The Immune Compromised Host in the Twenty-first Century: Management of Mucocutaneous Infections

Richard Allen Johnson

Infectious diseases encountered in dermatology have changed tremendously during the past few decades with the emergence of the immunocompromised host. This change is a result of the human immunodeficiency virus epidemic, use of immunomodulating drugs, bone marrow transplantation, increasing prevalence of diabetes mellitus, and an aging population. New pathogens have been discovered and new disorders have occurred. In the compromised host, infection can be more aggressive and widespread locally, be caused by opportunistic pathogens, and be disseminated hematogenously from or to the skin. The prevalence of nonmelanoma skin cancer has increased, and squamous cell carcinomas can be more aggressive with more rapid local growth as well as frequency of metastasis.

THE NUMBER OF individuals with an acquired immune compromised status continues to increase as we enter the 21st century. Major factors for this increase include the expanding human immunodeficiency virus (HIV) epidemic, chemotherapy of cancers, immunosuppressive therapy of organ (solid and bone marrow) transplant recipients and inflammatory disorders, and increasing numbers of individuals with diabetes mellitus (Table 1). These patients are subject to an exceptionally broad variety of potential microbial pathogens and a wide spectrum of clinical manifestations of disease resulting from the abnormal immune response. Cutaneous and subcutaneous tissues may be expected to be an important aspect of infection, for 3 reasons.[1,2] The skin and mucosal surfaces represent the body's first line of defense against the external environment. These barriers assume an even greater importance when secondary defenses, such as phagocytosis, cell-mediated immunity, and antibody production, are impaired. The rich blood supply of the skin provides a route of spread of infection both from the skin to other bodily locations and to the skin from infected sites. A skin lesion serves as an early warning system to alert the patient and the clinician to the existence of a systemic infection. Cutaneous lesions may be benign in appearance, presumably because of the impaired host immune response, and therefore be easily missed or dismissed as insignificant. Third, skin infections are common, occurring in up to one third of significantly compromised hosts.

Globally, the HIV epidemic continues to broaden, especially in Third World countries, with the total number of infected individuals approaching 40 million.[3] Untreated HIV-infected individuals in developing countries remain relatively asymptomatic, developing an acquired immunodeficiency syndrome (AIDS)-defining condition in 5 to 7 years after becoming infected; the estimated survival time once an AIDS-defining condition has occurred is 5 to 9 months. In contrast, in industrialized countries with access to all modalities of therapy, the average time after primary HIV infection to occurrence of an AIDS-defining illness ranges from 10 to 15 years; survival after AIDS diagnosis ranges from 9 to 26 months, and is increasing because of highly active antiretroviral therapy (HAART).

With use of HAART during the past few years, there has been a sharp decline in the rate of HIV disease as well as in the number of deaths. The age-adjusted death rate among HIV-infected individuals in 1997 (16,685) was only 40% of that in 1995 (43,115). This improved prognosis requires that individuals have access to treatment, can tolerate triple therapy, and can adhere to the therapeutic regimens. This dramatic decline in morbidity and mortality due to HIV disease in the

From the Department of Dermatology, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, MA.

Address reprint requests to Richard Allen Johnson, MD, 110 Francis St, Suite 7H, Beth Israel-Deaconess Medical Center, Boston, MA 02215.

1085-5629/00/1901-0004$10.00/0

doi:10.1053/sd.2000.7371

Table 1. Classification of Immunocompromise

HIV disease
Bone marrow and lymphatic cancers
Leukemia (acute and chronic)
Multiple myeloma
Lymphoma
Solid tumors
Diabetes mellitus
Transiently immunosuppressed after surgery
Solid organ transplantation: kidney, heart, lung, pancreas
Bone marrow transplantation
Immunosuppressive chemotherapy of inflammatory disorders
Cytotoxic chemotherapy
Old age

United States has also occurred in other developed nations with access to HAART (Canada, western Europe, and Australia). The death rate in Europe at the beginning of 1998 had decreased to less than 20% of that before 1995. HAART has altered natural history to an extraordinary degree. Nearly all mucocutaneous complications of HIV disease either improve or resolve if improved immune function is achieved by HAART. Kaposi's sarcoma (KS), which had caused great morbidity and some mortality, either does not occur or, if present, often resolves with immune reconstitution.

A new phenomenon, the immune restoration syndrome, is provoked by improved immune function following initiation of HAART. An exaggerated immune response occurs to presume subclinical or residual infection by pathogens such as mycobacteria, cytomegalovirus, and hepatitis virus at the time when CD4+ lymphocytes are increasing rapidly. Patients can also experience adverse cutaneous drug reaction to agents such as trimethoprim-sulfamethoxazole, which were previously tolerated.

PATHOGENESIS OF MUCOCUTANEOUS INFECTIONS

Skin as a Barrier to Infection

The skin is quite resistant to infection. The mechanisms by which the resistance occurs are not well understood. Several important components that contribute to microbial resistance are nonspecific: intact keratinized layers of the skin, which prevent penetration of microorganisms; dryness of the skin, which retards the growth of certain organisms such as aerobic gram-negative bacilli and *Candida* species; the suppressant effect of the normal skin flora, which appears to reduce colonization of pathogens, a phenomenon known as bacterial interference. Within this framework, then, one might expect potentially serious skin infections to develop under the following circumstances: destruction by trauma or bypass by introduction of intravascular catheters of the previously intact keratinized layer of skin; moistening of the skin, such as under occlusive dressings; alteration of the normal colonizing flora, such as after administration of antimicrobial agents. These types of events would represent some risk to the normal patient but are considerably more threatening to the compromised patient with impaired immunologic defenses that are likely to be more readily overwhelmed when the primary cutaneous barrier breaks down.

An example of these phenomena are the development of invasive fungal infection in compromised patients whose skin has been traumatized by tape holding intravascular lines in place. Infection with *Rhizopus* species has been associated with use of Elastoplast tape to secure intravascular catheters.[4] Skin infection with *Aspergillus* species has occurred at the site of boards to stabilize arms to protect intravenous lines.[5] Because of the occurrence of these types of infections, the following approach would seem warranted: Occlusive dressings in immunocompromised patients should be avoided when possible and skin covered by such dressings should be routinely inspected. Paper tape should be used in preference to cloth tape, and surgical dressings might be secured with girdles of elasticized netting rather than tape whenever possible.

The effect of chronic administration of corticosteroids (topical or systemic) on the skin is another factor that may contribute to increased susceptibility of compromised patients to infection. Steroid therapy appears to inhibit proliferation of fibroblasts, synthesis of mucopolysaccharides, and deposition of collagen. The net effect is thin and atrophic skin that heals poorly. Minor trauma generates lesions that tend to persist, providing potential portals of entry for pathogens. An example of the phenomenon that has been observed is recurrent staphylococcal cellulitis about the elbow in patients receiving chronic immunosuppressive therapy after renal transplantation. These patients exhibited 2 adverse effects of chronic corticosteroid administration: thinning of the skin leading to enhanced susceptibility of the tissue to trauma and steroid-induced proxi-

mal myopathy. Because of the myopathy, the patients tended to rise from the sitting position by pushing off with their elbows, thus traumatizing them. Cellulitis about the elbows recurs in these patients until their elbows are protected and the steroid dose is decreased.

Types of Skin Infection

Infection of the cutaneous and subcutaneous tissues in compromised patients can be classified in a variety of ways: by pathogen, by underlying immunologic defect, or by pace of illness. An additional categorization considers pathophysiological events and consists of 4 groups (Table 2): (1) infection originating in skin and typical of that which occurs in immunocompetent persons, albeit with the potential for more serious illness; (2) extensive cutaneous involvement with pathogens that normally produce trivial or well-localized disease in immunocompetent patients; (3) infection originating from a cutaneous source and caused by opportunistic pathogens that rarely cause disease in immunocompetent patients but that may cause either localized or widespread disease in compromised persons; (4) cutaneous or subcutaneous infection that represents metastatic spread from a noncutaneous site. Cutaneous and subcutaneous infections in compromised patients are discussed in this section within the framework of these 4 groups.

Primary Skin Infections With Common Pathogens

The incidence and severity of conventional forms of infections originating in the skin are often increased in the compromised host. Gram-positive organisms, such as *Staphylococcus aureus* and group A streptococci, most commonly cause these infections. In the healthy host, these organisms cause superficial infection of the epidermis or hair follicles. In the compromised host, superficial infections can quickly extend deeper, causing soft tissue infections and septicemia. Patients with granulocytopenia are more susceptible to cellulitis caused by less virulent bacterial pathogens, such as Enterobacteriaceae and *Pseudomonas* species and by anaerobic bacteria. Patients with leukemia or diminished cell-mediated immunity may have erysipelas-like infection, caused by organisms such as *Cryptococcus neoformans* or *Candida* species, mimicking cellulitis caused by common gram-positive bacteria. When evaluating cellulitis in a compromised patient, common as well as uncommon/rare pathogens must be considered as potential pathogens. If a patient does not respond to conventional antimicrobial therapy, an aggressive approach to diagnosis is warranted with biopsy of lesions for Gram and other stains, cultures, and dermatopathology, to identify the pathogen correctly.

Table 2. Types of Skin Infection by Pathophysiological Events

Type of Infection	Pathogen	Site of Infection	Healthy Host	Compromised Host
Primary skin infections with common pathogens	*S aureus*, group A streptococcus	Epidermis, hair follicles, dermis	Impetigo, ecthyma, folliculitis, abscess, intertrigo	Soft tissue infection, necrotizing soft tissue infection, septicemia
Unusually widespread cutaneous infection	Dermatophytes, *Candida* spp	Epidermis, intertriginous sites, hair follicles	Dermatophytosis: epidermal (limited), folliculitis	Dermatophytosis: epidermal (extensive), folliculitis
	Candida spp	Oropharynx, esophagus, genitalia	Candidiasis: intertrigo, genital	Candidiasis: intertrigo, folliculitis, mucosal
	HSV		Localized herpes; resolves spontaneously	Chronic herpetic ulcers
	VZV		HZ (mild)	Extensive HZ
	EBV			Hairy leukoplakia
	MCV		MCV (localized, nonfacial)	Widespread MC, resistant to therapy
	HPV		Common and mucosal warts	Widespread warts; SCC (in situ and invasive)
Opportunistic primary cutaneous infection	Atypical mycobacteria Nocardia Molds *Prototheca*	Dermis, hypodermis	Swimming pool granuloma	Soft tissue infection ± necrosis; septicemia
Systemic infection metastatic to cutaneous and subcutaneous sites	Bacteria Fungal pneumonitis with fungemia	Dermis, hypodermis	Soft tissue infection ± necrosis Nodules	Soft tissue infection ± necrosis Nodules

Unusually Widespread Cutaneous Infection

Nonvirulent skin fungi and viruses constitute the 2 major causes of infection in this category. These pathogens typically cause minor infections in immunocompetent persons, but in compromised patients tend to cause more extensive disease that may lead to more serious systemic illness. Viruses that cause exanthems (eg, those caused by rubella, measles, or enterovirus) do occur in compromised patients, but the more problematic pathogens include the family of herpesviruses and human papillomaviruses (HPV).

Nonvirulent fungi include the dermatophytes (*Trichophyton* species, *Microsporum* species, and *Epidermophyton*), *Candida* species, *Pityrosporum* species, *Fusarium solani*, and *Alternaria alternata*. These fungi frequently colonize human skin and cause localized, superficial skin infection in immunocompetent persons, particularly when the skin has been traumatized. The incidence and severity of infection may be increased in compromised patients. Topical corticosteroid preparations prescribed mistakenly for epidermal dermatophytoses compromise local immunity, facilitating growth of the fungus and causing extensive local epidermal infection (so-called tinea incognito in that the diagnosis of dermatophytosis is missed); dermatophytic folliculitis (Majocchi's granuloma) is commonly seen as an associated finding. Systemic corticosteroid therapy can also cause widespread epidermal dermatophytosis. These dermatomycoses are best treated with oral agents such as terbinafine, itraconazole, or fluconazole; secondary prophylaxis is often necessary.

Skin infections with members of the herpesvirus family, particularly herpes simplex virus (HSV) and varicella-zoster virus (VZV), are very common in compromised patients. Nasolabial or anogenital infections caused by HSV occur in as many as half of renal transplant recipients, patients with malignancy, those receiving chemotherapy, and HIV-infected individuals. Immunocompromised patients may have more serious forms of HSV infection, including chronic herpetic ulcers, esophageal or respiratory tract infection, or disseminated infection (patients with lymphoma, transplant recipients [bone marrow, renal, cardiac, or liver], and neonates).

In compromised patients, reactivation of VZV is common, occurring in 14% of persons with Hodgkin's disease, 8% of non-Hodgkin's lymphoma and renal transplant recipients, and 2% with solid tumors. Visceral dissemination occurs in 15% to 30% of patients with Hodgkin's disease with zoster; systemic dissemination, however, is uncommon in renal transplant recipients. Reactivated VZV infection is particularly problematic for bone marrow transplant recipients, of whom one half will develop herpes zoster (HZ). In one third of these, VZV will disseminate, and in one fourth, a generalized atypical recurrent varicella-like illness will develop.

Reactivated cytomegalovirus (CMV) causes hepatitis, pneumonitis, chorioretinitis, encephalitis, and gastroenteritis in transplant recipients and HIV-infected individuals; cutaneous CMV infections are rare. Cutaneous CMV infections are reported to present as nodules, ulcers, indurated plaques, vesicles, petechiae, or a maculopapular exanthem. Reactivation of Epstein-Barr virus (EBV) results in oral hairy leukoplakia (OHL) on the lateral aspects of the tongue, a lesion nearly pathognomonic for HIV disease.

In chronically immunosuppressed patients, HPV-induced lesions, ie, verrucae and condylomata, either may be extremely numerous or may form large confluent lesions. Up to 40% of renal transplant recipients develop warts after transplantation, half have more than 10 warts, and up to 1% have extensive disease. The incidence and severity of warts seem to be related to immunosuppression with previously acquired latent virus reactivating with institution of immunosuppressive therapy. In compromised patients, HPV-induced lesions have the potential for malignant transformation, particularly in sun-exposed areas of the body. Squamous cell carcinoma (SCC) arising in sites of chronic sun exposure occurs 36 times more frequently in renal transplant recipients than in the general population, some clearly arising within warts; HPV DNA is demonstrable within the tumors. Management of patients with extensive warts should include avoidance of sun exposure, use of strong sunscreens, reduction in immunosuppressive therapy when possible, and careful observation for the development of malignant lesions. HPV-induced anogenital in situ and invasive SCC are also more common in transplant recipients and HIV-infected individuals; these persons should also be screened for in situ and invasive SCC with a Pap test of the anus and cervix and lesional biopsy when indicated.

Opportunistic Primary Cutaneous Infection

Following inoculation into the skin, organisms of low virulence can cause local or disseminated infections in some persons with impaired immune defenses. Localized disease can be caused by atypical mycobacteria, *Paecilomyces,* and *Prototheca.* Environmental mycobacteria such as *Micobacterium, marinum, M chelonei, M kansasii,* and *M haemophilium* may cause cutaneous infection after inoculation. In the normal host, the infection is localized and may resolve without therapeutic intervention; however, in the compromised host, more extensive local infection may occur as well as lymphatic or hematogenous dissemination. Primary infection caused by *Aspergillus, Rhizopus,* or *Candida* species arises at localized cutaneous sites but has the potential for disseminated disease in the compromised host. Primary cutaneous infection with these fungi has been associated with the use of adhesive or Elastoplast tape, cardiac electrode leads, or extravasation of intravenous fluids. *Aspergillus* and *Rhizopus* species can invade blood vessels, resulting in infarction, hemorrhage, and hematogenous dissemination. Localized disease with life-threatening systemic spread may be caused by *Pseudomonas aeruginosa, Aspergillus* species, *Candida* species, and *Rhizopus* species. *Prototheca wickerhamii* is an algae-like organism ubiquitous in nature that may cause localized infection after trauma or surgery.

Systemic Infection Metastatic to Cutaneous and Subcutaneous Sites

In a report of dermatologic manifestations of infection in compromised patients, 8 of 31 patients (26%) had apparent spread of systemic infection to cutaneous and subcutaneous tissues.[2] In 6 of these 8 patients, cutaneous or subcutaneous lesions were the first clinical sign of disseminated infection. In compromised hosts, cutaneous lesions resulting from hematogenous spread of infection are caused in general by 3 classes of pathogens: (1) *P aeruginosa* and other bacteria; (2) the endemic systemic mycoses (*Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Penicillium marneffei* (southeast Asia); and (3) the ubiquitous opportunistic organisms *Aspergillus* species, *C neoformas, Candida* species, *Rhizopus* species, and *Nocardia* species.

OPPORTUNISTIC INFECTIONS BY PATHOGEN

Bacterial Infections

Staphylococcus Aureus

S aureus causes the majority of all pyodermas and soft tissue infections. *S aureus* is not one of the cutaneous resident flora. It colonizes the anterior nares in up to 25% of healthy individuals at any one time and more than 50% of chronically ill individuals. Intertriginous sites such as the axilla and perineum can also be colonized. The incidence of *S aureus* nasal carriage is higher in chronically ill individuals, especially those with HIV disease, diabetes mellitus, cancer (particularly hematologic malignancies), neutropenia, abnormal leukocyte function, chronic granulomatous disease, hyperimmunoglobulinemia E syndrome, and interleukin-2 therapy.

Ensconced in the nares, *S aureus* is able to colonize and infect superficial skin lesions by entering hair follicles or small breaks in the epidermis, by secondary infection of dermatologic disorders (scabies, eczematous dermatitis, herpetic ulcer, KS, molluscum contagiosum), or via vascular access line and drainage tubes, resulting in pyodermas (folliculitis, furuncles, carbuncles, abscess, impetigo, bullous impetigo, and ecthyma). Once established in the skin, *S aureus* is able to invade more deeply into the soft tissue with resultant erysipelas (horizontal spread in lymphatics) and cellulitis (vertical spread into subcutaneous fat). *S aureus* is the most common cause of wound infections. Risk factors for surgical wound infection depend on the following: host factors (immune status, diabetes mellitus); surgical factors (disruption of tissue perfusion that accompanies the surgical procedure, foreign body use); staphylococcal factors (substances that mediate tissue adherence and invasion or that enable staphylococci to survive host defenses and antibiotics in tissues; and antimicrobial prophylaxis). Bacteremia can result in deposition of *S aureus* in the skin, resulting in petechiae, hemorrhages, subcutaneous nodules, soft tissue infections, and pyomyositis.

Various strains of *S aureus* are capable of producing a variety of toxins, which cause the clinical syndromes of staphylococcal scalded skin syndrome (rare in infants older than 2 years of age), staphylococcal scarlet fever, and toxic shock syndrome (TSS). TSS is a febrile, multi-organ disease caused by the elaboration of staphylococ-

cal toxins, characterized by a generalized scarlatiniform eruption, hypotension, functional abnormalities of 3 or more organ systems, and desquamation in the evolution of the exanthem. Cellulitis caused by *S aureus* that produce TSS toxins can be accompanied by the cutaneous and systemic findings of staphylococcal scarlet fever or TSS.[6]

Streptococcus

Group A β-hemolytic streptococci (*Streptococcus pyogenes*) commonly colonize the upper respiratory tract and secondarily infect (impetiginize) minor skin lesions from which invasive infection can arise.[7-9] Certain strains of group A streptococci have a higher affinity for the skin than the respiratory tract and can colonize the skin, subsequently causing superficial pyodermas or soft tissue infections. Lymphatic obstruction/lymphedema predisposes to erysipelas or cellulitis. Individuals at higher risk are those who have had radical mastectomy with axillary node dissection or saphenous vein harvest.

Group B streptococci commonly colonize the perineum and may cause soft tissue infections at this site. Advanced age, cirrhosis, diabetes, stroke, breast cancer, surgical wounds, decubitus ulcer, neurogenic bladder, and foreign bodies (breast or penile implants) have all been associated with a significantly increased risk of acquiring group B *streptococcus* infection. An unusual form of recurrent cellulitis of the lower extremities in women results from impaired lymphatic drainage caused by neoplasia, radical vulvectomy or pelvic surgery, or radiation therapy. Morbidity and mortality are relatively high for group B *streptococcus* infections, with a high incidence of bacteremia.

S pneumoniae is a rare cause of cellulitis, occurring in individuals predisposed by connective tissue disease, alcoholism, drug abuse, HIV disease, or corticosteroid therapy.[10,11] Clinically, infected areas are characterized by bullae, brawny erythema, and a violaceous hue. Approximately 50% of cases are the result of pneumococcal bacteremia, often from a pulmonary source. Because of underlying medical conditions, and often pneumonia, the morbidity is high.

Other Gram-Positive Bacteria

Primary cutaneous *Bacillus cereus* infection presents as a single bulla with necrosis on the extremity of an immunocompromised patient.[12-14] The large gram-positive rods of *B cereus* may be mistaken for *Clostridium* species in lesional biopsy specimens and smears.

Skin and soft tissue infections caused by *Corynebacterium jeikeium* occur in granulocytopenic patients and take either of 2 forms: (1) primary infections (cellulitis at bone marrow biopsy sites, infection at insertion sites of intravascular catheters, skin fissures [perianal]),[12-14] and (2) secondary infections (erythematous or hemorrhagic papular rash, soft tissue abscess, or necrotic lesions) after bacteremia from primary infection sites.[15]

Escherichia Coli and Other Gram-Negative Bacilli

E coli and other gram-negative bacilli rarely cause soft tissue infection or hemorrhagic plaques associated with hematogenous dissemination, in individuals with cirrhosis, neutropenia, or leukocyte dysfunction.[16-22] In a report of 7 patients with gram-negative bacillary cellulitis and cirrhosis, soft tissue infections were characterized by bullous lesions, ulcers, abscesses, or extensive cutaneous necrosis. Bacteremia occurred in 6 patients who eventually died. Isolates from the skin included *Klebsiellae pneumonia, E coli, P aeruginosa, Proteus mirabilis,* and *Aeromonas hydrophila.*

Pseudomonas

P aeruginosa causes the necrotizing soft tissue infection ecthyma gangrenosum (EG), which occurs as a primary skin infection[23-25] or as a complication of pseudomonal bacteremia.[26] EG occurs commonly as a nosocomial infection, especially in immunocompromised patients with diabetes, neutropenia, or poor neutrophil function. *P aeruginosa* is the most common pathogen causing gangrenous cellulitis in childhood. *P aeruginosa* gains entry into the dermis and subcutaneous tissues via adnexal epidermal structures or areas of loss of epidermal integrity (pressure ulcers, thermal burns, and trauma). EG occurs most frequently in the axillae or anogenital regions but can arise at any cutaneous site. Clinically, EG presents initially as an erythematous, painful plaque that quickly undergoes necrosis. Established lesions show bulla formation, hemorrhage, necrosis, and surrounding erythema. If effective antibiotic therapy is not initiated promptly, the necrosis may often extend rapidly. Bacteremia occurs soon after the onset of EG, and

may result in metastatic spread of *P aeruginosa* with subcutaneous nodules and abscesses. Histologically, EG is characterized by a distinctive septic vasculitis. Hematogenous dissemination of *P aeruginosa* to the skin can result in multiple subcutaneous nodules, hemorrhagic bullae, multiple small hemorrhagic papules, and/or EG.[27]

Stenotrophomonas (formerly classified as *Xanthomonas* [formerly classified as *Pseudomonas*]) *maltophilia* is a significant cause of morbidity and mortality in hospitalized patients with neutropenia or cancer, and those undergoing chemotherapy. Primary cellulitis (often necrotizing), disseminated cutaneous nodules, and mucocutaneous ulcers caused by *Xanthomonas* are often associated with underlying malignancies.[28]

Aeromonas Species

A hydrophila, a gram-negative facultative rod found naturally in aqueous environments, causes soft tissue infections in healthy individuals and more serious infections in the compromised host.[29,30] *A hydrophila* soft tissue infections occur after injuries sustained in a contaminated aquatic environment or the "outdoors." *A hydrophila* (a normal inhabitant of the foregut of leeches) cellulitis has also followed the therapeutic use of leeches (in 7%-20% of patients) after reimplantation or flap surgery. In the compromised host, *Aeromonas* causes severe cellulitis and necrotizing soft tissue infections.

