Chapter 16

ATYPICAL MYCOBACTERIAL DISEASES

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INTRODUCTION

The group of acid-fast mycobacteria that do not cause tuberculosis or leprosy are a diverse collection of more than 30 facultative pathogens and saprophytes; they have been called by many names since first being recognized almost 70 years ago. Due to the medical importance of tuberculosis at the turn of the 20th century, designation as nontuberculous mycobacteria was and still is a common classification for this group. However, this designation was not altogether accurate because the leprosy bacillus should have been included in such a group of nontuberculous mycobacteria; nonetheless its exclusion is understandable, as it was not a culturable organism. Pseudotubercle bacilli, unusual mycobacteria, chromogenic or nonpathogenic acid-fast bacilli, saprophytic mycobacteria, and mycobacteria other than tuberculosis (MOTT) were some of the other terms used for this group of organisms. In 1954, Timpe and Runyon[1] called these organisms "atypical acid-fast bacteria" in their first attempt to classify them. In a 1959 refinement of this classification system, Runyon[2] referred to them as "anonymous mycobacteria." Thus, in reports about this group of organisms, any of these terms have been used to refer to what is now almost universally recognized as the atypical mycobacteria. This group includes both opportunistic pathogens as well as nonpathogenic, saprophytic, acid-fast mycobacteria; however, if the past is any indication of the future, some of the mycobacteria presently classified as nonpathogens will, under conducive host or environmental conditions, become facultative pathogens and be identified as such.

HISTORY

General History

The causative organism of leprosy was described in 1874 by Hansen,[3] from whose name the term Hansen's disease is derived; however, it was the identification of the tubercle bacillus as the cause of tuberculosis by Koch in 1882[4] that stole the mycobacterial disease spotlight for the next 50 years (Exhibit 16-1). A great effort was poured into research on epidemiology, diagnosis, and treatment of tuberculosis, then as now a significant worldwide medical menace. However, in many medical investigations of tuberculous disease, there began to emerge evidence for the existence of other "nontuberculous" mycobacterial infections. Probably the earliest hint of atypical mycobacterial infection was in 1897, with the description by Sir Albert Cook of slowly progressive ulcers of skin and underlying soft tissue in patients in Uganda.[5] More than 50 years later, in the Buruli District of Uganda, reports of multiple cases of *Mycobacterium ulcerans* infection would give it one of its eponyms, Buruli ulcer.

In the early 1900s, there were reports of rapidly growing, acid-fast organisms (as opposed to slow-growing tubercle bacilli) that were isolated from purulent sputum of patients with respiratory-tract disease.[6] Some clinicians called these organisms pseudotubercle bacilli, but their attempts to culture them were unsuccessful. Then, in 1904, came the report of a chronic injection-site abscess caused by an acid-fast bacillus. This organism was cultured and grew rapidly, in less than 1 week, and probably was what is presently classified as the group of rapid-growing atypical mycobacteria of the *Mycobacterium fortuitum–chelonae* complex. In 1926, *Mycobacterium marinum* was described and named as the cause of disease, not in humans, but in salt-water fish in the Philadelphia aquarium.[7] Years later, this same organism under a new name, *Mycobacterium balnei*, would be rediscovered as a cause of a human skin disease associated with swimming pools.

During the 1930s, further evidence for the existence of a group of "atypical" mycobacteria began to accumulate. In 1931, the Ryan strain, probably *M fortuitum*, was isolated from a pleural empyema. The organism was used to prepare a skin-test reagent that was reactive in that patient, who had not reacted to the usual *M tuberculosis* tuberculins of that day. Clinical laboratories began to isolate yellowish, pigmented, acid-fast organisms that were completely unlike the nonpigmented cultures of *M tuberculosis* or *M bovis*. In addition, inoculation of

EXHIBIT 16-1

MILESTONES IN THE HISTORY OF MYCOBACTERIAL DISEASE

Date	Event
1874	Leprosy bacillus is described by Hansen
1882	Tubercle bacillus is identified by Koch
1926	*Mycobacterium marinum* is identified by Aronson in Philadelphia aquarium fish
1938	*M fortuitum* is isolated and named by da Costa Cruz
1943	*M avium-intracellulare* is recovered from silicotuberculosis
1948	*M ulcerans* is reported isolated from skin ulcers in Australia
1951	*M balnei* (now called *M marinum*) is isolated from human skin lesions from swimming pool trauma
1953	*M kansasii* ("yellow bacillus") is isolated
1956	*M scrofulaceum*, so named because it resembled scrofula lymphadenitis in children
1959	Runyon Classification into Rapid Growers and Slow Growers (Groups I-IV) is established
1964	*M buruli* (now called *M ulcerans*) is isolated in Buruli District of Uganda
1965	*M kansasii* is first reported as skin infection
1965	*M fortuitum* is reported to produce abscesses
1972	*M szulgai* is first isolated and described
1977	*M malmöense* is reported as new species
1978	*M haemophilum* is described and named
1984	First report of skin infection with *M gordonae*
1984	*M ulcerans* is discovered in koalas in Australia
1990	*M malmöense* skin infection is reported

the atypical organisms into guinea pigs produced only local, self-healing lesions instead of the usual generalized involvement following *M tuberculosis* inoculations of guinea pigs. The "Mx" (mycobacteria x) strain was isolated from sputum from a lung abscess, and the "IP" strain originated from a case of chronic pneumonitis. Some variants of the "IP" strain produced pigmented colonies when exposed to light—again, completely unlike *M tuberculosis* colonies. A review of the literature published in 1935 revealed more than a dozen instances in which slow-growing, pigmented strains of acid-fast bacilli were recovered from humans without associated disease.[8] Then in 1938, da Costa Cruz isolated, described, and named the rapid-growing, acid-fast bacillus *M fortuitum*.[9] In that same year, there were reports of several cases of superficial abscesses from which rapid-growing, pigmented, acid-fast bacilli were isolated. From 1939 on, reports by Hellerström of facial granulomas, which followed abrasions in a swimming pool, implicated *M tuberculosis* as the cause of disease.[6] This was undoubtedly true in some of these cases, but in others the causative organism was probably *M marinum*. During the 1940s, manifestations of clinical disease were directly linked to atypical mycobacterial infections. In 1943, an acid-fast bacillus, later shown to be *M avium–intracellulare*, was recovered from a patient with silicotuberculosis. During that same year, a review of multiple pulmonary cases of normal or clinically nontuberculous patients revealed some positive *M tuberculosis* cultures and some "nonpathogenic" acid-fast bacilli. It was pointed out that "nonpathogenicity for animals did not preclude the ability to produce disease in the source patient."[6(p109)] In 1948, a new mycobacterial disease in humans was reported from the Bairnsdale district of Australia, with the first isolation and identification of *M ulcerans*.[10] Multiple reports of this infection in the same area gave it the eponym Bairnsdale ulcers. More than a decade later, what would eventually prove to be the same organism

was isolated from many patients in the Buruli District of Uganda with the disease they called Buruli ulcer.

