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133. INFECTIONS OF THE SKIN, MUSCLE, AND SOFT TISSUES - *Dennis L. Stevens*

ANATOMIC RELATIONSHIPS: CLUES TO THE DIAGNOSIS OF SOFT TISSUE INFECTIONS

Protection against infection of the epidermis is dependent on the mechanical barrier afforded by the stratum corneum, since the epidermis itself is devoid of blood vessels (Fig. 133-1). Disruption of this layer by burns, bites, abrasions, or foreign bodies allows penetration of bacteria to the deeper structures. Similarly, the hair follicle can serve as a portal either for components of the normal flora (e.g., *Staphylococcus*) or for extrinsic bacteria (e.g., *Pseudomonas* in hot-tub folliculitis). Intracellular infection of the squamous epithelium with vesicle formation may arise from cutaneous inoculation [as in infection with herpes simplex virus (HSV) type 1], from the dermal capillary plexus (as in varicella and infections due to other viruses associated with viremia), or from cutaneous nerve roots (as in herpes zoster). Bacteria infecting the epidermis, such as *Streptococcus pyogenes*, may be translocated laterally to deeper structures via lymphatics, an event that results in the rapid superficial spread of **erysipelas**. Later, engorgement or obstruction of lymphatics causes flaccid edema of the epidermis, another characteristic of **erysipelas**.

The rich plexus of capillaries beneath the dermal papillae provides nutrition to the stratum germinativum, and physiologic responses of this plexus produce important clinical signs and symptoms. For example, infective vasculitis of the plexus results in petechiae, Osler's nodes, Janeway lesions, and palpable purpura, which are important clues to the existence of endocarditis (Chap. 126). In addition, metastatic infection within this plexus can result in cutaneous manifestations of disseminated fungal infection (Chap. 207), gonococcal infection (Chap. 150), *Salmonella* infection (Chap. 158), *Pseudomonas* infection (i.e., ecthyma gangrenosum) (Chap. 157), meningococcemia (Chap. 149), and staphylococcal infection (Chap. 142). The plexus also provides access for bacteria to the circulation, thereby facilitating local spread or bacteremia. The postcapillary venules of this plexus are a major site of polymorphonuclear leukocyte sequestration, diapedesis, and chemotaxis to the site of cutaneous infection.

Exaggeration of these physiologic mechanisms by excessive levels of cytokines or bacterial toxins causes leukostasis, venous occlusion, and pitting edema. Edema with purple bullae and ecchymosis suggests loss of vascular integrity and necessitates exploration of the deeper structures for evidence of necrotizing fasciitis or myonecrosis.

To make an early diagnosis, one must exercise a high level of suspicion in instances of unexplained fever and of pain and tenderness in the soft tissue, even in the absence of acute cutaneous inflammation.

INFECTIONS ASSOCIATED WITH VESICLES (Table 133-1)

Vesicle formation due to infection is caused by viral proliferation within the epidermis. In varicella and variola, viremia precedes the onset of a diffuse centrifugal rash that progresses from macules to vesicles, then to pustules, and finally to scabs over the course of 1 to 2 weeks. Vesicles of varicella have a "dewdrop" appearance and develop in crops randomly about the trunk, extremities, and face over 3 to 4 days. Herpes zoster occurs in a single dermatome; the appearance of vesicles is preceded by pain for several days. Zoster may occur in persons of any age but is most common among immunosuppressed individuals and elderly patients, whereas most cases of varicella occur in young children. Vesicles due to HSV are found on or around the lips (HSV-1) or genitals (HSV-2) but may appear on the head and neck of young wrestlers (herpes gladiatorum) or on the digits of health care workers (herpetic whitlow). Coxsackievirus A16 characteristically causes vesicles on the hands, feet, and mouth of children. Orf is caused by a DNA virus related to smallpox virus and infects the fingers of individuals who work around goats and sheep. Molluscum contagiosum virus induces flaccid vesicles on the skin of healthy and immunocompromised individuals.

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Staphylococcal scalded-skin syndrome (SSSS) in neonates is caused by a toxin (exfoliatin) from phage group II *Staphylococcus aureus*. SSSS must be distinguished from toxic epidermal necrolysis (TEN), which occurs primarily in adults, is drug-induced, and has a higher mortality. Punch biopsy with frozen section is useful in making this distinction since the cleavage plane is the stratum corneum in SSSS (Fig. 133-1) and the stratum germinativum in TEN. Necrotizing fasciitis and gas gangrene also induce bulla formation (see "Necrotizing Fasciitis" below). Halophilic vibrio infection (see Chap. 161) can be as aggressive and fulminant as necrotizing fasciitis; a helpful clue in its diagnosis is a history of exposure to waters of the Gulf of Mexico or the Atlantic seaboard or (in a patient with cirrhosis) the ingestion of raw seafood. This organism is highly susceptible to tetracycline.

INFECTIONS ASSOCIATED WITH CRUSTED LESIONS (Table 133-1)

Impetigo contagiosa is caused by *S. pyogenes*, and bullous impetigo is due to *S. aureus*. Both skin lesions may have an early bullous stage but then appear as thick crusts with a golden-brown color. Streptococcal lesions are most common among children 2 to 5 years of age, and epidemics may occur in settings of poor hygiene, particularly among children of lower socioeconomic status in tropical climates. It is important to recognize impetigo contagiosa because of its relationship to poststreptococcal glomerulonephritis. Superficial dermatophyte infection (ringworm) can occur on any skin surface, and skin scrapings with KOH staining are diagnostic. Primary infections with dimorphic fungi such as

Blastomyces (Chap. 205) and *Sporothrix schenckii* (Chap. 210) can initially present as crusted skin lesions resembling ringworm. Disseminated infection with *Coccidioides immitis* (Chap. 204) also can involve the skin, and biopsy and culture should be performed on crusted lesions in patients from endemic areas. Crusted nodular lesions caused by *Mycobacterium chelonae* have recently been described in patients positive for human immunodeficiency virus. Treatment with clarithromycin looks promising.

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Hair follicles serve as a portal of entry for a number of bacteria, though *S. aureus* is the most common cause of localized folliculitis. Sebaceous glands empty into hair follicles and ducts and if blocked form sebaceous cysts, which may resemble staphylococcal abscesses or may become secondarily infected. Infection of sweat glands (hidradenitis suppurativa) can also mimic infection of hair follicles, particularly in the axillae. Chronic folliculitis is uncommon except in acne vulgaris, where constituents of the normal flora (e.g., *Propionibacterium acnes*) may play a role.

Diffuse folliculitis occurs in two settings. "Hot-tub folliculitis" is caused by *Pseudomonas aeruginosa* in waters that are insufficiently chlorinated and maintained at temperatures between 37 and 40°C. Infection is usually self-limited, though bacteremia and shock have been reported. Swimmer's itch occurs when a skin surface is exposed to water infested with freshwater avian schistosomes. Warm water temperatures and alkaline pH are suitable for molluscs that serve as intermediate hosts between bird and human. Free-swimming schistosomal cercariae (see Chap. 224) readily penetrate human hair follicles or pores but quickly die and elicit a brisk allergic reaction causing intense itching and erythema.

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Cutaneous anthrax begins as a pruritic papule, which develops within days into an ulcer with surrounding vesicles and edema and then into an enlarging ulcer with black eschar. Cutaneous diphtheria may cause chronic nonhealing ulcers with an overlying dirty-gray membrane, though lesions may also mimic psoriasis, eczema, or impetigo. Ulceroglandular tularemia may have associated ulcerated skin lesions with painful regional adenopathy. Although buboes are the major cutaneous manifestation of plague (see Chap. 164), in 25 percent of cases ulcers with eschars, papules, or pustules are also present.

Mycobacterium ulcerans typically causes chronic skin ulcers on the extremities of individuals living in the tropics. *Mycobacterium leprae* may be associated with cutaneous ulcerations in patients with lepromatous leprosy related to Lucio's phenomenon or during reversal reactions. *Mycobacterium tuberculosis* may also cause ulcerations, papules, or erythematous macular lesions of the skin in both normal and immunocompromised patients.

Decubitus ulcers are due to tissue hypoxia secondary to pressure-induced vascular insufficiency and may become secondarily infected with components of the skin and gastrointestinal flora, including anaerobes. Ulcerative lesions on the anterior shins may be due to pyoderma gangrenosum, which must be distinguished from similar lesions of infectious etiology by histologic evaluation of biopsy sites.