Vibrio Species

Vibrio vulnificus is a free-living gram-negative rod, occurring naturally in the marine environment, occasionally contaminating oysters and other shellfish. Marine *Vibrio* species can cause sepsis and soft tissue infections, particularly in patients with cirrhosis and/or diabetes mellitus.[31] *V damselae* may cause fulminant necrotizing soft tissue infections in immunocompetent patients. Either ingestion of raw seafood or exposure of open wounds to seawater can result in *Vibrio* bacteremia and soft tissue infections. Individuals with cirrhosis, hemochromatosis, and diabetes mellitus and other patients with chronic disease are advised to avoid eating raw seafood.

Marine *Vibrio* soft tissue infections occur by direct inoculation into a superficial wound or by bacteremic spread to the skin (metastatic infection). After ingestion of *V vulnificus* in contaminated seafood, the organism is capable of crossing the gut mucosa rapidly, invading the bloodstream without causing gastrointestinal symptoms. The clinical picture is one of abrupt onset of chills and fever, often followed by hypotension, usually complicated by development of metastatic cutaneous lesions within 36 hours after onset. The cutaneous lesions begin as erythematous plaques, rapidly evolving to hemorrhagic bullae, and then to necrotic ulcers. The lesions arise commonly on the extremities, occasionally bilaterally. Soft tissue infections can also arise following inoculation of *V vulnificus* or *V alginolyticus* directly into a site of soft tissue injury. Infection by either of these *Vibrio* species can be life-threatening in compromised hosts.

Helicobacter Cinaedi

Helicobacter cinaedi causes a syndrome characterized by fever, bacteremia, and recurrent and/or chronic cellulitis (resembling erythema nodosum) in compromised patients. In a series of 23 febrile patients with *H cinaedi* bacteremia (11 were HIV-infected; the others had underlying alcoholism, diabetes, or malignancy), 9 had cellulitis (some with a distinctive red brown or copper discoloration with minimal warmth). In a series of 7 patients (6 HIV-infected, 1 with a history of alcoholism) with *H cinaedi* soft tissue infections, cellulitis with adjacent arthritis occurred in 2 patients. The organism is carried as bowel flora in 10% of homosexual men (no carriage in other groups). Diagnosis is made by considering it in immunocompromised individuals, demonstrating cellulitis on lesional biopsy (excluding panniculitis), and failure to isolate other pathogens. Bacteremia is intermittent; the organism is difficult to isolate, requiring hydrogen in the culture vial. Ciprofloxacin 500 mg twice daily or clarithromycin 500 mg twice daily is effective, given for 6 to 8 weeks to prevent relapse.

Mycobacteria Infections

Mycobacterium tuberculosis. In developing countries, tuberculosis is the most common opportunistic infection in HIV disease; however, cutaneous tuberculosis is relatively uncommon. As has been true in the past, most cases of symptomatic tuberculosis represent reactivation of latent infection. In non–HIV-infected persons who have tuberculosis in some form, the incidence of extrapulmonary tuberculosis is 15%; in HIV disease, 20% to 40%. In advanced HIV

disease, the incidence of extrapulmonary disease increases to 70%.

The etiologic agents of human tuberculosis include *M tuberculosis, M bovis,* and occasionally bacillus Calmette-Guérin (BCG). Cutaneous tuberculosis is highly variable in its clinical presentation. Cutaneous tuberculosis occurs after *M tuberculosis* exposure to an exogenous source or by autoinoculation or endogenous spread from another site. Modes of endogenous spread to skin include: direct extension from underlying tuberculous infection, ie, lymphadenitis or tuberculosis of bones and joints results in scrofuloderma; lymphatic spread to skin results in lupus vulgaris; hematogenous dissemination results in either acute miliary tuberculosis,[32-34] lupus vulgaris, or metastatic tuberculosis abscess. Tuberculosis cutis miliaris disseminata is the lesion of miliary tuberculosis, presenting as 1- to 4-mm red-brown papules/papulovesicles/papulopustules.[35,36] On acid-fast stain of lesional skin biopsy specimens, numerous acid-fast bacilli are seen, however, giant cells and granulomas are absent. In HIV-infected individuals, prior bacillus Calmette-Guérin immunization can be followed by reactivation of and infection by BCG at the site of immunization, dissemination of BCG, or lymphadenitis.

Environmental mycobacteria. Mycobacteria other than tuberculosis (MOTT) (also known as nontuberculous mycobacteria, environmental mycobacteria, potentially pathogenic environmental mycobacteria, atypical mycobacteria, nonleprous mycobacteria) are widely distributed in soil, dust, and water. They are classified by Runyon groups: Group I (photochromogens), *M marinum, M kansasii;* Group II (scotochromogens), *M szulgai, M gordonae, M malmoense;* Group III (nonphotochromogens), *M avium-intracellulare* complex (MAC); Group IV (rapid growers), *M fortuitum* complex (*M fortuitum, M chelonae, M abscessus* [MFC]). In the immunocompetent host, injury (trauma or surgery) is followed by the development of localized cellulitis or abscess formation in 4 to 6 weeks. In the compromised host, the usual presentation is of multiple erythematous or violaceous subcutaneous nodules without history of trauma; lesions may progress to abscesses that drain and ulcerate.[37]

M kansasii,[38,39] *M marinum,*[40-42] *M gordonae,*[43] *M malmoense,*[44] *M fortuitum,*[45,46] and *M chelonae*[47,48] can cause infection in the healthy as well as the compromised host. Inoculation has occurred via puncture wounds (injection or traumatic) or surgical procedures (augmentation mammoplasty, median sternotomy,[47,48] percutaneous catheterization); rarely, primary cellulitis occurs without recognizable skin trauma. Contaminated gentian violet used for skin marking has been the source in some outbreaks. MFC soft tissue infections characteristically occur several weeks after the injury and appear as indolent wound infections (nodules, ulcers, granulomatous papules, or verrucous plaques). In immunocompromised individuals, MFC can disseminate hematogenously to skin (multiple recurring abscesses on the extremities) and joints.[49]

In advanced HIV disease, MAC commonly causes systemic infection; however, it rarely causes cutaneous infection.[50-52] Cutaneous MAC infections are usually complications of disseminated disease; lesions vary from papules, nodules, pustules, and soft tissue abscesses to ulcerations; localized infection without apparent disseminated infection has been reported.[51] Cutaneous ulcerations have occurred at the sites of underlying MAC-associated lymphadenitis. Subcutaneous abscesses and ulcers caused by localized MAC infection have also been described.

Interpretation of isolation of MAC and/or demonstration of acid-fast bacilli in skin biopsy specimens from patients with advanced HIV disease is difficult in that approximately 40% of these individuals have MAC bacteremia (if not on prophylaxis for MAC). In most cases, in patients in whom MAC is demonstrated on lesional biopsy specimen, the presence of MAC is incidental, having no part in the pathogenesis of the cutaneous lesion. MAC infection has been reported in 3 patients who presented with either submandibular, axillary, or inguinal lymphadenitis.[53] After incision and drainage or spontaneous rupture, scrofuloderma occurred with the formation of deep ulcerative lesions; resolution occurred after a short course of routine antituberculous therapy. Subcutaneous masses can also represent underlying osteomyelitis.

Cutaneous *M haemophilum* infection has been reported to induce erythema, swelling, painful nodules, and abscess formation and disseminated cutaneous lesions with systemic involvement of bones, joints, lymphatics, and lungs.[54-58] Recovery of *M haemophilum* requires a high level of

clinical suspicion and special handling of mycobacterial cultures by the microbiology laboratory, including cultivation on enriched chocolate agar or heme-supplemented media and incubation at 30°C for up to 8 weeks. Response to antimycobacterial therapy has been poor, as the disease tends to recur and progress.

Mycobacterium leprae. The interrelationship of *M leprae* and HIV in dually infected persons has not been adequately studied.[59-62] Tropical areas such as Africa and India that have a high prevalence of leprosy are expected to bear the brunt of the HIV epidemic during the next decade. It is probable that leprosy will accelerate the course of HIV disease and that HIV infection will result in a higher ratio of cases of lepromatous versus tuberculoid leprosy and resistance to antilepromatous therapy.[63,64] The natural history of leprosy in HIV disease has been reported in 275 patients from Haiti; 6.5% of the entire cohort was HIV seropositive. No difference in HIV seropositivity was detected in patients with either lepromatous or tuberculoid types of leprosy. Of the HIV-seropositive patients, 22% developed new skin lesions and lepromin anergy during the course of dapsone/rifampin leprosy therapy, as compared to 0.8% of HIV-seronegative patients.

Bacillary Angiomatosis

Bacillary angiomatosis (BA) and bacillary peliosis (BAP) occur most commonly in the setting of HIV-induced immunodeficiency, characterized by angioproliferative lesions resembling pyogenic granulomas or KS.[65] BAP is caused by infection with fastidious gram-negative bacilli of the genus *Bartonella, B henselae,* and *B quintana.* The vascular lesions are referred to as BA; those occurring in the liver or spleen, as peliosis (BAP). In immunocompetent individuals, *B henselae* also causes cat scratch disease. HIV-infected individuals with BAP usually have moderate to advanced disease; rarely, BA occurs in immunocompetent, non–HIV-infected individuals. The varied tissue response to *Bartonella* infection in the immunocompetent individual is analogous to the clinical patterns occurring in leprosy. Individuals with intact cellular immunity develop cat scratch disease or tuberculous leprosy; those with impaired cellular immunity develop BAP or lepromatous leprosy. Currently, the prevalence of BA is very low because of prophylaxis given for infections such as *Mycobacterium avium* complex (MAC) and improved immune function with HAART.

In a study of 49 individuals with BAP, 53% were infected with *B henselae* and 47% were infected with *B quintana.*[66] *B henselae* and *B quintana* were equally likely to cause cutaneous BA; only *B henselae* was associated with hepatosplenic peliosis. Patients with *B henselae* infection were epidemiologically linked to cat and flea exposure. Those with *B quintana* infections were linked to low income, homelessness, and exposure to head or body lice. Prior treatment with macrolide (erythromycin, clarithromycin, azithromycin) antibiotics appeared to be protective against infection with either species.

The domestic cat serves as a major persistent reservoir for *B henselae.* Cats experience prolonged, asymptomatic bacteremia and can transmit the infection to humans.[67] The cat flea is the vector of *B henselae* among cats. The domestic cat, however, appears to be a major vector (by scratch or bite) from cat to humans. Antibiotic treatment of infected cats and control of flea infestation are potential strategies for decreasing exposure to *Bartonella.*

Whether asymptomatic or latent infection occurs in humans is not known. The incubation period is unknown but is probably days to weeks. Patients with localized infection may be free of systemic symptoms. Cutaneous BA may be painful; in contrast, similar-appearing lesions of KS are usually not painful unless ulcerated or secondarily infected. Individuals with more widespread disseminated *Bartonella* infection often experience fever, malaise, and weight loss.

Clinically, the cutaneous lesions of BA are red to violaceous, dome-shaped papules, nodules, or plaques, ranging in size from a few millimeters to 2 to 3 cm in diameter (dermal vascular lesions with thinned or eroded epidermis). Less commonly, domed subcutaneous masses occur without the characteristic red color of more superficial vascular lesions.[68] Lesions are soft to firm and may be tender to palpation. The number of lesions can range from one to hundreds. Nearly any cutaneous site may be involved but the palms, soles, and oral cavity are usually spared. Following hematogenous or lymphatic dissemination, the spectrum of internal disease caused by *B henselae* and *B quintana* includes soft tissue masses, bone marrow, lymphadenopathy, splenomegaly,

and hepatomegaly; internal involvement can occur with or without cutaneous lesions.

The differential diagnosis of the cutaneous papulonodular lesions includes KS, pyogenic granuloma, epithelioid (histiocytoid) angioma, cherry angioma, sclerosing hemangioma, angiokeratomas, and disseminated deep fungal infections. Subcutaneous BA nodules and tumors must be differentiated from enlarged lymph nodes and subcutaneous masses.

The histopathology of lesional skin biopsy specimens of BA is characterized by 2 patterns of lobular proliferations of capillaries and venules. Pyogenic granuloma-like lesions are characterized by proliferation of small, round blood vessels with plump endothelial cells. The stroma is edematous and loose. The inflammatory infiltrate is composed of lymphocytes, histiocytes, and neutrophils. The overlying epidermis may show collarette formation, thinning, or ulceration. Few if any bacteria are visualized by silver stain. The second type of lesion, arising deeper in the dermis or subcutis, appears more cellular, made up of a myriad of small, round blood vessels lined by plump endothelial cells. The interstitium shows a granular amphophilic material. Abundant clusters of bacilli, corresponding to sites of granular material, are visualized by silver stain. Percutaneous liver biopsy in patients with peliosis hepatis may be contraindicated because of the vascular nature of the lesions and the risk for uncontrolled bleeding. Histology of liver lesions shows blood-filled cysts with clusters of bacilli in the connective tissue rims of the cysts.[69]

The infecting *Bartonella* species can be identified by molecular techniques on tissue samples. Isolation of *Bartonella* is possible from lesional tissue biopsy specimens and/or blood. The diagnosis can also be confirmed by detection of anti-*Bartonella* antibodies. The diagnosis of BAP is usually made by the demonstration of pleomorphic bacilli on a Warthin-Starry or similar silver stain or by electron microscopy.

The course of BA is variable. In some patients, lesions regress spontaneously. BA infection may spread hematogenously or via lymphatics to involve bone marrow, bone, spleen, and liver. Death may occur secondary to laryngeal obstruction, liver failure, or pulmonary infection. As with other opportunistic infections in HIV disease, BAP can recur. During the past decade, the incidence of BA has decreased because of use of antibiotics for MAC prophylaxis and improved immune function following HAART.

BAP is preventable. *B henselae* is contracted from cats; avoidance should prevent infection. *B quintana* occurs among homeless people; infection can be prevented by improved hygiene.[70] The antibiotics of choice are erythromycin 250 to 500 mg by mouth 4 times daily or doxycycline 100 mg twice daily, continued until the lesions resolve, usually in 3 to 4 weeks. Secondary prophylaxis is indicated in patients with recurrent BAP, especially if immune restoration is not possible.

Nocardiosis

Cutaneous nocardiosis can occur as a primary cutaneous infection (abscesses, ulcers, granulomas, soft tissue infection, mycetoma, sporotrichoid [lymphocutaneous] infection),[71,72] or secondary cutaneous infection (pustules, abscesses, nodules) complicating hematogenous dissemination from the lungs.[73-76] Nocardiosis in HIV disease is rare; prophylaxis for *Pneumocystis carinii* pneumonia (PCP) with sulfonamides may also provide primary prophylaxis for nocardiosis.[77] Primary cutaneous nocardiosis in HIV disease has been reported to occur at the site of heroin injection; abscesses appear initially and then evolve into large ulcerations. Primary cutaneous nocardiosis may result in lymphangitic proximal extension (sporotrichoid pattern).[78,79]

Fungal Infections

Superficial Fungal Infections (Dermatomycoses)

Dermatophytoses. Dermatophytes, ie, *Trichophyton, Microsporum,* and *Epidermophyton,* may occur on any keratinized epidermal structure, ie, epidermis (stratum corneum), nails, and hair. This group of fungi infect nonviable tissue in otherwise healthy individuals; however, in the compromised host direct invasion of the dermis may occur. Dermatophytoses are important for 3 reasons: the morbidity and disfigurement caused by the dermatophyte infection itself, which can be quite extensive; the breakdown in the integrity of the skin that can occur, providing a portal of entry for other pathogens, particularly *S aureus;* and clinical manifestations of such infections that mimic other dermatologic conditions.[80] Dermatophyte infections in the compromised host are more frequent, often widespread, atypical in appearance, or invasive.[81]

Epidermal dermatophytosis is often widespread in HIV-infected individuals and in transplant recipients. Local immunity to dermatophytic infection is commonly suppressed in patients who have been misdiagnosed as having an inflammatory dermatosis, such as eczema or psoriasis, and treated with topical corticosteroid preparations, so-called tinea incognito. Clinically, this presents as one or many plaque(s), in some cases with sharply marginated borders, in some cases without scaling, and variable degrees of erythema. Papules or nodules within tinea incognito represent a dermatophytic folliculitis (Majocchi's granuloma). Majocchi's granuloma does occur in the absence of topical corticosteroid use.[82] Inflammatory plaques, ± abscess formation, ± hemorrhage associated with dermal invasion have also been reported to occur in hairy and glabrous sites.[83-85] Epidermal dermatophytosis can also occur in sites of irradiation in which local immunosuppression has occurred.[86]

In immunocompromised individuals, *Trichophyton rubrum* causes proximal subungual onychomycosis (PSO) and infection of the undersurface of the proximal nail plate. PSO occurs most often in HIV-infected individuals and its diagnosis is an indication for HIV testing. PSO can also be seen in transplant recipients and Waldenstrom's macroglobulinemia. Clinically, PSO initially appears as a chalky white discoloration of the proximal nail plate. KOH preparation of the dorsal nail plate is negative for fungal elements; the undersurface of the nail plate obtained by collecting a core of nail with a skin punch shows fungal elements on the undersurface of the involved nail plate. Unless immunocompromise is restored, dermatophyte infections are chronic and recurrent.[87] In that many patients are taking oral imidazoles, such as fluconazole or itraconazole for candidiasis or cryptococcosis, dermatophytoses are inadvertently treated and kept under control. Terbinafine, which is highly efficacious for dermatophytic infection, is not predicatably effective for nondermatophytic fungal infections.

Pityrosporiasis. *Pityrosporum ovale* (*P orbiculare, Malassezia furfur*) can cause extensive pityriasis (tinea) versicolor, especially in diabetics and individuals treated with topical or systemic corticosteroids. *Pityrosporum* folliculitis, which occurs more commonly in HIV disease, transplant recipients, pregnancy, malignancy, and chronic renal failure, presents as multiple small folliculocentric papules and pustule (acneform) on the upper trunk.[88,89] Diagnosis is made by demonstration of yeast in the follicular infundibulum. *Pityrosporum* folliculitis must be differentiated from both cutaneous candidiasis and hematogenously disseminated candidiasis to skin in the compromised host.[90] *Pityrosporum* may have some role in the pathogenesis of seborrheic dermatitis, which is common in HIV disease.

Candidiasis. Oropharyngeal candidiasis (OPC) associated with PCP in young homosexual men marked the advent of the HIV epidemic.[91] OPC occurs in the majority of HIV-infected individuals during the natural course of HIV disease as a result of impaired cell-mediated immunity. The oropharynx is the most common site of mucosal candidiasis, which may extend into the esophagus and/or tracheobronchial tree in advanced HIV disease. Recurrent candidal vulvovaginitis (RVVC) is common in HIV-infected women and may be the first clinical expression of immunodeficiency.[92] In contrast, *Candida* intertrigo, which is more common than mucosal candidiasis in the normal host, is uncommon in adults with HIV disease. Candidiasis of moist, keratinized cutaneous sites, such as the anogenital region, occurs frequently. Systemic infection originating in the bowel occurs in individuals with prolonged neutropenia. Oropharyngeal candidiasis in the absence of predisposing local or systemic causes should always raise the issue of HIV serotesting.

Candida colonization of the oropharynx is common in HIV-infected individuals.[93] In a study of HIV-infected outpatients (median CD4-cell count 113/μL), *Candida* species were isolated from the oral swabs in 60% of individuals, in the absence of any clinical findings of thrush.[94] *C albicans* was the most prevalent colonizing species isolated from each individual. Five other species were also isolated, 22% of patients were colonized with 2 different *Candida* species. Isolation of non-*Albicans* species alone correlated with advanced HIV diseases with very low CD4-cell counts.

Oropharyngeal candidiasis is a marker of HIV disease progression.[95] In a study of the onset of oropharyngeal candidiasis after documented dates of HIV seroconversion, candidiasis was noted in 4% at 1 year after seroconversion, 8% at 2 years, 15% at 3 years, 18% at 4 years, 26% at 5 years; the median CD4-cell count was 392/μL when OPC

was first detected. OPC and esophageal candidiasis (EC) have been reported to occur as manifestations of primary HIV infection.[96] Esophageal candidiasis, an AIDS-defining condition, occurs only with advanced CD4 count reduction (<100/μL).

Although oropharyngeal candidiasis is often asymptomatic, the presence of white curd-like colonies of *Candida* in the mouth is a constant reminder of HIV disease to the patient. When symptomatic, common complaints associated with oropharyngeal candidiasis include a soreness or burning sensation in the mouth, sensitivity eating spicy foods, and/or reduced or altered sense of taste. Symptomatic esophageal candidiasis is less common than oropharyngeal infection and is usually, but not invariably, associated with oropharyngeal disease. The most common symptoms associated with esophageal candidiasis include retrosternal burning and odynophagia. Female patients with HIV infection are increasingly subject to vulvovaginal candidiasis associated with vulvar pruritus, dysuria, dyspareunia, and vaginal discharge.

On physical examination and esophagoscopy, oropharyngeal and esophageal candidiasis present most commonly with a pseudomembranous (thrush) pattern and less often with a chronic hyperplastic and/or atrophic pattern. Pseudomembranous candidiasis is characterized by white-to-creamy curd-like plaques on any surface of the oral mucosa, with these white areas being colonies of *Candida*. The "curds" are easily removed with a dry gauze (in contrast to the lesions of oral hairy leukoplakia that are relatively fixed to the underlying mucosa), with bleeding of the mucosa sometimes occurring. Atrophic candidiasis is often overlooked on examination of the mouth and is often the initial presentation of oropharyngeal candidiasis; it appears as patches of erythema, most commonly occurring in the vault of the mouth on the hard and/or soft palate. On the dorsal surface of the tongue, atrophic candidiasis causes areas of depapillation, resulting in a smooth red mucosa. There may be areas of pseudomembranous involvement at some sites, while others manifest the atrophic pattern. Chronic hyperplastic candidiasis presents as both red and white patches at any site in the oropharynx. In edentulous patients with dentures, pseudomembranous and/or atrophic candidiasis is typically seen under the mucosa occluded by dentures.

Candidal angular cheilitis occurs at the corners of the mouth as an intertrigo, unilaterally or bilaterally, and is more common in edentulous patients; it may occur in conjunction with oropharyngeal or esophageal disease or as the only manifestation of candidal infection.

Chronic and/or recurrent candidal vulvovaginitis is a common opportunistic infection in HIV-infected women with moderate-to-advanced immunodeficiency. Children with HIV infection commonly experience candidiasis in the diaper area, intertrigo in the axillae and neck fold.

The incidence of cutaneous candidiasis, ie, *Candida* intertrigo, may be somewhat increased in immunocompromised adults. Fingernail chronic *Candida* paronychia with secondary nail dystrophy (onychia) is common in HIV-infected children.[97]

Candidemia occurs in HIV-infected individuals undergoing total parenteral nutrition, intravenous antibiotic therapy through a central venous catheter, or cancer chemotherapy, having a central venous catheter for >90 days. In a study of HIV-infected children with fungemia, non-*C albicans* species and *Torulopsis glabrata* were isolated relatively commonly.[98]

Management of mucosal candidiasis should be directed at control of symptomatic candidiasis, which may be followed by secondary prophylaxis. Prolonged prophylaxis with topical or systemic agents increases the risk of azole-resistance infection. Topical treatments rely on high patient compliance in that they require administration 4 to 5 times daily, but they are usually preferred over systemic drugs for initial treatment. Agents for topical therapy of OPC include nystatin (suspension, tablets, pastilles),[99] clotrimazole (troche), itraconazole solution, fluconazole solution, and amphotericin B solution. The imidazoles, fluconazole (oral solution, tablets, intravenous solution), itraconazole (capsules, oral solution),[100] and ketoconazole (tablets) are available for systemic therapy. Terbinafine is an excellent agent for dermatophytoses but not for candidal infections.[101] OPC relapses in approximately 40% of cases within 4 weeks of discontinuing therapy.

