

Tropical dermatology: Bacterial tropical diseases

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Bacterial infections are common in tropical parts of the world and can include those species also seen regularly in temperate climates. Many tropical bacterial infections, however, are rarely diagnosed in temperate parts of the world and include bartonellosis, tropical ulcer, tropical pyomyositis, granuloma inguinale, lymphogranuloma venereum, yaws, pinta, melioidosis, and glanders. Some tropical bacterial diseases, eg, plague and anthrax, are associated with high mortality rates and are of potential use in bioterrorism. Some tropical bacterial diseases are closely associated with specific activities such as hunting (ie, tularemia) or eating raw seafood (*Vibrio vulnificus* infection). The bacterial diseases having the most severe medical impact in the tropics are those caused by members of the *Mycobacterium* genus. Millions of persons throughout the world suffer from tuberculosis and leprosy; Buruli ulcers are common causes of morbidity in many tropical countries. Because of the increasing frequency of travel to tropical parts of the world for tourism and work as well as the increasing number of immigrants and adoptees from these areas, it is imperative that physicians practicing in temperate climates be able to recognize the signs and symptoms of tropical bacterial diseases, carry out the proper diagnostic tests, and initiate appropriate therapy and prevention. (J Am Acad Dermatol 2006;54:559-78.)

Learning objective: At the completion of this learning activity, participants should be familiar with the clinical presentations, epidemiologies, diagnoses, therapies, and preventions of bacterial tropical diseases.

Bacterial tropical infections are the cause of multiple illnesses, such as bartonellosis, tropical ulcers, and tropical pyomyositis. Some sexually transmitted bacterial diseases, such as granuloma inguinale and lymphogranuloma venereum are important in some countries of the world. Another significant group of bacterial diseases is nonvenereal treponematoses, such as pinta and yaws.

Mycobacteriosis, caused by acid-fast, weakly gram-positive, nonsporogenic rods, has, however, a special impact in tropical countries. It has been estimated that the genus *Mycobacterium* causes more suffering for humans than all the other bacterial genera combined. Leprosy, as well as tuberculosis, is still a major challenge in most tropical countries. In addition, the so-called atypical mycobacteria are

Abbreviation used:

LGV: lymphogranuloma venereum

increasingly recognized as human pathogens and may be the cause of skin disease more frequently than *Mycobacterium tuberculosis*, especially Buruli ulcer. Rickettsial, ehrlichial, babesial, and other infections can have cutaneous manifestations but are not covered in this review.

Tropical bacterial diseases may be seen in tourists, workers, or soldiers who return from tropical parts of the world, as well as in immigrants and adoptees from countries in tropical areas. Other tropical bacterial diseases, such as plague, anthrax, and melioidosis, also have potential use in bioterrorism. Because these bacterial diseases have cutaneous manifestations, dermatologists in temperate parts of the world may have the first opportunity to diagnose and treat these infections. The objective of this review is to remind dermatologists of the clinical presentations of these bacterial diseases and to provide guidelines for their diagnoses and treatment.

BARTONELLOSIS

Bartonellosis is a bacterial disease with both acute and chronic forms.¹ It is transmitted by sandflies and

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Fig 1. Bartonellosis, miliary type. Courtesy of Francisco Bravo, MD, Lima, Peru.

is endemic in South America. The disease has been known since the 15th century. The first outbreak occurred during the construction of a railroad from Lima to Oroyo in the 1870s and killed more than 7,000 railway workers with acute fever (Oroyo fever).²

Bartonellosis is also known as Carrion disease, after a fatal experiment performed by a young medical researcher, Daniel Carrion, in 1885. The self-inoculation of the agent, recovered from a cutaneous lesion, proved that those verrucous lesions (Peruvian warts) were another manifestation of the same disease. *Bartonella bacilliformis*, the etiologic agent of bartonellosis, was isolated by Alberto Barton in 1909 but was not connected with the disease until 1940.³

The disease is limited to a small area of the Andes Mountains in western South America, mostly in Peru,⁴ Colombia,⁵ and Ecuador.⁵ It continues to be a public health problem in many mountain valleys in Peru, but the last outbreak occurred in 1941; since then only sporadic cases have been reported.^{2,6}

Reservoir hosts have been identified for other members of the genus *Bartonella*, including cats and rodents. However, no animal reservoirs of infection have been identified for *Bartonella bacilliformis* yet.⁷ It is still possible that human beings themselves are the principal reservoir, since some patients never develop the disease but remain persistently infected.⁶ Sandflies of the genus *Lutzomyia* are believed to transmit *B bacilliformis*, but other insects may also be involved, such as fleas that are important vectors for *Bartonella henselae*.⁸ Once in the bloodstream, the bacteria reproduce inside erythrocytes, causing massive hemolytic anemia.^{9,10} The anemia is accompanied by high fever, muscle pain, delirium, and sometimes coma, all characteristic of the acute phase of bartonellosis.¹⁰ One bacterial protein, deformin, causes pits and indentations in erythrocyte membranes and is probably involved in the hemolysis.¹⁰

Two to eight weeks after the febrile phase, an infected patient develops wartlike disseminated lesions that mainly affect the head and the limbs (Fig 1). The lesions may be painful, may bleed or ulcerate, and can last for several months.⁴⁻⁶

Isolation of *B bacilliformis* from either the skin lesions or the bloodstream is the key for diagnosis. Cultures on blood agar microbiologic media are useful in the isolation of the pathogen.¹¹ Serologic diagnosis is available with both enzyme-linked immunosorbent assay and immunofluorescent tests.^{9,11} The bacteria are susceptible to several antibiotics, including chloramphenicol, penicillins, and aminoglycosides.^{1,7,8}

TROPICAL ULCER

Tropical ulcer, or tropical phagedenic ulcer, is a painful, rapidly growing, sloughing ulcer, usually on the leg. It is mostly prevalent in hot, tropical regions, and trauma is always important in its development. The trauma may be trivial, such as a scratch or an insect bite.¹²

Tropical ulcer is a polymicrobial infection with *Fusobacterium* species,¹³ almost always present in the early stages, and anaerobic microorganisms (*Bacillus fusiformis*) and spirochetes (*Treponema vincenti*) playing a role in the late stages.^{12,13} Predisposing factors such as rural labor and malnutrition are important in the development of the disease.¹⁴ It most commonly occurs in undernourished youngsters and in rural laborers exposed to injury of their lower limbs. Deficiencies in calcium, vitamins, and proteins may predispose to the infection.^{12,14} Debilitating diseases such as malaria, chronic diarrhea, and intestinal parasites are also associated with tropical ulcer.^{15,16}

The single ulcer is very painful and grows quickly but is commonly superficial and the edges are undermined and violaceous (Fig 2).¹² Ulcers occur mainly on the lower limbs and may reach several centimeters in diameter after a couple of weeks.^{15,16} Some chronic tropical ulcers may reach the muscular fascia and even the periosteum.¹⁵ The most important differential diagnoses in the late stages should include cutaneous leishmaniasis, atypical mycobacteria, and pyoderma gangrenosum. Venous ulcers should be ruled out in the chronic stages.

Giemsa- or Gram-stained smears taken from the base and edges of the ulcer can show numerous *Fusobacterium* species, usually mixed with other gram-negative bacteria such as *Escherichia coli* and *Enterococcus* species.^{13,17} Treatment options include tetracycline (500 mg every 6 hours for 1 week) and metronidazole (250 mg every 8 hours for 10 days).¹⁵



Fig 2. Tropical ulcer. Ulcerative lesion in the lower limb.

TROPICAL PYOMYOSITIS

Tropical pyomyositis is a rare malady characterized by the presence of abscesses that arise primarily in the large muscles of the limbs and trunk.¹⁸ Scriba described the disease in 1885.¹⁹ The term *tropical pyomyositis* should be restricted to those cases in which is possible to find primary muscle abscesses arising within large bulky skeletal muscles beneath the deep fascia, usually in the tropics.²⁰ The disease is more prevalent in humid areas, mainly in Central Africa and Central America but also in certain parts of the Amazon rainforest and in the southeast provinces of Brazil.¹⁸ Walker described the first cases in South America as “myositis purulent tropical” in 1917.²¹

The disease mainly affects otherwise healthy children and young adults, with the highest incidence during the second decade, and is typically caused by *Staphylococcus aureus*.²² Some cases in temperate climates, known as nontropical pyomyositis,²³ seem to be more often associated with debilitated, elderly patients,²⁴ usually in the setting of a chronic immunosuppressive illness²⁵ such as diabetes mellitus, HIV infection,²⁶ connective tissue disease,²⁷ and neoplastic disease. The exact pathogenesis of tropical pyomyositis is uncertain. Clinical or subclinical involvement of skeletal muscle can occur in some cases and can be correlated with previous blunt muscle trauma, nutritional deficiencies, and parasitic infections.¹⁸



Fig 3. Tropical pyomyositis. Single localized abscess. Courtesy of Hospital Central do Exército in Rio de Janeiro, Brazil.