ERYSIPELAS (Table 133-1)

Erysipelas is due to *S. pyogenes* (see Chap. 143) and is characterized by an abrupt onset of fiery-red swelling of the face or extremities. The distinctive features of **erysipelas** are well-defined indurated margins, particularly along the nasolabial fold; rapid progression; and intense pain. Flaccid bullae may develop during the second or third day of illness, but extension to deeper soft tissues is rare. Treatment with penicillin is effective; swelling may progress despite appropriate treatment, though fever, pain, and the intense red color diminish. Desquamation of the involved skin occurs 5 to 10 days into the illness. Infants and elderly adults are most commonly afflicted, and the severity of systemic toxicity varies.

CELLULITIS

Cellulitis is an acute inflammatory condition of the skin that is characterized by localized pain, erythema, swelling, and heat. Cellulitis may be caused by indigenous flora colonizing the skin and appendages (e.g., *S. aureus* and *S. pyogenes*) or by a wide variety of exogenous bacteria. Because the exogenous bacteria involved in cellulitis occupy unique niches in nature, a thorough history provides important clues to etiology (see (Table 133-1 and text below).

Bacteria may gain access to the epidermis through cracks in the skin, abrasions, cuts, burns, insect bites, surgical incisions, and intravenous catheters. Cellulitis caused by *S. aureus* spreads from a central localized infection, such as an abscess, folliculitis, or an infected foreign body (e.g., a splinter, a prosthetic device, or an intravenous catheter). In contrast, cellulitis due to *S. pyogenes* is a more rapidly spreading, diffuse process frequently associated with lymphangitis and fever. Recurrent streptococcal cellulitis of the lower extremities may be caused by organisms of group A, C, or G in association with chronic venous stasis or with saphenous venectomy for coronary artery bypass surgery. Streptococci also cause recurrent cellulitis among patients with chronic lymphedema resulting from elephantiasis, lymph node dissection, or Milroy's disease. Recurrent staphylococcal cutaneous infections are more common among individuals who have eosinophilia and elevated serum levels of IgE (Job's syndrome) and among nasal carriers of staphylococci. Cellulitis caused by *Streptococcus agalactiae* (group B streptococci) occurs primarily in patients with diabetes mellitus or peripheral vascular disease. *Haemophilus influenzae* typically causes periorbital cellulitis in children in association with sinusitis, otitis media, or epiglottitis. It is unclear whether this form of cellulitis will (like meningitis) become less common as a result of the impressive efficacy of the *H. influenzae* type b vaccine.

Many other bacteria also cause cellulitis. Fortunately, these organisms occur in such characteristic settings that a good history provides useful clues to the diagnosis. Cellulitis associated with cat bites and, to a lesser degree, with dog bites is commonly caused by *Pasteurella multocida*, though in the latter case *Staphylococcus intermedius* and *Capnocytophaga canimorsus* (DF-2) must also be considered. Sites of cellulitis and abscesses associated with dog bites and human bites also contain a variety of anaerobic organisms. *Pasteurella* is notoriously resistant to dicloxacillin and nafcillin but is sensitive to all other β-lactam antimicrobials as well as to quinolones, tetracycline, and erythromycin. Ampicillin/clavulanate, ampicillin/sulbactam, and cefoxitin are good choices for the treatment of animal or human bite infections. *Aeromonas hydrophila* causes aggressive cellulitis in tissues surrounding lacerations sustained in fresh water (lakes, rivers, and streams). This organism remains sensitive to aminoglycosides, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and third-generation cephalosporins; it is resistant to ampicillin, however.

P. aeruginosa causes three types of soft tissue infection: ecthyma gangrenosum in neutropenic patients, hot-tub folliculitis, and cellulitis following penetrating injury. Most commonly, *P. aeruginosa* is introduced into the deep tissues when a person steps on a nail; this scenario is referred to as the "sweaty tennis shoe syndrome." Treatment includes surgical inspection and drainage, particularly if the injury also involves bone or joint capsule. Choices for empirical treatment while antimicrobial susceptibility data are awaited include an aminoglycoside, a third-generation cephalosporin (ceftazidime, cefoperazone, or cefotaxime), a semisynthetic penicillin (ticarcillin, mezlocillin, or piperacillin), or a fluoroquinolone (though drugs of the last class are not indicated for the treatment of children less than 13 years old).

Gram-negative bacillary cellulitis, including that due to *P. aeruginosa*, is most common among hospitalized, immunocompromised hosts. Cultures and sensitivity tests are critically important in this setting because of multidrug resistance (see Chap. 157).

The gram-positive aerobic rod *Erysipelothrix rhusiopathiae*, which causes cellulitis in bone renderers and fishmongers, remains susceptible to penicillin, erythromycin, clindamycin, tetracycline, and cephalosporins but is resistant to sulfonamides and chloramphenicol. Fish food containing the water flea *Daphnia* is sometimes contaminated with *Mycobacterium marinum*, which can cause cellutitis or granulomas on skin surfaces exposed to the water in aquariums or injured in swimming pools. Rifampin plus ethambutol has been an effective combination in some cases, though no comprehensive studies have been undertaken. In addition, some strains of *M. marinum* are susceptible to tetracycline or to trimethoprim-sulfamethoxazole.

The etiology of cellulitis can be suggested by epidemiologic data (see above). When there is drainage, an open wound, or an obvious portal of entry, Gram's stain and culture provide a definitive diagnosis. In the absence of these findings, the bacterial etiology of cellulitis is difficult to establish. Even with needle aspiration of the leading edge or a punch biopsy of the cellulitis tissue itself, cultures are positive in only 20 percent of cases. This observation suggests that relatively low numbers of bacteria may cause

cellulitis and that the expanding area of erythema within the skin may be a direct effect of extracellular toxins or of the soluble mediators of inflammation elicited by the host.

NECROTIZING FASCIITIS (Table 133-1)

Necrotizing fasciitis, formerly called streptococcal gangrene, may be associated with group A *Streptococcus* or mixed aerobic-anaerobic bacteria or may occur as part of gas gangrene caused by *Clostridium perfringens*. Early diagnosis may be difficult when pain or unexplained fever is the only presenting manifestation. Swelling then develops and is followed by brawny edema and tenderness. With progression, dark red induration of the epidermis appears along with bullae filled with blue or purple fluid. Later the skin becomes friable and takes on a bluish, maroon, or black color. By this stage, thrombosis of blood vessels in the dermal papillae is extensive (see Fig. 133-1). Extension of infection to the level of the deep fascia causes it to take on a brownish-gray appearance. Rapid spread occurs along fascial planes, through venous channels and lymphatics. Patients in the later stages are toxic and frequently manifest shock and multiorgan failure.

Necrotizing fasciitis caused by mixed aerobic-anaerobic bacteria begins with a breach in the integrity of a mucous membrane barrier, such as the mucosa of the gastrointestinal or genitourinary tract. The portal can be a malignancy, diverticulum, hemorrhoid, anal fissure, or urethral tear. Other predisposing factors include peripheral vascular disease, diabetes mellitus, surgery, and penetrating injury to the abdomen. Leakage into the perineal area results in a syndrome called *Fournier's gangrene*, characterized by massive swelling of the scrotum and penis with extension into the perineum or the abdominal wall and legs.

Necrotizing fasciitis caused by *S. pyogenes* has increased in frequency and severity since 1985. It frequently begins deep at the site of a nonpenetrating minor trauma such as a bruise or a muscle strain. Seeding of the site via transient bacteremia is likely, though most patients deny antecedent streptococcal infection. Alternatively, *S. pyogenes* may reach the deep fascia from a site of cutaneous infection or penetrating trauma. Toxicity is severe, and renal impairment may precede the development of shock. In 20 to 40 percent of cases, myositis occurs concomitantly, and, as in gas gangrene (see below), serum creatinine phosphokinase values may be markedly elevated. Necrotizing fasciitis due to mixed aerobic-anaerobic bacteria may be associated with gas in the deep tissue, but gas is not usually present when the cause is *S. pyogenes*. Prompt surgical exploration down to the deep fascia and muscle is essential. Necrotic tissue must be surgically removed, and Gram's staining and culture of excised tissue are useful in establishing whether group A streptococci, mixed aerobic-anaerobic bacteria, or *Clostridium* spp. are present (see "Treatment" below).