Secondary prophylaxis of OPC and EC is often indicated unless the immunocompromise is restored. Fluconazole-resistant oropharyngeal and/or esophageal candidiasis occurs relatively frequently in chronically treated patients.[102,103] HIV-infected individuals taking fluconazole 200

mg/d prophylactically experienced reduction in the frequency of cryptococcal infection, EC, and superficial fungal infection, especially those with CD4-cell counts ≤50/μL; but they did not experience reduction in overall mortality rate.[104] Despite fluconazole efficacy in preventing fungal infections, daily routine prophylaxis is not recommended for all individuals with advanced HIV disease because of cost, possible emergence of drug-resistant candidiasis, and potential drug interactions.[105]

Invasive Fungal Infections Involving the Skin

The major importance of the cutaneous manifestations of systemic mycotic infection is that these manifestations may be the first clue to the presence of such disseminated infection. The most important examples of this phenomenon are disseminated cryptococcal infection, which occurs in approximately 10% of patients with untreated advanced HIV disease, and infection due to *H capsulatum* or *C immitis*. The latter are seen much less frequently, since exposures to these organisms occur only in geographically restricted areas (*H capsulatum* being found in the east central portion of the United States, Ohio and Mississippi river valleys, Virginia and Maryland, as well as parts of Central America, and in the case of *H capsulatum var duboisii*, Africa; *C immitis* being found in the desert soil of the southwestern United States, Mexico, and parts of Central and South America). In southeast Asia, systemic infection with *P marneffei* in HIV disease has been reported.[106]

The pathogenesis of these infections resembles that of tuberculosis, in which the primary infection occurs in the lungs after the inhalation of air contaminated with these organisms. The initial response to this event is a polymorphonuclear leukocyte one, which serves to limit the extent of primary infection. However, the definitive host response is a cell-mediated immune response, which both limits the impact of postprimary systemic dissemination of the organisms and prevents the subsequent breakdown of sites of dormant infection. Thus, patients with advanced HIV disease are at risk for 3 patterns of infection: progressive, primary infection with systemic spread because of a failure of the normal cell-mediated immune response; reactivation of dormant sites of infection, with secondary systemic dissemination of the organisms; and reinfection in a patient who has lost the protective immunity engendered years previously on exposure to this same organism, with such reinfection resulting in a pattern of disease akin to that seen in patients with progressive primary infection. Whenever systemic dissemination of these organisms occurs, there is an approximately 10% incidence of mucocutaneous disease, often as the first recognizable manifestation of systemic infection.[107]

Skin lesions occurring in disseminated mycotic infections are, for the most part, asymptomatic apart from their cosmetic appearance. Thus, the symptom complex that the patient presents with is determined primarily by the other sites of involvement—symptoms referable to the respiratory tract in patients with active lung infection; symptoms referable to the central nervous system in patients with seeding of the central nervous system; and systemic complaints of fever, chills, sweats, weight loss, etc, dependent on the organism load and the intensity of the host inflammatory response.[108] Oral and/or esophageal ulcerations caused by *H capsulatum* may, however, be painful.

The most common appearance of skin lesions caused by systemic fungal infection in the HIV-infected individual is that of multiple molluscum contagiosum-like lesions, papules, or nodules occurring on the face.[109,110] On occasion, these lesions may become ulcerated, taking on a herpetiform appearance. Other reported cutaneous findings include erythematous macules; necrotic or keratin-plugged papules and nodules; pustules, folliculitis, or acneform lesions; vegetative plaques; or a panniculits.[111] Facial lesions are most common, but lesions are also seen on the trunk and extremities. Oral mucosal lesions occurring in HIV-infected patients with disseminated mycotic infections include nodules and vegetations; ulcerations may occur on the soft palate, oropharynx, epiglottis, and nasal vestibule. These occur most commonly with histoplasmosis, occasionally in cryptococcosis but not in coccidioidomycosis. Hepatosplenomegaly and/or lymphadenopathy occur commonly in patients with disseminated histoplasmosis.

The cornerstone of diagnosis in this clinical situation is skin biopsy for culture and pathological examination. It is important to recognize that such biopsies have 2 purposes: diagnosis of a particular skin lesion and early recognition of

disseminated infection in an compromised host. Because of these dual objectives, any unexplained skin lesion in these patients should be considered for biopsy. Histologically, diagnosis is made by demonstration of fungal forms with H&E, PAS, or methenamine silver stain of the lesional biopsy specimens or of a touch preparation. Tzanck smears obtained by scraping the top of a lesion, placing the material on a glass slide, fixing with methyl alcohol, and staining with rapid Giemsa technique show multiple encapsulated and budding yeast. India ink preparation of lesional skin scraping can also be used to show encapsulated and budding cryptococcal yeast forms. Fungi can also be isolated on culture of the skin biopsy specimen.

The differential diagnosis of patients with skin lesions possibly caused by systemic fungal infection includes molluscum contagiosum, verruca vulgaris, verruca plana, disseminated herpetic or varicella infection, bacillary angiomatosis, and furunculosis. The diagnosis of cutaneous infection with *C neoformans, C immitis,* or *H capsulatum* is *prima facie* evidence of disseminated infection and must be treated as such.

Ubiquitous Fungi

Invasive candidiasis. Invasive candidiasis is the most common invasive fungal infection. *C albicans* causes 75% of cases of disseminated candidal infections; *C tropicalis,* 20% of cases. *C tropicalis,* however, causes 60% of cases of disseminated candidal infections with cutaneous involvement; *C albicans,* only 20%.[112] The gastrointestinal tract is the site of primary invasion; *Candida* enters blood vessels and disseminates widely. Diagnosis is often delayed because of the nonspecific clinical manifestations and difficulty in identifying *Candida* isolated on culture as a pathogen. The usual clinical scenario is of a patient with fever, neutropenia, clinical deterioration, and failure of response to multiple antimicrobial agents.

The cutaneous findings are usually subtle with erythematous papules (single, multiple, localized, or diffuse) arising on the trunk and proximal extremities[113,114]; in some cases, papulonodules, purpura, central necrosis, ecthyma gangrenosum-like lesions, and nodular folliculitis occur in hair-bearing areas (heroin users).[115-118] Other clinical findings include endophthalmitis seen on fundoscopic examination, arthritis, and muscle abscess.[119,120] A touch preparation of a punch biopsy specimen examined with KOH or Gram stain may show *Candida,* allowing rapid diagnosis.[121] Lesional skin biopsy specimens show a range of inflammatory changes, ranging from a sparse perivascular mononuclear infiltrate to a leukocytoclastic vasculitis; *Candida* may be sparse or present in large numbers, in and around dermal blood vessels.

Cryptococcosis. C neoformans is the second most common fungal opportunist (*C albicans* being the most common, usually causing mucocutaneous infection as well as invasive disease) in the compromised host.[122,123] Disseminated cryptococcosis is by far the most common life-threatening fungal infection in HIV disease. Cutaneous cryptococcosis occurs in 5% to 10% of individuals with disseminated infection[124] and is essentially always associated with systemic infection in advanced HIV disease (CD4-cell count <50/μL). Cutaneous manifestations can present 2 to 6 weeks before signs of systemic infection.

Hematogenous dissemination of *C neoformans* to the skin results in lesions of various morphologies, which are generally asymptomatic. The most common morphology of cutaneous cryptococcosis is of molluscum contagiosum-like lesions, ie, umbilicated skin-colored or pink papules or nodules (54%); other types of cutaneous lesions include pustules, cellulitis,[125] ulceration, panniculitis, palpable purpura, subcutaneous abscesses, and vegetating plaques.[126,127] Lesions commonly occur on the face but may be widespread. Oral nodules and ulcers also occur alone or with cutaneous lesions. The papules and nodules of cryptococcosis range from solitary to >100 in number, are usually skin-colored, with little if any inflammatory erythema, and lack the central umbilication or keratotic plug characteristic of mollusca. Occasionally, crusting or ulceration occurs, resembling chronic herpetic ulcers. In more darkly pigmented individuals, lesions may be hypopigmented or hyperpigmented. Cutaneous cryptococcosis in some cases occurs in the absence of demonstrable fungal infection in the lung or meninges. Hematogenous dissemination of *H capsulatum* or *C immitis* can produce identical skin lesions on the face.

Cryptococcal cellulitis occurs after fungemia and most often occurs in the compromised host (corticosteroid therapy, systemic lupus, chronic lymphocytic leukemia, myeloma, chronic active hepatitis, cervical medullary tumor, congenital

lymphedema, congenital lymphedema with lymphopenia, liver transplantation, inflammatory bowel disease, and kidney transplantation). This fungal cellulitis presents with a single or multiple red, hot, tender plaque(s).[128,129] Primary cutaneous cryptococcosis has been reported, presenting as a nodule, plaque or ulcer, in some cases with sporotrichoid spread.[130-132]

Aspergillosis. *Aspergillus* species are ubiquitous in the environment, in food, water, soil, plants, and decaying vegetation. Aspergillosis can involve the skin either as a primary cutaneous infection or secondarily via invasion into the skin from an underlying infected site (nose, sinuses, and orbit) or hematogenous dissemination to the skin (usually from a primary lung infection). Aspergillosis occurs in the setting of severe or prolonged granulocytopenia caused by cytotoxic therapy for leukemia or lymphoma, high-dose or prolonged systemic corticosteroid therapy in transplant recipients, or those with collagen vascular disease. Primary cutaneous aspergillosis occurs at sites of intravascular catheters and drainage tubes, use of arm boards, and extensive trauma or burns.[5,133-136]

Primary cutaneous aspergillosis has been reported more commonly in children with acute lymphocytic leukemia. Lesions arise most commonly on the palm, initially with erythematous or purpuric papules that progress to violaceous plaques with hemorrhagic bullae, which, in turn, ulcerate and form necrotic eschars. Secondary cutaneous or disseminated aspergillosis presents as erythematous macules or papules that evolve to purpuric or necrotic lesions, hemorrhagic bullae, and subcutaneous nodules or abscesses.

Potassium hydroxide preparation of scraping from the inner aspect of the bulla roof shows large hyphae. Lesional skin biopsy shows regularly septate, dichotomously branching hyphal elements that may be angioinvasive, which must be differentiated from *Scopulariopsis, Pseudoallescheria, Fusarium,* and *Penicillium.* The majority of patients with invasive disseminated aspergillosis die, despite treatment with amphotericin B.[137]

Sporotrichosis. *Sporotrix schenkii* is ubiquitous in the environment in rotting organic matter. Percutaneous inoculation results in limited forms of cutaneous sporotrichosis in immunocompetent individuals. In the compromised host, dissemination of local infection to other organs occurs from lung or skin foci. Dissemination of sporotrichosis is associated with severe malnutrition, sarcoidosis, malignancy, diabetes mellitus, alcoholism, organ transplantation, and HIV disease. A range of cutaneous lesions includes papules to nodules, which may become eroded, ulcerated, crusted, or hyperkeratotic.[138,139] Individual lesions may remain discrete or become confluent. Lesions are often disseminated but sparing the palms, soles, and oral mucosa. Ocular involvement results in hypopeon, scleral perforation, and prolapse of the uvea.[140] Joint infection with frank arthritis is also common in the disseminated form of sporotrichosis occurring in HIV disease. Other organs involved in disseminated sporotrichosis in HIV disease include joints, lung, liver, spleen, intestine, and meninges.

Mucormycosis. Mucormycosis is a group of infectious syndromes caused by *Mucor, Rhizopus, Absidia,* and *Cunninghamella* species, which have identical presentations and appear morphologically identical in tissue. Conditions predisposing to cutaneous mucormycosis include diabetes, severe thermal burns, trauma, leukemia, organ transplantation, and use of Elastoplast dressing. Superficial cutaneous mucormycosis presents as erythematous plaque with subsequent vesicles, pustules, and ulceration at sites dressed with contaminated elasticized adhesive tape. The fungus can also enter the skin via breaks caused by intravascular lines, injections, macerated skin, burns, or insect bites. The fungus causes a necrotizing infection with subsequent vascular invasion, soft tissue infection, necrosis, and ulceration.

Rhinocerebral mucomycosis occurs in the setting of poorly controlled diabetes (especially with ketoacidosis) and systemic corticosteroid therapy, particularly in patients with leukemia, lymphoma, or organ transplant recipients. Infection begins on the palate or in the nose and paranasal sinuses, spreading rapidly to the central nervous system via the orbit and cribriform plate. Infected mucosal sites are black and necrotic. With extension of infection through the nasal turbinates, orbital cellulitis occurs associated with extraocular muscle paresis, proptosis, chemosis, and eyelid edema. Histologically, broad, irregularly shaped nonseptate hyphae with right angle branching are seen in the infected tissue.

Phaeohyphomycosis. The phaeohyphomycoses present as a clinically varied group of fungal infections caused by dematiaceous (pig-

mented or black) fungi that in tissue appear as yeast-like cells, branched or unbranched septate hyphae, or a combination of these forms. Chromomycosis appears clinically as verrucous, nodular, or tumorous plaques with pseudoepitheliomatous hyperplasia, showing large, pigmented, round, thick-walled cells with septation (sclerotic or Medlar bodies). Mycetoma appears clinically as a tumor with draining sinuses and granules in the abscesses. The clinical presentation varies with the host's immune response. The causative fungi include *Exophiala, Phialophora, Fonsecaea, Cladosporium, Alternaria, Bipolaris, Curvularia,* and *Exserohilum* species.

In the compromised host, infection with dematiaceous fungi can present as primary subcutaneous phaeohyphomycosis, localized inoculation cutaneous phaeohyphomycosis, and systemic or invasive phaeohyphomycosis with secondary or metastatic cutaneous lesions. Primary inoculation phaeohyphomycosis may present with a spectrum of clinical lesions: ulcer with necrosis, subcutaneous cyst, boggy verrucous plaque, crusted nodule with pustules, subcutaneous abscesses with sinus tracts, dermatomal vesicles and crusts, fluctuant abscess with surrounding cellulitis, and a necrotic ulcerated plaque resembling ecthyma gangrenosum. Disseminated phaeohyphomycosis involving the skin presents as tender erythematous nodules, ulcerated papules, hemorrhagic pustules, and scaling hyperpigmented plaques.

Hyalohyphomycosis. The hyalohyphomycoses are a variety of opportunistic fungal infections caused by nondematiaceous molds or yeasts, having a nonseptated tissue form. The fungi in this group include *Fusarium, Penicillium, Paecilomyces, Acremonium,* and *Scopulariopsis* species.

Fusarium species are ubiquitous soil saprophytes. Risk factors for infection are granulocytopenia and systemic corticosteroid therapy. Localized cutaneous infection is associated with thermal burns, punctures, and intravascular lines and can be the source of hematogenous dissemination. *Fusarium* onychomycosis can be the source of disseminated *Fusarium* infection in the compromised host.[141,142] Disseminated fusariosis is characterized by evolution of widespread cutaneous lesions from erythematous to necrotic lesions, propensity for vascular invasion and thrombosis with tissue infarction, and acute branching broad septate hyphae.[143] Tissue infarction is also seen in the lesions of *Aspergillus* and *Mucor* infections.

The dimorphic fungus *P marneffei* is the third most common opportunistic infection in HIV-infected residents of countries of southeast Asia and the southern part of China.[144,145] In a report of 92 patients,[146] the clinical presentation included fever, weight loss, cough, anemia, and disseminated papular skin lesions (71%). The most common skin lesions were umbilicated papules, occurring most frequently on the face, ears, upper trunk, and arms. Genital ulcers were also reported, ranging in size from <1 cm to 3 cm in diameter. Oral lesions included papules and ulcers. *P marneffei* preferentially disseminates to the lung and the liver as well.

Endemic Fungi

Fungi endemic to geographic regions cause primary pulmonary infection after inhalation of spores. Primary infection is usually asymptomatic, resolving undiagnosed. The organisms are normally contained by the immune system but not eradicated; immunosuppression late in life may lead to reactivation of the disease. In the immunocompromised host, the latent fungi reactivates in the pulmonary focus, causing infection in the lungs; invasion of blood vessels results in hematogenous dissemination to multiple organ systems. Alternatively, progressive primary infection can occur in the compromised host, again with systemic dissemination.

Blastomycosis. *B dermatitidis* is endemic to the south-central and midwestern United States, the central provinces of Canada, and Africa. Blastomycosis occurs most often in apparently immunocompetent individuals; more severe or disseminated infections occur in compromised persons. Disseminated blastomycosis presents with hundreds of erythematous papules that progress to pustules.[147-149]

Coccidioidomycosis. *C immitis* is limited to the semiarid areas of the southwestern United States, Mexico, and Central and South America. Latent pulmonary infection may become active and disseminate in pregnancy, those with African and Filipino ancestry, and immunocompromised individuals with advanced HIV disease, hematologic malignancies, or organ transplant. Cutaneous lesions of disseminated coccidioidomycosis are usually asymptomatic, beginning as papules,

evolving to pustules, plaques, or nodules with minimal surrounding erythema; lesions often resemble molluscum contagiosum.[150] In time, lesions may enlarge and become confluent, with formation of abscess, multiple draining sinus tracts, ulcers, subcutaneous cellulitis, verrucous plaques, granulomatous nodules, and, with healing, scars.[151] Lesional biopsy specimens show sporangia, hyphal forms, and arthroconidia. Disseminated coccidioidomycosis is diagnosed culturally by isolating the fungus from infected tissues. Serum complement fixation titers are often helpful in diagnosis but may be negative in the setting of immunocompromise.

Histoplasmosis. *H capsulatum* is restricted to the Ohio and Mississippi River valleys, Virginia, and Maryland as well as parts of Central America; *H capsulatum var duboisii* occurs in Africa. In endemic geographic areas, eg, Indiana, disseminated histoplasmosis is the leading opportunistic infection in HIV disease. In a report from Kansas City of HIV-infected individuals, the annual incidence of histoplasmosis was 4.7%.[152] The following were associated with an increased risk for histoplasmosis: a history of exposure to chicken coops, a positive baseline serology for complement-fixing antibodies to *Histoplasma mycelium* antigen, and a baseline CD4 of <150/μL. Disseminated histoplasmosis also occurs in young children, those with Hodgkin's disease, and patients treated with systemic corticosteroids or chemotherapy.

Disseminated histoplasmosis presents with a variety of cutaneous findings in approximately 10% of cases: erythematous macules; necrotic or keratin-plugged molluscum contagiosum-like papules and nodules; pustules, folliculitis, acneform lesions, a rosacea-like eruption, guttate psoriasis-like eruption; ulcers; vegetative plaques; or panniculitis.[111,153,154] Several different morphological lesions may occur on a patient. Lesions occur most commonly on the face, followed by the extremities and trunk. Oral mucosal lesions include nodules and vegetations; ulceration occurs on the soft palate, oropharynx, epiglottis, and nasal vestibule. A subtle, widespread, exanthematous or psoriasiform eruption may occasionally develop in HIV-infected patients already on systemic antifungal therapy and in whom systemic symptoms are completely lacking. Oral nodular and ulcerative lesions also occur in disseminated histoplasmosis.[155] Hepatosplenomegaly and/or lymphadenopathy occur commonly in patients with disseminated histoplasmosis.

Viral Infections

Viruses are major pathogens causing opportunistic infections (OIs) in the compromised host, many of which are manifested at mucocutaneous sites, ranging from cosmetically disfiguring facial molluscum contagiosum virus (MCV) to extensive common or genital warts to life-threatening or invasive HPV-induced SCC. In the great majority of cases, viral OIs represent reactivation of latent viral infection, ie, herpes family of viruses or of subclinical infection with HPV or MCV.

Measles

Measles had been rare in the industrialized nations because of childhood immunization; however, in Third World countries such as in Africa, measles is common and associated with significant morbidity and mortality. In the United States, focal epidemics have occurred because of immunization failure. Measles occurring in the setting of HIV disease in unvaccinated persons has high morbidity and mortality rates.[156] The immunogenicity of the measles vaccine in children with HIV infection is low, with only 25% of immunized HIV-infected children developing antibody.[157] Clinically, measles occurring in HIV disease may be atypical with a prolonged period of rash or absence of exanthem or enanthem.[158,159] Diagnosis of measles is usually made on clinical findings; however, in cases in which the exanthem is atypical, documentation of seroconversion is helpful. In some cases, seroconversion does not occur because of abnormal B-cell function; lesional skin biopsy is helpful, showing multinucleated keratinocytes. Children who develop measles may have a severe or an occasionally fatal infection.

Herpetoviridae (Human Herpesviruses)

Human herpesviruses (HHV), ie, HSV types 1 and 2, CMV,[160] VZV, EBV, HHV-6, HHV-7, and HHV-8, share 3 characteristics that make them particularly effective pathogens in the compromised host: latency (once infected with the virus, the individual remains infected for life, with immunosuppression being the major factor responsible for reactivation of the virus from a latent state); cell association (these viruses are

highly cell-associated, rendering humoral immunity inefficient as a host defense and cell-mediated immunity paramount in the control of these infections); and oncogenicity (all herpes group viruses should be regarded as potentially oncogenic, with the clearest demonstration of this being EBV-related lymphoproliferative disease).[161] Of the herpes group viruses, those with the greatest impact on the mucocutaneous tissues of the compromised host are HSV, VZV, HHV-8 and, to a lesser extent, EBV.

Reactivated HHV infection can be particularly severe in compromised hosts, resulting in chronic persistent disease, and in some cases, life-threatening disease. Reactivated HHV infections may contribute to increased HIV expression and potentially modify and accelerate the course of HIV disease. Acute or chronic infections caused by HSV or VZV are usually treated until lesions have resolved, secondary prophylaxis not usually being required. CMV infections, especially retinitis, may be devastating and require life-long prophylaxis.

Corticosteroid therapy in HIV disease is of concern because of the possible risk of reactivation of HHV. In a report of patients treated with prednisone, the incidence of clinically active infections caused by CMV, HSV, and VZV that occurred within a 30-day period of therapy was compared for each group; the median total dose of prednisone was 1,600 mg.[162] No statistically significant differences between the cases and controls were detected in terms of the incidence of clinically active herpesvirus infections, ie, CMV infection (2.5% v 5.0%), HSV (1.6% v 1.5%), and VZV (0% v 0.3%). Only CD4-cell count <50/μL was a significant risk factor for the development of any herpesvirus infection or for the development of a clinically active CMV infection. The risk of HHV infections was related to the stage of HIV infection and was not influenced by corticosteroid therapy.

Herpes simplex virus-1 and -2 infections. The greater majority of HSV-1 and HSV-2 infections occurring in the compromised host are reactivations of latent infections. With mild immunocompromise, lesions are self-limited and resolve within a week or 2. Extensive, local cutaneous infections, ie, eczema herpeticum (Kaposi's varicelliform eruption), can occur with locally impaired immune function (eg, atopic dermatitis) or in the systemically compromised host.[163]

With more advanced compromise, lesions tend to be subacute or chronic, indolent, atypical, responding less promptly to oral antiviral therapy. Clinically, reactivated infections (ulcers) are larger and deeper. Ulcerated, crusted lesions at perioral, anogenital, or digital locations are usually HSV in etiology, despite atypical clinical appearances. HSV is a treatable cause of intraoral ulcers and should always be identified and treated in the compromised host. Disseminated HSV infection can involve the skin only or, of more concern, the viscera (lungs, liver, and brain), which has significant associated morbidity and mortality.

In 1981, chronic perianal herpetic ulcers associated with a severe, previously undetected, acquired immune deficiency were an early harbinger of the impending HIV epidemic.[164] Genital herpes and other genital ulcerative diseases are risk factors for acquisition of HIV infection during sexual intercourse.[165] The seroprevalence of HSV-2 infection in the United States is indicative of unprotected sexual intercourse and increased risk of HIV transmission.[166] Reactivated latent HSV infection is one of the most common OIs in HIV disease. Reactivation of latent HSV infection has been documented to increase HIV plasma viral load level[167]; however, acyclovir use was not associated with prolonged survival.[168] Herpetic as well as other genital ulcers are risk factors for transmission of HIV.[165]

During the asymptomatic phase of HIV infection, the clinical manifestations of HSV infection are no different from those occurring in the normal host—orolabial lesions, usually caused by HSV-1, or anogenital lesions, usually caused by HSV-2, triggered by such factors as fever, stress, other viral infections, or exposure to intense ultraviolet light. The lesions heal within 1 to 2 weeks with or without antiviral treatment. However, with progression of the immunodeficiency, recurrence, even after effective therapy, delayed healing, and chronic ulcers, occasionally caused by treatment-resistant strains of HSV, become common. Intermittent asymptomatic shedding of HSV is common. In a report of patients with advanced HIV disease, HSV was isolated on periodic culture of the perianal region in 24% of patients in the absence of erosive or ulcerative lesions, even among those without a history of

perianal HSV lesions.[169] Shedding was short-lived, intermittent, and not associated with early subsequent development of perianal ulcers.

With increasing immunocompromise, recurrent HSV infection may become persistent and progressive. Erosions occurring at the typical sites (perioral, anogenital, and digital) enlarge and deepen into painful ulcers.[170,171] Oropharyngeal herpetic ulcers can occur alone or in association with lesions of the lip(s). Untreated, these ulcers may become confluent, forming large lesions.[172,173] Herpetic infection of one or more fingers can form severely painful, large whitlows.[174] HSV can be inoculated into nearly any site, including the ears and toes.[174,175] In addition to ulceration, chronic HSV infections can also present as proliferative lesions of the epidermis with or without scale. Herpetic ulcers on the buttocks, perineum, and anus can be associated with painful intra-anal or rectal HSV ulcerations. Genital herpetic ulcers are common. Untreated in individuals with advanced HIV disease, the ulcers persist and enlarge. Hematogenous dissemination with visceral infection is less common in HIV disease than in other compromised states. Large atrophic scars may follow healing of deep herpetic ulcers.