In 1951, self-limited skin lesions thought to be tuberculous developed in approximately 80 Swedish patients, from whom was isolated acid-fast bacilli that grew at 31°C and produced yellow pigment only after exposure to bright light. These culture results made tuberculosis an impossibility, because *M tuberculosis* grows at 37°C and produces no pigment—with or without exposure to light. The same acid-fast organism was isolated from the walls of a swimming pool used in common by several infected patients. This apparently newly isolated species of mycobacterium was named *M balnei* (from the Latin, meaning "of the bath"). To remove all doubt that indeed a new mycobacterial disease had been discovered, Linell and Norden inoculated themselves with the organism and produced identical skin lesions from which the same mycobacteria were then isolated. Later in 1959, Bojalil showed that *M balnei* was the same species as *M marinum,* which had been isolated by Aronson in 1926 from fish in the Philadelphia aquarium. Thus, the earlier name took precedence and this organism officially became *M marinum*.[11] In 1953, two cases of mycobacterial disease were described that were caused by the "yellow bacillus," later identified as *M kansasii*.[12] Three years later, a nontuberculous, acid-fast organism that produced cervical lymphadenitis in children was named *M scrofulaceum*, because it so resembled tuberculous scrofula.[13] A preliminary report in 1954 on the known facts about nontuberculous pulmonary disease published the Timpe-Runyon classification system for these nontuberculous organisms, which were termed "atypical" acid-fast bacteria. This system was limited to grouping these organisms into Groups I through III, based on colony color and texture, and on virulence in mice and absence of virulence in guinea pigs. Timpe and Runyon warned against "discard of an acid-fast organism isolated from a patient with pulmonary disease because it fails to fit the cultural or virulence pattern of *M tuberculosis*."[1(p208)]

Then in 1959 came Runyon's landmark refined classification system of anonymous mycobacteria based on both colony pigmentation and growth rate.[2] This was a very detailed, in-depth report on the epidemiology, culture characteristics varying with temperature and light, animal pathogenicity, and drug resistance of more than 400 patient strains of atypical mycobacteria from 93 laboratories in 30 states. It provided incontrovertible evidence refuting the dogma that an acid-fast bacillus, unable to produce disease in guinea pigs, was ipso facto a saprophyte and not a pathogen. For, only the year before, it had been suggested that "atypical variants" that produce lymphadenitis almost exclusively in children were actually "mutants of *M tuberculosis*" that had become predominant because of their higher drug resistance.[14]

Into the 1960s, widespread knowledge and acceptance of the identification of the various atypical mycobacteria were generally lacking. In a 1963 report of 12 orthopedic cases that grew out mycobacteria, the organisms were identified as "a mycobacterium, other than *M tuberculosis, M ulcerans, M balnei,* or *M leprae*."[15(p327)] In other words, these infections were identified as *not* due to tuberculosis, Buruli ulcer, swimming-pool granuloma, or leprosy. The cultures in these cases grew at 22°C to 24°C, 30°C, and/or 37°C, with most colonies producing smooth, cream-colored (or, in a few cases, yellow or orange) growth. Unfortunately, the time required for colony growth was not recorded; however, the nonpigmented ones were probably rapid growers in the *M fortuitum* complex, and the orange colonies, which grew at all three temperatures, may have been *M kansasii* from Group I photochromogens or *M szulgai*—a temperature-dependent photochromogen/scotochromogen not isolated until 1972. With all of the culture characteristics, excluding rate of growth, and without more modern metabolism, seroag-glutination, and chromatography methods, it is impossible to classify these atypical mycobacterial infections precisely. Use of Runyon's classification system, however crude it might appear by current standards, was and still is helpful in keying out general groups of organisms. Even though the yellow bacillus, *M kansasii*, had been isolated from autopsy material more than 10 years previously, it was not until 1965 that the first skin infection caused by *M kansasii* was reported.[16] Also in 1965, *M xenopi,* which has been commonly recovered from hospital hot-water storage tanks, was recognized first as a pulmonary pathogen. In that same year, subcutaneous abscesses due to *M fortuitum* were reviewed. Many reports of *M fortuitum* infections of skin, soft tissue, lung, and even the cornea were documented during this decade.[17]

The 1970s produced reports of pulmonary infections by *M simiae* and skin infections by two new atypical mycobacteria—*M szulgai* in 1972 and *M haemophilum* in 1978. In addition, work went forward on serotyping the various groups of atypical mycobacteria after more widespread use of differential culture techniques began to demonstrate the

more frequent occurrence of these acid-fast organisms in the production of disease. Additional biochemical tests were also developed to better differentiate the various species. Some species with differing names were found to be the same organism, while others were split into separate and distinct species. The acceptance of the atypical mycobacteria as separate and distinct species of mycobacteria became more widespread; the diagnosis of tuberculosis was restricted to slowly growing mycobacteria that (*a*) grew at 37°C, (*b*) did not produce yellow or orange colonies, (*c*) did give positive results for niacin and nitrate reduction, and (*d*) were virulent in guinea pigs.

In 1983, *M asiaticum*, which had been included among *M simiae* isolates from primates almost 20 years previously, was implicated as the cause of pulmonary disease; however, this particular newly identified organism did not, and has not been shown to, disseminate to the skin.[18,19] In 1984, *M gordonae*, a commonly encountered saprophyte in the laboratory, which has been referred to as the "tap-water bacillus" or *M aquae* in the past, was isolated as the cause of infection in the hand.[13] That same year, *M ulcerans*, thought only to infect humans, was isolated from koalas in Australia, thus stimulating speculation as to the epidemiology and transmissibility of this organism between humans and potential animal reservoirs.[20] Although *M malmöense* had been identified in 1977 in Malmö, Sweden, it had been associated solely with pulmonary disease and cervical adenitis until 1990, when it was isolated as the cause of skin nodules in a patient with chronic myeloid leukemia.[21] Prior to development of these skin nodules, this patient had developed a supraclavicular node that on biopsy was diagnosed as tuberculosis but was unresponsive to isoniazid, rifampicin, and pyrazinamide.

During the decade of the 1980s, increasing numbers of cases of atypical mycobacterial infections in immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS), were being reported. Many of these infections occurred in organs that had not previously been reported as being involved with atypical mycobacterial infections. Thus, it had become apparent that clinicians and researchers should maintain a high index of suspicion for unusual presentations of the atypical organisms, especially in immunocompromised patients. Nevertheless, diagnosis is accomplished through better and more sophisticated diagnostic classification tests such as thin-layer chromatography, plasmid profiling, enzyme-linked immunosorbent assay (ELISA), high-pressure liquid chromatography, radiometric culture system, and species-specific deoxyribonucleic acid (DNA) probes.[22–24]

Military History

There is no record of a single battle or military campaign whose outcome was determined by the presence of atypical mycobacterial infections. This is most likely due to their low overall clinical prevalence (< 2 / 100,000 in the United States) and to their lack of human-to-human or animal-to-human communicability.[22] Human infection occurs in an opportunistic fashion, with repeated or prolonged exposure of traumatized or compromised skin, soft tissue, or airway to adequate amounts of pathogenic, or in some cases, even saprophytic atypical mycobacteria. Water and soil appear to be their most common and most likely sources.[22] Therefore, on the battlefield or on the sea, wounded combatants may have a ready source of opportunistic infection if open wounds are allowed to come into repeated or prolonged contact with the environment. In 1918, chronic pustular skin lesions containing relatively rapidly growing, acid-fast bacilli were noted in a wounded English soldier who was being transported by ship. The ship was then sunk in the North Sea, which exposed his wounds directly to seawater.[6] The soldier's subsequent skin lesions were most likely caused by infection with organisms from the *M fortuitum–chelonae* complex or possibly *M marinum*.