MYOSITIS (Table 133-1)

Muscle involvement can occur with virus infection [influenza, dengue, coxsackievirus B (pleurodynia)]; or parasitic invasion [*Trichinella spiralis* (trichinosis), *Taenia solium* (cysticercosis), *Toxoplasma gondii* (toxoplasmosis)]. Although myalgia can occur in

most of these infections, severe muscle pain is the hallmark of pleurodynia, trichinosis, and bacterial infection. Acute rhabdomyolysis predictably occurs with clostridial and streptococcal myositis but may also be associated with influenza virus, echovirus, coxsackievirus, Epstein-Barr virus, and *Legionella* infection.

Pyomyositis is usually due to *S. aureus*, is common in tropical areas, and generally has no known portal of entry. Infection remains localized, and, unless organisms produce toxic shock syndrome toxin 1 or certain enterotoxins, shock does not develop. In contrast, *S. pyogenes* may induce primary myositis referred to as *streptococcal necrotizing myositis*, which is associated with severe systemic toxicity. Myonecrosis occurs concomitantly with necrotizing fasciitis in about 50 percent of cases. Both are part of the streptococcal toxic shock syndrome.

Gas gangrene usually follows severe penetrating injuries that result in interruption of the blood supply and introduction of soil into wounds. Such cases of traumatic gangrene are usually caused by *C. perfringens*, *Clostridium septicum*, or *Clostridium histolyticum*. Rarely, latent or recurrent gangrene can occur years after penetrating trauma, most likely owing to dormant spores that reside at the site of previous injury. Spontaneous nontraumatic gangrene among patients with neutropenia, gastrointestinal malignancy, diverticulosis, or recent radiation therapy to the abdomen is caused by *C. septicum*. The tolerance of this anaerobe to oxygen probably explains why it can initiate infection spontaneously in normal tissue anywhere in the body.

Synergistic nonclostridial anaerobic myonecrosis, also known as necrotizing cutaneous myositis and synergistic necrotizing cellulitis, is a variant of necrotizing fasciitis caused by mixed aerobic and anaerobic bacteria with the exclusion of clostridial organisms (see "Necrotizing Fasciitis" above).

TREATMENT

Early and aggressive surgical exploration is essential in patients with suspected necrotizing fasciitis, myositis, or gangrene in order to (1) visualize the deep structures, (2) remove necrotic tissue, (3) reduce compartment pressure, and (4) obtain suitable material for Gram's staining and for aerobic and anaerobic cultures. Appropriate empirical antibiotic treatment for mixed aerobic-anaerobic infections could consist of ampicillin/sulbactam, cefoxitin, or the following combination: (1) clindamycin (600 to 800 mg intravenously every 8 h) or metronidazole (750 mg every 6 h) plus (2) ampicillin or ampicillin/sulbactam (2 to 3 g intravenously every 6 h) plus (3) gentamicin (1.0 to 1.5 mg/kg every 8 h). Group A streptococcal and clostridial infection of the fascia and/or muscle carries a mortality rate of 20 to 50 percent with penicillin treatment. In experimental models of streptococcal and clostridial necrotizing fasciitis/myositis, clindamycin has exhibited markedly superior efficacy, but no comparative trials have been performed in humans. Hyperbaric oxygen treatment may also be useful in gas gangrene due to clostridial species. Antibiotic treatment should be continued until all signs of systemic toxicity have resolved, all devitalized tissue has been removed, and granulation tissue has developed (Chaps. 143, 148, and 169).

In summary, infections of the skin and soft tissues are diverse in presentation and severity and offer a great challenge to the clinician. This chapter provides an approach to diagnosis and understanding of the pathophysiologic mechanisms involved in these infections. More in-depth information is found in chapters on specific infections.

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CELLULITIS

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Bacteria may gain access to the epidermis through cracks in the skin, abrasions, cuts, burns, insect bites, surgical incisions, and intravenous catheters. Cellulitis caused by *S. aureus* spreads from a central localized infection, such as an abscess, folliculitis, or an infected foreign body (e.g., a splinter, a prosthetic device, or an intravenous catheter). In contrast, cellulitis due to *S. pyogenes* is a more rapidly spreading, diffuse process frequently associated with lymphangitis and fever. Recurrent streptococcal cellulitis of the lower extremities may be caused by organisms of group A, C, or G in association with chronic venous stasis or with saphenous venectomy for coronary artery bypass surgery. Streptococci also cause recurrent cellulitis among patients with chronic lymphedema resulting from elephantiasis, lymph node dissection, or Milroy's disease. Recurrent staphylococcal cutaneous infections are more common among individuals who have eosinophilia and elevated serum levels of IgE (Job's syndrome) and among nasal carriers of staphylococci. Cellulitis caused by *Streptococcus agalactiae* (group B streptococci) occurs primarily in patients with diabetes mellitus or peripheral vascular disease. *Haemophilus influenzae* typically causes periorbital cellulitis in children in association with sinusitis, otitis media, or epiglottitis. It is unclear whether this form of cellulitis will (like meningitis) become less common as a result of the impressive efficacy of the *H. influenzae* type b vaccine.

Many other bacteria also cause cellulitis. Fortunately, these organisms occur in such characteristic settings that a good history provides useful clues to the diagnosis. Cellulitis associated with cat bites and, to a lesser degree, with dog bites is commonly caused by *Pasteurella multocida*, though in the latter case *Staphylococcus intermedius* and *Capnocytophaga canimorsus* (DF-2) must also be considered. Sites of cellulitis and abscesses associated with dog bites and human bites also contain a variety of anaerobic organisms. *Pasteurella* is notoriously resistant to dicloxacillin and nafcillin but is sensitive to all other β-lactam antimicrobials as well as to quinolones, tetracycline, and erythromycin. Ampicillin/clavulanate, ampicillin/sulbactam, and cefoxitin are good choices for the treatment of animal or human bite infections. *Aeromonas hydrophila* causes aggressive cellulitis in tissues surrounding lacerations sustained in fresh water (lakes, rivers, and streams). This organism remains sensitive to aminoglycosides, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and third-generation cephalosporins; it is resistant to ampicillin, however.

P. aeruginosa causes three types of soft tissue infection: ecthyma gangrenosum in neutropenic patients, hot-tub folliculitis, and cellulitis following penetrating injury. Most commonly, *P. aeruginosa* is introduced into the deep tissues when a person steps on a nail; this scenario is referred to as the "sweaty tennis shoe syndrome." Treatment includes surgical inspection and drainage, particularly if the injury also involves bone or joint capsule. Choices for empirical treatment while antimicrobial susceptibility data are awaited include an aminoglycoside, a third-generation cephalosporin (ceftazidime, cefoperazone, or cefotaxime), a semisynthetic penicillin (ticarcillin, mezlocillin, or piperacillin), or a fluoroquinolone (though drugs of the last class are not indicated for the treatment of children less than 13 years old).

Gram-negative bacillary cellulitis, including that due to *P. aeruginosa*, is most common among hospitalized, immunocompromised hosts. Cultures and sensitivity tests are critically important in this setting because of multidrug resistance (see Chap. 157).

The gram-positive aerobic rod *Erysipelothrix rhusiopathiae*, which causes cellulitis in bone renderers and fishmongers, remains susceptible to penicillin, erythromycin, clindamycin, tetracycline, and cephalosporins but is resistant to sulfonamides and chloramphenicol. Fish food containing the water flea *Daphnia* is sometimes contaminated with *Mycobacterium marinum*, which can cause cellutitis or granulomas on skin surfaces exposed to the water in aquariums or injured in swimming pools. Rifampin plus ethambutol has been an effective combination in some cases, though no comprehensive studies have been undertaken. In addition, some strains of *M. marinum* are susceptible to tetracycline or to trimethoprim-sulfamethoxazole.

The etiology of cellulitis can be suggested by epidemiologic data (see above). When there is drainage, an open wound, or an obvious portal of entry, Gram's stain and culture provide a definitive diagnosis. In the absence of these findings, the bacterial etiology of cellulitis is difficult to establish. Even with needle aspiration of the leading edge or a punch biopsy of the cellulitis tissue itself, cultures are positive in only 20 percent of

cases. This observation suggests that relatively low numbers of bacteria may cause cellulitis and that the expanding area of erythema within the skin may be a direct effect of extracellular toxins or of the soluble mediators of inflammation elicited by the host.