Tropical pyomyositis follows a well-defined clinical course that involves an initial stage of diffuse pain with or without pyrexia.²⁰ Any of the skeletal muscles may be involved, but those of the trunk are most commonly affected, usually by a single localized abscess (Fig 3). The affected area will present progressive induration, pain, and overt enlargement of a mass over a period of 1 to 2 weeks.^{18,20} The involved muscles may eventually develop a firm, wooden texture at palpation. The last stage is characterized by painful muscle suppuration, with extension into an adjacent bone or joint, that leads to septicemia and death in 1.8% of patients.^{28,29} Multiple muscle involvement occurs in 12% to 60% of patients.¹⁸

The diagnosis of tropical pyomyositis is often overlooked, because most physicians are not familiar with the entity. Local signs of inflammation, fever, leukocytosis, and elevated erythrocyte sedimentation rate are common features.²³ The creatine kinase level may be normal or mildly elevated.²⁷ Blood cultures are positive for *Staphylococcus aureus* in 30% of patients,²⁸ and at autopsy, microscopic evidence of bronchopneumonia has been documented in 50% of patients.²⁹ The differential diagnosis with liposarcoma and osteomyelitis is difficult. Newer imaging modalities, such as gallium scanning, ultrasonography, computed tomography, and magnetic resonance imaging have greatly facilitated early diagnosis of tropical pyomyositis.^{30,31} The treatment of choice is surgical drainage of the abscess, along with appropriate intravenous antibiotics.^{18,20}

GRANULOMA INGUINALE

Granuloma inguinale is an indolent, progressive, ulcerative bacterial disease caused by *Calymmatobacterium granulomatis*. It mainly affects the skin and subcutaneous tissue of the genital and perianal areas. Untreated, it exhibits no tendency to go into spontaneous remission and in later stages may be severely debilitating.³²

McLeod, in Madras, India, who named it *serpiginous ulcer*, described the disease for the first time in 1882.³³ Many other names have been suggested since then, such as *venereum granuloma*, *ulcerating granuloma*, and *chronic venereum ulcer*, but aside from *granuloma inguinale*, only the term *donovanosis* persists. Aragao and Viana proposed the name *Calymmatobacterium granulomatis* in 1913 after the Greek word *kalymma*, which means hood.³⁴ They also first treated granuloma inguinale with antimony, but good clinical results were associated with severe side effects. In 1939, Greenblatt inoculated the pus from a pseudobubo of a patient with granuloma inguinale into a volunteer, obtaining in the resulting lesion a demonstration of the organism.³⁵ In 1950, Marmell and Santora proposed the term *donovanosis*, in homage to Donovan, who first demonstrated the causative agent as bipolar-staining intracellular inclusions in macrophages from lesion exudates.³⁶

The causative agent is a gram-negative rod with some antigenic properties in common with the *Klebsiella* group.³⁷ It has been demonstrated in fecal flora as a coccobacillus measuring 0.5-1.5 μm wide and 1.0 μm long, with round extremities.³⁸ The coccobacilli have a polysaccharide and fibrous capsule. *C granulomatis* demonstrates a chromatin condensation in one or both extremities, forming characteristic shapes in "halters" or "safety pins" when stained with Giemsa or Wright stains.^{37,38} The organisms appear isolated or form bunches in the interior of large mononuclear macrophages but are also found in extracellular spaces. The observation of intracytoplasmic granules was interpreted by Passos et al as bacteriophages³² and by Goldberg as important structures in the origin of the disease.³⁸ The demonstration of viral nucleic acid inside *C granulomatis* is significant, suggesting the possibility that the agent is a bacterium modified by phagocytosis, which also occurs with *Corynebacterium diphtheriae*.³² The transfection by phages may be the necessary prerequisite to transform the fecal bacteria contamination to a state of disease. These data support the hypothesis that disease transmission may occur through fecal contamination in environments with lower levels of hygiene and may also explain the high prevalence of the disease in males who practice rectal intercourse.^{32,37,39}

The sexually transmitted nature of granuloma inguinale is still controversial; however, the importance of sexual contact cannot be denied, since most of the lesions occur in the genital or anal region, the disease is more frequent in the most sexually active people, and donovanosis in homosexual males usually develops in the perianal area.^{32,39} Other observations, however, indicate the possibility of

transmission without sexual intercourse, such as sporadic cases in children who are not sexually active, the lack of transmission to a conjugal partner in some exuberant clinical cases, and the emergence of extragenital lesions.^{40,41}

Sporadic cases of granuloma inguinale occur worldwide,⁴¹ but endemic foci are usually seen only in tropical and subtropical countries, such as New Guinea, Brazil, French Guiana, Australia, South Africa, Zambia, Morocco, Madagascar, the Caribbean, and parts of India and China.^{40,42} Since 1989, fewer than 10 cases per year have been reported in the United States.⁴³

Although many authors affirm that the disease is more prevalent among males, Passos et al reported that the majority of their cases in Brazil occurred among females.³² Certain marked racial and ethnic predispositions have been noted, such as higher incidences in blacks than in whites in the United States,⁴³ in natives than in Europeans in Papua New Guinea, and in Hindus than in Muslims in India,³² but there is no evidence for specific racial susceptibility.⁴³ Rather, socioeconomic status and living conditions may be major risk factors. In most of the megacities, where it is possible to find places with subhuman living conditions, even in developed countries, it is possible to verify sporadic cases.⁴¹ It seems clear, however, that granuloma inguinale is one of a class of diseases causing genital ulceration, such as genital herpes, syphilis, and chancroid, that may predispose persons to the transmission of HIV.⁴⁴⁻⁴⁶

The incubation period is variable and can range from 2 weeks to 6 months.³² The disease begins as single or multiple subcutaneous nodules that erode through the skin, producing well-defined ulcerations that grow slowly and bleed readily on contact.⁴⁰ The subcutaneous nodule, if large enough, may be mistaken for a lymph node, giving rise to the term *pseudobubo*.⁴⁷ True adenopathy is rare. In men, the penis, scrotum, and glans are the most common sites of primary lesions; in females, they are the labia minora and the perigenital area.^{32,43} Lesions of the cervix may occur in as many as 10% of infected women, and the disease may involve the uterus and adnexa as well.³²

Jardim proposed a new clinical classification with eight major clinical varieties in 1987⁴⁸: ulcerous variety; ulcerative lesions with hypertrophic edges; ulcerative lesions with plane edges (Fig 4); ulcerovegetative lesions, which are the most common pattern of the disease (Fig 5); vegetating lesions; elephantine manifestations; extragenital disease; and systemic infection. The elephantine manifestations are due to the tendency of the disease to form fibrosis



Fig 4. Granuloma inguinale. Ulcerative vulvar lesion with plane edges.



Fig 5. Granuloma inguinale. Ulcerovegetative perianal lesion. Courtesy of Andreia Mateus, MD, Rio de Janeiro, Brazil.

and keloids, sometimes leading to deformity of the genitalia and paraphimosis.⁴⁰ The slowly developing lesions can be secondarily contaminated through other microorganisms. Extensive and deep ulcerations and necrosis of the soft tissues are likely to occur with subsequent fistulas and mutilation.⁴³

The extragenital manifestations are observed in about 5% of cases, almost all of them proceeding from endemic areas.⁴⁰ Hematogenous and lymphatic dissemination, as well as autoinoculation, can explain the extragenital sites. The disease shows no tendency toward spontaneous healing, though lesions may be stable for long periods.³² There is believed to be an increased incidence of squamous cell carcinoma of the genital skin in granuloma inguinale.