Almost certainly there were some cases of atypical mycobacterial infections during World War II, because tropical areas are endemic for many of the atypical organisms and wounded soldiers and sailors were undoubtedly directly exposed—sometimes for prolonged periods—to soil, water, or lush vegetation. However, the seriousness of their wounds, or the occurrence of more virulent infections in these wounds, may have displaced concern over relatively benign-appearing skin lesions, a chronic cough, or indolent soft-tissue infections such as might have been seen with atypical mycobacterial infections. In fact, if the casualty did survive his other injuries, many of the skin, pulmonary, or soft-tissue lesions of atypical mycobacterial infections would have healed spontaneously, after several months or even years, despite the lack of standard wound care. Some of the atypical mycobacteria might well have responded to timely debridement, surgical excision, incision and drainage or, in the years following World War II, to the administration

of antituberculous drugs or antibiotics as they became available. Mortality from these organisms was apparently small or was attributed to other types of infections, because during the 1940s, atypical mycobacteria were only beginning to be suspected as agents of infection. Usually, pulmonary disease and soft-tissue and lymphatic involvement that produced acid-fast bacilli were attributed to tuberculosis and treated as such. These treatment failures were then considered to be unresponsive or resistant cases of tuberculosis, and, without the special culture techniques for demonstrating atypical mycobacteria, their involvement went undetected. It was not until after World War II, in 1948, that *M ulcerans* was isolated and identified as the acid-fast bacillus that directly causes progressive ulcerative skin lesions (ie, Bairnsdale ulcers).

With the beginning of the Korean conflict came the first reports of the isolation of *M balnei* (the same organism as *M marinum*, which had been described earlier in fish) as the cause of the disease (in several patients in Sweden) that would later become known as swimming-pool granuloma. Little more was known about atypical mycobacterial infections in humans, except for suspicions that they might be secondary pathogens in chronic pulmonary disease. Soon after the Korean conflict, Runyon's detailed study and classification system for these organisms was published in 1959.[2] Fortunately, soldiers kept their exposure to water to a minimum during the harsh Korean winter, thereby decreasing the chances that casualties with even minor battle wounds would be contaminated by organisms such as *M marinum* or *M kansasii*. Certainly there must have been some soft-tissue infections with the atypical mycobacteria secondary to contamination associated with shrapnel and bullet wounds; however, as in World War II, surgical debridement, excision, incision and drainage, or amputation would have been curative of many atypical mycobacterial infections. Being far from the tropics, Korea was not an endemic area for *M ulcerans*, the cause of Buruli ulcer. Pulmonary infections with *M kansasii* or *M avium–intracellulare*, found to be positive for acid-fast bacilli, would have been treated as tuberculosis, with some success using antituberculous drugs. Most likely, these infections were recognized as somewhat resistant strains of tuberculosis that, when cultured with the usual mycobacterial techniques, unlike *M tuberculosis*, produced strangely pigmented yellowish colonies. For, in this war, as in prior wars, knowledge about atypical mycobacteria as possible pathogens was relatively uncommon throughout the medical community.

Although atypical mycobacterial infections per se are not mentioned in Lieutenant Colonel Alfred M. Allen's landmark volume on dermatology in the U.S. Army, *Skin Diseases in Vietnam, 1965–72*,[25] several reports of that era record infections with these organisms. In a report published in 1963,[15] 12 orthopedic cases were discussed, with atypical mycobacterial infections of tendon sheaths in one half of the patients and involvement of joints in the other half. Three of the tendon infections followed laceration or hydrocortisone injections, and three of the six joint infections followed repeated injections of hydrocortisone into the affected joint. The exact atypical mycobacteria species in these cases were not identified, but *M ulcerans* and *M marinum* were ruled out by bacteriological studies; thus, given the culture growth characteristics, the offending organisms were most likely *M fortuitum*, *M kansasii*, or *M szulgai*.

One report[17] recounted a *M fortuitum* infection following multiple gunshot wounds received by a 20-year-old army infantryman while in Vietnam in 1968. Interestingly, this organism was recovered from an abscess that developed proximally in the left thigh some 3 months after the initial wound and fracture of the left lower leg. Initial therapy with isoniazid and pyrazinamide for 2 months had shown no effect; therefore, extensive debridement, sequestrectomy of the involved bone, and split-thickness skin grafting finally produced sustained healing of the area after 4 more months. Another report[26] described *M fortuitum* infections in three severely wounded Vietnam veterans with deep soft-tissue abscesses; all eventually healed following extensive debridement, incision and drainage, and local wound care. These three cases were the only ones found among the large number of injured patients returning from Vietnam and treated at Valley Forge (Pennsylvania) General Hospital. The low number of cases may have been attributed to the aeromedical evacuation system that was used during the Vietnam conflict, which rapidly removed the accessible wounded from the battlefield, thus preventing continued contact of open wounds with water or soil contaminated with atypical mycobacteria. Rapid removal of patients with extensive open wounds to relatively sophisticated treatment facilities with good laboratory capabilities is essential in minimizing delays in diagnosis and effective treatment of atypical mycobacterial infections.

EPIDEMIOLOGY

Atypical mycobacterial diseases are not communicable: human-to-human transmission has rarely, if ever, been known to occur. Instead, these diseases occur when an individual made susceptible by trauma, a deep wound, a surgical procedure—with or without compromise of the immune system—comes in sufficient contact with these saprophytic organisms. Atypical mycobacteria can be found almost worldwide in soil, water, vegetation, and indigenous animals. Therefore, the incidence of disease caused by these organisms is relatively low, even rare, unless the scales are tipped in their favor due to exposure of susceptible tissue to these organisms in their endemic locales.

Due to their similar clinical, etiologic, and antigenic characteristics, two groups of atypical mycobacteria are considered together as "complexes." For example, *M intracellulare* and *M avium* produce almost identical human pathogenicity and are found together endemically. They differ in their ability to produce disease in animals and can be distinguished from one another by sophisticated laboratory techniques; however, their human clinical course, histology, and response to treatment are essentially identical. They are grouped together as the *M avium–intracellulare* complex. *M scrofulaceum* is sometimes included in the *M avium–intracellulare* complex because it also produces cervical adenitis—one of the clinical signs seen in both children and adults with *M avium–intracellulare* complex infection.

Although *M fortuitum* and *M chelonae* each contain several separate and identifiable subgroups, the human diseases that they produce have such similar clinical courses and culture characteristics that these organisms, too, are usually grouped together as the *M fortuitum–chelonae* complex.

Because atypical mycobacteria are ubiquitous, they were not readily associated with clinical disease. However, under circumstances that are precisely right for them and wrong for the host, these saprophytes take their place as true pathogens in the production of human disease.

Incidence

The true incidence of atypical mycobacterial disease is difficult to ascertain: because they are not communicable diseases, they are not reportable in the United States. However, several laboratory surveys of pathogenic mycobacteria have been reported (Table 16-1). One such survey, published in 1982 by the Centers for Disease Control in Atlanta, Georgia, suggests that 65.2% of the total mycobacterial pathogens isolated were *M tuberculosis* and 34.8% were atypical mycobacteria. Of the atypical mycobacterial isolates, about 60% were *M avium–intracellulare* complex; 20% *M fortuitum–chelonae* complex; 10% *M kansasii*; with *M scrofulaceum, M marinum, M xenopi, M szulgai,* and *M malmöense* comprising the remaining 10%.[27] In 1990, the overall prevalence of atypical mycobacterial infections was estimated at about 2/100,000 population in the United States, with over one half the cases due to *M avium–intracellulare* complex, and the largest population of patients being white males who are not infected with AIDS.[22] If *M avium–intracellulare* complex infections in AIDS patients were included, the percentage of infection in white males would be even higher. Even though the *M avium–intracellulare* complex is the most prevalent atypical mycobacterium in the United States and is also common in western Australia and Japan, it is rare in Europe: the predominant atypical organisms there are *M kansasii* and *M xenopi*.