NECROTIZING FASCIITIS (Table 133-1)

Necrotizing fasciitis, formerly called streptococcal gangrene, may be associated with group A *Streptococcus* or mixed aerobic-anaerobic bacteria or may occur as part of gas gangrene caused by *Clostridium perfringens*. Early diagnosis may be difficult when pain or unexplained fever is the only presenting manifestation. Swelling then develops and is followed by brawny edema and tenderness. With progression, dark red induration of the epidermis appears along with bullae filled with blue or purple fluid. Later the skin becomes friable and takes on a bluish, maroon, or black color. By this stage, thrombosis of blood vessels in the dermal papillae is extensive (see Fig. 133-1). Extension of infection to the level of the deep fascia causes it to take on a brownish-gray appearance. Rapid spread occurs along fascial planes, through venous channels and lymphatics. Patients in the later stages are toxic and frequently manifest shock and multiorgan failure.

Necrotizing fasciitis caused by mixed aerobic-anaerobic bacteria begins with a breach in the integrity of a mucous membrane barrier, such as the mucosa of the gastrointestinal or genitourinary tract. The portal can be a malignancy, diverticulum, hemorrhoid, anal fissure, or urethral tear. Other predisposing factors include peripheral vascular disease, diabetes mellitus, surgery, and penetrating injury to the abdomen. Leakage into the perineal area results in a syndrome called *Fournier's gangrene*, characterized by massive swelling of the scrotum and penis with extension into the perineum or the abdominal wall and legs.

Necrotizing fasciitis caused by *S. pyogenes* has increased in frequency and severity since 1985. It frequently begins deep at the site of a nonpenetrating minor trauma such as a bruise or a muscle strain. Seeding of the site via transient bacteremia is likely, though most patients deny antecedent streptococcal infection. Alternatively, *S. pyogenes* may reach the deep fascia from a site of cutaneous infection or penetrating trauma. Toxicity is severe, and renal impairment may precede the development of shock. In 20 to 40 percent of cases, myositis occurs concomitantly, and, as in gas gangrene (see below), serum creatinine phosphokinase values may be markedly elevated. Necrotizing fasciitis due to mixed aerobic-anaerobic bacteria may be associated with gas in the deep tissue, but gas is not usually present when the cause is *S. pyogenes*. Prompt surgical exploration down to the deep fascia and muscle is essential. Necrotic tissue must be surgically removed, and Gram's staining and culture of excised tissue are useful in establishing whether group A streptococci, mixed aerobic-anaerobic bacteria, or *Clostridium* spp. are present (see "Treatment" below).

MYOSITIS (Table 133-1)

Muscle involvement can occur with virus infection [influenza, dengue, coxsackievirus B (pleurodynia)]; or parasitic invasion [*Trichinella spiralis* (trichinosis), *Taenia solium*

(cysticercosis), *Toxoplasma gondii* (toxoplasmosis)]. Although myalgia can occur in most of these infections, severe muscle pain is the hallmark of pleurodynia, trichinosis, and bacterial infection. Acute rhabdomyolysis predictably occurs with clostridial and streptococcal myositis but may also be associated with influenza virus, echovirus, coxsackievirus, Epstein-Barr virus, and *Legionella* infection.

Pyomyositis is usually due to *S. aureus*, is common in tropical areas, and generally has no known portal of entry. Infection remains localized, and, unless organisms produce toxic shock syndrome toxin 1 or certain enterotoxins, shock does not develop. In contrast, *S. pyogenes* may induce primary myositis referred to as *streptococcal necrotizing myositis*, which is associated with severe systemic toxicity. Myonecrosis occurs concomitantly with necrotizing fasciitis in about 50 percent of cases. Both are part of the streptococcal toxic shock syndrome.

Gas gangrene usually follows severe penetrating injuries that result in interruption of the blood supply and introduction of soil into wounds. Such cases of traumatic gangrene are usually caused by *C. perfringens*, *Clostridium septicum*, or *Clostridium histolyticum*. Rarely, latent or recurrent gangrene can occur years after penetrating trauma, most likely owing to dormant spores that reside at the site of previous injury. Spontaneous nontraumatic gangrene among patients with neutropenia, gastrointestinal malignancy, diverticulosis, or recent radiation therapy to the abdomen is caused by *C. septicum*. The tolerance of this anaerobe to oxygen probably explains why it can initiate infection spontaneously in normal tissue anywhere in the body.

Synergistic nonclostridial anaerobic myonecrosis, also known as necrotizing cutaneous myositis and synergistic necrotizing cellulitis, is a variant of necrotizing fasciitis caused by mixed aerobic and anaerobic bacteria with the exclusion of clostridial organisms (see "Necrotizing Fasciitis" above).

TREATMENT

Early and aggressive surgical exploration is essential in patients with suspected necrotizing fasciitis, myositis, or gangrene in order to (1) visualize the deep structures, (2) remove necrotic tissue, (3) reduce compartment pressure, and (4) obtain suitable material for Gram's staining and for aerobic and anaerobic cultures. Appropriate empirical antibiotic treatment for mixed aerobic-anaerobic infections could consist of ampicillin/sulbactam, cefoxitin, or the following combination: (1) clindamycin (600 to 800 mg intravenously every 8 h) or metronidazole (750 mg every 6 h) plus (2) ampicillin or ampicillin/sulbactam (2 to 3 g intravenously every 6 h) plus (3) gentamicin (1.0 to 1.5 mg/kg every 8 h). Group A streptococcal and clostridial infection of the fascia and/or muscle carries a mortality rate of 20 to 50 percent with penicillin treatment. In experimental models of streptococcal and clostridial necrotizing fasciitis/myositis, clindamycin has exhibited markedly superior efficacy, but no comparative trials have been performed in humans. Hyperbaric oxygen treatment may also be useful in gas gangrene due to clostridial species. Antibiotic treatment should be continued until all

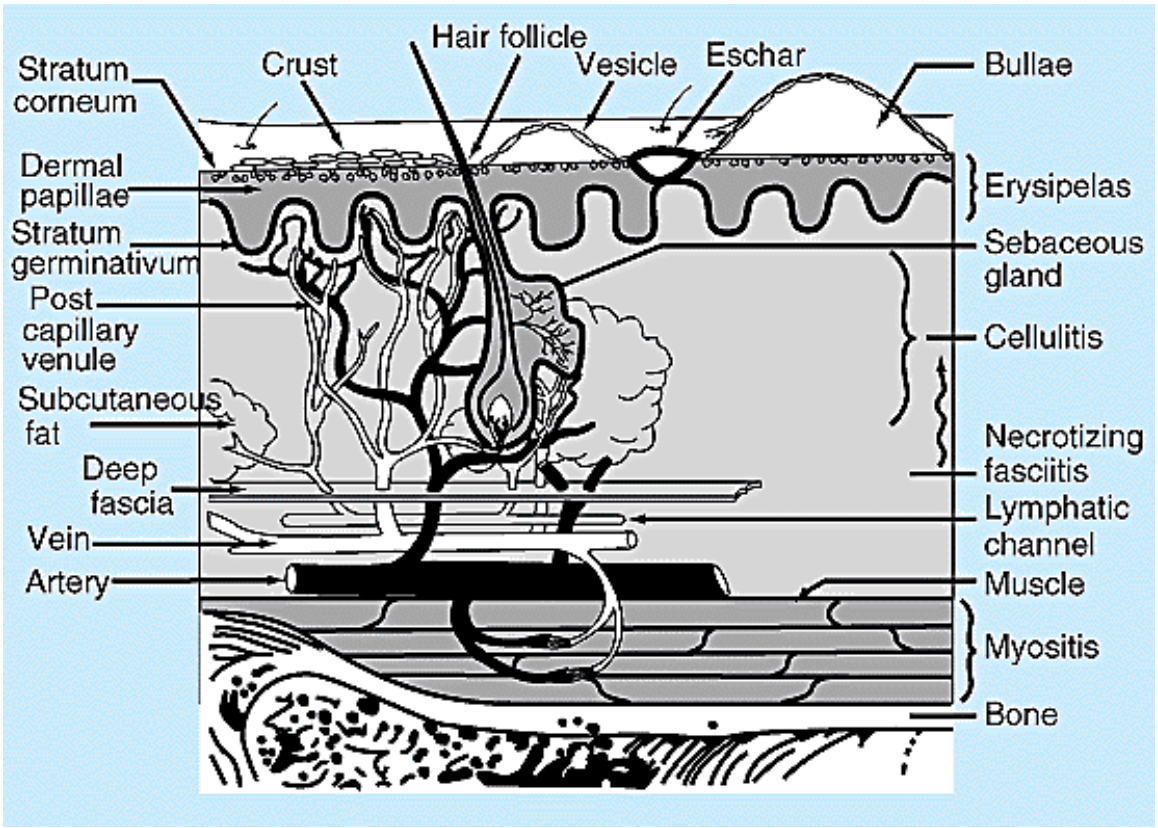
signs of systemic toxicity have resolved, all devitalized tissue has been removed, and granulation tissue has developed (Chaps. 143, 148, and 169).