The clinical diagnosis of granuloma inguinale, based on history and appearance, may be fairly accurate in endemic areas. Laboratory diagnosis requires a crush or touch preparation stained with Wright or Giemsa stain from a punch biopsy specimen.³² The biopsy specimen should be obtained before cleaning the lesion and removing necrotic tissues with saline solution and sterilized gauze. Scrapings from the base of the ulcer or exudate aspirated from pseudobuboes can also be used. One can observe the diagnostic Donovan bodies in the direct examination of these materials, dried or fixed

with methyl alcohol, and stained with Giemsa or Wright stain.^{32,43} They are seen as deeply staining, bipolar, safety pin-shaped rods in the cytoplasm of macrophages. *C granulomatis* was successfully cultured in vitro by infecting macrophage monolayers from the peritoneum with lysates of donovanosis-infected tissues.⁴⁹

Histologically, the skin exhibits a massive cellular reaction, predominantly polymorphonuclear, with occasional plasma cells and, rarely, lymphocytes.⁴³ The marginal epithelium demonstrates acanthosis and pseudoepitheliomatous hyperplasia. Hypertrophic and cicatricial forms demonstrate an increase in fibrous tissue. Donovan bodies are scattered throughout the lesions. Serologic tests, such as the use of complement fixation have little practical application.³²

Differential diagnoses for early lesions should include primary syphilis, chancroid, condyloma acuminatum, leishmaniasis, deep mycosis, and cutaneous amebiasis. Late lesions can mimic squamous cell carcinoma, scrofuloderma, and lymphogranuloma venereum.

Numerous drugs have been found useful in treating granuloma inguinale, including streptomycin (1g/d intramuscularly for 20 to 30 days), chloramphenicol or tetracycline (500 mg every 6 hours for 15 days), doxycycline (100 mg twice a day for



Fig 6. LGV. Enlarged inguinal lymph node.

30 to 60 days), and gentamicin (30 mg intramuscularly twice a day for 15 days).^{32,43} Response may be monitored by clinical appearance and serial biopsy specimens examined for persistent presence of Donovan bodies. In late cases, irreparable tissue destruction may have supervened and radical surgery may be required.^{40,43}

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is an acute to chronic sexually transmitted disease with transient early genital lesions followed by significant regional lymphadenopathy, as well as systemic manifestations.⁵⁰ LGV may progress to late fibrosis and tissue destruction in untreated cases. The causative agent is *Chlamydia trachomatis*.^{50,51} The disease was given numerous names and has been known since antiquity by the Romans, who called it *struma*, and by the Arabians, who called it *althaun*.⁵⁰ The more modern descriptions tried to point out its main characteristics: regional adenopathy, almost always inguinal; subacute evolution; suppuration in multiple sites; and a possible climatic influence, since the disease is much more prevalent in the tropics. The designations for LGV are tropical bubo, d'embré bubo, scrofulous bubo, benign suppurative inguinal paradenitis, and inguinal lymphogranuloma.

Rake performed the first cultivation of the agent in the yolk sacs of embryonate eggs, in 1940.⁵² The etiologic agent belongs to the *Chlamydia* genus, gram-negative intracellular parasites that measure

0.3 to 1.0 μm .⁵¹ They produce infection in man and fowl (psittacosis, ornithosis) with a remarkable tropism for ganglia and ocular structures, lungs, and the genitourinary and gastrointestinal tracts. The causative organism is *C trachomatis* serotypes L1, L2, and L3. Other serotypes cause trachoma, inclusion conjunctivitis, and ophthalmia of neonates (serotypes A–C), as well as urethritis, cervicitis, and Reiter syndrome (serotypes D–K).^{51,53}

LGV is more usual in the tropical and subtropical regions but does occur in low incidence throughout the Western world. In Paris, Scieux et al detected only 27 cases in 6 years.⁵⁴ An investigation in prostitutes in a northeastern province of Brazil, however, showed that 11% of all genital ulcers were due to LGV.⁵⁵ Two epidemiologic inquiries performed in Rio de Janeiro, Brazil, led to the identification of more than 400 cases of LGV in 6 years, representing 0.26% of persons who sought dermatologic care. About 91% of the cases occurred among men, 63% were unmarried, and there was no significant difference as to the ethnic group. The main complaint was inguinal adenopathy. The primary ulcer was present in 20% of patients, and fever was observed in 8.3% of them. The incidence was higher among servants and merchants. Both studies showed a gradual decline in LGV but it is still the sixth most frequent sexually transmitted disease in Brazil, after gonococcal urethritis, human papillomavirus infection, genital herpes, syphilis, and chancroid.⁵⁰

The incubation period is uncertain but has been estimated to be anywhere from 1 to 2 weeks.⁵⁶ The site of the primary chancre is not commonly noticed. This transient primary lesion usually appears as a small erosion, an eroded papule, or an ulcerated area. The coronal sulcus, glans, and internal face of labia minora are the usual locations.⁵⁰ The lesion will last only 2 to 3 days and is followed by adenopathy after 1 to 3 weeks. In its earlier stages the adenopathy syndrome is manifested by discrete, tender movable nodes.^{50,56} The overlying skin is often slightly reddened and edematous but may become thickened and develop a purple hue.⁵⁷ In a short time the lymph nodes become tender and fluctuant and are referred to as buboes (Fig 6). They usually undergo necrosis, and spontaneous fistula tracts may develop (Fig 7). These nodules may also become fluctuant and discharge purulent material from multiple fistulous orifices, such as a "watering can."⁵⁰ Painful elongated sausage-shaped swellings may occur in the inguinal area above and below the Poupart ligament. The linear depressions are the so-called groove sign.⁵⁰

Fever and chills are common findings during this stage of the disease and can be associated with other



Fig 7. LGV. Buboer after spontaneous fistulization.

nonspecific systemic symptoms such as headache, nausea, weight loss, and myalgia.^{50,56} Females may present with rectitis, tenesmus, and mucosanguineous rectal discharge due to the rupture of perirectal or pelvic adenopathy, whereas infection in males results in inguinal adenopathy.⁵⁸ The lymph nodes rupture, causing hemorrhage and friability of the anorectal mucosa. Later, as healing occurs, there is formation of strictures, fistulas, and abscesses, with destruction of anal and rectal structures.⁵⁹ The genitoanorectal syndrome occurs after late fibrosis in untreated cases. Elephantiasis of the vulva and of the penis and scrotum represents late manifestations, which are rare today.⁵⁰ Esthiomene, composed of vulvar enlargement, thickening, and ulceration followed by sclerosis, can occur not only in LGV patients but also in those with tuberculosis or syphilis. Perirectal abscesses, fistulas, rectovaginal fistulas, ulceration, strictures, and sclerosis of the skin compose the anorectal syndrome, also known as Jersild syndrome.^{50,58,59}

The differential diagnoses should include chancroid, syphilis, and genital herpes in the late stage. Ganglionic tuberculosis and Hodgkin disease may be ruled out in patients with severe adenopathy and genital swelling.^{50,57} Squamous cell carcinoma and hidradenitis can be difficult to differentiate from Gersild syndrome. Direct bacteriologic examination and culture can be performed with pus from affected lymph nodes. The material can be collected by inserting a needle into the fluctuant area from a point of normal skin.⁵⁰ Staining the smear with Giemsa or fuchsin stain reveals the intracellular corpuscles of Gamma-Miyagawa, which occur in some chlamydial infections.^{50,58} Culture of the agent can be performed in yolk sacs of embryonate eggs or in McCoy culture cells. A complement fixation test, using group-specific antigens, is reactive within 1 month of onset of infection.^{50,58} A titer greater than or equal to 1:16, in the presence of a compatible clinical syndrome, is suggestive of LGV. Indirect immunofluorescence represents a sensitive method but is not widely available.⁵⁸

LGV can be treated with tetracycline (500 mg every 6 hours for 2 to 4 weeks), doxycycline (100 mg every 12 hours for 3 weeks), or erythromycin (500 mg every 6 hours for 2 to 3 weeks).⁵⁰ Tense and fluctuant nodules should be aspirated rather than incised and drained, with a thick needle through healthy adjacent normal skin to prevent rupture and formation of fistulous tracts. Dilation and partial amputation of the rectum are measures occasionally indicated to correct rectal stricture. Vulvectomy and colostomy are seldom necessary.⁵⁰

YAWS

Yaws, also known as frambesia, parangi, paru, pian, and boubia, is a contagious, nonvenereal, endemic treponematosis in humans.⁶⁰ The disease is transmitted by *Treponema pertenue*, a subspecies of *Treponema pallidum* with different pathogenic properties.⁶¹ The relationship between both bacteria has been the subject of much debate for several years. Both are noncultivable and morphologically identical in that they cannot be distinguished by means of fluorescent or treponemal immobilization tests. To date, only minor genetic differences between these two parasites have been reported, but clinically, they differ in several aspects.^{61,62}