Sources of Organisms

Mycobacteria exist and probably multiply in a wide variety of natural sources such as soil, water,

TABLE 16-1

PATHOGENIC MYCOBACTERIA ISOLATES IN THE UNITED STATES (1980)

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and wild and domestic animals and birds; therefore, it seems reasonable to believe that most human disease comes from the environment.[6] Even potable water supplies harbor some of these organisms: *M gordonae* (the tap-water bacillus) and *M xenopi* (isolated almost exclusively from water, especially from hospital hot-water systems, and called the hot-water bacillus).[13,22]

Although *M ulcerans* has recently been isolated in Australia from koalas, there have been no isolates from samplings of soil, water, or vegetation; however, Buruli (Uganda) and Bairnsdale (Australia) ulcers, both caused by *M ulcerans*, are known to be endemic in tropical or subtropical areas where wet, marshy terrain produces lush vegetation—usually without koalas in the environment.[20] *M marinum* is not only found in both fresh and salt water, it is also found in fresh- and salt-water fish. In addition, *M marinum* is found in swimming pools, aquariums, and mud and is capable of multiplying in soil.[28]

Although not isolated from soil or natural water supplies, *M kansasii* has been isolated many times from tap water and is found in wild and domestic animals such as cattle and pigs.[22,29] Organisms from the *M fortuitum–chelonae* complex have been isolated from soil, natural water supplies, tap water, house dust, distilled water, hemodialysis equipment, and even gentian violet skin-marking solutions.[22,30] *M scrofulaceum* organisms have been found in soil, water, raw milk, dairy products, and oysters.[13] Researchers in one report pooled together shucked oysters from several oyster beds. The oyster homogenate, inoculated on mycobacteria cultures, grew *M scrofulaceum*.[31]

The pulmonary route of infection is probably the most common for *M avium–intracellulare* complex. Interestingly enough, the highest numbers of these isolates are found aerosolized in air samples when compared to soil, dust, sediment, or even water samples (*M avium* and *M intracellulare* can remain viable for years in soil and water).[13] Even though the organisms are known to cause disease in birds, poultry, pigs, cattle, and monkeys, the disease has not been shown to be communicable from these animals to humans.

With the possible exception of pulmonary infections with *M xenopi*, human-to-human infections by atypical mycobacteria do not occur.[32]

Distribution

Distribution of atypical mycobacteria appears to be worldwide; however, some organisms are found only in limited areas (eg, *M ulcerans* in Central Africa, Australia, New Guinea, Mexico, Central America, and South America). Some species are common in relatively similar geographical areas. For example, although *M avium–intracellulare* and *M fortuitum–chelonae* complexes are found almost worldwide, in the United States they are more common in the southeastern and Gulf-coast states, while *M kansasii* is more prevalent in the midwestern and central parts of the country.[22,29] A 1967 report,[33] which consolidated data from two previous reports[34,35] on the incidence of skin-test reactions to specific atypical mycobacterial antigens in healthy U.S. Navy recruits, gave the following results: in 257,476 recruits, *M avium–intracellulare* produced fewer than 30% reactors from northern, western, and far-western regions, and approximately 70% reactors from the southeastern United States. Similarly, in 31,479 recruits, *M scrofulaceum* produced about 30% to 50% reactors in most areas of the United States, while it produced more than 80% reactors in the southeastern United States.[33] Likewise, *M avium–intracellulare* complex infections are generally more common in rural areas, while *M kansasii* is most common atypical mycobacterium found in sputum specimens from urban areas.[36]

The relatively uncommon occurrence of *M malmöense* has been reported only rarely outside a relatively limited area that includes Sweden, Ireland, England, and Wales.[13,21] The occurrence of *M scrofulaceum* is worldwide, but generally in the more temperate climatic zones, while *M marinum* is found worldwide in association with either fresh or salt water.[13,37] Causing only rare cases of pulmonary disease, *M asiaticum* has been found in Queensland, Australia, and Los Angeles, California.[19]

CLASSIFICATION SYSTEMS

Due to the variability in organ systems involved and in the clinical expression of disease in the atypical mycobacteria group, standardization of a logical, understandable classification system is difficult at best. However, some semblance of order has developed since 1954, with the first attempt by Timpe and Runyon to group these organisms into meaningful categories. In that first attempt at classification, organisms were not named by their species but instead were placed in Groups I, II, or III

according to their colony color, texture, rate of growth, virulence in guinea pigs and mice, and how these characteristics compared with those of organisms from other microbiology laboratories from around the country.[1] Runyon's much more sophisticated system was proposed in 1959, when he placed more than 400 atypical strains in the following three slow-growing groups (ie, Groups I, II and III, which grew in 3–4 wk), based mainly on colony color and the effects of light and darkness; and in Group IV, based solely on how rapidly the colonies grew[2]:

- Group I: Photochromogens (color forms only with light),
- Group II: Scotochromogens (color forms even in darkness),
- Group III: Nonphotochromogens (weak to no color forms in both darkness and light), and
- Group IV: Rapid Growers (colonies grow within 48 h, with little to no color).

Additional features that were recorded included pretreatment drug resistance; strong colony catalase activity; growth at room temperature; lack of virulence in guinea pigs; and colony characteristics, including intense pigmentation, smooth surface, easy dispersion in liquid, and growth within 3 days. Several of the then-known species of atypical mycobacteria were then placed in one of these four simple groups according to their colony-growth characteristics; others (eg, *M ulcerans*) were not placed in the groups because their features overlapped.

Since then, many additional tests for species separation have been developed that can be used by specialty laboratories to determine (*a*) the exact species of atypical mycobacteria causing a specific disease and (*b*) its drug sensitivities. Using readily available media and incubating at the appropriate temperatures, a relatively accurate appraisal of suspected atypical mycobacteria can be made, using tables based on the original Runyon groups. The recently identified species have been inserted into their appropriate groups (Exhibit 16-2) for the reader's convenience. The most commonly isolated organisms are listed toward the top of each group; special or unique characteristics are noted in parentheses for some species; and, for the more uncommon pathogens, the most significant investigations are referenced. Although not included with the atypical mycobacteria because it was always the "typical" one, *M tuberculosis*, if it were listed, would go into Group III: its colonies are slow growing and produce no pigmentation. At present, *M leprae* is not culturable by routine methods and therefore is not placed in a classification group based on colony characteristics.

Some classification schematics differentiate organisms solely on their pigment production without reference to the rate of colony growth, while

EXHIBIT 16-2

RUNYON CLASSIFICATION OF ATYPICAL MYCOBACTERIA

Slow Growers (> 7 d)

Group I, Photochromogens
- *M marinum*[*]
- *M kansasii*
- *M szulgai* (at 25°C)[1]

Group II, Scotochromogens[†]
- *M scrofulaceum* (cervical adenitis with ulcerations)
- *M szulgai* (at 37°C)[1]
- *M xenopi* (adenitis, sinus tracts)[2]
- *M gordonae*[3]

Group III, Nonchromogens
- *M avium–intracellulare*[‡]
- *M ulcerans*
- *M heamophilum* (seen in immunocompromised patients)[2]
- *M malmöense* [4]

Rapid Growers (< 7 d)

Group IV, Buff colored
- *M fortuitum–chelonae* complex (after surgery and trauma)[*]
- *M smegatis* (after cardiac bypass surgery)[5]

[*]Most commonly seen
[†]All in this group are rare
[‡]Seen with increasing frequency with HIV infections

The following are the most significant investigations for particular organisms:

1. Cross GM, Guill MA, Aton JK. Cutaneous *Mycobacterium szulgai* infection. *Arch Dermatol.* February 1985;121:247-249.
2. Woods GL, Washington JA II. Mycobacteria other than *Mycobacterium tuberculosis*: Review of microbiologic and clinical aspects. *Rev Infect Dis.* Mar-Apr 1987;9(2):275-294.
3. Shelley WB, Folkens AT. *Mycobacterium gordonae* infection of the hand. *Arch Dermatol.* 1984;120:1064-1065.
4. Gannon M, Otridge B, Hone R, Dervan P, O'Loughlin S. Cutaneous *Mycobacterium malmöense* infection in an immunocompromised patient. *Int J Dermatol.* March 1990;29(2):149-150.
5. Wallace RJ Jr, Musser JM, Hull SI, et al. Diversity and sources of rapidly growing mycobacteria associated with infections following cardiac surgery. *J Infect Dis.* 1989;159(4):708-716.

others are based on characteristic clinical and radiographic findings and skin tests (eg, purified protein derivative of tuberculin [PPD]).[36] A recently suggested classification system for cutaneous mycobacteriosis, which includes mostly tuberculous infections, is based on the clinical *source* of the infection: whether exogenous, endogenous, or hematogenous.[38] A disadvantage of this particular system is that the atypical mycobacteria can fall into any of these three categories, and identification of the particular organism is not the goal of this system. A more recent, clinically useful classification system divides atypical mycobacterial infections into clinical disease groups based on the organ system involved—pulmonary, lymphatic, cutaneous, or disseminated.[22] In this classification system, common and unusual etiologic species in each group are then listed along with their growth rates, colony pigmentation characteristics, and references to the medical literature. One limitation of this system is that only the more common skin pathogens are included; therefore, if a patient's disease is caused by a rare, atypical organism, it might not be considered in the clinical or laboratory differential.

One of the main objectives of organism classification is to expedite the initiation of effective therapy. In nonimmunocompromised patients who have atypical mycobacterial skin infections, time may be on the side of the patient. However, should the infection disseminate or spread to deeper structures—or, in immunocompromised patients, to soft tissue—time may be of the essence in preventing severe morbidity or even mortality. Additionally, the ability to rule in certain atypical mycobacterial infections and to rule out others by culture classification is significant in managing these patients with confidence and effectiveness. In most cases of mycobacterial infection, the histopathology alone will not be completely diagnostic; therefore, in cases with borderline or overlapping histopathological findings, the bacteriological classification of the involved organism may become vital.

HISTOPATHOLOGY

As occurs in *M tuberculosis*, seven different patterns of reaction may be seen on histological examination of the atypical mycobacteria (see Chapter 15, Cutaneous Tuberculosis, for further discussion of these patterns):

1. classic tuberculoid granulomas,
2. abscess formation,
3. diffuse infiltrate of histiocytes,
4. panniculitis,
5. nonspecific chronic inflammation,
6. sarcoidal granulomas, and
7. rheumatoid-like nodules.

These patterns are not pure but represent a spectrum of changes. For example, well-formed granulomas are seen less commonly in atypical mycobacterial diseases than they are in *M tuberculosis* infections, and a classic tuberculoid pattern is not commonly seen. Therefore, instead of relying on a classic tuberculoid granuloma, the medical officer should be sufficiently familiar with the general patterns to suspect a mycobacterial infection in routine stained material, then obtain special acid-fast stains to identify the causative organism. In most atypical mycobacterial infections, acid-fast organisms are sparse (Figure 16-1). However, in early necrotic areas of Buruli ulcer and in immunocompromised patients, many organisms—sometimes even clumps—can be seen.

The features most commonly seen with each specific atypical mycobacterial infection are discussed later in this chapter.

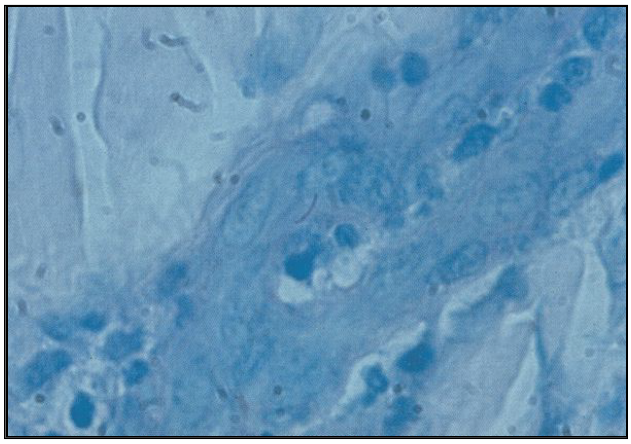

Fig. 16-1. Note the acid-fast bacillus in the center of this positive acid-fast stain of atypical mycobacteria.

MYCOBACTERIOLOGY

In 1896, the genus name *Mycobacterium* was given to a group of bacteria that grew moldlike pellicles when cultured on liquid media.[39] This genus of bacteria was already large, and many additional species, including the atypical mycobacteria, have been added during the 20th century. All atypical mycobacteria are nonmotile, aerobic, nonencapsulated, nonsporulating, usually slender bacilli that have a waxy coating that resists acid-alcohol decolorizing once they are stained, thus their designation *acid fast*.

Useful acid-fast stains for these organisms include Ziehl-Neelsen and Kinyoun, a modified Ziehl-Neelsen stain that is milder and better suited to atypical mycobacteria. The Fite (Fite-Ferraco) stain, usually used in staining for *M leprae*, is useful as a screening acid-fast stain for all mycobacteria. The auramine-rhodamine stain using a fluorochrome technique is approximately 100-fold more sensitive than the Fite stain and is very useful for detecting sparse numbers of atypical mycobacteria; *M fortuitum–chelonae* organisms, however, do not take this fluorochrome stain well. The routine Gram's stain is usually positive, to some degree, for atypical mycobacteria. The organisms vary in size, ranging from 0.2 to 0.6 μm in diameter and 1.0 to 4.0 μm in length; however, there may be some variability even within the same species (eg, *M malmöense* can be coccoid to short to moderately long).[13]

Routine culture media, such as blood or chocolate agar, will support growth of many of the atypical mycobacteria including *M haemophilum*, which requires a source of hemoglobin or hemin; however, these media dry out within 5 to 7 days, making them suboptimal for all except the rapid-growing group. Lowenstein-Jensen medium, with contaminant-inhibiting antibiotics, is the preferable medium, with 2% ferric ammonium citrate added if *M haemophilum* is suspected. The hemin requirement of this organism can be met by using standard chocolate agar, 5% sheep-blood Columbia agar, or by using the more specialized Mueller-Hinton agar with Fildes supplement. The growth of mycobacteria, especially *M haemophilum*, is stimulated by the presence of 5% to 10% carbon dioxide during culture growth. A new biphasic culture system (Septi-Chek AFB [SCAFB], manufactured by Roche Diagnostic Systems, Nutley, New Jersey) is a specially designed bottle containing four selected media (7H11, Lowenstein-Jensen, chocolate agars, and 7H9 broth) for mycobacterial culture that requires only the addition of the homogenized specimen and then incubation at the appropriate temperature. A slow-release carbon dioxide process is built into the system. Culture results from early testing have given results as good as or better than those with regular Lowenstein-Jensen medium. When an inoculum is placed on any culture, the surface of the medium should be scratched to ensure good contact with the medium and optimum growth conditions. For the first 2 weeks, the inoculated surface should be kept almost horizontal to prevent the colonies from loosening from the medium, and the container cap should be kept loose to allow circulation of the carbon dioxide.