In summary, infections of the skin and soft tissues are diverse in presentation and severity and offer a great challenge to the clinician. This chapter provides an approach to diagnosis and understanding of the pathophysiologic mechanisms involved in these infections. More in-depth information is found in chapters on specific infections.

Table 133-1. Skin And Soft Tissue Infections

Lesion, Clinical Syndrome	Infectious Agent
Vesicles	
Smallpox	Variola virus
Chickenpox	Varicella-zoster virus
Shingles (herpes zoster)	Varicella-zoster virus
Cold sores, herpetic whitlow, herpes gladiatorum	Herpes simplex virus
Hand-foot-and-mouth disease	Coxsackievirus A16
Orf	Parapoxvirus
Molluscum contagiosum	Pox-like virus
Bullae	
Staphylococcal scalded-skin syndrome	*Staphylococcus aureus*
Necrotizing fasciitis	*Streptococcus pyogenes, Clostridium* spp., mixed aerobes and anaerobes
Gas gangrene	*Clostridium* spp.
Halophilic vibrio	*Vibrio vulnificus*
Crusted lesions	
Bullous impetigo	*S. aureus*
Impetigo contagiosa	*S. pyogenes*
Ringworm	Superficial dermatophyte fungi
Sporotrichosis	*Sporothrix schenckii*
Histoplasmosis	*Histoplasma capsulatum*
Coccidioidomycosis	*Coccidioides immitis*
Blastomycosis	*Blastomyces dermatitidis*
Cutaneous leishmaniasis	*Leishmania* spp.
Cutaneous tuberculosis	*Mycobacterium tuberculosis*
Nocardiosis	*Nocardia asteroides*
Folliculitis	
Furunculosis	*S. aureus*
Hot-tub folliculitis	*Pseudomonas aeruginosa*
Swimmer's itch	*Schistosoma* spp.
Acne vulgaris	*Propionibacterium acnes*
Ulcers with or without eschars	
Anthrax	*Bacillus anthracis*

Ulceroglandular tularemia	*Francisella tularensis*
Bubonic plague	*Yersinia pestis*
Buruli ulcer	*Mycobacterium ulcerans*
Leprosy	*Mycobacterium leprae*
Cutaneous tuberculosis	*M. tuberculosis*
Erysipelas	*S. pyogenes*
Necrotizing fasciitis	
Streptococcal gangrene	*S. pyogenes*
Fournier's gangrene	Mixed aerobic and anaerobic bacteria
Myositis and myonecrosis	
Pyomyositis	*S. aureus*
Streptococcal necrotizing myositis	*S. pyogenes*
Gas gangrene	*Clostridium* spp.
Nonclostridial (crepitant) myositis	Mixed aerobic and anaerobic bacteria
Synergistic nonclostridial anaerobic myonecrosis	Mixed aerobic and anaerobic bacteria



Cellulitis Inoculation of organisms into the skin may lead to infection involving the skin and subcutaneous tissues, or cellulitis (Fig. 143-CD3). The portal of entry may be a traumatic or surgical wound, an insect bite, or any other break in the skin's integrity. Often, no entry site is apparent.

One form of streptococcal cellulitis, known as ***erysipelas*** (Fig. 143-CD4), is characterized by a bright red appearance of the involved skin, which forms a plateau sharply demarcated from the surrounding normal skin. The lesion is warm to the touch, may be tender, and appears shiny and swollen. The skin often has a *peau d'orange* texture, which is thought to reflect involvement of superficial lymphatics; superficial blebs or bullae may form, usually 2 or 3 days after onset. The lesion typically develops over a few hours and is associated with fever and chills. **Erysipelas** tends to occur in certain characteristic locations: the malar area of the face (often with extension over the bridge of the nose to the contralateral malar region) and the lower extremities. After one episode, recurrence at the same site/sometimes years later/is not uncommon.

Classic cases of **erysipelas**, with the typical features described above, are almost always due to group A streptococci. Often, however, the appearance of streptococcal cellulitis is not sufficiently distinctive to permit a specific diagnosis on clinical grounds. The area of involvement may not be one of the typical sites for **erysipelas**; the lesion may be less intensely red than usual and may fade into surrounding skin; and/or the patient may appear only mildly ill. In such cases, it is prudent to broaden the spectrum of empirical antimicrobial therapy to include other pathogens, particularly *S. aureus*, that can produce cellulitis with the same appearance.

Streptococcal cellulitis tends to develop at anatomic sites in which normal lymphatic drainage has been disrupted, such as sites of prior episodes of cellulitis, the arm ipsilateral to a mastectomy and axillary lymph-node dissection, a lower extremity previously involved in deep venous thrombosis or chronic lymphedema, and the leg from which a saphenous vein has been harvested for coronary artery bypass grafting. The organism may enter via a breach in the dermal barrier at a location some distance from the eventual site of clinical cellulitis. For example, some patients with recurrent episodes of leg cellulitis following saphenous vein removal have stopped having recurrent episodes only after treatment of tinea pedis on the foot of the affected extremity, fissures in the skin presumably having served as a portal of entry for streptococci, which then produced infection more proximally in the leg at the site of previous injury. Streptococcal cellulitis may also involve recent surgical wounds. Group A streptococci are among the few bacterial pathogens that typically produce signs of wound infection and surrounding cellulitis within the first 24 h after surgery. These wound infections are usually associated with a thin exudate and may spread rapidly, either as cellulitis in the skin and subcutaneous tissue or as a deeper tissue infection (see below). Streptococcal wound infection or localized cellulitis may also be associated with *lymphangitis* (Fig. 143-CD3B), manifested by red streaks extending proximally along superficial lymphatics from the site of infection.

Deep Soft Tissue Infections *Necrotizing fasciitis* (Fig. 143-CD5), also referred to as *hemolytic streptococcal gangrene*, is an infection involving the superficial and/or deep fascia investing the muscles of an extremity or the trunk. The source of the infection is either the skin, with organisms introduced into the tissue as a result of trauma (which may be trivial), or the bowel flora, with organisms released during abdominal surgery or from an occult enteric source, such as a diverticular or appendiceal abscess. The site of

inoculation in both forms of necrotizing fasciitis may be inapparent and often is some distance from the site of clinical involvement; for example, the introduction of organisms via minor trauma to the hand may be associated with clinical infection of the tissues overlying the shoulder or chest. In cases associated with the bowel flora, the infection is usually polymicrobial, involving a mixture of anaerobic bacteria (such as *Bacteroides fragilis* or anaerobic streptococci) and facultative organisms (usually gram-negative bacilli). Cases unrelated to contamination from bowel organisms are most commonly caused by group A streptococci, either alone or in combination with other organisms (most often *S. aureus*). Overall, group A streptococci are implicated in about 60 percent of cases of necrotizing fasciitis.

The onset of symptoms is usually quite acute and is marked by severe pain at the site of involvement, malaise, fever, chills, and a toxic appearance. The physical findings, particularly early in the illness, may not be striking, with only minimal erythema of the overlying skin. Pain and tenderness are usually severe; in contrast, in more superficial cellulitis, the appearance of the skin is more abnormal, but pain and tenderness are only mild or moderate. As the infection progresses (often in a matter of several hours), the severity and extent of symptoms worsen, and skin changes become more evident, with the appearance of dusky or mottled erythema and edema. The marked tenderness of the involved area may evolve into anesthesia as the spreading inflammatory process produces infarction of cutaneous nerves. Once the diagnosis is suspected, early surgical exploration is both diagnostically and therapeutically indicated. Surgery reveals necrosis and inflammatory fluid tracking along the fascial planes above and between muscle groups, without involvement of the muscles themselves. The process usually is found to extend beyond the area of clinical involvement, and extensive debridement is required. Drainage and debridement are central to the management of necrotizing fasciitis; antibiotic treatment is a useful adjunct (Table 143-2), but surgery is life-saving.