Symptomatically, recurrent herpetic infection is characterized by an itching or tingling sensation at the site, often before any visible alteration. Vesicles and pustules frequently rupture, leaving superficial erosions and ulcers, which are associated with varying degrees of discomfort and pain. A herpetic whitlow, for example, occurring on the distal finger is often associated with excruciating pain because of the closed tissue spaces involved and the extensive enervation of the site.[176] Herpetic ulcers on the anorectal mucosa cause pain on defecation, tenesmus, and constipation and, at times, are associated with HSV colitis and diarrhea. HSV from labial or oropharyngeal ulcers is swallowed in saliva and can infect the esophageal epithelium, usually in patients with very low CD4 counts. Esophageal herpetic ulcers present with odynophagia and/or chest pain.[177] Predisposing factors include nasogastric procedures, corticosteroid therapy, and cancer chemotherapy. Extraesophageal herpetic lesions (labial, oropharyngeal) are present in one third of patients with esophageal ulcers.

In patients with advanced immunodeficiency, recurrent lesions may fail to heal and continue to enlarge, thus forming large, chronic ulcers.[178] In the absence of other causes of immunocompromise, chronic herpetic ulcers present for more than a month's duration is an AIDS-defining opportunistic infection. Such ulcers may develop on any mucocutaneous epithelium but are seen most commonly in perineal, anal, buttock, genital, perioral, and digital sites. Untreated or acyclovir-resistant HSV ulcers may become confluent, forming lesions up to 20 cm in diameter, involving half the face or perineum.

HSV infections can be diagnosed by isolation of the virus or identification of HSV antigen in lesional smears or biopsy specimens. If indicated, the isolate can be tested for sensitivity to various antiviral agents. Histology shows multinucleated giant epidermal cells indicative of HSV or VZV infection. The Tzanck test, which looks for giant epithelial or adnexal cells, preferably multinucleated, in smears of lesional exudate, is useful but is not always positive even in frank herpetic lesions; its reliability is completely dependent on the skill of the microscopist. Lesional biopsy is helpful when giant epidermal cells are detected but cannot distinguish HSV from VZV infection. Viral culture of a lesion has a high yield in making the diagnosis. The polymerase chain reaction can detect VZV and HSV-DNA sequences from a variety of sources including formalin-fixed tissue specimens.[179]

Currently, 3 drugs are available for oral therapy of HSV infections; famciclovir[180] and valaciclovir are absorbed much better than acyclovir. These agents can be given to treat primary or reactivated infection or to suppress reactivation. In the management of chronic herpetic ulcers, immunosuppressive therapy should be reduced when possible. Intravenous acyclovir (5 mg/kg every 8 hours) may be given for severe infections; the improved blood levels of famciclovir and valaciclovir make oral therapy more effective than with oral acyclovir. Foscarnet and cidofovir are administered intravenously for infections caused by acyclovir-resistant HSV. Cidofovir gel has been effective as a topical therapy of acyclovir-resistant HSV infections.[181] The use of chronic HSV suppression is controversial. The oral antiviral agents are indicated for frequently recurring HSV infection.

Varicella-zoster virus infections. Primary VZV infection manifests as varicella (chicken-

pox); reactivation of VZV from a dorsal root ganglion or cranial nerve ganglion manifests as HZ. In the compromised host, VZV infection can present as severe varicella, dermatomal HZ, disseminated HZ (sometimes without dermatomal HZ), and chronic or recurrent HZ. Disseminated HZ is defined as cutaneous involvement by >3 contiguous dermatomes or >20 lesions scattered outside the initial dermatome or systemic infection (hepatitis, pneumonitis, encephalitis). Disseminated VZV infection in an individual harboring latent VZV can present with a clinical pattern of scattered vesicles in the absence of dermatomal HZ. The compromised host previously infected with VZV is subject to exogenous reinfection with VZV.[182] Underlying conditions of immunocompromise associated with an increased incidence of HZ include Hodgkin's disease, non-Hodgkin's lymphoma, solid tumors (eg, small cell carcinoma of the lung), solid organ and bone marrow transplantation, and HIV disease. Local immunosuppression related to irradiation, nodal involvement by tumor, or surgical sites is also associated with an increased incidence of HZ.[183]

Primary VZV infection is nearly always symptomatic (ie, varicella or chickenpox)[184]; reactivated infection presents as HZ. Children with HIV disease represent the largest reservoir of VZV-susceptible immunodeficient children in the world, numbering several million in Africa. Varicella occurring in HIV-infected children and adults can be severe, prolonged,[185] and complicated by VZV dissemination (pneumonia, hepatitis, encephalitis, and pancreatitis), disseminated intravascular coagulation, bacterial superinfection, and death. Primary, recurrent, and persistent VZV infections are a frequent cause of morbidity and hospitalization for HIV-infected children. Rather than resolving, persistent crusted lesions can occur at sites of initial vesicle formation, lasting for weeks or months. In a report of HIV-infected children with varicella, the most common complication was recurrence of VZV infection, in 53% of cases.[186-188] Sixty-one percent of children experienced HZ during the first episode of reactivated VZV infection; 32% had dissemination of HZ, associated with a low CD4-cell count. A second episode of varicella can occur, presumably after exposure to a different VZV strain than that which caused varicella initially. In a study of 30 cases of varicella in HIV-infected children, 27% developed HZ an average of 1.9 years after varicella (range, 0.8-3.7).[186-188] Children with <15% CD4-cell levels at onset of varicella were at very high risk of reactivation. Of the children with HZ, 50% developed recurrent HZ episodes.

HIV-infected individuals who are seronegative for VZV, and hence are at risk for primary infection, should promptly receive zoster immune globulin on exposure to the virus and high-dose intravenous acyclovir (10 mg/kg every 8 hours) instituted at the earliest signs of primary infection. This disastrous illness is of primary concern in HIV-infected children, as >90% of the adult population in the United States is seropositive for VZV. Acute varicella does not appear to worsen the course of HIV infection with regard to CD4- or CD8-cell levels.

The more common problem in the compromised host is reactivated infection, where a latent virus present in the dorsal nerve root ganglia becomes reactivated.[189] Typically zoster occurs for the first time relatively early in the course of HIV disease, even before oral hairy leukoplakia and oropharyngeal candidiasis.[190,191] Thus, among a group of 112 HIV-infected homosexual men with zoster, 23% had developed AIDS 2 years later, 46% 4 years later, and 73% 6 years later.[192] The more extensive the dermatomal involvement, the greater the pain and involvement of cranial and cervical dermatomes, the more advanced the HIV infection is found to be. HZ is also common in other compromised hosts.[193,194]

The first manifestation of zoster is often pain in the dermatome that subsequently manifests the classical grouped vesicles on an erythematous base. At times, multidermatomal involvement, either contiguous or noncontiguous, may occur. Zoster may also recur within the same dermatome or persist chronically for many months.[195] Occasionally in these patients, the dermatomal eruption may be bullous, hemorrhagic, necrotic, and accompanied by severe pain. Not infrequently, patients with zoster experience hematogenously borne cutaneous dissemination, without visceral involvement or inordinate morbidity. Persistent disseminated VZV lesions are often very painful and appear as crusted-to-hyperkeratotic plaques, 1 to 2 cm in diameter, occasionally with marginal vesicles.[196] These ecthymatous or chronic VZV infections are sparse, typically 5 to 15 in number, appearing on the trunk or proximal extremi-

ties.[197,198] The majority of HIV-infected patients with zoster have an uneventful recovery.

HZ can be the initial clinical presentation of HIV disease. Those who acquire HIV infection sexually are reported to experience HZ more commonly than with those who acquire it by injecting drug use.[199] In a report from Kenya, 85% of patients (16-50 years old) presenting with HZ were HIV-infected.[200] The duration of illness was longer in HIV-infected patients compared with non–HIV-infected cases of HZ (32 *v* 22 days). Seventy-four percent of HIV-infected individuals with HZ had generalized lymphadenopathy compared with only 3% in the noninfected group. Severe pain (69% *v* 39%), bacterial superinfection (15% *v* 6%), more than one affected dermatome (38% *v* 18%), and cranial nerve involvement were all more common in HIV-infected individuals with HZ. The mean CD4-cell count at presentation was 333/μL in the HIV-infected group and 777/μL in the HIV-negative group. Recovery was generally complete and uncomplicated. In Ethiopia, 95% of patients (mean age 35 years) with HZ ophthalmicus were reported to be HIV-infected.[201] Severe eyelid involvement occurred in 25%, ocular involvement in 78%, visual loss in 56%, and postherpetic neuralgia in 55%. Severity of HZ ophthalmicus was associated with delay in presentation, lack of antiviral therapy, and advanced HIV disease.

In a report of homosexual men observed after HIV-1 seroconversion, 20% had an episode of HZ after a mean follow-up of 54 months; 10% of those experienced one recurrence.[202] In a report of patients with advanced HIV disease (CD4-cell count <25/μL) treated with zidovudine, 16% had a history of HZ on enrollment and 13% of these had a recurrence during the 2-year follow-up.[203] HZ was not associated with a more rapid progression to AIDS.

Major complications of HZ occur in one fourth of cases and include blindness (HZ ophthalmicus), neurological complications, chronic cutaneous infection, postherpetic neuralgia, and bacterial superinfection, all of which occur more commonly if the CD4-cell count is <200/μL.

HZ is a clinical indicator of faltering immunity and its occurrence should always raise the issue of HIV serotesting. The incidence of HZ in HIV disease is approximately 25%. In a cohort study of 287 homosexual men with well-defined dates of HIV seroconversion and 419 HIV-seronegative homosexual men, the incidence of HZ was 15 times greater in HIV-seropositive men (29.4 cases/1,000 person-yr) than in HIV-seronegative men (2.0 cases/1,000 person-yr).[204] The overall age-adjusted relative risk was 16.9.

HZ often occurs early in the course of HIV disease and can occur soon after varicella in children. In several studies, HZ was not predictive of faster progression to advanced HIV disease. Extent of dermatomal involvement, severity of pain, and involvement of cranial or cervical dermatomes have been correlated with a poor outcome of HIV disease.

In a study of men with HZ, the incidence of first episode was 52/1,000 person-yr in HIV-infected men and 3.3/1,000 person-yr in non–HIV-infected men.[205] HZ recurred in 26% of HIV-infected men. The incidence of HZ increased by 31.2/1,000 PY at CD4 cells ≥500/μL, 47.2/1,000 PY at CD4 cells 200 to 499/μL, and 97.5/1,000 PY at CD4 cells <200/μL. The incidence of HZ increases with the decrease in CD4 cell counts and T-cell reactivity, but HZ is not an independent predictor of disease progression.

Clinically, HZ is typical in most cases. In advanced HIV disease, the spectrum of lesions is much wider. Solitary or a few ulcerations can occur. Epidermal proliferative lesions, either solitary or a few, resemble basal cell or SCCs.[206] Scattered or zosteriform verrucous lesions also occur.[207] In advanced HIV disease, VZV can also infect the neural tissue of the central nervous system (encephalitis), retina (acute retinal necrosis), or the spinal cord, with or without cutaneous lesions.[208-211] HZ precedes the onset of acute retinal necrosis by several days in 60% to 90% of cases.

In that zoster often occurs early in HIV disease, the course is fairly uneventful for the majority of patients. It is most often unidermatomal but may be multidermatomal, recurrent within the same dermatome, or disseminated. The eruption may be bullous, hemorrhagic and/or necrotic, and accompanied by severe pain. The majority of HIV-infected patients with HZ experience an uneventful recovery but atypical clinical courses are not uncommon. Limited cutaneous dissemination of zoster secondary to viremia is common in some patients with zoster but uneventful recovery is the rule. Ophthalmic zoster has the highest

incidence of serious complications, which include corneal ulceration, variable decrease of visual acuity,[212,213] and retinal necrosis.[214] Viral encephalitis can occur via entry into the brain by VZV infection of the optic nerve,[215] or follow hematogenous dissemination.[216] Cutaneous dissemination of VZV in patients with HZ is relatively common[217]; however, significant visceral involvement is rare. Viscerally disseminated HZ in a compromised host can be life-threatening.

In HIV disease individuals, cutaneous VZV lesions can persist[198] for months after either primary[197] or reactivated VZV infection with a pattern of zoster[195,218] or disseminated infection,[196,219] referred to as chronic verrucous or ecthymatous VZV infection. Lesions may persist for months, either in the localized or disseminated form, appearing as hyperkeratotic, ulcerated, painful nodules often with central crusting and/or ulceration with a border of vesicles.[189] A rare complication of zoster is the occurrence of a granulomatous vasculitis in the involved dermatome, without persistence of the VZV genome, possibly as a reaction to minute amounts of viral proteins.[220]

The diagnosis of varicella and HZ can be confirmed by detection of viral antigen on a smear of the base of a vesicle or erosion or in a section of a lesional biopsy specimen. A positive Tzanck test confirms the diagnosis of either VZV or HSV. Isolation of VZV on culture is more difficult than isolation of HSV. Lesional biopsy is also helpful to establish a diagnosis, especially in unusual manifestations of VZV infection such as ecthymatous or chronic verrucous lesions; the diagnosis is confirmed by detection of VZV antigen.

Administration of varicella vaccine in early HIV disease in children appears safe and beneficial. HIV-infected children exposed to VZV, whether varicella or zoster, may benefit by treatment with varicella-zoster immune globulin prophylactically, as well as acyclovir. Most persons with zoster occurring in early HIV disease do well without antiviral therapy. The same drugs approved for treatment of HSV are approved for treatment of VZV infection: famciclovir, valaciclovir, and acyclovir. Intravenous acyclovir (10 mg/kg every 8 hours) is given for severe infections. Because of the risk of visual impairment after ophthalmic zoster, intravenous acyclovir is usually given. As with HSV infections, acyclovir-resistant strains emerge after prolonged acyclovir treatment; most of these resistant strains respond to foscarnet therapy. Secondary prophylaxis is usually not indicated after VZV infection resolves.

The cornerstone of treatment for serious VZV infection is intravenous acyclovir. Valacyclovir and famciclovir, as well as acyclovir, are effective orally after initial intravenous therapy or for less severe VZV infections. As with HSV infection, acyclovir-resistant VZV has been reported after chronic acyclovir therapy for persistent or recurrent VZV infection.[221,222]

Epstein-barr virus infections. EBV selectively infects cells of the B-lymphocyte lineage and certain types of squamous epithelium. The majority of adults have been infected with EBV and harbor the latent virus. EBV infection plays an important role in the pathogenesis of 3 important clinical conditions in the HIV-infected patient population: OHL, classic Burkitt's lymphoma, and EBV-positive large cell lymphoma. Of these, OHL is the one with primary effects on the mucocutaneous tissues and correlates with moderate-to-advanced HIV-induced immunodeficiency.[223,224] EBV DNA can be detected in the oral epithelium in HIV-infected patients without clinical signs of OHL and its detection may be a marker for symptomatic HIV disease.[225] Whether OHL develops after reactivation of latent EBV or superinfection is uncertain.[226]

OHL is a lesion specific to HIV disease. OHL has been reported in up to 28% of HIV-infected patients and is more common in males.[227,228] In a study of OHL as a clinical marker of HIV disease progression, OHL was detected in 9% of individuals 1 year after seroconversion, in 16% at 2 years, 15% at 3 years, 35% at 4 years, and 42% at 5 years.[95] The median CD4-cell count when OHL was first detected was 468/μL. In individuals without an AIDS-defining illness when OHL is first detected, the probability of developing AIDS (without HAART) has been reported to be 48% by 16 months after detection and 83% by 31 months.[223] Persons with OHL and a history of hepatitis B virus infection have a 4-fold risk for early progression to AIDS; those with syphilis have nearly a 3-fold risk for early AIDS diagnosis.[229] In a study of HIV-associated mucocutaneous disorders in 456 patients (1982-1992),[230] OHL was diagnosed in 16% of cases, when the

median CD4-cell count was 235/μL. Median survival time after OHL diagnosis was 20 months. In patients with a CD4-cell count ≥300/μL, the detection of OHL was associated with shorter median survival time of 25 months compared with 52 months in those without OHL.

OHL typically presents as hyperplastic, verrucous, whitish, epithelial plaques on the lateral aspects of the tongue, frequently extending onto the contiguous dorsal or ventral surfaces.[231] Usually, a single lesion or 3 to 6 discrete plaques separated by normal-appearing mucosa is observed. Much less commonly, OHL occurs on the buccal mucosa opposing the tongue and on the soft palate. Although described as hairy, the most frequently noted appearance of the lesion occurring on the tongue is a corrugated appearance, with parallel white rows arranged nearly vertically. Useful diagnostic criteria for OHL are: a white lesion, involvement of the lateral aspect of the tongue, lack of change in appearance with rubbing, and no response to antifungal therapy. Differential diagnostic considerations include hyperplastic oral candidiasis, condyloma acuminatum, geographic (migratory) glossitis, lichen planus, tobacco-assisted leukoplakia, the mucous patch of secondary syphilis, SCC, and occlusal trauma.

For the most part, OHL is asymptomatic but its presence may be associated with some degree of anxiety. Patients should be reassured and advised that OHL is not thrush. With HAART, OHL usually resolves without additional interventions. In concerned patients with persistent lesions, topically applied podophyllin in benzoin is effective; recurrence within weeks to months is common. Acyclovir, valacyclovir, famciclovir, ganciclovir, or foscarnet given for other indications are often effective therapies for OHL.

Posttransplant cutaneous B-cell lymphoma, associated with EBV infection, is an uncommon complication of solid organ transplantation.[232] Findings are usually confined to the limited regions of the skin; systemic involvement is not common. Treatment is usually directed at the lesions, with surgery or radiotherapy.

Cytomegalovirus. Seroprevalence studies of CMV infection indicate that 50% of the general population is infected by age 50. The seroprevalence is much higher in lower socioeconomic groups and among injecting drug users. Most cases of primary CMV infection are asymptomatic; after primary infection, CMV enters a latent phase of infection, during which asymptomatic viral shedding in saliva, semen, and/or urine is extremely common. In the compromised host, CMV disease occurs via primary CMV infection, reactivation of latent CMV infection, or reinfection with a new CMV subtype. In most cases, CMV disease represents reactivation of latent virus. CMV infection often occurs soon after immune suppression associated with cancer chemotherapy, organ transplantation, and systemic corticosteroid therapy. CMV is the most common viral pathogen in patients with advanced HIV-induced immunodeficiency. In a study of 82 HIV-1–seropositive persons, 51.7% of those with either AIDS-related complex (ARC) or AIDS had evidence of CMV infection of circulating polymorphonuclear cells, whereas no infection was detected among the 50 asymptomatic HIV-infected persons.

Manifestations of CMV infection include retinitis, esophagitis, colitis, gastritis, hepatitis, and encephalitis. In a multicenter study of 1,002 persons with AIDS or ARC, median survival after diagnosis of CMV disease was 173 days, and CMV was an independent predictor of death.[233] Disseminated CMV has been shown in 93% of patients with AIDS; at autopsy, however, association with skin lesions was not reported. CMV reactivation and dissemination are common events as immunodeficiency worsens. As an opportunistic organism CMV commonly infects the retina, causing a sight-threatening retinitis,[234] and the large intestine, causing colitis manifested by intractable diarrhea. Widespread infection is associated with a generalized wasting syndrome, pneumonitis, and encephalitis. CMV infection, although present within various organs as documented by viral culture, is not necessarily the cause of the tissue dysfunction.[160]

Specific CMV-induced skin lesions have not been identified in compromised individuals. Cutaneous ulcers and a morbilliform eruption are the most common presentation of cutaneous CMV involvement.[31,235-237] Evidence for CMV infection in a variety of mucous membrane lesions, implied by specific cytopathic changes in biopsy specimens by light and electron microscopy, immunofluorescence, immunoperoxidase, and in situ hybridization techniques, has been

reported[238,239]; however, the role of CMV in pathogenesis of the lesions is not certain. Perianal ulceration caused by CMV occurs as the infection spreads from contiguous gastrointestinal sites. CMV was considered to be the cause of perianal and oral ulceration in 5 patients with advanced disease studied, based on typical histological changes and positive fluorescent monoclonal anti-CMV antibody studies. Empirical treatment with acyclovir failed, but all ulcers healed with either foscarnet or ganciclovir treatment. Other reported presentations of CMV infection in skin of HIV-infected individuals include macular purpura of the extremities associated with leukocytoclastic vasculitis and small, keratotic, verrucous lesions, 1 to 3 cm in diameter, scattered on the trunk, limbs, and face.

Human herpesvirus-8 (Kaposi's sarcoma-associated herpes virus). KS is a hemangioma-like proliferation of endothelial-derived cells, first reported by Moritz Kaposi in 1872 as "idiopathic pigmented sarcoma of the skin." Classical KS occurs in men of Mediterranean or Eastern European ancestry and presents clinically as slowly growing tan-to-violaceous papules, nodules, and tumors on the lower extremities. In the 1950s, African KS was described in children from equatorial Africa. In the 1960s, a third variant of KS was described in patients on long-term immunosuppressive therapy (ie, recipients of organ transplants). Most recently, in 1981, epidemic or HIV-associated KS was one of the first disorders to be identified in patients with AIDS. Most cases of HIV-associated KS occurred in homosexual or bisexual men. Early in the HIV epidemic, approximately 40% of homosexual or bisexual men with AIDS had KS; however, more recently the prevalence of KS appears to have declined. In all other groups at risk for HIV infection, the prevalence of KS has been and remains at the 1% to 3% level.

Although the clinical course of HIV-associated KS may be quite variable, it is far more aggressive than other variants of KS with the frequent occurrence of widespread cutaneous and visceral lesions.[240] Early lesions of HIV-associated KS present as slight discolorations of the skin, usually barely palpable papules and, if very early, macules. These lesions arise within the dermis, lacking any epidermal change, and are pinkish in color, with faint hues of tan, yellow, and green (biliverdin), giving the appearance of a bruise. Over a period of weeks-to-months-to-years, these early lesions enlarge into nodules or frank tumors, and the color darkens to a violaceous, "Concord grape" color, often with a yellow-green halo. As lesions enlarge, epidermal changes may occur, showing a shiny, atrophic appearance if stretched or, at times, hyperkeratosis with scale formation. In late lesions, tumor necrosis may occur with erosion or ulceration of the surface. Oral lesions are common and may be the first site of involvement, occurring typically on the hard palate as a violaceous stain of the mucosa.

Although HIV-associated KS can occur at any site on the skin, certain sites are much more common than others. On the head and neck, lesions commonly develop on the tip of the nose, cheeks, eyelids, and ears. In time, discrete lesions may coalesce, forming large plaques. Occasionally, KS lesions may form on the bulbar conjunctiva, appearing as a subconjunctival hemorrhage. Facial edema is common, caused by lymphatic obstruction by the KS lesions, and is sometimes extreme, causing gross distortion of the patient's appearance. In some patients, visible lesions are scanty or absent and the presentation of the KS is predominantly that of edema isolated to the face and/or one or more of the extremities. In a study of 173 patients with epidemic KS the distribution of mucocutaneous lesions were: trunk, 52%; legs, 45%; arms, 38%; face, 33%; and oral cavity, 40%. Koebnerization of KS lesions has been reported at sites of venipuncture, BCG injection, abscess formation, and contusions.

Although the diagnosis of KS can usually be suspected clinically, in most instances histological diagnosis on a lesional punch biopsy specimen should be accomplished. The differential diagnosis of possible KS lesions depends on the stage of disease encountered. An early, nearly macular (patch stage) lesion can be mistaken for a bruise, a hemangioma, a dermatofibroma, an insect bite, or a benign nevus. More advanced, nodular or plaque KS lesions must be differentiated from psoriasis, lichen planus, secondary syphilis, insect bites, benign nevi, nonmelanoma cancer, melanoma, and metastatic visceral malignancies. Once the individual KS plaque or tumorous lesions have coalesced to form tuberous lesions, the major alternative diagnosis is lymphoma.