Children under 15 years of age in Central and West Africa are affected most.^{60,63} Countries that have been especially affected include Ghana, Ivory Coast, and Mali.⁶⁰ Other areas that have shown susceptibility to yaws are Southeast Asia, the Pacific Islands, and Indonesia.^{64,65} South America is the site of sporadic cases. The route of infection is through direct person-to-person contact. The ulcerative skin lesions present early in the disease are teeming with spirochetes that can be transmitted via skin-to-skin contact and via breaks in the skin barrier such as traumas, bites, or excoriations.⁶⁵ Early stages of yaws and syphilis bear some similarities, but late lesions of yaws are thought to be limited to skin, bones, and joints.^{63,65} Late active syphilis, on the other hand, may involve any tissue or organ system. Congenital and neurosyphilis are the consequence of untreated or improperly treated syphilis, whereas in yaws, reports of congenital, visceral, or central nervous system involvement are rare.⁶²

The primary lesion of yaws, also called “mother yaw,” develops at the inoculation site after an incubation period of 3 weeks. The initial lesion is a papule that enlarges to become the so-called frambesioma and resolves spontaneously after 3 to 6 months.^{63,64} The widespread dissemination of *T pertenue* results in multiple skin lesions (Fig 8) similar to the primary ones, and disseminated lesions can last for longer than 6 months and are highly



Fig 8. Disseminated papules of yaws. Courtesy of Ross Barnetson, MD, Sydney, Australia.

infective.⁶⁴ Macules, papules, nodules, and hyperkeratotic lesions, mainly on palms and soles (“dry crab yaws”), may appear for the next few weeks.^{63,64} The climate influences the morphology and the number of the lesions; in the dry season, lesions are fewer in number and macular in appearance. Secondary yaws lesions are painless and may ulcerate but tend to heal spontaneously without scarring.⁶⁵

During latent periods, some skin lesions may relapse for as long as 5 years after infection.⁶³ Most patients remain in a noninfectious latent stage for their lifetime, but late yaws develops in 10% of cases, usually 5 to 10 years after disease onset.⁶⁴ During this tertiary stage of yaws, bone, joint, and soft-tissue deformities may occur. Chronic untreated periostitis of the tibia can result in bone deformities (“saber shins”); hydrarthrosis of yaws and juxta-articular nodules are also common. Rhinopharyngitis mutilans, also known as gangosa, is characterized by massive and progressive destruction of the nasal cartilage and other midface structures.^{66,67}

The diagnosis is based on clinical findings. Serodiagnostic tests for venereal syphilis are also used to diagnose yaws.⁶⁵ Dark-field examination of early lesions will be positive. It is not possible to perform the differential diagnosis between syphilis and yaws on only a laboratory basis.⁶⁰ The dermatologic lesions and the epidemiologic pattern are critical in the correct diagnosis. Benzathine penicillin G

is the drug of choice for yaws, as it is for syphilis, since the drug is able to interfere with cell wall synthesis during active multiplication, resulting in bactericidal activity. After a single penicillin dose, early lesions become noninfectious after 24 hours and heal within 1 to 2 weeks.^{64,67,68}

PINTA

Pinta, also known as puru-puru or carate, is an endemic treponematosis caused by *Treponema carateum*. The disease is characterized by a relatively benign course, chronic skin lesions, and no systemic involvement.⁶⁹ The disease has been endemic in Central and South America for several centuries, affecting Aztec and Caribbean Amerindians. It is a rural disease restricted to some endemic foci in Mexico, Venezuela, Colombia, Bolivia, Peru, Honduras, Guatemala, and Brazil.^{69,70} According to Padilha-Goncalves,^{71,72} the disease was prevalent in the 1940s and 1950s in some Brazilian towns along the rivers of the Amazon rain forest. Currently, the prevalence of pinta is decreasing in all the endemic areas of South America, and according to Talhari,⁶⁹ only a few cases among Brazilian Amerindians have been reported in the last decade.

The exact mode of transmission is unknown, but pinta probably is transmitted by direct skin or mucous membrane contact. Insect bites can be an important source of transmission, since they break the skin. Biocca,⁷³ in 1945, evaluated the possible ritual transmission of pinta due to the use of contaminated whips in Indian rituals. Talhari^{69,74} also studied the possible transmission of the disease among Baniwa Indians during the same kind of ritual ceremonies. Indians also referred to the criminal transmission of pinta by infected persons (“pintados”) who mixed their blood with some fruits or food. These alternative ways of transmission, however, were not confirmed.

Pinta affects children and young adults mainly, and both sexes are affected equally. The peak age of incidence is 15-30 years.⁷⁵ The initial lesion is a papule that slowly enlarges to become a pruritic erythematous, squamous plaque. The incubation period (7-20 days) was determined by Padilha-Goncalves.⁷² The dorsa of the feet, legs, forearms, and hands are the most common sites of lesions, and regional lymph nodes may enlarge. No constitutional symptoms exist, however. Late lesions occur after a period of 6 months to 3 years and can be both achromic or hyperpigmented (“pintids”).^{75,76}

The differential diagnoses should include psoriasis, indeterminate leprosy, and pityriasis alba during the early stages of the disease, as well as vitiligo during the late stages. Dark-field examination of



Fig 9. Scrofuloderma.



Fig 10. Scrofuloderma.

exudates from early lesions is rich in *T carateum*.⁷⁶ It is not possible to distinguish pinta from yaws and venereal syphilis serologically. Otherwise, both non-treponemal and treponemal serologic tests are useful and reliable.⁷⁵ The histologic findings of pinta and yaws are similar, with mild acanthosis and an infiltrate rich in lymphocytes. Treponemes can be demonstrated in the epidermis in primary and secondary but not late lesions of both diseases using silver stain.^{75,76} The treatment is identical to that of yaws, using benzathine penicillin G, and the lesions become noninfectious in 24 hours. Alternative therapies, as in other treponematoses, are tetracycline or erythromycin.⁷⁵ Early lesions heal within a few months, but pigmentary changes persist in late lesions.

CUTANEOUS TUBERCULOSIS

Tuberculosis of the skin is caused predominantly by *Mycobacterium tuberculosis* but can also be produced by *Mycobacterium bovis* and, under certain conditions, by the bacille Calmette-Guérin, an attenuated strain of the former.^{77,78} It can be transmitted through inhalation, ingestion, or direct inoculation to the skin.⁷⁹ The dermatologic manifestations are polymorphous and common worldwide,⁷⁹⁻⁸¹ both in temperate climates and in tropical areas. The involvement may be either as primary tuberculosis (tuberculous chancre and acute military tuberculosis) or as secondary infection (lupus vulgaris, Bazin nodules, scrofuloderma, verrucous tuberculosis).^{82,83} Another possibility is the tuberculids, cutaneous manifestations due to hypersensitivity to an extracutaneous focus of *M tuberculosis*.⁸²

Scrofuloderma is, however, a typical pattern of cutaneous tuberculosis in tropical countries.^{79,80} *Scrofula* is a Latin word meaning "weak resistance to disease."⁸¹ This clinical presentation is also known as *tuberculosis colliquativa cutis*, after the recognition of the existence of subcutaneous abscesses that lead to a secondary breakdown of the overlying skin.⁸⁴ Scrofuloderma results from contiguous

involvement of the skin overlying another tuberculous process, usually tuberculous lymphadenitis or tuberculosis of bones and joints.^{78,81} It may affect all age groups, although prevalence is greater among children, adolescents, and the aged. Scrofuloderma is the most common skin manifestation of tuberculosis in Brazil⁸² and is common in most of the tropical countries of the New World. In a large 10-year study performed in Brazil in the 1980s, 43,579 cases of tuberculosis were noted.⁸² About 8.7% (3,809) were evaluated as extrapulmonary cases, and the reference university hospital for that study observed that scrofuloderma was the most common manifestation of cutaneous tuberculosis.