Although this syndrome is due more commonly to *S. aureus* infection, group A streptococci occasionally produce abscesses in skeletal muscles (*streptococcal myositis*), with little or no involvement of the surrounding fascia or overlying skin. The presentation is usually subacute, but a fulminant form has been described in association with severe systemic toxicity, bacteremia, and a high mortality rate. The fulminant form may reflect the same basic disease process as that seen in necrotizing fasciitis, but with the necrotizing inflammatory process extending into the muscles themselves rather than remaining limited to the fascial layers. Treatment for streptococcal myositis consists of surgical drainage/usually by an open procedure that permits evaluation of the extent of the infection and ensures adequate debridement of involved tissues/and high-dose penicillin (Table 143-2).

Steroids

Physiological Functions and Pharmacological Effects

Physiological Actions. The effects of corticosteroids are numerous and widespread. Their diverse effects include: alterations in carbohydrate, protein, and lipid metabolism; maintenance of fluid and electrolyte balance; and preservation of normal function of the cardiovascular system, the immune system, the kidney, skeletal muscle, the endocrine system, and the nervous system. In addition, by mechanisms that are still not fully understood, corticosteroids endow the organism with the capacity to resist stressful circumstances such as noxious stimuli and environmental changes. In the absence of the adrenal cortex, survival is made possible only by maintaining an optimal environment, including adequate and regular feedings, ingestion of relatively large amounts of sodium chloride, and maintenance of an appropriate environmental temperature.

Until recently, corticosteroid effects were viewed as physiological (reflecting actions of corticosteroids at doses corresponding to normal daily production levels) or pharmacological (representing effects seen only at doses exceeding the normal daily production of corticosteroids). More recent concepts suggest that the antiinflammatory and immunosuppressive actions of corticosteroids, one of the major "pharmacological" uses of this class of drugs, also provide a protective mechanism in the physiological setting, since many of the immune mediators associated with the inflammatory response decrease vascular tone and could lead to cardiovascular collapse if unopposed by the adrenal corticosteroids. This hypothesis is supported by the fact that the daily production rate of cortisol can rise markedly (at least 10-fold) in the setting of severe stress. In addition, as discussed below, the pharmacological actions of corticosteroids in different tissues and many of their physiological effects seem to be mediated by the same receptor. Thus, the various glucocorticoid derivatives used as pharmacological agents have side effects on physiological processes that parallel their therapeutic effectiveness.

The actions of corticosteroids are related in complex ways to those of other hormones. For example, in the absence of lipolytic hormones, cortisol has virtually no effect on the rate of lipolysis by adipocytes. Likewise, in the absence of glucocorticoids, epinephrine and norepinephrine have only minor effects on lipolysis. Administration of a small dose of a glucocorticoid, however, markedly potentiates the lipolytic action of these amines. These effects of corticosteroids that involve concerted actions with other hormonal regulators are termed *permissive* and most likely reflect steroid-induced changes in protein synthesis that, in turn, modify tissue responsiveness.

Corticosteroids are grouped according to their relative potencies in Na^+ retention, effects on carbohydrate metabolism (*i.e.*, hepatic deposition of glycogen and gluconeogenesis), and antiinflammatory effects. In general, potencies of **steroids** as judged by their ability to sustain life in the adrenalectomized animal closely parallel those determined for Na^+ retention. Potencies based on effects on glucose metabolism closely parallel those for antiinflammatory effects. The effects on Na^+ retention and the carbohydrate/antiinflammatory actions are not closely related. Based on these differential

potencies, the corticosteroids traditionally are divided into mineralocorticoids and glucocorticoids. Estimates of potencies of representative **steroids** in these actions are listed in Table 59-2. It should be kept in mind, however, that a number of **steroids** that are predominantly classified as glucocorticoids, such as cortisol and prednisone, also possess modest but significant mineralocorticoid activity. Clinically significant changes in fluid and electrolyte handling can result from the mineralocorticoid effects of these "glucocorticoids." In contrast, aldosterone is exceedingly potent with respect to Na^+ retention but has only modest potency for effects on carbohydrate metabolism. At normal rates of secretion by the adrenal cortex or in doses that maximally affect electrolyte balance, aldosterone has no significant glucocorticoid activity and thus acts as a pure mineralocorticoid.

Table 59-2
Relative Potencies and Equivalent Doses of Representative Corticosteroids

COMPOUND	ANTI-INFLAMMATORY POTENCY	Na^+-RETAINING POTENCY	DURATION OF ACTION[a]	EQU DO
Cortisol	1	1	S	
Cortisone	0.8	0.8	S	
Fludrocortisone	10	125	S	
Prednisone	4	0.8	I	
Prednisolone	4	0.8	I	
6α-methylprednisolone	5	0.5	I	
Triamcinolone	5	0	I	
Betamethasone	25	0	L	
Dexamethasone	25	0	L	

[a] S, short (*i.e.*, 8-12 hour biological half-life); I, intermediate (*i.e.*, 12-36 hour biological half-life); L, long (*i*
biological half-life).

[b] These dose relationships apply only to oral or intravenous administration, as glucocorticoid potencies may
following intramuscular or intraarticular administration.

[c] This agent is not used for glucocorticoid effects.

Withdrawal of Therapy. Withdrawal of corticosteroid therapy poses a number of difficult decisions. It is important to remember that the most frequent problem in steroid withdrawal is flare-up of the underlying disease for which **steroids** were prescribed. There are several complications associated with steroid withdrawal, as discussed by Sullivan (1982). The most severe complication of steroid cessation, acute adrenal insufficiency, results from too rapid withdrawal of corticosteroids after prolonged therapy, where the HPA axis has been suppressed. The therapeutic approach to acute

adrenal insufficiency is detailed below. There is significant variation among patients with respect to the degree and duration of adrenal suppression following corticosteroid therapy, making it difficult to establish the relative risk in any given patient. Many patients recover from corticosteroid-induced HPA suppression within several weeks to months; however, in some individuals, the time to recovery can be 1 year or longer.

In an effort to diminish the risk of iatrogenic acute adrenal insufficiency, protocols for discontinuing corticosteroid therapy in patients receiving long-term treatment with corticosteroids have been proposed (for example, *see* Byyny, 1976). In general, patients who have received supraphysiological doses of glucocorticoids for a period of 2 weeks within the preceding year should be considered to have some degree of HPA impairment in settings of acute stress and should be treated accordingly

ADRENOCORTICAL STEROIDS

Introduction

The adrenal cortex synthesizes two classes of **steroids**: the *corticosteroids* (*glucocorticoids* and *mineralocorticoids*), which have 21 carbon atoms, and the *androgens*, which have 19 (Figure 59-3). The actions of corticosteroids historically were described as glucocorticoid (carbohydrate metabolism-regulating) and mineralocorticoid (electrolyte balance-regulating). The adrenal corticosteroids differ in their relative glucocorticoid and mineralocorticoid activities. In human beings, hydrocortisone (*cortisol*) is the main glucocorticoid, and *aldosterone* is the main mineralocorticoid. The mechanisms by which glucocorticoid biosynthesis is regulated by ACTH have been discussed above, and the regulation of aldosterone production is described in Chapter 31. Table 59-1 shows typical rates of secretion of the physiologically most significant corticosteroids in human beings/cortisol and aldosterone/as well as their normal concentrations in peripheral plasma. Although earlier studies had suggested that cortisol was produced at a daily rate of 20 mg, more recent studies indicate that the actual rate is closer to 10 mg/day (Esteban *et al.*, 1991).

Carbohydrate and Protein Metabolism. Corticosteroids have profound effects on carbohydrate and protein metabolism. Teleologically, these effects of glucocorticoids on intermediary metabolism can be viewed as protecting glucose-dependent tissues (*e.g.*, the brain and heart) from starvation. This is achieved by stimulating the liver to form glucose from amino acids and glycerol and by stimulating the deposition of glucose as liver glycogen. In the periphery, glucocorticoids diminish glucose utilization, increase protein breakdown, and activate lipolysis, thereby providing amino acids and glycerol for

gluconeogenesis. The net result is to increase blood glucose levels. Because of these effects on glucose metabolism, treatment with glucocorticoids can worsen control in patients with overt diabetes and can precipitate the onset of hyperglycemia in patients who are otherwise predisposed.

The mechanisms by which glucocorticoids inhibit glucose utilization in peripheral tissues are not fully understood. Glucocorticoids decrease glucose uptake in adipose tissue, skin, fibroblasts, thymocytes, and polymorphonuclear leukocytes; these effects are postulated to result from translocation of the glucose transporters from the plasma membrane to an intracellular location. These peripheral effects are associated with a number of catabolic actions, including atrophy of lymphoid tissue, decreased muscle mass, negative nitrogen balance, and thinning of the skin.