The course of KS depends on restitution of immune function. Few patients die from compli-

cations directly related to KS. Currently, individuals with untreated HIV disease still present with KS. With effective response to HAART, KS is relatively uncommon and, if present, usually regresses or resolves without specific therapy for KS. Without immune restitution by HAART, however, established KS lesions tend to enlarge in size and deepen in color, at times coalescing, while more and more lesions appear. An occasional patient will develop KS lesions involving internal organs in the absence of any visible mucocutaneous involvement. At postmortem examination, most patients with KS will be found to have lesions in the gastrointestinal tract, lymph nodes, liver, lung, spleen, and/or kidneys. In addition, there appears to be an increased incidence of second malignancies in patients with AIDS-associated KS.

In the management of KS, the initial therapeutic focus is reduction in immune compromise by changing immunosuppressive drug therapies or by effective treatment of HIV disease with HAART. In many cases, KS will regress or resolve. For persistent KS, a spectrum of increasingly aggressive therapies is available.

Localized cutaneous disease is best treated with application of a retinoid gel, intralesional injection of vinblastine,[241] cryotherapy,[242] surgical excision, or radiation. Indolent, disseminated cutaneous KS is best treated with systemic immunotherapy or chemotherapy. Systemic α interferon is effective in indolent or slowly growing KS in patients with CD4-lymphocyte counts >400/mm who have few systemic symptoms and no opportunistic infections (40%-50% response rate, although this rate may be higher when zidovudine is also administered). Because of its slow onset of action, usually requiring 6 to 8 weeks for an initial response, systemic α interferon is inappropriate therapy for rapidly growing KS. In such patients, and those who fail to respond to interferon therapy, chemotherapy akin to that used for the more aggressive forms of the disease may then be employed. Systemic chemotherapy is indicated for aggressive disseminated and/or visceral KS. The chemotherapeutic agents of choice are vincristine and bleomycin, both of which are marrow-sparing agents, usually in combination with adriamycin. Such regimens yield a significant response in 79% of cases. Liposome-encapsulated doxorubicin has enhanced tumor uptake and lesser systemic side effects. Paclitaxel may be effective as a single agent. Antiviral agents, effective in treatment of HHV-8 infection, may be effective in treatment of KS.[243,244]

Molluscum Contagiosum

MCV commonly infects keratinized skin subclinically and can cause lesions at sites of minor trauma and in the infundibular portion of the hair follicle.[245] Transmission is usually via skin-to-skin contact, occurring commonly in children and sexual partners. The clinical course of MCV infection in HIV disease differs significantly from that in the normal host and is an excellent clinical marker of the degree of immunodeficiency.[246] In adults with multiple mollusca occurring outside of the genital area, especially head and neck lesions, HIV infection should be considered. Large and confluent lesions cause significant morbidity and disfigurement. Extensive MCV infection is uncommon in other compromised adults such as those with atopic dermatitis,[247] sarcoidosis,[248] cutaneous T-cell lymphoma,[249] lymphatic leukemia, lymphoma,[250] and thymoma.[251]

Prior to HAART, MCV infections were detected in 10% of individuals with HIV disease, and in 30% of those with CD4-cell counts <100/μL, the number of lesions being inversely related to the CD4-cell count.[252] In a study of 27 HIV-infected patients with MCV infection,[246] mean CD4-cell count was 85.7 cells/μL within 60 days of mollusca diagnosis; 52% of patients had facial and neck lesions alone and 26% had lesions in areas associated with sexual transmission. PCP had previously occurred in 30% of individuals and KS had been diagnosed in 56%.

Clinically, MCV infection presents as skin-colored papules or nodules, often with a characteristic central umbilicated keratotic plug. Lesions are usually 2 to 6 mm in diameter but may be >1 cm in diameter (giant molluscum). Large lesions may mimic epidermal inclusion cysts, arising on or about the ear or on the trunk. Shortly after their appearance, lesions may be solitary; in time, multiple lesions are more typical (50+ lesions). With persistent and progressive immunodeficiency, mollusca may continue to enlarge and proliferate, resulting in confluent masses of lesions, eg, involving the entire beard area. Large and/or multiple confluent facial lesions cause

significant cosmetic disfigurement. The most characteristic sites of occurrence in HIV-infected adults are on the face, beard area, neck, and scalp; anogenital and intertriginous (axillae, groins) involvement is also common. In men, lesions are often confined to the beard area, the skin having been inoculated during the process of shaving. Occasionally, lesions become secondarily infected with *S aureus,* resulting in abscess formation or with *P aeruginosa* with resultant necrotizing cellulitis. Significant postinflammatory hyperpigmentation or hypopigmentation, more pronounced in more heavily melanized skin, may occur after cryosurgery of lesions, adding to the cosmetic disfigurement of the mollusca.

The diagnosis of MCV infection in the HIV-infected patient is usually made on clinical grounds but histological confirmation is required in some patients. The differential diagnosis of solitary molluscum contagiosum includes verruca vulgaris, condyloma acuminatum, basal cell carcinoma, keratoacanthoma, and SCC. The differential diagnosis of multiple facial mollusca contagiosa includes hematogenous dissemination to the skin of invasive fungal infections (cryptococcosis, histoplasmosis, coccidioidomycosis, and penicilliosis). Lesional skin biopsy is indicated in patients with sudden appearance of mollusca-like facial papules associated with fever, headache, confusion, or pulmonary infiltrate to rule out deep mycosis with hematogenous dissemination to the skin.

In HIV-infected individuals, MCV infection tends to be progressive and recurrent after the usual therapies. MCV has been shown within clinically normal epidermis surrounding lesions, suggesting the mechanism by which new lesions recur at treatment sites in HIV-infected individuals.[253,254] With response to HAART, MCV infections regress or resolve completely, associated with increased CD4-cell counts and reduced viral load level.[255]

Therapeutically, the most efficacious approach toward MCV infection is correction of the underlying immunodeficiency; if this can be accomplished lesions regress. If correction of immunodeficiency is not possible, treatment is directed at controlling the numbers and bulk of cosmetically disturbing lesions rather than at eradication of all lesions. Liquid nitrogen cryospray is the most convenient therapy and usually must be repeated every 2 to 4 weeks. Electrosurgery is more effective than cryosurgery; local anesthesia is required by most subjects with either injected lidocaine or eutectic mixture of local anesthetics cream. CO_2 or pulse-dye laser ablation is also effective but relatively costly. Five percent imiquimod cream applied 3 times a week is an effective patient administered therapy in children and adults. Cidofovir, a nucleotide analog with activity against several DNA viruses, given either intravenously or topically as a cream, may be an effective therapy.[256]

Human Papillomavirus Infections

Subclinical infection with HPV is nearly universal in humans. With immunocompromise, cutaneous and/or mucosal HPV infection (re)emerges from latency, presenting clinically as verruca, condyloma acuminatum, squamous intraepithelial lesion (SIL), SCC in situ (SCCIS), or invasive SCC.[257] HPV colonizes keratinized skin of all humans producing common warts (verruca vulgaris, verruca plantaris, verruca plana) in many healthy individuals during the course of lifetime. The greater majority of sexually active individuals are subclinically infected with one or multiple HPV types. HPV-6 and -11 infect mucosal sites (genitalia, anus, perineum, oropharynx) and cause genital warts (condyloma acuminatum); HPV-16 and -18 cause precancerous lesions SIL, SCCIS, and invasive SCC.

In organ transplant recipients, HIV-infected individuals, and other compromised hosts, verrucae are not unusual in morphology, number, or response to treatment; however, with advancing disease, verrucae can enlarge, become confluent and unresponsive to therapy.[258] HPV-5 can cause an unusual pattern of extensive verruca plana and pityriasis (tinea) versicolor-like warts, similar to the pattern seen in epidermodysplasia verruciformis. With moderate or advanced immunodeficiency, warts and condyloma may become much more numerous, confluent, and refractory to usual treatment modalities. Precancerous lesions identical to mucosal lesions, namely SIL and SCCIS, can occur periungually on the fingers. In some cases, invasive SCC can arise at one or multiple sites on the fingers and/or nail bed. These tumors are aggressive and invade to the underlying periosteum and bone relatively early

caused by the proximity of the underlying bony structures.

HPV-induced SIL, SCCIS, and invasive SCC of mucosal sites, especially the transitional epithelium of the cervix and anus, are increasingly more common in HIV disease. SIL and SCCIS occur despite maintained or improved immune function as a result of HAART. Invasive cervical SCC has been added to the list of AIDS-defining conditions. HPV-induced neoplasms may well be diagnosed more frequently as the lifespan of persons with HIV diseases is increased with treatment.

HPV DNA is 2 to 3 times as frequent in cervicovaginal-lavage specimens and almost 15 times as common in anal-swab specimens from HIV-infected women as in those from HIV-seronegative women.[259,260] HIV-seropositive women are 5 times as likely as HIV-seronegative women to have vulvovaginal condyloma and oral or anal SIL.[261,262] The increased prevalence of HPV-induced lesions in HIV disease probably is related to deficient cell-mediated immunity rather than impaired specific antibody formation.[263] Increased HPV replication of the more oncogenic HPV types occurs with more advanced immunosuppression.[264]

In a study of the association between anal SIL, HPV infection, and immunosuppression among HIV-seropositive and HIV-seronegative homosexual men, anal HPV DNA was detected in 55% of HIV-seropositive and 23% of HIV-seronegative men by Southern transfer hybridization and in 92% and 78% by polymerase chain reaction.[265] Anal SIL was noted in 26% of HIV-seropositive and in 8% of HIV-seronegative men; high-grade SIL was noted in 4% of HIV-seropositive and in 0.5% of HIV-seronegative men. Among HIV-infected men, anal SIL, detection of specific anal HPV types, and detection of high levels of anal HPV DNA were all associated with advanced HIV disease. The risk of anal SIL among HIV-seropositive men with CD4 <500 was increased 2.9-fold over that of HIV-seropositive men with CD4 counts >500.

In a study of HPV infection in HIV-seronegative and -seropositive women, HPV DNA was detected in 83% of the seropositive and 62% of the seronegative women.[259] Twenty percent of seropositive women and 3% of seronegative women had persistent infections with HPV-16–associated viral types (16, 31, 33, 35, 58) or HPV-18–associated types (18 or 45), which are most strongly associated with cervical cancer. HIV-infected women were noted to have a high rate of persistent HPV infections with the types of HPV that are strongly associated with the development of high-grade SIL and invasive SCC.

The degree of immunosuppression correlates with the presence of HPV DNA, extent of HPV infection, and potential for malignant transformation, individuals with CD4-cell counts <200/mL being at greatest risk.[266] The potential for malignant transformation varies considerably according to the type and site of HPV-infected epithelium, being greatest for the transitional epithelium of the cervix and anus, lesser for vulvar epithelium, and least for the epithelium of the male genitalia, perineum, inguinal folds, and perianal regions. The immune mechanisms underlying the increased rates of anogenital neoplasia in HIV-infected individuals[267-270] are not well understood but are thought to be related to high prevalence of HPV infection, impairment of cellular immunity, activation of latent HPV replication, and local suppression of cytokine production.

With advanced immunodeficiency, low-grade SIL or high-grade SIL, caused most frequently by HPV-16 and -18, can arise on epithelium of the cervix, external genitalia, perineum, anus, oropharynx, or keratinized skin, especially the nail-beds. Although differentiation from condyloma cannot be made on clinical grounds alone, SIL and SCCIS often present as multiple, smooth, pink or skin colored to tan/brown macules or papules, which may form confluent, cobblestoned, well-demarcated plaques. Lesions are usually multifocal but may be unifocal. In some cases, multiple foci of epithelial erosion occur and concomitant herpetic infection must be ruled out. Massive HPV-induced lesions (older terminology giant condyloma of Buschke-Lōwenstein) have a much greater chance of showing foci of SIL, SCCIS, or invasive SCC histologically. Extragenital HPV-induced SIL, SCCIS, and invasive SCC also occur in keratinized skin, such as the nail beds.[271,272]

Oropharyngeal HPV-induced lesions resemble anogenital condyloma, pink or white in color, but never the tan-to-brown color of some genital lesions. Extensive intraoral condyloma acuminatum (oral florid papillomatosis) presents as mul-

tiple large plaques, analogous to anogenital giant condylomata acuminata of Buschke-Löwenstein, and can also transform to verrucous carcinoma.

The diagnosis of verrucae and condylomata is usually made on clinical findings. In individuals with advanced HIV disease, biopsy of suspected HPV infections of the anogenital region is recommended because of the high prevalence of SIL and SCCIS. Exfoliative cytology is very effective at detecting SIL or SCC of the cervix and may also be helpful with anal involvement.[273] External anogenital SIL and SCCIS, unlike cervical and anal lesions, cannot be screened for by the Pap test using exfoliative cytology. Lesional biopsy specimens should be obtained from several sites, especially in individuals at higher risk for malignant transformation. In most patients, histological findings are relatively uniform at multiple biopsy sites, ranging from low-grade or high-grade SIL to SCCIS. At one point in time, invasive SCC is, however, usually unifocal within a field of SCCIS. A larger nodule within a field of SIL or SCCIS should be excised to rule out invasive SCC. Over the course of HPV-induced neoplasia, multiple invasive SCCs may arise at various anogenital epithelial sites.

The natural history of external anogenital HPV-induced neoplasia is probably similar to that of condyloma acuminatum. Prolonged, severe immunodeficiency provides the necessary milieu for the emergence of HPV-induced anogenital neoplasia. The incidence of transformation of SCC in situ to invasive SCC appears to be low. The relative risk for HPV-related anal SCC is much higher in HIV-infected than in non–HIV-infected homosexual men and is more likely in advanced HIV disease.

Invasive cervical SCC is an AIDS-defining condition; however, a documented increase in incidence has not yet been reported. Cervical and anal neoplasias are likely to become more common manifestations of HIV disease as patients with profound immunodeficiency, who would previously have succumbed to OIs, are now surviving for extended periods because of increasingly effective antiretroviral prophylaxis of OIs and newer antimicrobial therapies. External anogenital SIL and SCCIS may also become more common in long-term survivors of HIV disease.

Low-grade or high-grade SIL of the external anogenital epithelium can be treated by several methods: topical chemotherapy (5% 5-fluorouracil or 5% imiquimod cream, especially for extensive multifocal lesions); surgical excision of single or several lesions; focal destruction of lesions by cryosurgery, electrosurgery, or lasersurgery. Unlike topical 5-fluorouracil or imiquimod, surgical modalities treat only clinically detectable lesions and not subclinical infection. For minimally invasive SCC arising in an area of external anogenital SCCIS, surgical excision is recommended with adequate borders around the lesion. The role for adjunctive radiotherapy has neither been defined nor has the use of combined modality therapy with external beam radiotherapy and chemotherapy.

Individuals with documented external anogenital high-grade SIL or SCCIS should be observed by periodic follow-up examinations (every 3 to 4 months), noting the appearance of new lesions at these sites or an enlarging nodule or ulcerated site; biopsy of these sites is recommended. In that HPV-induced neoplasia may extend to the cervix and/or anus, direct examination by speculum and anoscope should also be performed; samples for cytology should be obtained using a cervical brush and cytofix solution.

The number of individuals with SIL/SCCIS of the external anogenital region is expected to grow with the increasing numbers of long-term survivors of HIV disease. The prevalence of HPV infection of nonkeratinized and mucous epithelium in HIV-infected homosexual men is high, up to 20% having clinically detectable anogenital condylomata and up to 50% having infection detectable by cytological smears of anal canal mucosa.[274] HPV types 6 and 11, which in the normal host infect the anogenital epithelium and are of low oncogenic risk, can be shown in extensive verruca on the hands and feet and in invasive anogenital SCC of HIV-infected men. Similarly, HIV-infected women have rates of cervical dysplasia 5 to 10 times higher than non–HIV-infected women. Thus, in one group of HIV-infected women, three fourths had vulvar HPV infection, two thirds of these having condylomata, and one third vulvar intraepithelial neoplasia.[275,276]

Verrucae occurring in HIV-infected individuals are usually asymptomatic, with the most common complaint being a cosmetic one. Warts on the plantar aspect of the foot can become large and

painful. Verruca vulgaris and verruca plantaris appear as well-demarcated keratotic papules or nodules, usually with multiple tiny red-brown dots representing thrombosed capillaries; palmar and plantar warts characteristically interrupt the normal dermatoglyphics. They may be numerous and confluent, giving the appearance of a mosaic. Verruca plana appears as a well-demarcated, flat-topped papule, which lacks the dots seen in other types of verrucae.[277,278] When present in the beard area, hundreds of flat warts may be present. All types of verrucae may have a linear arrangement due to koebnerization or autoinoculation.

Condylomata acuminata are usually asymptomatic, although voluminous lesions may be painful and bleed.[279] Pain associated with HPV infection most commonly is caused by therapy but is also sensed in voluminous verrucous masses. Condylomata appear as well-demarcated papular or nodular lesions arising anywhere on the anogenital, vaginal, cervical, rectal, or oropharyngeal epithelium. Lesions may be numerous and become confluent. The prevalence of cervical intraepithelial neoplasia is increased in HIV disease; however, the prevalence of invasive SCC of the cervix is not certain at this time.[276] Intraepithelial neoplasia involving the anogenital skin is also increased; there may also be an increase in the incidence of invasive SCC.[280,281]

The diagnosis of verrucae and condylomata is usually made on a clinical basis. Acetowhitening, the appearance of white micropapules or macules after the application of 5% acetic acid (white vinegar) to the anogenital epithelium, can be helpful in defining the extent of HPV infection. The diagnosis of intraepithelial neoplasia and invasive SCC can only be made histologically, and atypical lesions should be biopsied. The differential diagnosis of verrucae includes molluscum contagiosum, various benign and malignant epidermal neoplasms, KS, deep mycotic lesions hematogenously disseminated to the skin, and bacillary angiomatosis. The differential diagnosis of condylomata acuminata includes various benign and malignant mucocutaneous neoplasms, condylomata lata of secondary syphilis, and molluscum contagiosum.

Efficacy of treatment of verruca vulgaris and condyloma acuminatum in HIV disease varies with the degree of immunocompromise. In patients with early disease, these lesions should be managed as in the normal host. In patients with advanced HIV-induced immunodeficiency complete eradication of benign HPV-induced lesions is unlikely, and aggressive treatment such as laser surgery is contraindicated.[282] Cytological smears and/or lesional biopsies should be obtained to monitor the evolution from cytological atypia to intraepithelial neoplasia or invasive SCC.

Sexually Transmitted Diseases

Genital ulcer disease caused by syphilis, genital herpes, and chancroid has been associated with increased transmission of HIV.

Syphilis

Coinfection with *Treponema pallidum* and HIV interact at several levels.[283,284] Both are sexually transmitted diseases and may be acquired from a dually infected sex partner. Primary syphilis (characterized by chancres or ulcers on the vulva, cervix, penis, anus, rectum, or oropharynx) facilitates acquisition of HIV because of the break in the integrity of the epithelium. Syphilis occurring in more advanced HIV disease can present with highly atypical findings: the immunologic defects associated with HIV infection may block the appearance of the usual antibody response to *T pallidum* infection, so that false negative serological tests for syphilis can be observed in the face of active and even progressive infection; the clinical manifestations of the disease may be altered, the response to therapy decreased; the duration of the stages of syphilis may be greatly telescoped, all caused by the immunocompromised state of the host.

Shortly after *T pallidum* penetrates the intact mucous membrane or abraded skin, it spreads via lymphatics and the systemic circulation. Healing of the primary chancre, control of the infection in draining lymph nodes, the development of lesions at metastatic sites, the rapidity with which normally late manifestations of syphilis develop, the clinical manifestations of the infection, and the response to antimicrobial therapy are all influenced by the degree of immunocompromise present. Thus, the greater the immunocompromise, the slower the healing, the greater the organism burden, the more common systemic spread, the more rapid the development of "late stage" disease, and the more likely the failure of conventional antimicrobial therapy, particularly if

bacteriostatic drugs such as doxycycline or erythromycin are used.

The majority of HIV-infected persons who acquire syphilis have the expected clinical course of disease and the expected serological findings in serum and cerebrospinal fluid (CSF), and they respond to the recommended therapeutic regimens. In a small percentage, however, the clinical manifestations, clinical course, serological response, and response to antibiotic treatment are unusual, especially with moderate-to-advanced HIV-induced immunodeficiency. In that unusual clinical presentations or failures of treatment are reported as single or a few cases, the percentage of cases of syphilis in HIV-infected patients with an unusual clinical course of disease is unknown. An inadequate immune response to *T pallidum* is considered to cause the various abnormalities in the course of syphilis in the HIV-infected patient.[285,286]

Not uncommonly, however, the extent of ulceration is far greater than normally seen, and multiple chancres may be observed.[287] Instead of healing within 3 to 6 weeks, persistent ulceration may occur.

Any of the clinical manifestations of secondary syphilis that occur in the normal host may occur in HIV patients.[288] In addition, lues maligna, a rare form of secondary syphilis characterized by pleomorphic skin lesions including pustules, nodules, ulcers, and a necrotizing vasculitis may be seen.[289] However, the most notable aspect of syphilis in the HIV-infected individual is the rapid progression of disease, such that normally late sequelae of *T pallidum* infection may be observed in <6 months after primary infection, even in the face of normally adequate therapy.[290,291]

In general, HIV-infected individuals with syphilis have a higher incidence of systemic symptoms, simultaneous multiorgan involvement, atypical rashes, and are particularly prone to the development of neurosyphilis and uveitis. Because of the malignant course of the disease and the unreliability of traditional diagnostic and therapeutic approaches, both an aggressive biopsy and treatment program are essential.

The cornerstone of the diagnostic approach to syphilis in non–HIV-infected individuals is serological testing.[292,293] However, since both false-positive and false-negative results occur in HIV-infected persons,[294,295] such testing must be supplemented by biopsies of suspicious lesions.[296] Fluid from such lesions should be examined immediately by dark-field microscopy. In addition, specific immunofluorescent or immunoperoxidase staining of the pathological specimens can lead to the definitive diagnosis. The differential diagnosis of syphilitic cutaneous lesions is quite broad, depending on the particular lesion being considered. Thus, the differential diagnosis of primary lesions of syphilis mainly includes herpes simplex infection, chancroid, and bacterially infected genital lesions of any cause, although, under appropriate epidemiological conditions entities such as donovanosis, lymphogranuloma venereum, mycobacterial infection, and tularemia must be considered. The differential diagnosis of secondary syphilis includes drug eruption (eg, captopril), pityriasis rosea, infectious exanthems, infectious mononucleosis, tinea corporis, tinea versicolor, scabies, "id" reaction, condylomata acuminata, acute guttate psoriasis, and lichen planus. The differential diagnosis of tertiary syphilis includes lymphoma, tuberculosis, sarcoidosis, and deep fungal infections.

In HIV-infected patients with syphilis, 2 rules of clinical management apply: (1) disseminated infection, particularly with central nervous system involvement, should be assumed and appropriate therapy for neurosyphilis should be prescribed for any patient coinfected with syphilis and HIV who has evidence of compromised immune function, regardless of the apparent clinical stage of syphilis observed; (2) close follow-up with repeated clinical, serological, and cerebrospinal fluid examinations are necessary, as even the best of regimens will sometimes fail in HIV-infected patients with significant immunocompromise.[297,298]

In a report of syphilis and HIV infection, 23% of individuals who presented with syphilis were concurrently HIV-infected.[299] The clinical presentation of syphilis in patients with HIV infection differs from that of patients without HIV infection in that patients with HIV infection present more often in the secondary stage (53% v 33%) and those with secondary syphilis are more likely to have chancres (43% v 15%).

HIV testing is advised for all sexually active patients with syphilis. Although uncommon, seronegative primary and secondary syphilis have been reported in HIV-infected individuals.[294]

Nearly all HIV-infected individuals with symptomatic neurosyphilis have positive syphilis serologies.[295] Normally, treponemal tests remain positive throughout life. However, 7% of asymptomatic HIV-infected patients with a history of syphilis and 38% of those with symptomatic HIV infection with a history of syphilis have been reported to lose reactivity of treponemal tests.[300]

Neurosyphilis should be considered in the differential diagnosis of neurological disease in HIV-infected persons. When clinical findings suggest syphilis but serological tests are negative or confusing, alternative tests such as biopsy of lesions, dark-field examination, and direct fluorescent antibody staining of lesion material should be used.

In comparison with HIV-seronegative individuals, HIV-infected patients who have early syphilis may be at increased risk for neurological complications and may have higher rates of treatment failure with currently recommended regimens. The magnitude of these risks, although not defined precisely, is probably minimal. No treatment regimens for syphilis are demonstrably more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-seronegative individuals. Careful follow-up after therapy is essential.