Scrofuloderma most often occurs in the parotid, submandibular, and supraclavicular regions, as well as on the lateral aspect of the neck (Figs 9 and 10); owing to the involvement of lymph nodes in these areas, the lesions are often bilateral.⁸¹ They begin as firm, deep-seated nodules that subsequently become adherent to surrounding tissue. As the infiltrate enlarges it becomes doughy, but months may elapse before there is liquefaction with subsequent perforation.^{81,85} Ulcers and sinuses develop and discharge watery and purulent or caseous material. The margins of the ulcers are purple, and edges are serpiginous and undermined, with granulating floors. Sinusoidal tracts undermine the skin, and clefts and dissecting subcutaneous pockets alternate with soft gummatous nodules; scar tracts develop and bridge ulcerative areas or even stretches of normal skin.^{79,86}

The Mantoux intradermal test, performed in vivo with *M tuberculosis* antigens (tuberculin), is reliable to indicate active tuberculosis and history of contact with the bacillus.⁸⁷ Histopathologic examination of skin samples may depict a tuberculous granuloma composed of epithelioid cells and a few giant cells, with a central area of caseation necrosis surrounded by a mantle of lymphocytes.⁸⁷ The demonstration of acid-fast bacilli at Ziehl staining is, however, an absolute criterion for the diagnosis of tuberculosis.

The polymerase chain reaction is also effective in the determination of tuberculous etiology.⁸⁸

The differential diagnoses should include some deep fungal infections, particularly paracoccidioidomycosis and some severe cases of sporotrichosis, as well as actinomycosis.⁸⁶ Histopathologic analysis will show massive necrosis and abscess formation in the center of the lesion. However, the periphery of the abscesses or the margins of the sinuses contain tuberculoid granulomas and true tubercles, and *M tuberculosis* can be found. Tuberculin sensitivity is usually pronounced. Sarcoidosis is another important differential diagnosis, but results of the Mantoux test are negative and histopathologic assessment shows "naked" epithelioid cell granulomas with only a few lymphocytes at the periphery.⁷⁷

Treatment of cutaneous tuberculosis is the same as that for systemic tuberculosis. The multidrug "RIP" treatment regimen involves use of rifampicin (10 mg/kg/d), isoniazid (5 mg/kg/d), and pyrazinamide (30 mg/kg/d) for at least 9 months.^{77,78} Spontaneous healing in scrofuloderma does occur, but the course is protracted, and it may take years for scar tissue to completely replace the inflammatory and ulcerative lesions.⁷⁷ The typical scars facilitate a correct diagnosis, even after the process has become quiescent.

LEPROSY

The first historical descriptions of leprosy came from India in about 600 BC.⁸⁹ The disease was called *kushta* and was described as being different from vitiligo. The disease spread to Egypt, China, and Japan.⁸⁹ The origin of leprosy is, however, still a mystery, and some recent evaluations pointed out that *Mycobacterium leprae*, the etiologic microorganism, is a degenerative form of *Mycobacterium bovis* that came in contact with humans when the first farmers settled the Middle East, Europe, and Asia thousands of years ago.⁹⁰ The organism gradually lost many genes since then and became fully dependent on the host cellular metabolism for its metabolism.⁹⁰

Leprosy is also known as Hansen disease, after the demonstration of *M leprae* by Gerhard Armauer Hansen in 1873.⁹¹ The discovery of the leprosy bacillus preceded that of the tubercle bacillus by 1 decade; moreover, *M leprae* was the first bacterium to be identified as causing disease in man. The microorganism has never been cultivated on artificial medium or in tissue culture. Classified in the family Mycobacteriaceae, *M leprae* is a rod-shaped organism with parallel sides and rounded ends, 1 to 8 μm long and 0.3 μm in diameter.⁹² It is an obligatory intracellular parasite that divides by means of binary fission. Macrophages are the main target of infection, where the bacteria occur in clumps ("globi") with

hundreds of individuals.⁹¹ Another remarkable characteristic is its capability to infect peripheral nerves, especially Schwann cells. It is a gram-positive bacterium that is also strongly acid-fast after staining with carbol-fuchsin.⁹²

In the footpads of mice, *M leprae* has a generation time of 11 to 13 days, extremely slow even for slow-growing mycobacteria (*M tuberculosis* having a generation time of 20 hours).⁹² This slow rate of multiplication is consistent, however, with the chronicity of the disease. The clinical distribution of lesions, predominantly affecting the skin, nasal mucosa, and peripheral and superficial nerves, was the initial evidence for suggesting that the organism preferred a growth temperature of less than 37°C.⁹³ The confirmation came with the observation that the highly susceptible nine-banded armadillo (*Dasypus novemcinctus*), where *M leprae* multiplies in the liver, spleen, and lymph nodes, has a core temperature of 30 to 36°C.⁹³ Consistent with these observations is the determination that the maximal growth rate for *M leprae* in the mice footpad was over a temperature range of 27-30°C.⁹²

Estimates of the total number of cases of leprosy worldwide varies from 8 million to 10 million.⁹⁴ Most of the cases are in Southeast Asia, especially in India (10 cases per 1,000 inhabitants), and in sub-Saharan Africa, where the disease reaches high endemic levels (>40 cases per 1,000 inhabitants).⁹⁴ The disease is also common in South America, especially in certain provinces of Brazil.⁹⁵ Leprosy affects males more frequently than females in a ratio of 2:1.⁹³ Socioeconomic factors play an important role in leprosy around the world and account for the failure of imported cases to produce secondary cases in Europe and the United States.^{96,97}

Although leprosy is a chronic infectious disease, it may be considered an immunologic disease to a great extent, partially explaining the different clinical patterns.⁹³ Two different classifications are used: the Madrid classification,⁹⁸ accurate for clinical evaluation of leprosy patients, and the Ridley-Jopling immunologic classification,^{99,100} useful for research purposes. According to the Madrid classification, leprosy can be subdivided into 4 different types: lepromatous, tuberculoid, borderline, and indeterminate forms.⁹⁸ The Ridley-Jopling classification involves the use of clinical, histopathologic, and immunologic parameters to create a 7-group spectrum for leprosy between the typical lepromatous and tuberculoid poles. This whole classification includes the polar tuberculoid form, an indefinite tuberculoid presentation, the borderline-tuberculoid form, truly borderline forms, a borderline-lepromatous pattern, indefinite lepromatous presentation,

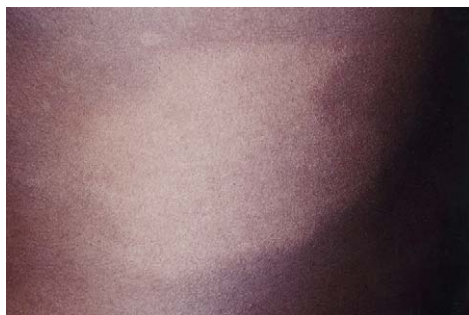


Fig 11. Indeterminate leprosy. Hypopigmented macule with mild infiltration.



Fig 12. Tuberculoid leprosy with "tricophytoid" aspect.

and finally the true lepromatous pole.^{99,100} For the treatment of a large population, patients may be divided into paucibacillary cases (tuberculoid and indeterminate leprosy) and multibacillary ones (lepromatous and borderline leprosy).^{95,101,102} Tuberculoid and lepromatous lesions express distinct immunologic patterns. Tuberculoid lesions express Th1 cytokines (eg, interleukin-2, interleukin-12, and interferon- γ), which activate macrophages and circulating monocytes, producing the granulomatous response against intracellular pathogens. Lepromatous lesions demonstrate primarily Th2 cytokines (eg, interleukin-4 and interleukin-10). The Th2 cytokines result in impaired cell-mediated immune responses to *M leprae* and a significant humoral response to the mycobacteria.

The clinical presentation of leprosy is polymorphous and can vary from hypopigmented macules that heal spontaneously to widespread damage to peripheral nerves, skin, eyes, and bone, with deformity and disability. Most people have, or quickly develop, resistance to infection with *M leprae*.^{93,94} The incubation time is 2 to 5 years and most infections, in endemic areas, are acquired in early childhood.¹⁰³ Much leprosy, however, presents only in early adult life. The early lesion is commonly an area of numbness on the skin or a visible and well-defined hypopigmented macule (Fig 11), usually affecting the trunk or buttocks (indeterminate leprosy). The evolution is variable and will depend on the immunologic capability of the host to fight the *M leprae*. The initial lesion can become infiltrated, either diffusely or as localized papules. Neuritic pain or paresthesia, from infection of peripheral nerves and the skin, can also be the first symptom of leprosy.⁹³

Patients with an effective specific immunity against *M leprae* might develop the tuberculoid form of leprosy. This presentation is characterized by single or few skin lesions with sharp borders and some erythema. The elevated edges and the aspect



Fig 13. Souza Campos nodule of tuberculoid leprosy with spontaneous healing.

of central healing can easily mimic a lesion of tinea with a "tricophytoid" aspect (Fig 12). The lesions are hypoesthetic or definitely anesthetic, except when on the face, because of the rich sensory innervation.⁹³ Hairs are reduced in number or are absent, and sweating is lost. A rare form of tuberculoid leprosy can be observed in endemic areas of Brazil, where a lepromatous patient may infect children during a kiss, and the highly resistant child develops a nodule at the site of the inoculation (Souza Campos nodule; Fig 13).