Tissue being prepared for culture can be minced in a sterile Petri dish with a sterile number 10 or number 15 scalpel blade. Also available is the handheld Sterile Disposable Tissue Grinder (number 3505, manufactured by Sage Products, Inc., Cary, Ill). This disposable plastic tissue grinder makes homogenization of tissue fast and simple. Great care must be taken to prevent contamination with environmental bacteria and ubiquitous saprophytic atypical mycobacteria, which, under proper conditions, can be opportunistic pathogens and, if grown out as a contaminant, could cloud the diagnostic picture.

Overgrowth of cultures by contaminants is a major problem in culturing of mycobacteria, because all are relatively slow growers compared to most bacteria. Even the rapid growers, which take only 3 to 7 days to grow, are slow compared to most other bacterial cultures (which, having no apparent colonies at 48 h, are called "no growth"). If any mycobacterial species are suspected, the laboratory should be advised to retain the special cultures for at least 8 weeks, as the usual laboratory procedure is to dispose of no-growth cultures after 48 to 72 hours. The laboratory procedures necessary to isolate and diagnose atypical mycobacteria can be described schematically (Figure 16-2).

Once suspected atypical mycobacterial colonies do grow, they should be checked for acid-fastness by using the Kinyoun or auramine-rhodamine staining technique. If the culture is acid-fast staining, the organism is most likely a mycobacterium; however, *Nocardia* (a genus of actinomycetes; see Chapter 18, Deep Fungal Skin Diseases) with its uneven acid-fast staining, could be present. All suspected

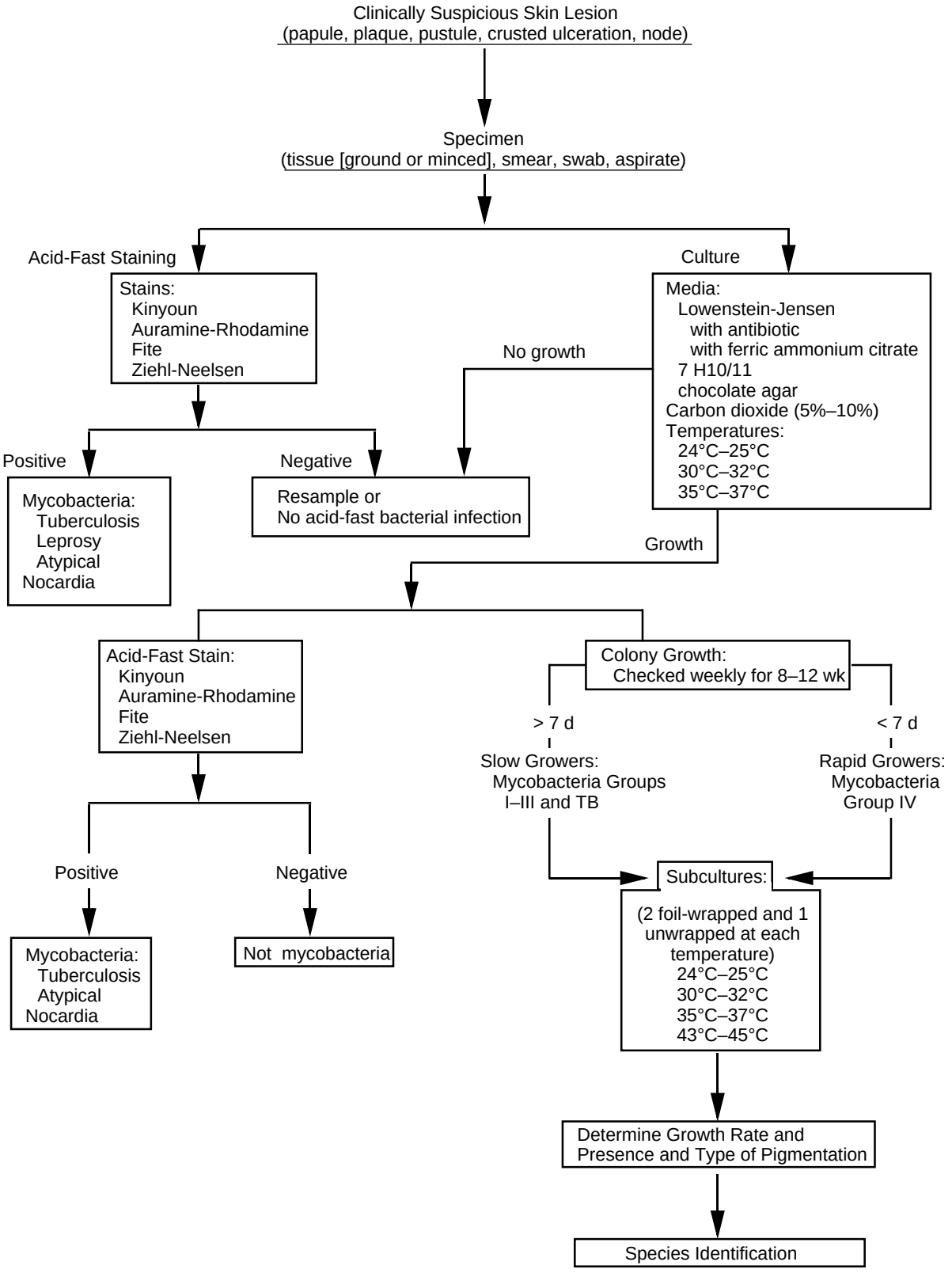

Fig. 16-2. Algorithm for the laboratory diagnosis and isolation of atypical mycobacteria.

TABLE 16-2

COLONY GROWTH AS A FUNCTION OF TEMPERATURE

Atypical Mycobacteria	Temperature Range (in °C)			
	24–25	**30–32**	**35–37**	**42–43**
Group I				
M marinum	+	+ (7–14)*	N	N
M kansasii	S	S	+ (10–20)*	N
Group II				
M szulgai	S	S	+ (12–25)*	N
M scrofulaceum	S	S	+ (> 10)*	N
M xenopi	N	N	+	+ (14–28)*
M gordonae	S	S	+ (20–50)*	N
Group III				
M avium-intracellulare	±	+	+ (10–21)*	±
M haemophilum	S	+ (15–30)*	N	N
M ulcerans	N	+ (28–60)*	S	N
M malmöense	S	S	+ (15–60)*	N
Group IV				
M fortuitum–chelonae complex	+	+	+ (3–5)*	N
M smegmatis	+	+	+	+ (3–5)*

*number of days necessary for growth at the optimum temperature
+: good growth; ±: growth may or may not occur; S: slow growth; N: no growth

mycobacterial cultures should be saved under refrigeration for sensitivity testing and positive biochemical identification procedures by a specialty laboratory, or by a referral laboratory such as the National Jewish Center, Denver, Colorado.