The current Centers for Disease Control (Atlanta, GA) recommendations for treating early syphilis appear adequate for most patients, whether or not HIV infection is present.[301,302]

Penicillin regimens should be used whenever possible for all stages of syphilis in HIV: benzathine penicillin G, 2.4 million U intramuscular, as for HIV-seronegative individuals. Some authorities advise CSF examination and/or treatment with a regimen appropriate for neurosyphilis for all patients coinfected with syphilis and HIV, regardless of the clinical stage of syphilis. Patients should be observed clinically and with quantitative nontreponemal serological tests (venereal diseases research laboratory, rapid plasma reagin) at 1, 2, 3, 6, 9, and 12 months after treatment. Patients with early syphilis whose titers increase or fail to decrease 4-fold within 6 months should undergo CSF examination and be retreated. In such patients, CSF abnormalities could be caused by HIV-related infection, neurosyphilis, or both.[283] In that *T pallidum* may persist in the central nervous system of the HIV-infected patient despite adequate antibiotic treatment, the possibility of chronic maintenance treatment, analogous to secondary prophylaxis of cryptococcal meningitis, has been raised.

Parasitic Infestations

Protozoan infections are among the most common opportunistic infections in HIV disease; mucocutaneous involvement, however, is uncommon.[303]

Extrapulmonary Pneumocystosis

P carinii is a common opportunistic pathogen in untreated HIV disease with CD4 counts <200 cells/μL, most commonly causing pneumonia (PCP). Extrapulmonary pneumocystosis can be rare at the initial presentation of HIV infection, manifested by unilateral or bilateral polypoid masses, and may be accompanied by loss of hearing. Similar lesions may occur at the tympanic membrane, middle ear, and mastoid air cells, associated with retrograde spread via the eustachian tube. Gangrene of the foot has been reported in a patient with widespread pneumocystosis; microemboli containing *P carinii* were present in smaller arterioles and capillaries within necrotic skin of the toes. Widespread violaceous papules and nodules arising on the torso, arms, and legs, resembling KS, have been reported.[304]

Strongyloidiasis

Once infected with *Strongyloides stercoralis*, the organism persists in the host via autoinoculation. In the compromised host with underlying conditions such as chronic infection (HIV disease, tuberculosis, lepromatous leprosy), neoplasms (lymphoma, leukemia), or organ transplantation, the number of filariform larvae can increase tremendously resulting in disseminated strongyloidiasis or hyperinfection syndrome.

Disseminated strongyloidiasis should be considered in the following circumstances[305]: (1) eosinophilia may be modest or absent; systemic corticosteroids and host debilitation may suppress this characteristic finding; the presence of eosinophilia should initiate a vigorous search for parasites; (2) unexplained and/or persistent bacteremia with enteric organisms despite administration of appropriate antibiotics; (3) serious infection (pneumonia, meningitis, bacteremia) from a suspected intra-abdominal source; (4) nonspecific gastroin-

testinal symptoms (abdominal pain and distention, diarrhea, nausea, and vomiting); (5) nonspecific pulmonary symptoms and signs (cough, wheezing, hemoptysis, transient interstitial infiltrates); (6) concurrent infection or prior therapy for other intestinal parasites; (7) history of residence or travel to an endemic area even many years previously.

Clinically, periumbilical purpura is suggestive of disseminated strongyloidiasis. The ecchymoses are said to resemble multiple thumbprints on the abdominal wall, radiating from the umbilicus to the flanks and lower extremities.[306] Fine petechiae are also seen having a reticulated pattern of linear and serpiginous purpuric streaks.[307]

Leishmaniasis

Following asymptomatic or symptomatic primary infection, *Leishmania* often remains latent in the reticuloendothelial system. Subclinical *Leishmania* infection is common in Mediterranean countries; 5% to 15% of adults in parts of Italy have a positive leishmanin skin test.[308] In previously infected individuals, antigen-specific T cells and natural killer cells interact with parasitized phagocytes in an equilibrium such that only a very low level of replication of *Leishmania* occurs. In HIV-infected persons the equilibrium is lost.[309] As immunodeficiency progresses, the protozoans may escape confinement by immune surveillance and cause visceral leishmaniasis (VL) (kala-azar). Reactivated leishmaniasis also occurs in organ transplant recipients.

Coinfection with HIV and *Leishmania* has been reported in >700 patients living in the Mediterranean basin, with the greatest number in Spain. In southern Europe, 50% of adult VL cases have occurred in HIV-infected individuals; 1.5% to 9% of HIV-infected individuals have either newly acquired or reactivated VL. More than 400 cases of coinfection with HIV and *Leishmania* have been reported from Spain, 85% in injecting drug users (IDU). Person-to-person transmission of *Leishmania,* as well as HIV, has been suggested in IDUs. VL may be the presenting manifestation of HIV disease. The course of persons who harbor *Leishmania* and HIV remains poorly defined. Coinfection of HIV and *Leishmania* in other sites of endemic leishmaniasis such as Kenya, Sudan, India, and Brazil is not well defined.

No characteristic skin lesions have been described in HIV disease. Normal skin may also be parasitized. Cutaneous leishmaniasis (CL) usually represents primary infection presenting in multiple crusted papulonodules in sites exposed to insect vectors, disseminated nodules,[310] as well as an erythrodermic and dermatomyositis-like eruption.[311] A generalized psoriasiform eruption has been reported in a patient with VL.[312] Leishmaniasis can also present at sites of HSV or VZV infection or of KS in HIV-infected individuals with CL or VL.[313] Digital necrosis has been reported associated with leishmanial vasculitis.[314]

Diagnosis may be confirmed by demonstration of *Leishmania* on lesional skin biopsy and/or bone marrow aspiration. Leishmanial serology is often negative. The incidence of relapse of visceral leishmaniasis is high in HIV-infected individuals.

American Trypanosomiasis (Chagas' Disease)

American trypanosomiasis can reactivate in patients with cardiomyopathy treated with cardiac transplantation and present with lesions resembling soft tissue infection.[315-319] In transplant recipients, trypanosomiasis reactivates with clinical presentation of fever, heart failure, and soft tissue infection on the trunk and/or lower extremities. *Trypanosoma cruzi* can be detected on lesional skin biopsy.

Acanthamoebiasis

Acanthamoebae are free-living amoebae, which can enter the upper respiratory tract, disseminate hematogenously, and cause encephalitis and disseminated cutaneous lesions in advanced HIV disease. Cutaneous lesions initially appear as erythematous dermal-to-subcutaneous papules and/or nodules that suppurate, forming abscesses and ulcerations.[320-323] Acanthamoebic cysts and trophozoites, which resemble macrophages, can be visualized in lesional biopsy specimens with periodic acid-Schiff (PAS) or Gomori's methenamine silver stain and immunofluorescence techniques.[324] A leukocytoclastic vasculitis can also occur. The organism can be isolated on culture of a biopsy specimen.

Protothecosis

Prototheca species are algae found in water, sewage, soil, and trees; *P wickerhamii* is the only

one capable of infecting humans. Human infection occurs at sites of traumatic inoculation, producing localized infection in the olecranon bursa in the normal host. In the compromised host, lesions occur at the site of inoculation and have a widely varied clinical appearance, ranging from papules, vesicles, ulcers, or verrucous plaques.[325,326] Disseminated infection can occur after localized cutaneous lesions, such as an insect bite in the compromised host.[327] *Prototheca* can be identified by PAS and silver stains of lesional biopsy specimens and isolated on Sabouraud's dextrose agar.

Arthropod Infestations

Crusted (Norwegian) Scabies

Crusted or hyperkeratotic or Norwegian scabies occurs in compromised hosts. Currently in the United States, HIV disease is the most common associated immunocompromised state; crusted scabies also occurs in leprosy (the original report of crusted or Norwegian scabies was in lepers from Norway), Down syndrome, transplant recipients,[328] chronic lymphocytic leukemia,[329] adult T-cell leukemia,[330] solid tumors, and vasculitis.

In obtunded or compromised individuals, pruritus may be diminished or absent in crusted scabies. Scabetic infestation can be severe, with millions of mites infesting the skin, presenting as a hyperkeratotic dermatitis but resembling atopic erythroderma, psoriasis vulgaris, keratoderma blennorrhagicum, keratosis follicularis (Darier's disease), or seborrheic dermatitis (in infants).[331] Thickly crusted plaques occur on the ears, buttocks, and extensor surfaces of the extremities, palms, and soles. Heavy infestation occurs around the nails with nail dystrophy and subungual and periungual scale-crust.[332,333] Scabetic infestation, which usually spares the head and neck in adults, can be generalized. *S aureus* and gram-negative superinfection can occur, which has been complicated by septicemia and death.[288,334,335] Because of the number of organisms in crusted scabies, recurrences are common and hospital epidemics may occur.

Use of potent topical corticosteroids for such previously diagnosed pruritic conditions may mask the presence of scabetic infestation. Eradication of the infestation is difficult because of the number of organisms. Topical treatment with gamma benzene hexachloride, permethrin lotion, or 10% sulfur ointment is effective; total body application is required. Keratolytic agents are needed to debride hyperkeratotic areas, in conjunction with debridement of involved nails. Orally administered ivermectin has been reported to be effective in scabies.[336,337]

INFLAMMATORY DISORDERS THAT SIMULATE INFECTION IN THE COMPROMISED HOST

Several inflammatory cutaneous disorders occur in the compromised host, which can be mistaken for infections. These disorders are treated with anti-inflammatory agents such as corticosteroids. Antibiotics are ineffective for treating these disorders; surgical debridement is contraindicated.

HIV-Associated Eosinophilic Folliculitis

Eosinophilic folliculitis (EF) is a relatively common pruritic eruption of sterile pruritic papules and pustules on the face, trunk, and extremities.[338] The eruption occurs nearly exclusively in HIV disease, presenting in either advanced HIV disease or during immune reconstitution after initiation of HAART.[339] Histologically, neutrophilic and eosinophilic infiltration of the hair follicles is observed. A clinical entity (Ofuji's disease) with identical histology occurs in non–HIV-infected individuals. Clinically, however, nonfollicular pustules, coalescing plaques, and urticarial lesions are seen. A 1- to 2-week course of oral corticosteroids is highly effective in providing symptomatic relief of EF. Agents used for long-term suppression of EF included topical corticosteroid preparations, ultraviolet B phototherapy, and oral agents, such as isotretinoin and itraconazole.

Neutrophilic Dermatoses

Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome)

Acute febrile neutrophilic dermatosis presents as painful inflammatory plaques often accompanied by fever, arthralgia, and peripheral leukocytosis (neutrophilia). Multiple lesions arise acutely, are tender and/or painful, and occur most commonly on the face, neck, arms, and legs. Systemic symptoms of fever, headache, arthralgia, and malaise often accompany the cutaneous manifestations. Sweet's syndrome occurs as a paraneoplas-

tic reaction pattern and is associated with various infections and inflammatory disorders (parainflammatory). Approximately 10% of cases of Sweet's syndrome are associated with malignancies, ie, preleukemias (myelodysplastic syndrome, leukemias, and solid tumors). When associated with an underlying malignancy, Sweet's syndrome persists for months or years. The treatment of choice for Sweet's syndrome is prednisone 70 mg tapered over 1 to 2 weeks. Lesions recur unless the underlying malignancy is effectively treated.

Pyoderma Gangrenosum

Pyoderma gangrenosum is a rapidly evolving, idiopathic, chronic, and severely disabling skin disease, characterized by the sudden occurrence of single or multiple inflammatory plaques. Approximately half of cases are idiopathic, whereas others are associated with paraproteinemia, myeloma, and leukemia. Surgical debridement is contraindicated, for any trauma to the skin of these individuals can cause the lesions to flare at that site. The most effective agents for management are oral corticosteroids and cyclosporin A.

CONCLUSION

Both the physician and the compromised patient should routinely examine the skin for cutaneous and subcutaneous lesions. This evaluation enables the skin to be used as an early warning system of serious infection. Unexplained skin lesions should be evaluated by biopsy for culture and histological examination.

REFERENCES

1. Wolfson JS, Sober AJ, Rubin RH: Dermatologic manifestations of infection in the compromised host. Annu Rev Med 34:205-217, 1983

2. Wolfson JS, Sober AJ, Rubin RH: Dermatologic manifestations of infections in immunocompromised patients. Medicine (Baltimore) 64:115-133, 1985

3. Fauci AS: The AIDS epidemic—considerations for the 21st century. N Engl J Med 341:1046-1050, 1999

4. Dennis JE, Rhodes KH, Cooney DR, et al: Nosocomical Rhizopus infection (zygomycosis) in children. J Pediatr 96:824-828, 1980

5. Grossman ME, Fithian EC, Behrens C, et al: Primary cutaneous aspergillosis in six leukemic children. J Am Acad Dermatol 12:313-318, 1985

6. Cone LA, Woodard DR, Byrd RG, et al: A recalcitrant, erythematous, desquamating disorder associated with toxin-producing staphylococci in patients with AIDS. J Infect Dis 165:638-643, 1992

7. Cupps TR, Cotton DJ, Schooley RT, et al: Facial erysipelas in the immunocompromised host. Report of two cases. Arch Dermatol 117:47-49, 1981

8. Hewitt WD, Farrar WE: Bacteremia and ecthyma caused by Streptococcus pyogenes in a patient with acquired immunodeficiency syndrome. Am J Med Sci 295:52-54, 1988

9. Janssen F, Zelinsky-Gurung A, Caumes E, et al: Group A streptococcal cellulitis-adenitis in a patient with acquired immunodeficiency syndrome. J Am Acad Dermatol 24:363-365, 1991

10. Patel M, Ahrens JC, Moyer DV, et al: Pneumococcal soft-tissue infections: A problem deserving more recognition [see comments]. Clin Infect Dis 19:149-151, 1994

11. Rodriguez Barradas MC, Musher DM, Hamill RJ, et al: Unusual manifestations of pneumococcal infection in human immunodeficiency virus-infected individuals: The past revisited. Clin Infect Dis 14:192-199, 1992

12. Jaruratanasirikul S, Kalnauwakul S, Lekhakula A: Traumatic wound infection due to Bacillus cereus in an immunocompromised patient: A case report. Southeast Asian J Trop Med Public Health 18:112-114, 1987

13. Khavari PA, Bolognia JL, Eisen R, et al: Periodic acid-Schiff-positive organisms in primary cutaneous Bacillus cereus infection. Case report and an investigation of the periodic acid-Schiff staining properties of bacteria. Arch Dermatol 127:543-546, 1991

14. Henrickson KJ, Shenep JL, Flynn PM, et al: Primary cutaneous bacillus cereus infection in neutropenic children. Lancet 1:601-603, 1989

15. Jerdan MS, Shapiro RS, Smith NB, et al: Cutaneous manifestations of Corynebacterium group JK sepsis. J Am Acad Dermatol 16:444-447, 1987

16. Chapman RA, Van Slyck EJ, Madhavan T: Skin lesions associated with E. Coli sepsis in a patient with acute leukemia. Henry Ford Hosp Med J 28:47-48, 1980

17. Dreizen S, McCredie KB, Bodey GP, et al: Unusual mucocutaneous infections in immunosuppressed patients with leukemia—expansion of an earlier study. Postgrad Med 79:287-294, 1986

18. Livingston W, Grossman ME, Garvey G: Hemorrhagic bullae in association with Enterobacter cloacae septicemia. J Am Acad Dermatol 27:637-638, 1992

19. DiGioia RA, Kane JG, Parker RH: Crepitant cellulitis and myonecrosis caused by Klebsiella. JAMA 237:2097-2098, 1977

20. Bagel J, Grossman ME: Hemorrhagic bullae associated with Morganella morganii septicemia. J Am Acad Dermatol 12:575-576, 1985

21. Bonner MJ, Meharg JG, Jr: Primary cellulitis due to Serratia marcescens. JAMA 250:2348-2349, 1983

22. Hartmann F, Gheorghiu T, Leupold H, et al: Serratia infections in patients with neutropenia. Klin Wochenschr 69:491-494, 1991

23. Blumenthal NC, Sood UR, Aronson PJ, et al: Facial ulcerations in an immunocompromised patient. Ecthyma gangrenosum. Arch Dermatol 126:529-532, 1990

24. Huminer D, Siegman-Igra Y, Morduchowicz G, et al:

Ecthyma gangrenosum without bacteremia. Report of six cases and review of the literature. Arch Intern Med 147:299-301, 1987

25. Sangeorzan JA, Bradley SF, Kauffman CA: Cutaneous manifestations of Pseudomonas infection in the acquired immunodeficiency syndrome [letter]. Arch Dermatol 126:832-833, 1990

26. Collini FJ, Spees EK, Munster A, et al: Ecthyma gangrenosum in a kidney transplant recipient with Pseudomonas septicemia. Am J Med 80:729-734, 1986

27. Bagel J, Grossman ME: Subcutaneous nodules in Pseudomonas sepsis. Am J Med 80:528-529, 1986

28. Pham BN, Aractingi S, Dombret H, et al: Xanthomonas (formerly Pseudomonas) maltophilia—induced cellulitis in a neutropenic patient [letter] [published erratum appears in Arch Dermatol 128:1378, 1992]. Arch Dermatol 128:702-704, 1992

29. Francis YF, Richman S, Hussain S, et al: Aeromonas hydrophila infection: Ecthyma gangrenosum with aplastic anemia. NY State J Med 82:1461-1464, 1982

30. Gold WL, Salit IE: Aeromonas hydrophila infections of skin and soft tissue: Report of 11 cases and review. Clin Infect Dis 16:69-74, 1993

31. Bhawan J, Gellis S, Ucci A, et al: Vesiculobullous lesions caused by cytomegalovirus infection in an immunocompromised adult. J Am Acad Dermatol 11:743-747, 1984

32. Antinori S, Galimberti L, Tadini GL, et al: Tuberculosis cutis miliaris disseminata due to multidrug-resistant Mycobacterium tuberculosis in AIDS patients. Eur J Clin Microbiol Infect Dis 14:911-914, 1995

33. Libraty DH, Byrd TF: Cutaneous miliary tuberculosis in the AIDS era: Case report and review [see comments]. Clin Infect Dis 23:706-710, 1996

34. Hudson CP, Wood R, O'Keefe EA: Cutaneous miliary tuberculosis in the AIDS era [letter; comment]. Clin Infect Dis 25:1484, 1997

35. Stack RJ, Bickley LK, Coppel IG: Miliary tuberculosis presenting as skin lesions in a patient with acquired immunodeficiency syndrome. J Am Acad Dermatol 23:1031-1035, 1990

36. Rohatgi PK, Palazzolo JV, Saini NB: Acute miliary tuberculosis of the skin in acquired immunodeficiency syndrome [see comments]. J Am Acad Dermatol 26:356-359, 1992

37. Patel R, Roberts GD, Keating MR, et al: Infections due to nontuberculous mycobacteria in kidney, heart, and liver transplant recipients. Clin Infect Dis 19:263-273, 1994

38. Stellbrink HJ, Koperski K, Albrecht H, et al: Mycobacterium kansasii infection limited to skin and lymph node in a patient with AIDS. Clin Exp Dermatol 15:457-458, 1990

39. Nandwani R, Shanson DC, Fisher M, et al: Mycobacterium kansasii scalp abscesses in an AIDS patient [letter]. J Infect 31:79-80, 1995

40. Gombert ME, Goldstein EJ, Corrado ML, et al: Disseminated Mycobacterium marinum infection after renal transplantation. Ann Intern Med 94:486-487, 1981

41. Enzenauer RJ, McKoy J, Vincent D, et al: Disseminated cutaneous and synovial Mycobacterium marinum infection in a patient with systemic lupus erythematosus. South Med J 83:471-474, 1990

42. Lambertus MW, Mathisen GE: Mycobacterium marinum infection in a patient with cryptosporidiosis and the acquired immunodeficiency syndrome. Cutis 42:38-40, 1988

43. Rusconi S, Gori A, Vago L, et al: Cutaneous infection caused by Mycobacterium gordonae in a human immunodeficiency virus-infected patient receiving antimycobacterial treatment [letter] [see comments]. Clin Infect Dis 25:1490-1491, 1997

44. Claydon EJ, Coker RJ, Harris JR: Mycobacterium malmoense infection in HIV positive patients [see comments]. J Infect 23:191-194, 1991

45. Sack JB: Disseminated infection due to Mycobacterium fortuitum in a patient with AIDS. Rev Infect Dis 12:961-963, 1990

46. Shafer RW, Sierra MF: Mycobacterium xenopi, Mycobacterium fortuitum, Mycobacterium kansasii, and other nontuberculous mycobacteria in an area of endemicity for AIDS. Clin Infect Dis 15:161-162, 1992

47. Wallace RJ, Jr, Brown BA, Onyi GO: Skin, soft tissue, and bone infections due to Mycobacterium chelonae chelonae: importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. J Infect Dis 166:405-412, 1992

48. Jopp-McKay AG, Randell P: Sporotrichoid cutaneous infection due to Mycobacterium chelonei in a renal transplant patient. Australas J Dermatol 31:105-109, 1990

49. Swetter SM, Kindel SE, Smoller BR: Cutaneous nodules of Mycobacterium chelonae in an immunosuppressed patient with preexisting pulmonary colonization. J Am Acad Dermatol 28:352-355, 1993

50. Friedman BF, Edwards D, Kirkpatrick CH: Mycobacterium avium-intracellulare: Cutaneous presentations of disseminated disease. Am J Med 85:257-263, 1988

51. Esteban J, Gorgolas M, Fernandez-Guerrero ML, et al: Localized cutaneous infection caused by Mycobacterium avium complex in an AIDS patient. Clin Exp Dermatol 21:230-231, 1996

52. Meadows JR, Carter R, Katner HP: Cutaneous Mycobacterium avium complex infection at an intramuscular injection site in a patient with AIDS. Clin Infect Dis 24:1273-1274, 1997

53. Barbaro DJ, Orcutt VL, Coldiron BM: Mycobacterium avium-Mycobacterium intracellulare infection limited to the skin and lymph nodes in patients with AIDS. Rev Infect Dis 11:625-628, 1989

54. Rogers PL, Walker RE, Lane HC, et al: Disseminated Mycobacterium haemophilum infection in two patients with the acquired immunodeficiency syndrome. Am J Med 84:640-642, 1988

55. Kristjansson M, Bieluch VM, Byeff PD: Mycobacterium haemophilum infection in immunocompromised patients: case report and review of the literature. Rev Infect Dis 13:906-910, 1991

56. Dever LL, Martin JW, Seaworth B, et al: Varied presentations and responses to treatment of infections caused by Mycobacterium haemophilum in patients with AIDS. Clin Infect Dis 14:1195-2000, 1992

57. Mycobacterium haemophilum infections—New York City metropolitan area, 1990-1991. MMWR Morb Mortal Wkly Rep 40:636-637, 643, 1991

58. Straus WL, Ostroff SM, Jernigan DB, et al: Clinical and epidemiologic characteristics of Mycobacterium haemophi-

lum, an emerging pathogen in immunocompromised patients. Ann Intern Med 120:118-125, 1994

59. Lamfers EJ, Bastiaans AH, Mravunac M, et al: Leprosy in the acquired immunodeficiency syndrome [letter]. Ann Intern Med 107:111-119, 1987

60. Meeran K: Prevalence of HIV infection among patients with leprosy and tuberculosis in rural Zambia. BMJ 298:364-365, 1989

61. Turk JL, Rees RJ: AIDS and leprosy [editorial]. Lepr Rev 59:193-194, 1988

62. Leonard G, Sangare A, Verdier M, et al: Prevalence of HIV infection among patients with leprosy in African countries and Yemen. J Acquir Immune Defic Syndr 3:1109-1113, 1990

63. Gormus BJ, Murphey-Corb M, Martin LN, et al: Interactions between simian immunodeficiency virus and Mycobacterium leprae in experimentally inoculated rhesus monkeys. J Infect Dis 160:405-413, 1989

64. Kennedy C, Lien RA, Stolz E, et al: Leprosy and human immunodeficiency virus infection. A closer look at the lesions. Int J Dermatol 29:139-140, 1990

65. Wong R, Tappero J, Cockerell CJ: Bacillary angiomatosis and other Bartonella species infections. Semin Cutan Med Surg 16:188-199, 1997

66. Koehler JE, Sanchez MA, Garrido CS, et al: Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis [see comments]. N Engl J Med 337:1876-1883, 1997

67. Koehler JE, Glaser CA, Tappero JW: Rochalimaea henselae infection. A new zoonosis with the domestic cat as reservoir [see comments]. JAMA 271:531-535, 1994