Polar lepromatous leprosy is characterized by massive proliferation of *M leprae* in tissues.⁹³ Insidious onset and steady progression, however, may allow the advance of leprosy for years before the diagnosis. The early lesions of lepromatous leprosy are macules or papules symmetrically distributed over the body surface. They are usually ill defined, slightly hypopigmented, and erythematous.⁹³ The skin in warmer areas, such as the axillae, the midline of the back, the perineum, and the neck are usually spared. The nerve damage is still discrete by this time, but infiltration of the skin is widely distributed. Loss of eyelashes and eyebrows (madarosis) is characteristic, as is progressive infiltration of the earlobes (Fig 14) and the central portion of the face (Fig 15). Invasion of the mucosa and the upper respiratory tract is found in about 80% of lepromatous patients.⁹³



Fig 14. Lepromatous leprosy with massive infiltration of the earlobe. Courtesy of HCEX.

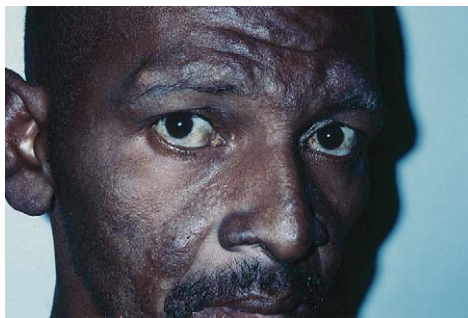


Fig 15. Lepromatous leprosy with madarosis and diffuse infiltration of the face (leonine face).

Palatal ulcerations and nasal mucosal infiltrations, with collapse of the nose, are common, and when the patient coughs, the droplets are full of bacteria. In lepromatous disease the hands and feet take on a characteristic appearance, with swollen digits, but the clinical signs of nerve damage on the large peripheral nerves will appear only when the disease is well advanced. When anesthesia finally develops, the extremities are susceptible to trauma, which leads to ulcerations, chronic osteomyelitis, deformities, and bone destruction.⁹³ These changes occur more readily when there is claw formation that results from weakness of small muscles. There are, however, some uncharacteristic presentations of lepromatous leprosy, such as the Wade histoid leprosy¹⁰⁴ (dome-shaped disseminated nodules) and Lucio leprosy⁹³ (diffuse infiltration and madarosis, without papules or nodules).



Fig 16. Borderline leprosy.

Borderline leprosy spans the spectrum between the lepromatous and tuberculoid poles.⁹⁸ It causes most disability and deformity seen in leprosy owing to the great proportion of patients affected and because of the severity of nerve damage. Instability is the predominant characteristic of borderline leprosy, and the patients can present a clinical pattern of both poles.⁹³ Some skin lesions, however, are typical of this form, presenting an infiltrated plaque with central healing, similar to the tuberculoid lesion, but the external margin is less defined and may taper off gradually into normal skin. A coppery brown coloration is usually present, and the paresthesia is prominent (Fig 16). The nerve damage is much more widespread and severe than in other forms of leprosy, and sometimes most of the large peripheral nerves are irregularly enlarged and tender in an asymmetric pattern.⁹³ The most severe complication of leprosy, known as leprosy reaction, is extremely common in borderline patients.¹⁰⁵ Type 1 reaction, characterized by raised swelling of skin lesions, can produce skin ulceration and severe neuritis, with loss of function (Fig 17). Type 2 reactions, also common in borderline patients and in lepromatous ones, are characterized by systemic illness, fever, malaise, and erythema nodosum leprosum, usually on the lower limbs.¹⁰⁵

Differential diagnosis is dependent on the clinical form of leprosy and the stage of the disease. Indeterminate leprosy lesions can mimic vitiligo,



Fig 17. Type 1 leprosy reaction with nerve damage.

onchocerciasis, and pityriasis alba, while tuberculoid lesions are similar to tinea corporis or psoriasis. Mycosis fungoides, diffuse cutaneous leishmaniasis, and disseminated infiltration due to leukemia can be difficult to differentiate from lepromatous leprosy.¹⁰⁶ Borderline lesions can be similar to granuloma annulare, Leiker granuloma multiforme, and sarcoidosis. Even the neurologic features can be hard to differentiate from some hereditary sensory neuropathy syndromes (Thévenard syndrome, Dejerine-Sottas disease, and Charcot-Marie-Tooth disease), primary amyloidosis of nerves (Corino de Andrade syndrome), syringomyelia, and other causes of polyneuropathy (brucellosis, infectious mononucleosis, and gold poisoning).⁹³

Diagnosis is based on the clinical picture and on the histopathologic features that can present as a spectrum with a close correlation with the clinical form of the disease. Granulomas rich in lymphocytes and epithelioid and Langerhans giant cells are common in the tuberculoid patients, while lepromatous patients will present foamy macrophages with large vacuoles rich in *M leprae*.¹⁰⁷ Borderline cases can present some epithelioid cells and macrophages separated by edema, without giant cells and with few lymphocytes. Indeterminate leprosy usually shows only sparse lymphocyte infiltration around nerve bundles or vessels.¹⁰⁷ Acid-fast bacilli, with the typical agglomeration in globi, can be easily visualized within vacuolated macrophages with Fite's method or Ziehl-Neelsen stain.¹⁰⁷ Tissue collected from the earlobes is usually rich in *M leprae* in multibacillary patients. Mitsuda reaction (lepromin reaction) is prepared with an emulsion of autoclaved *M leprae* obtained from skin lesions of patients with lepromatous leprosy and is used as a skin-test material.⁹³ Its positivity is not diagnostic of leprosy but is useful to analyze the immune responsiveness to the bacilli, since tuberculoid patients present a positive result, while lepromatous cases present no response at all.⁹³



Fig 18. Buruli ulcer. Courtesy of Ross Barnetson, MD, Sydney, Australia.

Leprosy is treated with a multidrug therapy regimen with a daily dose of dapsone (100 mg/d) and clofazimine (50 mg/d), plus a monthly controlled dose of rifampicin (300 mg).¹⁰¹ The duration of treatment is dependent on the clinical and histopathologic picture and can vary from 6 months among paucibacillary patients to 24 months among the multibacillary ones. Reactions are common during treatment and may be managed with corticosteroids, thalidomide, or clofazimine in higher doses.^{95,101}

BURULI ULCER

Buruli ulcer, a disease caused by *Mycobacterium ulcerans*, is the third most common mycobacterial infection in healthy people, after tuberculosis and leprosy. It is a chronic, indolent, necrotizing disease of the skin and underlying tissues that was first described among farmers in Australia (Bairnsdale ulcer). The term *Buruli ulcer* was taken, however, after the recognition of many cases of the disease in Buruli, a province of Uganda.¹⁰⁸

Buruli ulcer is found in many parts of the tropical and subtropical regions of Africa, Asia, South America, and the Western Pacific.¹⁰⁸⁻¹¹⁰ Cases have been reported from Australia, French Guiana, Mexico, all countries along the Gulf of Guinea in Africa, and Malaysia and Papua New Guinea.¹⁰⁸⁻¹¹⁰ In Ivory Coast, approximately 15,000 cases have been recorded since 1978.¹¹¹ In Benin, up to 15% of the whole population in some villages are affected.¹¹⁰ In 1999 there were 6,000 new cases in Ghana, and there is evidence of huge underreporting of the disease.¹¹¹ A few cases reported in non-endemic areas in North America and Europe have been linked to international travel.¹¹⁰

Buruli ulcer is manifest initially as firm, nontender subcutaneous nodules 1 to 2 cm in diameter at sites of penetrating skin trauma.¹¹² Unlike other mycobacteria, *M ulcerans* produces a soluble polyketide toxin, called mycolactone, that has cytotoxic effects and immunosuppressive properties, which explain

the lack of host symptoms, such as fever, malaise, and adenopathy, and the extent of tissue undermining and destruction within the subsequent few weeks.^{113,114} The affected area becomes fluctuant, and later, painless, undermined ulcerations are formed. These ulcerations can be extensive, destroying nerves and blood vessels, and may occasionally invade bones.¹⁰⁹ Characteristic ulcerations affect the lower limbs and have a scalloped border and a sloughing, necrotic base (Fig 18). Undermining necrosis along the panniculus may extend several centimeters.^{108,109}