Temperature effects on atypical mycobacterial growth are crucial for both colony survival and for differentiation among the various species. (As discussed previously, the difference in temperature requirements and the production of colony pigmentation with and without exposure to light are the two characteristics that originally raised scientific awareness that atypical mycobacteria existed and were different from the tubercle bacillus.) With some species of atypical mycobacteria, colony growth to any degree hinges on the ambient temperature. The first objective in culturing is to obtain some colony growth; therefore, only a few parameters require attention. The properly inoculated Lowenstein-Jensen cultures are incubated at 25°C (usual room temperature), at 30°C, and at 37°C, with a 5% to 10% carbon dioxide atmosphere. If colonies appear between 3 to 7 days and are acid-fast on staining, then rapid-growing atypical mycobacteria are most likely present. If acid-fast colonies appear from 8 days to 8 weeks, then either a tuberculosis or a slow-growing atypical mycobacterium is most likely present. As mentioned above,

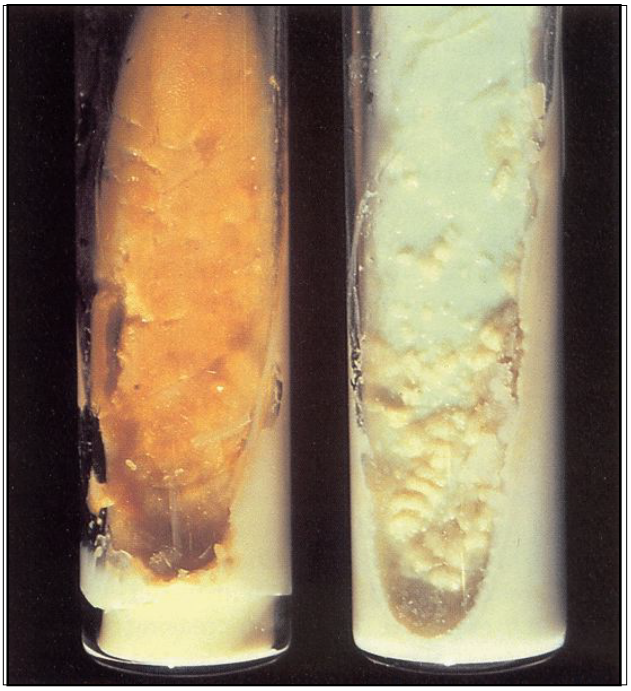

Fig. 16-3. These Lowenstein-Jensen cultures contain orange scotochromogen (*Mycobacterium gordonae*) colonies (left) and buff-colored, nonpigmented, rapid-grower (*Mycobacterium chelonae*) colonies (right). Cultures supplied by Deanne Harley, Supervisor, Microbiology Section, Laboratory Medicine Department, Naval Hospital, San Diego, California.

Nocardia can grow on Lowenstein-Jensen medium and is acid-fast; however, the staining is usually in an uneven pattern.

To further differentiate the organism, a saline or broth suspension from the initial culture is inoculated onto Lowenstein-Jensen medium cultures at 24°C, 32°C, 35°C, and 42°C (Table 16-2). For each temperature setting, two foil-wrapped and one unwrapped Lowenstein-Jensen cultures are used. After colony growth is noted in the unwrapped, light-exposed cultures, one of the foil-wrapped slants with growth is exposed to a strong light (eg, a 100-W light bulb at a distance that does not heat the culture, approximately 50–60 cm). The other culture tube remains foil-wrapped and serves as a control for comparison. After 3 to 5 hours of exposure to light, the cultures are returned to their respective incubators and examined at 24, 48, and 72 hours for evidence of yellow or orange colonies (Figure 16-3) as compared to the covered control. With this information, using Table 16-2 and Exhibit 16-2, cutaneous atypical mycobacteria may be grossly classified to guide initial or continuing therapy. Positive cultures should always be saved under refrigeration for later use in definitive classification and drug sensitivity testing, if necessary.

ATYPICAL MYCOBACTERIAL INFECTIONS

Because its first pathogenic representative was not identified until 1938, the recorded history of atypical mycobacterial infections is relatively short. In comparison with the other mycobacteria, leprosy and tuberculosis, they pose a much lower risk of serious disease. With little or no human-to-human contagion among the more than 30 species, infection usually is the result of an opportunistic encounter between patient and pathogen. These soil and water saprophytes will infect humans only under certain conducive conditions. In the operational military setting, traumatized skin is a portal of entry for *M marinum*, *M kansasii*, *M smegmatis*, and possibly *M ulcerans*. Penetrating wounds allow for deep inoculation of organisms such as *M gordonae* or *M fortuitum–chelonae* complex. Cardiac bypass surgery has been an avenue for infection by *M smegmatis*[24]; therefore, with cardiothoracic surgery of any type, whether in the military or civilian setting, it is prudent to be on guard for infection by this organism.

Atypical mycobacterial infections are slow in their progression and, occasionally, slow in regression. They can be widely destructive, as seen with deep infections with *M ulcerans* and *M scrofulaceum*. Having invaded tendons, joints, or even bone, *M kansasii*, *M szulgai*, or *M fortuitum–chelonae* complex organisms can be difficult to identify and even more difficult to eradicate. With the increasing frequency of organ transplantation and associated iatrogenic immunosuppression, the risk for opportunistic infection by several organisms such as *M haemophilum*, *M xenopi*, *M avium–intracellulare* complex, and even *M marinum* has correspondingly increased. Patients with AIDS are particularly susceptible to the *M avium–intracellulare* complex, which is found at autopsy in more than half of AIDS victims.[40]

As noted, mycobacterial infections have not played a pivotal role in military history. However, with the possibility that the military will be deployed anywhere in the world for brief or extended peacekeeping or combat missions, infections with these organisms should be kept in mind when military planners consider the biological threats in an operational arena. Otherwise, the failure to suspect, and thus to diagnose, infections by these organisms will lead to delayed diagnoses and treatment—with resultant increases in patient morbidity and even mortality.

Mycobacterium marinum Disease (Group I, Photochromogen)

The synonyms for *M marinum* include *M balnei*, *M platypoecilus* (recognized early as the cause of tuberculosis in Mexican platyfish), swimming-pool granuloma, fish-tank granuloma, fish-fancier's finger, aquarium granuloma, and oyster-shucker's palm.

Epidemiology

Although first isolated from salt-water fish in the Philadelphia, Pennsylvania, aquarium in 1926, and named *M marinum* then, this mycobacterium was not identified as a human skin pathogen until 1951.[7] The overall incidence in the United States is only about 0.05/100,000[41]; however, it is the most common atypical mycobacterium to cause skin disease in the United States, with about 600 cases reported since 1951. The natural habitat is worldwide, in temperate fresh or salt water (eg, harbors, bays, rivers, brackish coastal waters, inadequately chlorinated pools, aquariums, and even the Dead Sea).

This organism has been readily cultured from masonry cracks and chinks in pools as well as from the mud in natural water sources. It is pathogenic for, and has been isolated from, marine animals, frogs, fishes, and even the water flea *Daphnia*. Humans acquire the infection through (*a*) traumatized skin lesions exposed to contaminated water or (*b*) wounds inflicted by, or in contact with, marine animals or their products (eg, fish bone). Occasionally, what seems to be epidemics of infection have occurred in patients using the same swimming pool; however, person-to-person transmission has not been reported and is assumed not to occur.[7]

Diagnostic Features

A slightly tender, red, indurated area develops in the skin within a 1- to 6-week incubation period (usually about 3 wk) and then progresses to single or, occasionally, grouped multiple, brownish red papulonodules that slowly become violaceous (Figure 16-4). The skin lesions may eventually ulcerate to drain pus or they may form slightly verrucous papules or plaques resembling psoriasis (Figure 16-5). These papules are usually located, in decreasing order of occurrence, on the elbows (most common by far), knees, hands, or feet that have been traumatized during water-related work or leisure activities (Figure 16-6). Uncommonly in *M marinum* infection, underlying bursae, bone, or synovia may become involved. Systemic spread occurs in about 2% of infections, in immunocompromised or immunocompetent patients.[7,42] In about 25% of cases, tender, red, centrally spreading, secondary nodules can be seen along the course of the lymphatics of the involved extremity in a sporotrichoid pattern (Figure 16-7).[7]