68. Schwartz RA, Nychay SG, Janniger CK, et al: Bacillary angiomatosis: Presentation of six patients, some with unusual features. Br J Dermatol 136:60-65, 1997

69. Perkocha LA, Geaghan SM, Yen TS, et al: Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection [see comments]. N Engl J Med 323:1581-1586, 1990

70. Tompkins LS: Of cats, humans, and Bartonella [editorial; comment]. N Engl J Med 337:1916-1917, 1997

71. Nishimoto K, Ohno M: Subcutaneous abscesses caused by Nocardia brasiliensis complicated by malignant lymphoma. A survey of cutaneous nocardiosis reported in Japan. Int J Dermatol 24:437-440, 1985

72. Moeller CA, Burton CSD: Primary lymphocutaneous Nocardia brasiliensis infection. Arch Dermatol 122:1180-1182, 1986

73. Kalb RE, Kaplan MH, Grossman ME: Cutaneous nocardiosis. Case reports and review. J Am Acad Dermatol 13:125-133, 1985

74. Shapiro PE, Grossman ME: Disseminated Nocardia asteroides with pustules. J Am Acad Dermatol 20:889-892, 1989

75. Christoph I: Pulmonary Cryptococcus neoformans and disseminated Nocardia brasiliensis in an immunocompromised host. Case report. N C Med J 51:219-220, 1990

76. Hodohara K, Fujiyama Y, Hiramitu Y, et al: Disseminated subcutaneous Nocardia asteroides abscesses in a patient after bone marrow transplantation. Bone Marrow Transplant 11:341-343, 1993

77. Javaly K, Horowitz HW, Wormser GP: Nocardiosis in patients with human immunodeficiency virus infection. Report of 2 cases and review of the literature. Medicine (Baltimore) 71:128-138, 1992

78. Shelkovitz-Shilo I, Feinstein A, Trau H, et al: Lymphocutaneous nocardiosis due to Nocardia asteroides in a patient with intestinal lymphoma. Int J Dermatol 31:178-179, 1992

79. Yang LJ, Chan HL, Chen WJ, et al: Lymphocutaneous nocardiosis caused by Nocardia caviae: The first case report from Asia. J Am Acad Dermatol 29:639-641, 1993

80. Almeida L, Grossman M: Widespread dermatophyte infections that mimic collagen vascular disease. J Am Acad Dermatol 23:855-857, 1990

81. Elewski BE, Sullivan J: Dermatophytes as opportunistic pathogens. J Am Acad Dermatol 30:1021-1022, 1994

82. Sequeira M, Burdick AE, Elgart GW, et al: New-onset Majocchi's granuloma in two kidney transplant recipients under tacrolimus treatment. J Am Acad Dermatol 38:486-488, 1998

83. Squeo RF, Beer R, Silvers D, et al: Invasive Trichophyton rubrum resembling blastomycosis infection in the immunocompromised host. J Am Acad Dermatol 39:379-380, 1998

84. Demidovich CW, Kornfeld BW, Gentry RH, et al: Deep dermatophyte infection with chronic draining nodules in an immunocompromised patient. Cutis 55:237-240, 1995

85. Novick NL, Tapia L, Bottone EJ: Invasive trichophyton rubrum infection in an immunocompromised host. Case report and review of the literature. Am J Med 82:321-325, 1987

86. Maor MH: Dermatophytosis confined to irradiated skin. A case report [letter]. Int J Radiat Oncol Biol Phys 14:825-826, 1988

87. Wright DC, Lennox JL, James WD, et al: Generalized chronic dermatophytosis in patients with human immunodeficiency virus type I infection and CD4 depletion [letter]. Arch Dermatol 127:265-266, 1991

88. Bufill JA, Lum LG, Caya JG, et al: Pityrosporum folliculitis after bone marrow transplantation. Clinical observations in five patients. Ann Intern Med 108:560-563, 1988

89. Yohn JJ, Lucas J, Camisa C: Malassezia folliculitis in immunocompromised patients. Cutis 35:536-538, 1985

90. Klotz SA, Drutz DJ, Huppert M, et al: Pityrosporum folliculitis. Its potential for confusion with skin lesions of systemic candidiasis. Arch Intern Med 142:2126-2129, 1982

91. Gottlieb MS, Schroff R, Schanker HM, et al: Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: Evidence of a new acquired cellular immunodeficiency. N Engl J Med 305:1425-1431, 1981

92. Imam N, Carpenter CC, Mayer KH, et al: Hierarchical pattern of mucosal candida infections in HIV-seropositive women [see comments]. Am J Med 89:142-146, 1990

93. Carlin EM, Hannan M, Walsh J, et al: Nasopharyngeal flora in HIV seropositive men who have sex with men. Genitourin Med 73:477-480, 1997

94. McNeil J, Kan V: Oral yeast colonization of HIV-infected outpatients [letter]. AIDS 9:301-302, 1995

95. Lifson AR, Hilton JF, Westenhouse JL, et al: Time from HIV seroconversion to oral candidiasis or hairy leukoplakia among homosexual and bisexual men enrolled in three prospective cohorts. AIDS 8:73-79, 1994

96. Decker CF, Tiernan R, Paparello SF: Esophageal candidiasis associated with acute infection due to human immuno-

deficiency virus [letter; comment]. Clin Infect Dis 14:791, 1992

97. Prose NS: HIV infection in children. J Am Acad Dermatol 22:1223-1231, 1990

98. Walsh TJ, Gonzalez C, Roilides E, et al: Fungemia in children infected with the human immunodeficiency virus: New epidemiologic patterns, emerging pathogens, and improved outcome with antifungal therapy. Clin Infect Dis 20:900-906, 1995

99. MacPhail LA, Hilton JF, Dodd CL, et al: Prophylaxis with nystatin pastilles for HIV-associated oral candidiasis. J Acquir Immune Defic Syndr Hum Retrovirol 12:470-476, 1996

100. Graybill JR, Vazquez J, Darouiche RO, et al: Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. Am J Med 104:33-39, 1998

101. Nandwani R, Parnell A, Youle M, et al: Use of terbinafine in HIV-positive subjects: Pilot studies in onychomycosis and oral candidiasis. Br J Dermatol 134:22-24, 1996 (suppl 46, discussion 39)

102. Laguna F, Rodriguez-Tudela JL, Martinez-Suarez JV, et al: Patterns of fluconazol susceptibility in isolates from human immunodeficiency virus-infected patients with oropharyngeal candidiasis due to Candida albicans. Clin Infect Dis 24:124-130, 1997

103. Maenza JR, Merz WG, Romagnoli MJ, et al: Infection due to fluconazole-resistant Candida in patients with AIDS: Prevalence and microbiology. Clin Infect Dis 24:28-34, 1997

104. Powderly WG, Finkelstein D, Feinberg J, et al: A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group [see comments]. N Engl J Med 332:700-705, 1995

105. Schuman P, Capps L, Peng G, et al: Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS [see comments]. Ann Intern Med 126:689-696, 1997

106. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al: Penicillium marneffei infection in patients infected with human immunodeficiency virus [see comments]. Clin Infect Dis 14:871-874, 1992

107. Diamond RD: The growing problem of mycoses in patients infected with the human immunodeficiency virus. Rev Infect Dis 13:480-486, 1991

108. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al: Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. Medicine (Baltimore) 69:361-374, 1990

109. Rico MJ, Penneys NS: Cutaneous cryptococcosis resembling molluscum contagiosum in a patient with AIDS. Arch Dermatol 121:901-902, 1985

110. Picon L, Vaillant L, Duong T, et al: Cutaneous cryptococcosis resembling molluscum contagiosum: A first manifestation of AIDS. Acta Derm Venereol 69:365-367, 1989

111. Cohen PR, Bank DE, Silvers DN, et al: Cutaneous lesions of disseminated histoplasmosis in human immunodeficiency virus-infected patients. J Am Acad Dermatol 23:422-428, 1990

112. Wingard JR, Merz WG, Saral R: Candida tropicalis: A major pathogen in immunocompromised patients. Ann Intern Med 91:539-543, 1979

113. Bodey GP, Luna M: Skin lesions associated with disseminated candidiasis. JAMA 229:1466-1468, 1974

114. Grossman ME, Silvers DN, Walther RR: Cutaneous manifestations of disseminated candidiasis. J Am Acad Dermatol 2:111-116, 1980

115. File TM, Jr, Marina OA, Flowers FP: Necrotic skin lesions associated with disseminated candidiasis. Arch Dermatol 115:214-215, 1979

116. Fine JD, Miller JA, Harrist TJ, et al: Cutaneous lesions in disseminated candidiasis mimicking ecthyma gangrenosum. Am J Med 70:1133-1135, 1981

117. Benson PM, Roth RR, Hicks CB: Nodular subcutaneous abscesses caused by Candida tropicalis [letter]. J Am Acad Dermatol 16:623-624, 1987

118. Collignon PJ, Sorrell TC: Disseminated candidiasis: Evidence of a distinctive syndrome in heroin abusers. Br Med J (Clin Res Ed) 287:861-862, 1983

119. Jarowski CI, Fialk MA, Murray HW, et al: Fever, rash, and muscle tenderness. A distinctive clinical presentation of disseminated candidiasis. Arch Intern Med 138:544-546, 1978

120. Marcus J, Grossman ME, Yunakov MJ, et al: Disseminated candidiasis, Candida arthritis, and unilateral skin lesions. J Am Acad Dermatol 26:295-297, 1992

121. Held JL, Berkowitz RK, Grossman ME: Use of touch preparation for rapid diagnosis of disseminated candidiasis. J Am Acad Dermatol 19:1063-1066, 1988

122. Currie BP, Casadevall A: Estimation of the prevalence of cryptococcal infection among patients infected with the human immunodeficiency virus in New York City. Clin Infect Dis 19:1029-1033, 1994

123. Dromer F, Mathoulin S, Dupont B, et al: Epidemiology of cryptococcosis in France: A 9-year survey (1985-1993). French Cryptococcosis Study Group. Clin Infect Dis 23:82-90, 1996

124. Murakawa GJ, Kerschmann R, Berger T: Cutaneous Cryptococcus infection and AIDS. Report of 12 cases and review of the literature. Arch Dermatol 132:545-548, 1996

125. Anderson DJ, Schmidt C, Goodman J, et al: Cryptococcal disease presenting as cellulitis [see comments]. Clin Infect Dis 14:666-672, 1992

126. Manfredi R, Mazzoni A, Nanetti A, et al: Morphologic features and clinical significance of skin involvement in patients with AIDS-related cryptococcosis. Acta Derm Venereol 76:72-74, 1996

127. Dimino-Emme L, Gurevitch AW: Cutaneous manifestations of disseminated cryptococcosis. J Am Acad Dermatol 32:844-850, 1995

128. Hall JC, Brewer JH, Crouch TT, et al: Cryptococcal cellulitis with multiple sites of involvement. J Am Acad Dermatol 17:329-332, 1987

129. Goldman M, Pottage JC, Jr: Cryptococcal infection of the breast. Clin Infect Dis 21:1166-1169, 1995

130. Shuttleworth D, Philpot CM, Knight AG: Cutaneous cryptococcosis: Treatment with oral fluconazole. Br J Dermatol 120:683-687, 1989

131. Cusini M, Cagliani P, Grimalt R, et al: Primary

cutaneous cryptococcosis in a patient with the acquired immunodeficiency syndrome [letter]. Arch Dermatol 127: 1848-1849, 1991

132. Antony SA, Antony SJ: Primary cutaneous Cryptococcus in nonimmunocompromised patients. Cutis 56:96-98, 1995

133. Hunt SJ, Nagi C, Gross KG, et al: Primary cutaneous aspergillosis near central venous catheters in patients with the acquired immunodeficiency syndrome. Arch Dermatol 128: 1229-1232, 1992

134. Allo MD, Miller J, Townsend T, et al: Primary cutaneous aspergillosis associated with Hickman intravenous catheters. N Engl J Med 317:1105-1108, 1987

135. Arikan S, Uzun O, Cetinkaya Y, et al: Primary cutaneous aspergillosis in human immunodeficiency virus-infected patients: two cases and review [see comments]. Clin Infect Dis 27:641-643, 1988

136. Thakur BK, Bernardi DM, Murali MR, et al: Invasive cutaneous aspergillosis complicating immunosuppressive therapy for recalcitrant pemphigus vulgaris. J Am Acad Dermatol 38:488-490, 1998

137. Pursell KJ, Telzak EE, Armstrong D: Aspergillus species colonization and invasive disease in patients with AIDS. Clin Infect Dis 14:141-148, 1992

138. Oscherwitz SL, Rinaldi MG: Disseminated sporotrichosis in a patient infected with human immunodeficiency virus [letter]. Clin Infect Dis 15:568-569, 1992

139. Dong JA, Chren MM, Elewski BE: Bonsai tree: Risk factor for disseminated sporotrichosis. J Am Acad Dermatol 33:839-840, 1995

140. Heller HM, Fuhrer J: Disseminated sporotrichosis in patients with AIDS: Case report and review of the literature. AIDS 5:1243-1246, 1991

141. Girmenia C, Iori AP, Boecklin F, et al: Fusarium infections in patients with severe aplastic anemia: Review and implications for management. Haematologica 84:114-118, 1999

142. Girmenia C, Arcese W, Micozzi A, et al: Onychomycosis as a possible origin of disseminated Fusarium solani infection in a patient with severe aplastic anemia [letter]. Clin Infect Dis 14:1167, 1992

143. June CH, Beatty PG, Shulman HM, et al: Disseminated Fusarium moniliforme infection after allogeneic marrow transplantation. South Med J 79:513-515, 1986

144. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, et al: Case-control study of risk factors for Penicillium marneffei infection in human immunodeficiency virus-infected patients in northern Thailand. Clin Infect Dis 24:1080-1086, 1997

145. Duong TA: Infection due to Penicillium marneffei, an emerging pathogen: Review of 155 reported cases [see comments]. Clin Infect Dis 23:125-130, 1996

146. Supparatpinyo K, Khamwan C, Baosoung V, et al: Disseminated Penicillium marneffei infection in southeast Asia. Lancet 344:110-113, 1994

147. Butka BJ, Bennett SR, Johnson AC: Disseminated inoculation blastomycosis in a renal transplant recipient. Am Rev Respir Dis 130:1180-1183, 1984

148. Pappas PG: Blastomycosis in the immunocompromised patient. Semin Respir Infect 12:243-251, 1997

149. Pappas PG, Threlkeld MG, Bedsole GD, et al: Blastomycosis in immunocompromised patients. Medicine (Baltimore) 72:311-325, 1993

150. Prichard JG, Sorotzkin RA, James RED: Cutaneous manifestations of disseminated coccidioidomycosis in the acquired immunodeficiency syndrome. Cutis 39:203-205, 1987

151. Vartivarian SE, Coudron PE, Markowitz SM: Disseminated coccidioidomycosis. Unusual manifestations in a cardiac transplantation patient. Am J Med 83:949-952, 1987

152. McKinsey DS, Spiegel RA, Hutwagner L, et al: Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: Incidence, risk factors, and pathophysiology. Clin Infect Dis 24:1195-1203, 1997

153. Carme B, Ngaporo AI, Ngolet A, Ibara JR, Ebikili B: Disseminated African histoplasmosis in a Congolese patient with AIDS. J Med Vet Mycol 30:245-248, 1992

154. Bellman B, Berman B, Sasken H, et al: Cutaneous disseminated histoplasmosis in AIDS patients in south Florida. Int J Dermatol 36:599-603, 1997

155. Eisig S, Boguslaw B, Cooperband B, et al: Oral manifestations of disseminated histoplasmosis in acquired immunodeficiency syndrome: Report of two cases and review of the literature. J Oral Maxillofac Surg 49:310-313, 1991

156. Kaplan LJ, Daum RS, Smaron M, et al: Severe measles in immunocompromised patients. JAMA 267:1237-1241, 1992

157. Krasinski K, Borkowsky W: Measles and measles immunity in children infected with human immunodeficiency virus. JAMA 261:2512-2516, 1989

158. Markowitz LE, Chandler FW, Roldan EO, et al: Fatal measles pneumonia without rash in a child with AIDS. J Infect Dis 158:480-483, 1988

159. McNutt NS, Kindel S, Lugo J: Cutaneous manifestations of measles in AIDS. J Cutan Pathol 19:315-324, 1992

160. Horn TD, Hood AF: Cytomegalovirus is predictably present in perineal ulcers from immunosuppressed patients. Arch Dermatol 126:642-644, 1990

161. Stewart JA, Reef SE, Pellett PE, et al: Herpesvirus infections in persons infected with human immunodeficiency virus. Clin Infect Dis 21:S114-S120, 1995 (suppl 1)

162. Keiser P, Jockus J, Horton H, et al: Prednisone therapy is not associated with increased risk of herpetic infections in patients infected with human immunodeficiency virus. Clin Infect Dis 23:201-202, 1996

163. Masessa JM, Grossman ME, Knobler EH, et al: Kaposi's varicelliform eruption in cutaneous T cell lymphoma. J Am Acad Dermatol 21:133-135, 1989

164. Siegal FP, Lopez C, Hammer GS, et al: Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. N Engl J Med 305:1439-1444, 1981

165. Hook EWD, Cannon RO, Nahmias AJ, et al: Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals [see comments]. J Infect Dis 165:251-255, 1992

166. Fleming DT, McQuillan GM, Johnson RE, et al: Herpes simplex virus type 2 in the United States, 1976 to 1994 [see comments]. N Engl J Med 337:1105-1111, 1997

167. Mole L, Ripich S, Margolis D, et al: The impact of active herpes simplex virus infection on human immunodeficiency virus load. J Infect Dis 176:766-770, 1997

168. Torres RA, Neaton JD, Wentworth DN, et al: Acyclovir

use and survival among human immunodeficiency virus-infected patients with CD4 cell counts of 500/mm3. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Clin Infect Dis 26:85-90, 1998

169. Pannuti CS, Cristina M, Finck DS, et al: Asymptomatic perianal shedding of herpes simplex virus in patients with acquired immunodeficiency syndrome. Arch Dermatol 133: 180-183, 1997

170. Burgoyne M, Burke W: Atypical herpes simplex infection in patients with acute myelogenous leukemia recovering from chemotherapy. J Am Acad Dermatol 20:1125-1126, 1989

171. Kalb RE, Grossman ME: Chronic perianal herpes simplex in immunocompromised hosts. Am J Med 80:486-490, 1986

172. Toback AC, Grossman ME: Chronic intraoral herpes simplex infection in renal transplant recipients. Transplant Proc 18:966-969, 1986

173. Grossman ME, Stevens AW, Cohen PR: Brief report: Herpetic geometric glossitis [see comments]. N Engl J Med 329:1859-1860, 1993

174. Zuretti AR, Schwartz IS: Gangrenous herpetic whitlow in a human immunodeficiency virus-positive patient. Am J Clin Pathol 93:828-830, 1990

175. Weaver G, Kostman JR: Inoculation herpes simplex virus infections in patients with AIDS: Unusual appearance and location of lesions. Clin Infect Dis 22:141-142, 1996

176. Norris SA, Kessler HA, Fife KH: Severe, progressive herpetic whitlow caused by an acyclovir-resistant virus in a patient with AIDS [letter]. J Infect Dis 157:209-210, 1988

177. Genereau T, Lortholary O, Bouchaud O, et al: Herpes simplex esophagitis in patients with AIDS: Report of 34 cases. The Cooperative Study Group on Herpetic Esophagitis in HIV Infection. Clin Infect Dis 22:926-931, 1996

178. Stone WJ, Scowden EB, Spannuth CL, et al: Atypical herpesvirus hominis type 2 infection in uremic patients receiving immunosuppressive therapy. Am J Med 63:511-516, 1977

179. Nahass GT, Mandel MJ, Cook S, et al: Detection of herpes simplex and varicella-zoster infection from cutaneous lesions in different clinical stages with the polymerase chain reaction. J Am Acad Dermatol 32:730-733, 1995

180. Schacker T, Hu HL, Koelle DM, et al: Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. Ann Intern Med 128:21-28, 1998

181. Lalezari J, Schacker T, Feinberg J, et al: A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. J Infect Dis 176:892-898, 1997

182. McNamara MP, LaCrosse S, Piering WF, et al: Exogenous reinfection with varicella-zoster virus [letter]. N Engl J Med 317:511, 1987

183. Rusthoven JJ, Ahlgren P, Elhakim T, et al: Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med 148:1561-1566, 1988

184. Kelley R, Mancao M, Lee F, et al: Varicella in children with perinatally acquired human immunodeficiency virus infection. J Pediatr 124:271-273, 1994

185. Baran J, Jr, Khatib R: Recrudescence of initial cutaneous lesions after crusting of chickenpox in an adult with advanced AIDS suggests prolonged local viral persistence. Clin Infect Dis 24:741-742, 1997

186. Leibovitz E, Cooper D, Giurgiutiu D, et al: Varicella-zoster virus infection in Romanian children infected with the human immunodeficiency virus. Pediatrics 92:838-842, 1993

187. Gershon AA, Mervish N, LaRussa P, et al: Varicella-zoster virus infection in children with underlying human immunodeficiency virus infection. J Infect Dis 176:1496-5000, 1997

188. von Seidlein L, Gillette SG, Bryson Y, et al: Frequent recurrence and persistence of varicella-zoster virus infections in children infected with human immunodeficiency virus type 1. J Pediatr 128:52-57, 1996

189. Gulick RM, Heath-Chiozzi M, Crumpacker CS: Varicella-zoster virus disease in patients with human immunodeficiency virus infection [comment]. Arch Dermatol 126:1086-1088, 1990

190. Colebunders R, Mann JM, Francis H, et al: Herpes zoster in African patients: A clinical predictor of human immunodeficiency virus infection. J Infect Dis 157:314-318, 1988

191. Friedman-Kien AE, Lafleur FL, Gendler E, et al: Herpes zoster: A possible early clinical sign for development of acquired immunodeficiency syndrome in high-risk individuals. J Am Acad Dermatol 14:1023-1028, 1986

192. Melbye M, Grossman RJ, Goedert JJ, et al: Risk of AIDS after herpes zoster. Lancet 1:728-731, 1987

193. Dolin R, Reichman RC, Mazur MH, et al: NIH conference. Herpes zoster-varicella infections in immunosuppressed patients. Ann Intern Med 89:375-388, 1978

194. Feld R, Evans WK, DeBoer G: Herpes zoster in patients with small-cell carcinoma of the lung receiving combined modality treatment. Ann Intern Med 93:282-283, 1980

195. Hoppenjans WB, Bibler MR, Orme RL, et al: Prolonged cutaneous herpes zoster in acquired immunodeficiency syndrome [see comments]. Arch Dermatol 126:1048-1050, 1990

196. Gilson IH, Barnett JH, Conant MA, et al: Disseminated ecthymatous herpes varicella-zoster virus infection in patients with acquired immunodeficiency syndrome. J Am Acad Dermatol 20:637-642, 1989

197. Leibovitz E, Kaul A, Rigaud M, et al: Chronic varicella zoster in a child infected with human immunodeficiency virus: case report and review of the literature. Cutis 49:27-31, 1992

198. LeBoit PE, Limova M, Yen TS, et al: Chronic verrucous varicella-zoster virus infection in patients with the acquired immunodeficiency syndrome (AIDS). Histologic and molecular biologic findings. Am J Dermatopathol 14:1-7, 1992

199. Alliegro MB, Dorrucci M, Pezzotti P, et al: Herpes zoster and progression to AIDS in a cohort of individuals who seroconverted to human immunodeficiency virus. Italian HIV Seroconversion Study. Clin Infect Dis 23:990-995, 1996

200. Tyndall MW, Nasio J, Agoki E, et al: Herpes zoster as the initial presentation of human immunodeficiency virus type 1 infection in Kenya. Clin Infect Dis 21:1035-1037, 1995

201. Bayu S, Alemayehu W: Clinical profile of herpes zoster ophthalmicus in Ethiopians. Clin Infect Dis 24:1256-1260, 1997

202. McNulty A, Li Y, Radtke U, et al: Herpes zoster and the stage and prognosis of HIV-1 infection. Genitourin Med 73:467-470, 1997

203. Glesby MJ, Moore RD, Chaisson RE: Herpes zoster in patients with advanced human immunodeficiency virus infection treated with zidovudine. Zidovudine Epidemiology Study Group. J Infect Dis 168:1264-1268, 1993

204. Buchbinder SP, Katz MH, Hessol NA, et al: Herpes zoster and human immunodeficiency virus infection [see comments]. J Infect Dis 166:1153-1156, 1992

