococcal toxin directed against the kidneys.
   E. All of the above.
6. All of the following are true of Rocky Mountain spotted fever, *except*
   A. the disease is most prevalent in the western United States.
   B. it is caused by an obligate intracellular bacterium.
   C. it is a zoonosis transmitted to human beings by ticks.
   D. those with the disease characteristically develop a hemorrhagic rash.
   E. antibiotic therapy is usually curative if given early in the disease.

7. All of the following are true of Lyme disease, *except*
   A. it is caused by a spirochete.
   B. it is transmitted by certain species of ticks.
   C. it occurs only in the region around Lyme, Connecticut.
   D. most cases get a rash that looks like a target.
   E. it can cause heart and nervous system damage.

8. Which of the following statements is more likely to be true of measles (rubeola) than German measles (rubella)?
   A. Koplik's spots are present.
   B. It causes birth defects.
   C. It causes only a mild illness.
   D. Human beings are the only natural host.
   E. Attenuated virus vaccine is available for prevention.

9. All of the following must be cultivated in cell cultures instead of cell-free media, *except*
   A. *Rickettsia rickettsii*.
   B. rubella virus.
   C. varicella-zoster virus.
   D. *Borrelia burgdorferi*.
   E. rubeola virus.

10. All of the following might contribute to development of ringworm or other superficial cutaneous mycoses, *except*
    A. obesity.
    B. playing with kittens.
    C. rubber boots.
    D. using skin powder.
    E. dermatophyte virulence.

Applications

1. A school administrator in a small Iowa community prohibited a child with chickenpox from attending school. He claimed that this was the first case of chickenpox seen in the school in 6 years and that he did not want to have an outbreak at the school. Several parents argued to the school board that an outbreak would benefit the school in the long term. Discuss the pros and cons of allowing this child to attend school.
2. A public health official was asked to speak about immunization during a civic group luncheon. One parent asked if rubella was still a problem. In answering the question, the official cautioned women planning to have another child to have their present children immunized against rubella. Why did the official make this statement to the group?

Critical Thinking

1. A microbiology instructor stated that the presence of large numbers of *Propionibacterium acnes* in the same areas where acne develops illustrates that occurrence of a bacterium and a disease together does not necessarily imply cause and effect. Why would the instructor make this statement?
2. When Lyme disease was first being investigated, the observation that frequently only one person in a household was infected was a clue leading to the discovery that the disease was spread by arthropod bites. Why was this so?
3. Why might it be more difficult to eliminate a disease like Lyme disease or Rocky Mountain spotted fever from the earth than rubeola or rubella?