Diagnosis is based mainly on the clinical and epidemiologic data. The most important differential diagnoses are cutaneous leishmaniasis, tertiary syphilis, and tropical ulcer. A smear from the necrotic base of the lesion may be stained with Ziehl-Neelsen stain, revealing clumps of acid-fast bacilli. *M ulcerans* can be cultured from ulcer exudate or fresh tissue samples. Inocula must be incubated at 30°C to 35°C for 6 to 8 weeks before the colonies can be visualized.¹⁰⁹

Despite often-extensive host involvement, little mortality occurs with *M ulcerans* infection. Healing with fibrosis may lead to significant deformity, with secondary lymphedema, scarring, and contractures of the lower limbs.¹¹⁵ Treatment of Buruli ulcer with antibiotics has been unsuccessful to date, although the organism is sensitive in vitro to some of the antituberculous drugs.¹¹⁶ The combination of an aminoglycoside (amikacin or streptomycin) and rifampicin cures ulcerative lesions due to *M ulcerans* in mice.¹⁰⁹ Most of the cases are treated with surgical excision of the infected tissue, followed by a skin graft, if necessary. Bacille Calmette-Guérin vaccination appears to offer some short-term protection from the disease.¹¹⁰

PLAGUE

For many centuries, plague has appeared in epidemics with significant mortality. Due to the understanding of the epidemiology of plague and the responsible organism, *Yersinia pestis*, control of the responsible rodents and fleas has markedly decreased the incidence of this infection. The availability of antibiotics in the second half of the twentieth century has allowed effective therapy of plague if the signs and symptoms are recognized in a timely manner.

About 15 countries report plague to the World Health Organization each year. These cases are primarily from the western United States, Peru, East Africa, and Southeast Asia and India. *Yersinia pestis* exists in nature as a zoonotic infection in rodents and their fleas, and humans are incidentally infected,

usually by flea bites and occasionally by the handling of infected animals or by inhalation.¹¹⁷ After gaining entrance into the body via a flea bite or inhalation, the organism causes bacteremia and septicemia, resulting in death by disseminated intravascular coagulation, refractory hypotension, renal shutdown, and shock. Pneumonic plague results in acute respiratory distress syndrome and multilobar confluence.

Approximately 2 to 6 days after infection, the patient with bubonic plague experiences fever to 38°C or greater, chills, headache, myalgias, arthralgias, and lethargy.¹¹⁸ During the next day or two the patient has pain and tenderness in the regional lymph nodes that drain the area of the flea bite. The bite often results in a papule, pustule, ulcer, or eschar. The skin over the involved lymph nodes becomes erythematous, edematous, tense, and warm to the touch. The bubo of plague differs from the lymphadenopathy of most other causes by its rapid onset, marked tenderness, and systemic toxemia, as well as the absence of cellulitis or ascending lymphangitis. If appropriate antibiotic therapy is initiated in the acute state, bubonic plague usually responds rapidly, with decrease of fever and resolution of systemic symptoms in 2 to 5 days. The buboes, however, remain enlarged, tender, and sometimes fluctuant for 1 or more weeks after successful therapy.

If therapy is not initiated early, bubonic plague progresses to systemic toxemia, tachycardia, prostration, agitation, confusion, convulsions, delirium, and death. Patients with septicemic plague often present with endotoxemia and gastrointestinal symptoms but without regional lymphadenitis.^{119,120} Plague is often not suspected initially, until laboratory results indicate its presence. Without intensive supportive care and antibiotic therapy, septicemic plague can rapidly progress to disseminated intravascular coagulation manifested as petechiae, ecchymoses, and acral gangrene. In addition to disseminated intravascular coagulation, refractory hypotension, renal shutdown, and acute respiratory distress syndrome usually result in shock and death in the absence of therapy.

The most rapidly developing and deadly form of plague is pneumonic plague. Within 2 to 4 days of infection, fever, chills, myalgias, arthralgias, dizziness, and lethargy develop. By the second day, the patient suffers from productive cough, tachypnea, dyspnea, hemoptysis, respiratory distress, chest pain, cardiopulmonary insufficiency, circulatory collapse, and sudden death. For the diagnosis to be made in time to initiate life-saving therapy, the physician must have a high index of suspicion

from the patient's history of exposure to *Yersinia pestis*—carrying rodents and fleas, as well as signs and symptoms suggestive of plague. Intensive supportive care and appropriate antibiotic therapy must be initiated immediately upon reasonable suspicion of plague. Gram, Wayson, or Giemsa staining and culturing must be performed with buboes, blood, lymph node aspirates, sputum, tracheal samples, cerebrospinal fluid, and so forth. The clinical specimens should also be examined with fluorescent antibody testing. Acute and convalescent serologic testing¹²¹ and chest radiography should be performed. The peripheral leukocyte count is usually between 15,000 and 25,000 per microliter and sometimes exceeds 100,000 per microliter.

The differential diagnosis of bubonic plague includes lymphogranuloma venereum or localized lymphadenopathy due to other regional infections, but the symptoms of plague would not be expected in these conditions. The differential diagnosis of septicemic plague can include various gastrointestinal infections, and the differential diagnosis of pneumonic plague includes other causes of pneumonia. The drug of choice in treatment of plague is streptomycin, although gentamicin, tetracycline, and chloramphenicol can also be used. Buboes may require surgical drainage. Patients with plague also need intensive supportive care. Without antibiotic therapy, more than 50% of patients with bubonic plague will die, as will almost 100% of patients with septicemic or pneumonic plague.

A safe and effective vaccine for *Yersinia pestis* is not available for human beings,¹²² but control of plague is best achieved through avoidance of areas with known epizootic plague, avoidance of diseased or dead animals, and use of repellents, insecticides, protective clothing, and masks. Persons with suspected pneumonic plague must be isolated, and respiratory precautions must be used. Antibiotic prophylaxis can be used for persons who must work in areas of plague outbreaks or must care for plague patients.

ANTHRAX

Anthrax is found throughout tropical Africa, Asia, Central and South America, and the Caribbean; it is due to the gram-positive bacillus, *Bacillus anthracis*. Incidental infection of human beings is usually due to contact with infected livestock or wild herbivores or animal products (eg, meat, hides, wool). Dying and dead animals contaminate the soil with spores that subsequently infect other animals or people. Recently, the potential of the use of anthrax spores as weapons of bioterrorism has become a reality. More than 95% of all clinical anthrax is cutaneous, resulting

from spores that enter abraded skin of persons who skin or butcher infected animals or of persons who subsequently handle the meat, hides, or wool. Other presentations of anthrax include oropharyngeal or gastrointestinal (from eating raw or undercooked meat) and inhalational (from contaminated wool or hides or from bioterrorism). The majority of these systemic presentations are fatal if not treated. Hematogenous spread can lead to meningoencephalitis. Death is from edema, hemorrhage, and necrosis secondary to anthrax toxins.

After entering the skin, anthrax spores germinate, resulting in a "malignant pustule," although pus is usually seen only if there is secondary bacterial infection. Histologic assessment of the skin lesions reveals marked tissue destruction with extensive subepidermal edema, thrombosis of vessels, and hemorrhagic interstitium. Toxin production results in generalized edema and nonpitting edema around the lesion.

Although the draining lymph nodes respond to the infection, the bacterial capsule is antiphagocytic and bacteremia often results. Inhalation anthrax results in phagocytosis of spores by alveolar macrophages, mediastinal widening, and bacteremia. As seen in the victims in Sverdlovsk, Russia, death is due to primary pneumonia.^{123,124} Anthrax is not found in the sputum of persons with inhalational anthrax. Ingestion of meat contaminated with anthrax results in ulceration and hemorrhage at the points of entry in the submucosa, especially in the oropharynx and the ileocecal regions. Hemorrhagic ascites and diseased bowel segments are associated with bacteremia. Hemorrhagic meningitis can result from bacteremia in any clinical form of anthrax.

Although reinfection with anthrax has been reported, immunity can develop from subclinical infection, and lasting protection usually results in survivors of clinical anthrax.^{125,126} Measurable antibodies to the toxin and the capsule are found after infection. Anthraxin is a skin test for delayed-type hypersensitivity that has been reported to be useful.