205. Veenstra J, Krol A, van Praag RM, et al: Herpes zoster, immunological deterioration and disease progression in HIV-1 infection. AIDS 9:1153-1158, 1995

206. Tsao H, Tahan SR, Johnson RA: Chronic varicella zoster infection mimicking a basal cell carcinoma in an AIDS patient. J Am Acad Dermatol 36:831-833, 1997

207. Nikkels AF, Rentier B, Pierard GE: Chronic varicella-zoster virus skin lesions in patients with human immunodeficiency virus are related to decreased expression of gE and gB. J Infect Dis 176:261-264, 1997

208. Batisse D, Eliaszewicz M, Zazoun L, et al: Acute retinal necrosis in the course of AIDS: study of 26 cases [see comments]. AIDS 10:55-60, 1996

209. Galindez OA, Sabates NR, Whitacre MM, et al: Rapidly progressive outer retinal necrosis caused by varicella zoster virus in a patient infected with human immunodeficiency virus. Clin Infect Dis 22:149-151, 1996

210. Manian FA, Kindred M, Fulling KH: Chronic varicella-zoster virus myelitis without cutaneous eruption in a patient with AIDS: Report of a fatal case. Clin Infect Dis 21:986-988, 1995

211. Lionnet F, Pulik M, Genet P, et al: Myelitis due to varicella-zoster virus in two patients with AIDS: Successful treatment with acyclovir. Clin Infect Dis 22:138-140, 1996

212. Kestelyn P, Stevens AM, Bakkers E, et al: Severe herpes zoster ophthalmicus in young African adults: A marker for HTLV-III seropositivity. Br J Ophthalmol 71:806-809, 1987

213. Shuler JD, Engstrom RE, Jr, Holland GN: External ocular disease and anterior segment disorders associated with AIDS. Int Ophthalmol Clin 29:98-104, 1989

214. Seiff SR, Margolis T, Graham SH, et al: Use of intravenous acyclovir for treatment of herpes zoster ophthalmicus in patients at risk for AIDS. Ann Ophthalmol 20:480-482, 1988

215. Rostad SW, Olson K, McDougall J, et al: Transsynaptic spread of varicella zoster virus through the visual system: A mechanism of viral dissemination in the central nervous system [published erratum appears in Hum Pathol 20:820, 1989]. Hum Pathol 20:174-179, 1989

216. Ryder JW, Croen K, Kleinschmidt-DeMasters BK, et al: Progressive encephalitis three months after resolution of cutaneous zoster in a patient with AIDS. Ann Neurol 19:182-188, 1986

217. Cohen PR, Grossman ME: Clinical features of human immunodeficiency virus-associated disseminated herpes zoster virus infection—a review of the literature. Clin Exp Dermatol 14:273-276, 1989

218. Disler RS, Dover JS: Chronic localized herpes zoster in the acquired immunodeficiency syndrome [letter] [see comments]. Arch Dermatol 126:1105-1106, 1990

219. Janier M, Hillion B, Baccard M, et al: Chronic varicella zoster infection in acquired immunodeficiency syndrome [letter]. J Am Acad Dermatol 18:584-585, 1988

220. Langenberg A, Yen TS, LeBoit PE: Granulomatous vasculitis occurring after cutaneous herpes zoster despite absence of viral genome. J Am Acad Dermatol 24:429-433, 1991

221. Safrin S, Berger TG, Gilson I, et al: Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. Ann Intern Med 115:19-21, 1991

222. Safrin S, Assaykeen T, Follansbee S, et al: Foscarnet therapy for acyclovir-resistant mucocutaneous herpes simplex virus infection in 26 AIDS patients: Preliminary data. J Infect Dis 161:1078-1084, 1990

223. Greenspan D, Greenspan JS, Hearst NG, et al: Relation of oral hairy leukoplakia to infection with the human immunodeficiency virus and the risk of developing AIDS. J Infect Dis 155:475-481, 1987

224. Greenspan D, Greenspan JS: Oral manifestations of HIV infection. Dermatol Clin 9:517-522, 1991

225. Webster-Cyriaque J, Edwards RH, Quinlivan EB, et al: Epstein-Barr virus and human herpesvirus 8 prevalence in human immunodeficiency virus-associated oral mucosal lesions. J Infect Dis 175:1324-1332, 1997

226. Triantos D, Porter SR, Scully C, et al: Oral hairy leukoplakia: Clinicopathologic features, pathogenesis, diagnosis, and clinical significance. Clin Infect Dis 25:1392-1396, 1997

227. Shiboski CH, Hilton JF, Neuhaus JM, et al: Human immunodeficiency virus-related oral manifestations and gender. A longitudinal analysis. The University of California, San Francisco Oral AIDS Center Epidemiology Collaborative Group. Arch Intern Med 156:2249-2254, 1996

228. Shiboski CH, Hilton JF, Greenspan D, et al: HIV-related oral manifestations in two cohorts of women in San Francisco. J Acquir Immune Defic Syndr 7:964-971, 1994

229. Greenspan D, Greenspan JS, Overby G, et al: Risk factors for rapid progression from hairy leukoplakia to AIDS: A nested case-control study. J Acquir Immune Defic Syndr 4:652-658, 1991

230. Husak R, Garbe C, Orfanos CE: Oral hairy leukoplakia in 71 HIV-seropositive patients: Clinical symptoms, relation to immunologic status, and prognostic significance [see comments]. J Am Acad Dermatol 35:928-934, 1996

231. Alessi E, Berti E, Cusini M, et al: Oral hairy leukoplakia [see comments]. J Am Acad Dermatol 22:79-86, 1990

232. McGregor JM, Yu CC, Lu QL, et al: Posttransplant cutaneous lymphoma. J Am Acad Dermatol 29:549-554, 1993

233. Gallant JE, Moore RD, Richman DD, et al: Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group [see comments]. J Infect Dis 166:1223-1227, 1992

234. Heinemann MH: Characteristics of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Am J Med 92:12S-16S, 1992

235. Pariser RJ: Histologically specific skin lesions in disseminated cytomegalovirus infection. J Am Acad Dermatol 9:937-946, 1983

236. Patterson JW, Broecker AH, Kornstein MJ, et al: Cutaneous cytomegalovirus infection in a liver transplant

patient. Diagnosis by in situ DNA hybridization. Am J Dermatopathol 10:524-530, 1988

237. Curtis JL, Egbert BM: Cutaneous cytomegalovirus vasculitis: An unusual clinical presentation of a common opportunistic pathogen. Hum Pathol 13:1138-1141, 1982

238. Walker JD, Chesney TM: Cytomegalovirus infection of the skin. Am J Dermatopathol 4:263-265, 1982

239. Swanson S, Feldman PS: Cytomegalovirus infection initially diagnosed by skin biopsy. Am J Clin Pathol 87:113-116, 1987

240. Friedman-Kien AE, Saltzman BR: Clinical manifestations of classical, endemic African, and epidemic AIDS-associated Kaposi's sarcoma. J Am Acad Dermatol 22:1237-1250, 1990

241. Boudreaux AA, Smith LL, Cosby CD, et al: Intralesional vinblastine for cutaneous Kaposi's sarcoma associated with acquired immunodeficiency syndrome. A clinical trial to evaluate efficacy and discomfort associated with infection. J Am Acad Dermatol 28:61-65, 1993

242. Tappero JW, Berger TG, Kaplan LD, et al: Cryotherapy for cutaneous Kaposi's sarcoma (KS) associated with acquired immune deficiency syndrome (AIDS): A phase II trial. J Acquir Immune Defic Syndr 4:839-846, 1991

243. Morfeldt L, Torssander J: Long-term remission of Kaposi's sarcoma following foscarnet treatment in HIV-infected patients. Scand J Infect Dis 26:749-752, 1994

244. Hammoud Z, Parenti DM, Simon GL: Abatement of cutaneous Kaposi's sarcoma associated with cidofovir treatment [see comments]. Clin Infect Dis 26:1233, 1998

245. Weinberg JM, Mysliwiec A, Turiansky GW, et al: Viral folliculitis. Atypical presentations of herpes simplex, herpes zoster, and molluscum contagiosum [see comments]. Arch Dermatol 133:983-986, 1997

246. Myskowski PL: Molluscum contagiosum. New insights, new directions [editorial; comment]. Arch Dermatol 133:1039-1041, 1997

247. Pauly CR, Artis WM, Jones HE: Atopic dermatitis, impaired cellular immunity, and molluscum contagiosum. Arch Dermatol 114:391-393, 1978

248. Ganpule M, Garretts M: Molluscum contagiosum and sarcoidosis: Report of a case. Br J Dermatol 85:587-589, 1971

249. Rosenberg EW, Yusk JW: Molluscum contagiosum. Eruption following treatment with prednisone and methotrexate. Arch Dermatol 101:439-441, 1970

250. Redfield RR, James WD, Wright DC, et al: Severe molluscum contagiosum infection in a patient with human T cell lymphotrophic (HTLV-III) disease. J Am Acad Dermatol 13:821-824, 1985

251. Cotton DW, Cooper C, Barrett DF, et al: Severe atypical molluscum contagiosum infection in an immunocompromised host. Br J Dermatol 116:871-876, 1987

252. Koopman RJ, van Merrienboer FC, Vreden SG, et al: Molluscum contagiosum; a marker for advanced HIV infection [letter]. Br J Dermatol 126:528-529, 1992

253. Smith KJ, Skelton HGD, Yeager J, et al: Molluscum contagiosum. Ultrastructural evidence for its presence in skin adjacent to clinical lesions in patients infected with human immunodeficiency virus type 1. Military Medical Consortium for Applied Retroviral Research [see comments]. Arch Dermatol 128:223-227, 1992

254. Smith KJ, Yeager J, Skelton H: Molluscum contagiosum: Its clinical, histopathologic, and immunohistochemical spectrum. Int J Dermatol 38:664-672, 1999

255. Hicks CB, Myers SA, Giner J: Resolution of intractable molluscum contagiosum in a human immunodeficiency virus-infected patient after institution of antiretroviral therapy with ritonavir. Clin Infect Dis 24:1023-1025, 1997

256. Meadows KP, Tyring SK, Pavia AT, et al: Resolution of recalcitrant molluscum contagiosum virus lesions in human immunodeficiency virus-infected patients treated with cidofovir [see comments]. Arch Dermatol 133:987-990, 1997

257. Cohen LM, Tyring SK, Rady P, et al: Human papillomavirus type 11 in multiple squamous cell carcinomas in a patient with subacute cutaneous lupus erythematosus. J Am Acad Dermatol 26:840-845, 1992

258. Viac J, Chardonnet Y, Euvrard S, et al: Langerhans cells, inflammation markers and human papillomavirus infections in benign and malignant epithelial tumors from transplant recipients. J Dermatol 19:67-77, 1992

259. Sun XW, Kuhn L, Ellerbrock TV, et al: Human papillomavirus infection in women infected with the human immunodeficiency virus [see comments]. N Engl J Med 337:1343-1349, 1997

260. Sun XW, Ellerbrock TV, Lungu O, et al: Human papillomavirus infection in human immunodeficiency virus-seropositive women. Obstet Gynecol 85:680-686, 1995

261. Hillemanns P, Ellerbrock TV, McPhillips S, et al: Prevalence of anal human papillomavirus infection and anal cytologic abnormalities in HIV-seropositive women. Aids 10:1641-1647, 1996

262. Chiasson MA, Ellerbrock TV, Bush TJ, et al: Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with the human immunodeficiency virus. Obstet Gynecol 89:690-694, 1997

263. Hagensee ME, Kiviat N, Critchlow CW, et al: Seroprevalence of human papillomavirus types 6 and 16 capsid antibodies in homosexual men. J Infect Dis 176:625-631, 1997

264. Palefsky JM, Holly EA, Ralston ML, et al: Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis 177:361-367, 1998

265. Kiviat NB, Critchlow CW, Holmes KK, et al: Association of anal dysplasia and human papillomavirus with immunosuppression and HIV infection among homosexual men. AIDS 7:43-49, 1993

266. Chopra KF, Tyring SK: The impact of the human immunodeficiency virus on the human papillomavirus epidemic. Arch Dermatol 133:629-633, 1997

267. Palefsky JM, Shiboski S, Moss A: Risk factors for anal human papillomavirus infection and anal cytologic abnormalities in HIV-positive and HIV-negative homosexual men. J Acquir Immune Defic Syndr 7:599-606, 1994

268. Maiman M, Fruchter RG, Guy L, et al: Human immunodeficiency virus infection and invasive cervical carcinoma. Cancer 71:402-406, 1993

269. Palefsky JM: Anal human papillomavirus infection and anal cancer in HIV-positive individuals: An emerging problem [editorial]. AIDS 8:283-295, 1994

270. Carter PS, de Ruiter A, Whatrup C, et al: Human immunodeficiency virus infection and genital warts as risk

factors for anal intraepithelial neoplasia in homosexual men. Br J Surg 82:473-474, 1995

271. Fader DJ, Stoler MH, Anderson TF: Isolated extragenital HPV-thirties-group-positive bowenoid papulosis in an AIDS patient. Br J Dermatol 131:577-580, 1994

272. Tosti A, La Placa M, Fanti PA, et al: Human papillomavirus type 16-associated periungual squamous cell carcinoma in a patient with acquired immunodeficiency syndrome [letter]. Acta Derm Venereol 74:478-499, 1994

273. Palefsky JM, Holly EA, Hogeboom CJ, et al: Anal cytology as a screening tool for anal squamous intraepithelial lesions. J Acquir Immune Defic Syndr Hum Retrovirol 14:415-422, 1997

274. Critchlow CW, Holmes KK, Wood R, et al: Association of human immunodeficiency virus and anal human papillomavirus infection among homosexual men. Arch Intern Med 152:1673-1676, 1992

275. Schrager LK, Friedland GH, Maude D, et al: Cervical and vaginal squamous cell abnormalities in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr 2:570-575, 1989

276. Feingold AR, Vermund SH, Burk RD, et al: Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr 3:896-903, 1990

277. Berger TG, Sawchuk WS, Leonardi C, et al: Epidermodysplasia verruciformis-associated papillomavirus infection complicating human immunodeficiency virus disease. Br J Dermatol 124:79-83, 1991

278. Prose NS, von Knebel-Doeberitz C, Miller S, et al: Widespread flat warts associated with human papillomavirus type 5: A cutaneous manifestation of human immunodeficiency virus infection. J Am Acad Dermatol 23:978-981, 1990

279. Laraque D: Severe anogenital warts in a child with HIV infection [letter]. N Engl J Med 320:1220-1221, 1989

280. Kiviat N, Rompalo A, Bowden R, et al: Anal human papillomavirus infection among human immunodeficiency virus- seropositive and -seronegative men. J Infect Dis 162:358-361, 1990

281. Ampel NM, Stout ML, Garewal HS, et al: Persistent rectal ulcer associated with human papillomavirus type 33 in a patient with AIDS: Successful treatment with isotretinoin. Rev Infect Dis 12:1004-1007, 1990

282. Beck DE, Jaso RG, Zajac RA: Surgical management of anal condylomata in the HIV-positive patient. Dis Colon Rectum 33:180-183, 1990

283. Musher DM: Syphilis, neurosyphilis, penicillin, and AIDS. J Infect Dis 163:1201-1206, 1991

284. Hicks CB: Syphilis and HIV infection. Dermatol Clin 9:493-501, 1991

285. Tramont EC: Syphilis in the AIDS era [editorial]. N Engl J Med 316:1600-1601, 1987

286. Tramont EC: Syphilis in adults: From Christopher Columbus to Sir Alexander Fleming to AIDS. Clin Infect Dis 21:1361-1369, 1995

287. Gregory N, Sanchez M, Buchness MR: The spectrum of syphilis in patients with human immunodeficiency virus infection. J Am Acad Dermatol 22:1061-1067, 1990

288. Glover RA, Piaquadio DJ, Kern S, et al: An unusual presentation of secondary syphilis in a patient with human immunodeficiency virus infection. A case report and review of the literature. Arch Dermatol 128:530-534, 1992

289. Tosca A, Stavropoulos PG, Hatziolou E, et al: Malignant syphilis in HIV-infected patients [see comments]. Int J Dermatol 29:575-578, 1990

290. Johns DR, Tierney M, Felsenstein D: Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. N Engl J Med 316:1569-1572, 1987

291. Holtom PD, Larsen RA, Leal ME, et al: Prevalence of neurosyphilis in human immunodeficiency virus-infected patients with latent syphilis [see comments]. Am J Med 93:9-12, 1992

292. Recommendations for diagnosing and treating syphilis in HIV-infected patients. MMWR Morb Mortal Wkly Rep 37:600-2, 607-8, 1988

293. Rompalo AM, Cannon RO, Quinn TC, et al: Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis 165: 1124-1126, 1992

294. Hicks CB, Benson PM, Lupton GP, et al: Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. A diagnostic dilemma [published erratum appears in Ann Intern Med 107:946, 1987] [see comments]. Ann Intern Med 107:492-495, 1987

295. Matlow AG, Rachlis AR: Syphilis serology in human immunodeficiency virus-infected patients with symptomatic neurosyphilis: Case report and review. Rev Infect Dis 12:703-707, 1990

296. Tikjob G, Russel M, Petersen CS, et al: Seronegative secondary syphilis in a patient with AIDS: Identification of Treponema pallidum in biopsy specimen. J Am Acad Dermatol 24:506-508, 1991

297. Fiumara N: Human immunodeficiency virus infection and syphilis. J Am Acad Dermatol 21:141-142, 1989

298. Musher DM, Hamill RJ, Baughn RE: Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann Intern Med 113:872-881, 1990

299. Hutchinson CM, Hook EW, 3rd, Shepherd M, et al: Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. Ann Intern Med 121:94-100, 1994

300. Haas JS, Bolan G, Larsen SA, et al: Sensitivity of treponemal tests for detecting prior treated syphilis during human immunodeficiency virus infection [see comments]. J Infect Dis 162:862-866, 1990

301. 1998 guidelines for treatment of sexually transmitted diseases. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 47:1-111, 1998

302. Rolfs RT, Joesoef MR, Hendershot EF, et al: A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group [see comments]. N Engl J Med 337:307-314, 1997

303. Curry A, Turner AJ, Lucas S: Opportunistic protozoan infections in human immunodeficiency virus disease: Review highlighting diagnostic and therapeutic aspects [see comments]. J Clin Pathol 44:182-193, 1991

304. Litwin MA, Williams CM: Cutaneous Pneumocystis

carinii infection mimicking Kaposi sarcoma. Ann Intern Med 117:48-49, 1992

305. Scowden EB, Schaffner W, Stone WJ: Overwhelming strongyloidiasis: An unappreciated opportunistic infection. Medicine (Baltimore) 57:527-544, 1978

306. Bank DE, Grossman ME, Kohn SR, et al: The thumbprint sign: Rapid diagnosis of disseminated strongyloidiasis. J Am Acad Dermatol 23:324-326, 1990

307. Kalb RE, Grossman ME: Periumbilical purpura in disseminated strongyloidiasis. JAMA 256:1170-1171, 1986

308. Davidson RN: AIDS and leishmaniasis [editorial]. Genitourin Med 73:237-239, 1997

309. Desjeux P: Global control and Leishmania HIV coinfection. Clin Dermatol 17:317-325, 1999

310. Da-Cruz AM, Machado ES, Menezes JA, et al: Cellular and humoral immune responses of a patient with American cutaneous leishmaniasis and AIDS. Trans R Soc Trop Med Hyg 86:511-512, 1992

311. Dauden E, Penas PF, Rios L, et al: Leishmaniasis presenting as a dermatomyositis-like eruption in AIDS. J Am Acad Dermatol 35:316-319, 1996

312. Rubio FA, Robayna G, Herranz P, et al: Leishmaniasis presenting as a psoriasiform eruption in AIDS [letter]. Br J Dermatol 136:792-794, 1997

313. Barrio J, Lecona M, Cosin J, et al: Leishmania infection occurring in herpes zoster lesions in an HIV-positive patient [see comments]. Br J Dermatol 134:164-166, 1996

314. Caballero-Granado FJ, Lopez-Cortes LF, Borderas F, et al: Digital necrosis due to Leishmania species infection in a patient with AIDS. Clin Infect Dis 26:198-199, 1998

315. Stolf NA, Higushi L, Bocchi E, et al: Heart transplantation in patients with Chagas' disease cardiomyopathy. J Heart Transplant 6:307-312, 1987

316. Libow LF, Beltrani VP, Silvers DN, et al: Post-cardiac transplant reactivation of Chagas' disease diagnosed by skin biopsy. Cutis 48:37-40, 1991

317. Kirchhoff LV, Gam AA, Gilliam FC: American trypanosomiasis (Chagas' disease) in Central American immigrants. Am J Med 82:915-920, 1987

318. Kirchhoff LV: Chagas disease. American trypanosomiasis. Infect Dis Clin North Am 7:487-502, 1993

319. Kirchhoff LV: American trypanosomiasis (Chagas' disease). Gastroenterol Clin North Am 25:517-533, 1996

320. Murakawa GJ, McCalmont T, Altman J, et al: Disseminated acanthamebiasis in patients with AIDS. A report of five cases and a review of the literature. Arch Dermatol 131:1291-1296, 1995

321. Tan B, Weldon-Linne CM, Rhone DP, et al: Acanthamoeba infection presenting as skin lesions in patients with the acquired immunodeficiency syndrome. Arch Pathol Lab Med 117:1043-1046, 1993

322. Helton J, Loveless M, White CR, Jr: Cutaneous acanthamoeba infection associated with leukocytoclastic vasculitis in an AIDS patient. Am J Dermatopathol 15:146-149, 1993

323. Chandrasekar PH, Nandi PS, Fairfax MR, et al: Cutaneous infections due to Acanthamoeba in patients with acquired immunodeficiency syndrome. Arch Intern Med 157: 569-572, 1997

324. May LP, Sidhu GS, Buchness MR: Diagnosis of Acanthamoeba infection by cutaneous manifestations in a man seropositive to HIV. J Am Acad Dermatol 26:352-355, 1992

325. Woolrich A, Koestenblatt E, Don P, et al: Cutaneous protothecosis and AIDS. J Am Acad Dermatol 31:920-924, 1994

326. Goldstein GD, Bhatia P, Kalivas J: Herpetiform protothecosis. Int J Dermatol 25:54-55, 1986

327. Wirth FA, Passalacqua JA, Kao G: Disseminated cutaneous protothecosis in an immunocompromised host: A case report and literature review. Cutis 63:185-188, 1999

328. Anolik MA, Rudolph RI: Scabies simulating Darier disease in an immunosuppressed host. Arch Dermatol 112:73-74, 1976

329. Tibbs CJ, Wilcox DJ: Norwegian scabies and herpes simplex in a patient with chronic lymphatic leukemia and hypogammaglobulinemia [letter]. Br J Dermatol 126:523-524, 1992

330. Suzumiya J, Sumiyoshi A, Kuroki Y, et al: Crusted (Norwegian) scabies with adult T-cell leukemia. Arch Dermatol 121:903-904, 1985

331. Donabedian H, Khazan U: Norwegian scabies in a patient with AIDS. Clin Infect Dis 14:162-164, 1992

332. Portu JJ, Santamaria JM, Zubero Z, et al: Atypical scabies in HIV-positive patients. J Am Acad Dermatol 34:915-917, 1996

333. Arico M, Noto G, La Rocca E, et al: Localized crusted scabies in the acquired immunodeficiency syndrome. Clin Exp Dermatol 17:339-341, 1992

334. Hulbert TV, Larsen RA: Hyperkeratotic (Norwegian) scabies with gram-negative bacteremia as the initial presentation of AIDS [letter]. Clin Infect Dis 14:1164-1165, 1992

335. Glover A, Young L, Goltz AW: Norwegian scabies in acquired immunodeficiency syndrome: Report of a case resulting in death from associated sepsis [letter]. J Am Acad Dermatol 16:396-399, 1987

336. Meinking TL, Taplin D, Hermida JL, et al: The treatment of scabies with ivermectin. N Engl J Med 333:26-30, 1995

337. Taplin D, Meinking TL: Treatment of HIV-related scabies with emphasis on the efficacy of ivermectin. Semin Cutan Med Surg 16:235-240, 1997

338. Rosenthal D, LeBoit PE, Klumpp L, et al: Human immunodeficiency virus-associated eosinophilic folliculitis. A unique dermatosis associated with advanced human immunodeficiency virus infection. Arch Dermatol 127:206-209, 1991

339. Bachmeyer C, Cordier F, Cazier A, et al: Eosinophilic folliculitis associated with AIDS after antiretroviral tri-therapy [letter]. Presse Med 28:2226, 1999