Similarly, the mechanisms by which the glucocorticoids promote gluconeogenesis are not fully defined. Amino acids mobilized from a number of tissues in response to glucocorticoids reach the liver and provide substrate for the production of glucose and glycogen. In the liver, glucocorticoids induce the transcription of a number of enzymes involved in gluconeogenesis and amino acid metabolism, including phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, and fructose-2,6-bisphosphatase (Pilkis and Granner, 1992). Analyses of the molecular basis for regulation of PEPCK gene expression have identified complex regulatory influences involving an interplay among glucocorticoids, insulin, glucagon, and catecholamine. The effects of these hormones and amines on PEPCK gene expression mirror the complex regulation of gluconeogenesis in the intact organism.

Electrolyte and Water Balance. Aldosterone is by far the most potent naturally occurring corticosteroid with respect to fluid and electrolyte balance. Evidence for this comes from the relatively normal electrolyte balance found in hypophysectomized animals, despite the loss of glucocorticoid production by the inner cortical zones. Mineralocorticoids act on the distal tubules and collecting ducts of the kidney to enhance reabsorption of Na^+ from the tubular fluid; they also increase the urinary excretion of both K^+ and H^+. Conceptually, it is useful to think of aldosterone as stimulating a renal exchange between Na^+ and K^+ or H^+, although the molecular mechanism of monovalent cation handling is not a simple 1:1 exchange of cations in the renal tubule.

These renal actions on electrolyte transport, in conjunction with similar effects in other tissues (*e.g.*, colon, salivary glands, and sweat glands), appear to account for the physiological and pharmacological activities that are characteristic of mineralocorticoids. Thus, the primary features of hyperaldosteronism are positive Na^+ balance with consequent expansion of the extracellular fluid volume, normal or slight increases in plasma Na^+ concentration, hypokalemia, and alkalosis. Mineralocorticoid deficiency, in contrast, leads to Na^+ wasting and contraction of the extracellular fluid volume,

hyponatremia, hyperkalemia, and acidosis. Chronically, hyperaldosteronism can cause hypertension, whereas aldosterone deficiency can lead to hypotension and vascular collapse. Because of the effects of mineralocorticoids on electrolyte handling by sweat glands, patients who are adrenal insufficient are especially predisposed to Na^+ loss and volume depletion through excessive sweating in hot environments.

Aldosterone exerts its effects on Na^+ and K^+ homeostasis primarily via its actions on the principal cells of the distal renal tubules and collecting ducts, while the effects on H^+ excretion are largely exerted in the intercalated cells. Although the precise mechanisms have not been defined, aldosterone increases the number of open Na^+ and K^+ channels in the luminal membrane, thus leading to an increase in Na^+ uptake into the tubular cells. Aldosterone also directly increases the activity of the Na^+,K^+-ATPase in the basolateral membrane, returning Na^+ to the systemic circulation in exchange for K^+. Recent studies have established the β subunit of the amiloride-sensitive Na^+ channel as an important component of mineralocorticoid action (Shimkets *et al*., 1994). The gene encoding this subunit is mutated in patients with *Liddle's syndrome (pseudoaldosteronism),* an autosomal dominant disease manifested by hypertension and hypokalemia in the setting of low plasma renin and aldosterone levels. Presumably, constitutive activity of the Na^+ channel due to this mutation mimics the effect of hyperaldosteronism.

Glucocorticoids also exert effects on fluid and electrolyte balance, largely due to permissive effects on tubular function and actions that maintain glomerular filtration rate. Glucocorticoids play a permissive role in the renal excretion of free water; the ability to excrete a water challenge was used at one time to diagnose adrenal insufficiency. In part, the inability of Addisonian patients to excrete free water results from the increased secretion of AVP, which stimulates water reabsorption in the kidney.

In addition to their effects on monovalent cations and water, glucocorticoids also exert multiple effects on Ca^{2+} metabolism. In the gut, **steroids** interfere with Ca^{2+} uptake by undefined mechanisms, while there is increased Ca^{2+} excretion at the level of the kidney. These effects collectively lead to decreased total body Ca^{2+} stores.

Cardiovascular System. As noted above, the most striking effects of corticosteroids on the cardiovascular system result from mineralocorticoid-induced changes in renal Na^+ excretion as is evident in primary aldosteronism. The resultant hypertension can lead to a diverse group of adverse effects on the cardiovascular system, including increased atherosclerosis, cerebral hemorrhage, stroke, and hypertensive cardiomyopathy. The mechanism underlying the hypertension remains incompletely understood, but restriction of dietary Na^+ can lower the blood pressure considerably.

The second major action of corticosteroids on the cardiovascular system is to enhance vascular reactivity to other vasoactive substances. Hypoadrenalism generally is associated with hypotension and reduced response to vasoconstrictors such as

norepinephrine and angiotensin II. This diminished pressor response is explained partly by recent studies in experimental systems showing that glucocorticoids increase expression of adrenergic receptors in the vascular wall. Conversely, hypertension is seen in patients with excessive glucocorticoid secretion, occurring in most patients with Cushing's syndrome and in a subset of patients treated with synthetic glucocorticoids (even those lacking any significant mineralocorticoid action).

The underlying mechanisms in glucocorticoid-induced hypertension also are unknown; in hypertension related to the endogenous secretion of cortisol, as seen in patients with Cushing's syndrome, it is not known if the effects are mediated by the glucocorticoid or mineralocorticoid receptor. Unlike hypertension caused by high aldosterone levels, the hypertension secondary to excess glucocorticoids is generally resistant to Na^+ restriction.

Recent studies also have shown direct effects of aldosterone on both the heart and vascular lining; treating rats with aldosterone induced hypertension and interstitial cardiac fibrosis (Young *et al.*, 1994). The increased cardiac fibrosis was proposed to result from direct mineralocorticoid actions in the heart rather than from the effect of hypertension, because treatment with spironolactone, a mineralocorticoid antagonist, blocked the fibrosis without altering blood pressure. To the extent that this finding is relevant to human beings, it may provide another mechanism by which chronic mineralocorticoid excess can lead to deleterious cardiovascular effects.

Snake Bites

Formed Elements of Blood. Glucocorticoids exert minor effects on hemoglobin and erythrocyte content of blood, as evidenced by the frequent occurrence of polycythemia in Cushing's syndrome and of normochromic, normocytic anemia in Addison's disease. More profound effects are seen in the setting of autoimmune hemolytic anemia, where the immunosuppressive effects of glucocorticoids can diminish the self-destruction of erythrocytes.

Corticosteroids also affect circulating white blood cells. Addison's disease, as noted by Addison in his initial report, is associated with an increased mass of lymphoid tissue and lymphocytosis. In contrast, Cushing's syndrome is characterized by lymphocytopenia and decreased mass of lymphoid tissue. The administration of glucocorticoids leads to a decreased number of circulating lymphocytes, eosinophils, monocytes, and basophils. A single dose of hydrocortisone leads to a decline of these circulating cells within 4 to 6 hours; this effect persists for 24 hours and results from the redistribution of cells away from the periphery rather than from increased destruction. In contrast, glucocorticoids increase circulating polymorphonuclear leukocytes as a result of increased release from the marrow, diminished rate of removal from the circulation, and increased demargination from vascular walls. Certain lymphoid malignancies, however, are destroyed by glucocorticoid treatment. This latter effect may be related to the rapid lytic effect of glucocorticoids on lymphatic tissues in rodents not seen in normal human tissues.