In approximately 90% of cutaneous anthrax cases, there is only one lesion, and it is usually on an exposed part of the body.¹²⁷ The initial symptom is pruritus, which follows infection by 3 to 10 days. The first sign, a papule a few millimeters in diameter, usually follows pruritus by only 1 day. During the next day, vesicles surround the papule. The vesicles coalesce, and the papule ruptures, resulting in a 4- to 6-cm-diameter ulcer.

During the next few days, the ulcer develops a thick, depressed, brown to black eschar that adheres to the underlying tissue. Nonpitting edema forms

around the eschar, and regional lymphadenopathy develops. If the lesion is on the neck, edema may become so extensive as to compromise respiration. The patients are usually afebrile, and the skin lesions are usually painless. Some patients, however, do develop fever, headache, anorexia, nausea, and lethargy associated with the systemic effects of the toxin. More than 80% of untreated cutaneous lesions remain localized and heal within 2 to 6 weeks, often resulting in scar formation. Almost 20% of untreated cutaneous lesions and the majority of systemic infections develop systemic bacteremia and are fatal.¹²⁸

In the setting of the signs or symptoms of anthrax or a history of potential exposure to the bacteria or spores, Gram staining should be carried out on material from the vesicle fluid, ulcer base, or other appropriate clinical material for large, gram-positive bacilli. Bacterial culture should be inoculated on the appropriate media and serologic evaluation performed using a specific inhibition enzyme immunoassay for antibodies directed against purified protective antigen. A biopsy specimen should be taken from a characteristic cutaneous lesion and examined for the changes described above. Therapy must be initiated immediately to prevent the high mortality and to reduce morbidity. The differential diagnosis of cutaneous anthrax includes orf, tularemia, plague, burns, cutaneous diphtheria, rickettsial eschar, ecthyma gangrenosum, and staphylococcal skin lesions such as bullous impetigo.

Considering the high mortality associated with anthrax, treatment must be started as soon as possible. Therapy of cutaneous anthrax usually involves use of oral potassium penicillin V or intramuscular procaine penicillin G. If the patient has a penicillin allergy, alternatives include tetracycline, ciprofloxacin, erythromycin, and chloramphenicol. Intravenous penicillin G, along with intensive supportive care, is the therapy of choice for systemic anthrax. Alternative antibiotics in penicillin-allergic persons include streptomycin, erythromycin, and tetracycline. Surgical excision or incision of the cutaneous lesions is not beneficial and can even exacerbate the injury.

Use of control measures for animal anthrax will help prevent human anthrax. These measures include quarantine of animals suspected to have been exposed to anthrax, use of antibiotics or destruction and incineration of infected animals, and vaccination of livestock at risk of anthrax. Prevention of human anthrax also requires public awareness programs and vaccination for persons at high risk (ie, the military).¹²⁹ Antibiotic prophylaxis can be protective if used properly.

MISCELLANEOUS BACTERIA

A number of other tropical bacterial diseases with cutaneous manifestations occasionally present to physicians in temperate countries and are included in this review. These diseases include melioidosis, glanders, tularemia, *Vibrio vulnificus* infections, typhoid fever, psittacosis, and Q fever.

Melioidosis

Melioidosis is an opportunistic infection caused by the gram-negative bacillus *Burkholderia* (formerly *Pseudomonas*) *pseudomallei* and is most often reported from Southeast Asia in persons who have frequent contact with soil or surface water, such as in rice paddies.¹³⁰ Because of this association, melioidosis is four times more common in males than in females. It is also strongly associated with diabetes mellitus. The infection may be subclinical in otherwise healthy persons or fulminant and rapidly fatal in immunocompromised patients. In addition, melioidosis may be acute or chronic and localized or disseminated. It may be latent and reappear clinically at times of stress as reported in American veterans of the Vietnam War.¹³¹ Clinical manifestations develop after an incubation period of 6 days (range, 1 day to 2 months), with high fever and rigors as well as occasional confusion, stupor, jaundice, and diarrhea. Common laboratory findings include anemia, neutrophil leukocytosis, coagulopathy, and renal and hepatic abnormalities.

Cutaneous manifestations, seen in 10% to 20% of patients, include cutaneous pustules or subcutaneous abscesses. The most common cutaneous manifestation in children is acute suppurative parotitis. Treatment of melioidosis is intensive supportive care, draining of abscesses, and antibiotic therapy using β -lactam agents such as ceftazidime or amoxicillin and clavulanate, with or without cotrimoxazole. Antibiotics must be given for 20 weeks to avoid relapses.

Glanders

Glanders is caused by a gram-negative bacterium, *Burkholderia* (formerly *Pseudomonas*) *mallei* and is usually acquired from horses but may be transmitted person to person. It is most common in Asia, Africa, and South America but was reported in an American research microbiologist in 2001.¹³² After an incubation period of 1 day to 2 weeks, patients with glanders can present with fever and any of 4 clinical manifestations: a nodule with lymphangitis at the site of inoculation, the nodule eventually breaking down and ulcerating; mucous membrane ulceration and granulomatous reaction; septicemia with cutaneous papules and pustules; and pulmonary form with

malaise, headache, and pleurisy. The treatment of glanders is with sulfadiazine.

Tularemia

Although not usually classified as a tropical disease, tularemia can be seen in Mexico and in the Far East. It is more likely to be acquired in the United States, Europe, and the former Soviet Union. Tularemia is a zoonosis due to infection with a gram-negative coccobacillus, *Francisella* (formerly *Pasteurella*) *tularensis*; it is usually acquired from infected animals such as wild rodents, carnivores, and some species of birds. It can be seen in hunters who prepare animal carcasses, (eg, "rabbit fever") or can be acquired from the bites of mosquitos, tabanid flies, or ixodid ticks. Clinical symptoms can be manifested as ulceration at the site of primary infection, followed by lymphadenopathy and fever (ulceroglandular disease). The majority of infections remain subclinical, but septicemia as well as abdominal and pleuropulmonary forms can develop.¹³³ Streptomycin is the drug of choice, but other aminoglycosides can be used successfully, as can tetracyclines, chloramphenicol, third-generation cephalosporins, rifampin, and erythromycin.

The spread of tularemia may be prevented with the use of gloves when handling wild animals, avoidance of ticks, and use of insect and tick repellents.

Vibrio vulnificus

Cutaneous manifestations can result from puncture wounds from shrimp, crabs, or various other sources of trauma (eg, fishhooks) in salt water. Cellulitis, necrosis, and hemorrhagic bullae can develop, especially if the patient has alcoholic cirrhosis or diabetes mellitus. Ingestion of seafood contaminated with *V vulnificus*, especially raw oysters, in patients with such immunocompromising conditions can result in septicemia with widespread hemorrhagic bullae and can be fatal if not treated with intensive supportive care and systemic antibiotics.¹³⁴ Other species of *Vibrio* can rarely have similar clinical manifestations.¹³⁵

Other bacterial diseases

Cutaneous manifestations can be seen in a number of other tropical bacterial diseases, such as the erythematous macules known as "rose spots" of typhoid fever due to *Salmonella typhi*.¹³⁶ Extrapulmonary manifestations of psittacosis include Horder spots (pink macules that resemble rose spots of typhoid), acrocyanosis, superficial venous thrombosis, splinter hemorrhages, erythema multiforme, and erythema nodosum.¹³⁷ In addition, Q fever, due to

Coxiella burnetii, can occasionally cause erythema nodosa and erythema annulare centrifugum.¹³⁸

CONCLUSION

Patients with bacterial infections that are endemic to the tropics occasionally present to dermatologists in North America, Europe, and other areas with temperate climates. As more immigrants move from tropical to temperate areas and as more persons from temperate climates travel to or work in the tropics, it is expected that such infections will become increasingly common outside their usual range. Therefore it is important that physicians be familiar with the mucocutaneous manifestations of such infections and that they be prepared to diagnose these diseases and treat these patients.

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Answers to CME examination

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Questions 1-30, Lupi O, Madkan V, Tyring SK. *J Am Acad Dermatol* 2006;54:559-78.

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| 2. c | 17. a |
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| 4. b | 19. d |
| 5. a | 20. c |
| 6. d | 21. d |
| 7. a | 22. a |
| 8. d | 23. b |
| 9. c | 24. d |
| 10. a | 25. b |
| 11. b | 26. c |
| 12. c | 27. a |
| 13. a | 28. b |
| 14. b | 29. c |
| 15. b | 30. d |