BITES AND STINGS
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SNAKEBITES
Epidemiology
An estimated 50,000 to 100,000 individuals die each year worldwide from venomous snakebites. The population at greatest risk includes agricultural workers and hunters living in tropical countries. 39 In the United States, approximately 45,000 snakebites occur annually, and poisonous snakes are responsible for some 8000 bites, of which 9 to 15 are fatal. 32 Venomous species indigenous to the United States can be found in all states except Alaska, Maine, and Hawaii. Most snakebites occur on the extremities of males. 32 Accidentally stepping near a snake can cause bites to the lower extremity, whereas purposeful handling of a snake produces bites to the upper extremity. Snakes are poikilothermic, explaining the high incidence of bites during July and August. 32
Species
In the United States, the rattlesnakes, copperheads, and cottonmouths of the Crotalidae (pit viper) family account for 99% of medically significant bites; the coral snakes of the

Elapidae family are responsible for less than 1% of bites. 18 Colubrid (rear-fanged) snakes also account for less than 1%. Several characteristics distinguish pit vipers from nonvenomous snakes. Pit vipers have triangle-shaped heads, elliptic pupils, heat-sensing pits, and a single row of subcaudal scales. Nonpoisonous snakes have rounded heads with round pupils, no fangs, and a double row of subcaudal scales (Fig. 16–1 Fig. 16–1). Coral snakes have a red, black, and yellow band pattern similar to that of many nonpoisonous snakes. The unique placement of red bands next to yellow bands identifies the coral snake. Snakes brought in for identification should be handled cautiously, because a bite reflex may still be present.

Toxicology

Chemically, venom is quite complex, consisting of many enzymes and peptides. Damage to the endothelium by peptides increases vascular permeability, which may lead to edema and hypovolemic shock. The enzymes include proteases and L-amino acid oxidase, which cause tissue necrosis; hyaluronidase, which facilitates the spread of venom through tissues; and phospholipase A 2, which damages erythrocytes and muscle cells. Other enzymes include endonucleases, alkaline phosphatase, acid phosphatase, and cholinesterase. 18, 31 Besides causing local injury, these components also have deleterious effects on the cardiovascular, pulmonary, renal, and neurologic systems. 14 Other components of the venom profoundly affect coagulation, fibrinolysis, platelet function, and vascular integrity, sometimes producing either hemorrhagic or thrombotic sequelae. 22

Clinical Manifestations

Local. Approximately 20% of bites by pit vipers do not cause envenomation. 36 These may appear as puncture wounds and lacerations associated with minimal pain only. Inoculation with venom produces burning pain within minutes, followed by edema and erythema. Edema progresses over the next few hours, with development of ecchymoses and hemorrhagic bullae. Involvement of the lymphatic system is common, causing lymphangitis and lymphadenopathy. 18, 35 Without treatment, the patient may develop severe extremity necrosis.

Systemic. Patients typically complain of weakness, nausea, vomiting, perioral paresthesias, metallic taste, and fasciculations. 35, 42 Continuing capillary leak leads to pulmonary edema, hypotension, and eventually shock. Victims of significant bites can develop coagulopathy within an hour, manifested as spontaneous bleeding from the gingivae, the bite site, venipuncture areas, and recent wounds. If untreated, progression to fulminant disseminated intravascular coagulation (DIC) can occur. 22 Acute renal failure secondary to direct nephrotoxins, circulatory collapse, and consumption coagulopathy is possible. Laboratory abnormalities include hypofibrinogenemia, thrombocytopenia, prolonged prothrombin and partial thromboplastin times, increased fibrin split products, creatinine and creatine phosphokinase, proteinuria, hematuria, and anemia or hemoconcentration. 22, 42

Coral snakes produce primarily a neurotoxic venom. Local injury is generally minimal or absent. Systemic signs of coral snake bites, including cranial nerve dysfunction and loss of deep tendon reflexes, may progress to respiratory depression and paralysis over several hours. 14, 18 The differences in therapy make it important to distinguish between Elapidae and Crotalidae bites.

Management

Field Treatment. The patient should be placed at rest in an area away from the snake's territory. The wound should be cleansed and immobilized below the level of the heart. Cryotherapy, incision and suction, tourniquets, and electric shock therapy are not recommended and have, in certain circumstances, proved to be harmful. 18 Suction syringe devices now on the market successfully extract venom from the bite site if applied within 5 minutes and continued for at least 30 minutes. 18 A constriction band should be used, especially if a delay in treatment is anticipated. The band is applied 5 cm. above the bite, tight enough to occlude only lymphatic flow, and removed after antivenin therapy has been initiated. 18 Distal pulses and venous return should not be interrupted. These measures should not delay transport to the nearest hospital.

Hospital Management. A detailed history of the incident, type of snake, field management, and prior antivenin therapy is important. A rapid physical assessment should emphasize vital signs, wound appearance and size, and neurologic examination. Necessary laboratory analyses include a complete blood count (CBC), DIC panel, electrolytes, blood urea nitrogen, creatinine, creatine phosphokinase, urinalysis, and electrocardiogram. If the patient remains asymptomatic 6 hours after a pit viper bite or 24 hours after a coral snake bite, it is unlikely that envenomation occurred, so discharge is acceptable. 14

Antivenin Therapy. Antivenin can neutralize venom at the bite site, making it the primary treatment modality. However, this therapy is not benign; severe hypersensitivity reactions can occur. In one study, 23% of the patients suffered acute anaphylaxis, and 50% suffered delayed serum sickness. 24 The use of antivenin for minor envenomation is controversial. Skin testing predicts hypersensitivity in most patients; this is performed by administering 0.02 ml. of 1:10 dilution of antivenin with 0.9% sodium chloride intradermally. Options for patients demonstrating hypersensitivity reactions or with known allergy to horse serum include premedication with diphenhydramine hydrochloride (25 to 50 mg. intravenously) and an epinephrine drip (2 to 20 mg. per minute) during antivenin administration in an intensive care setting.

Best results are achieved when an adequate amount of antivenin is administered within 4 hours of the bite. 18 Antivenin doses are determined by the severity of the envenomation (Table 16–1 Table 16–1) and are administered over a 2- to 4-hour period. The patient's clinical condition should be re-evaluated every 2 hours, and, if necessary, a repeat dose of antivenin should be recalculated and given. Persistent hemodynamic instability and coagulopathy indicate inadequate antivenin dosage. Blood products are needed only if the antivenin is ineffective. Some experts recommend that in children, the dose of antivenin be increased by 50% because of the higher ratio of venom to body mass. 14, 18 Pregnancy is not a contraindication to antivenin therapy. 18

A separate antivenin is available for coral snakes, excluding snakes from Arizona. Administration is similar to that of Crotalidae antivenin except that therapy should be initiated even when a coral snake bite is only strongly suspected because there are frequently no local manifestations. Poison control centers and zoos can provide information regarding the occasional exotic snakebite.

Wound Care. The wound should be cleansed thoroughly and the extremity splinted. Soaking the affected area in Burow's solution (1:20 aluminum acetate) three times a day is recommended. 18 Surgical débridement should be performed as necessary. Tetanus toxoid and tetanus immune globulin should be administered as indicated. Both gram-

negative and -positive rods have been cultured from snakes' mouths and bite abscesses; therefore, a broad-spectrum antibiotic is recommended for 3 to 5 days after the bite. Fasciotomy. Most snakebites cause subcutaneous deposition of venom. Clinically, differentiating true compartment syndrome from these local reactions is difficult, requiring the measurement of compartment pressures. Fasciotomies should be performed only if compartment pressures are over 30 mm. Hg. 18 Compartment syndrome in areas too small to measure pressures, such as the digits, can be diagnosed by pricking the skin of the affected extremity. Dark venous blood flow indicates increased pressure. 38 Routine fasciotomies to prevent compartment syndrome have not proved to be beneficial.

Anatomy – Cauda Equina

The tip of the spinal cord (conus medullaris) ends at the T12 or L1 level of the spinal canal. Caudal to the conus medullaris, the nerve roots of the cauda equina lie immersed in cerebrospinal fluid within the subarachnoid space, surrounded by concentric cylindrical sheaths, the arachnoid and the dura mater. The dural-arachnoidal sac usually ends at about the level of the first sacral vertebra. The space that surrounds the dura within the spinal canal, the epidural space, is filled with fat and is traversed by veins. The spinal nerves leave the dural sac in pairs, with one nerve on each side exiting at each vertebral level. Each nerve lies along the caudal border of the pedicle as it exits through the intervertebral foramen; in this position, it lies between the intervertebral disc anteromedially and the facet joint posterolaterally (Fig. 41–24 Fig. 41–24). The nerve roots, however, do not exit directly transversely. Each nerve root exits from the main dural sac and then lies immediately lateral to it for 1 to 2 cm. before it turns further laterally to leave the bony spinal canal about one vertebral level below where it left the dural sac. For example, the left L5 nerve root ordinarily leaves the dural sac at the level of the L4–L5 intervertebral disc (where it is most likely to be involved by a left-sided L4–L5 disc herniation), but it leaves the bony spinal canal below the left L5 pedicle, opposite the L5–S1 disc (Fig. 41–25 Fig. 41–25).