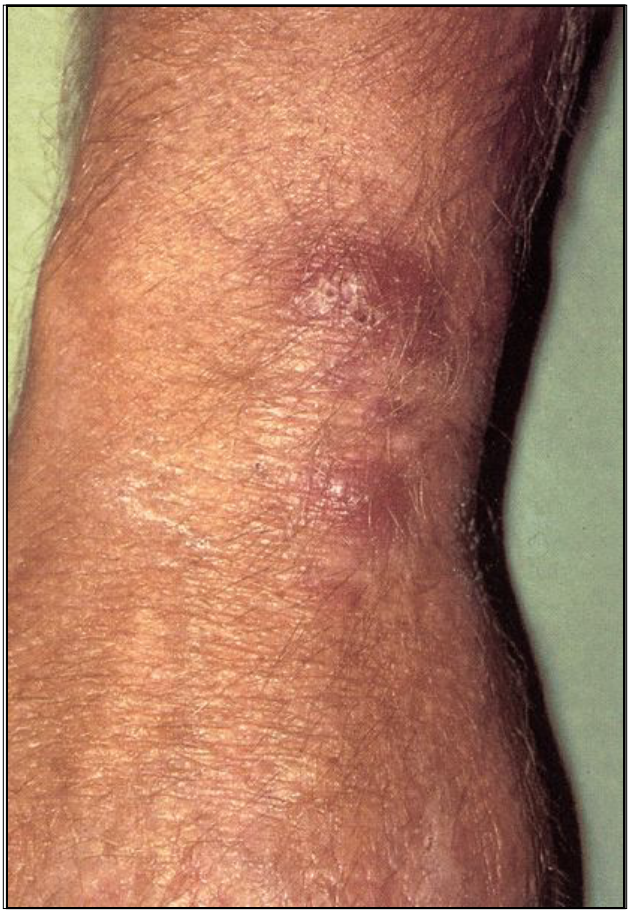

Fig. 16-4. The early lesion of *Mycobacterium marinum* infection appears approximately 3 weeks after exposure to the organism in a water environment. Here, a brownish red papulonodule on the wrist is the first sign of infection.

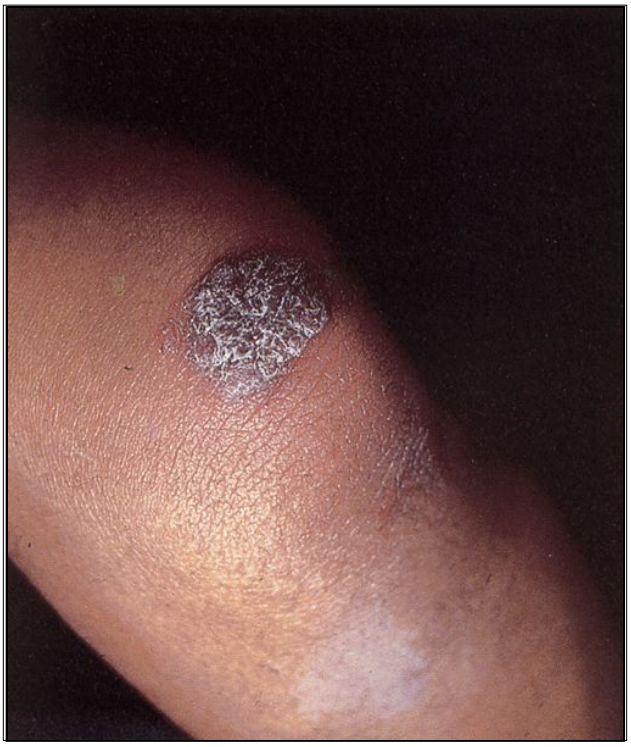

Fig. 16-5. As an unrecognized, untreated infection with *Mycobacterium marinum* becomes chronic, over a several-week period, a verrucous plaque, like the one shown on this patient's knee, develops.

Differential Diagnosis. The differential diagnosis for *M marinum* infection includes sporotrichosis, nocardiosis, blastomycosis, chromoblastomycosis, other mycobacterioses, cutaneous leishmaniasis, coccidioidomycosis, tularemia, foreign body granu-

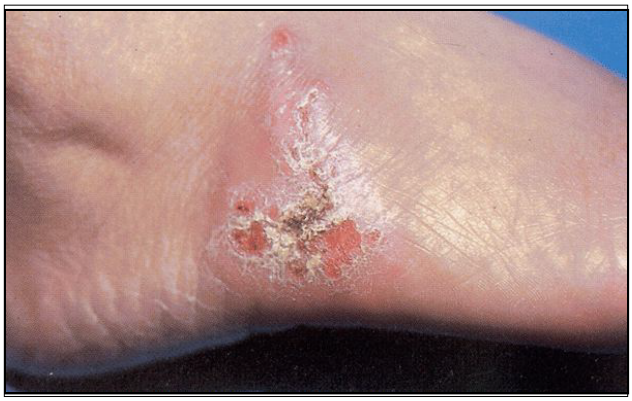

Fig. 16-6. The feet may be affected if they are traumatized during water-related work or leisure activities. The enlarging plaque on this patient's foot is due to infection with *Mycobacterium marinum*. Photograph: Courtesy of Captain E. C. Oldfield, Medical Corps, US Navy, Naval Hospital, San Diego, Calif.

loma, posttraumatic hypertrophic scar, iodine and bromine granuloma, granuloma annulare, hypertrophic lichen planus, sarcoidosis, psoriasis, ecthyma, favus, syphilis, cutaneous tuberculosis, warts, and skin cancer.[7,43]

Histopathology. In only about 10% of cases does the histopathology reveal acid-fast bacilli, which are usually located within histiocytes. The granulomatous pattern is that of an epithelioid granuloma that usually does not exhibit caseation necrosis.

Laboratory Features. *M marinum* is one of the faster slow-growing atypical mycobacteria, such that in 7 to 10 days, cultures grown in the dark produce nonpigmented colonies; these then become yellow-orange within 24 to 48 hours after exposure to the proper light (see Figure 16-3). In fact, in early classification schemata, *M marinum* was occasionally classified as a rapid grower; however, a more restricted growth time (ie, < 7 d) now excludes this organism from the rapid growers. Culture media include Middlebrook 7H10 and 7H11, and Lowenstein-Jensen with antibiotic. Temperature control is a critical factor for growth of this organism since it typically grows best at 30°C to 32°C and not at the usual laboratory level of 37°C (see Table 16-2); however, this organism can show some eventual growth at 37°C.[11,44] If the culture conditions are optimum, *M marinum* can be isolated by culture in about 70% of the involved cases with the earlier clinical lesions producing the greatest number of positive cultures.

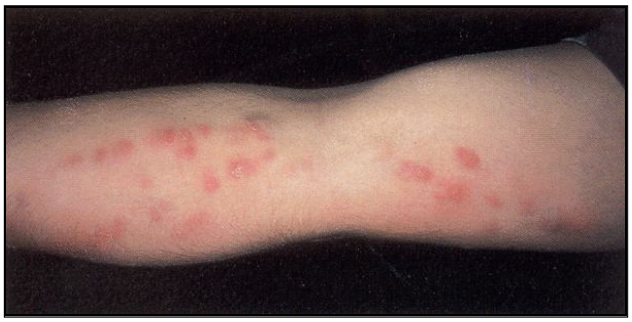

Fig. 16-7. As the infection ascends the lymphatics, multiple inflamed papulonodules develop proximal to the initial site. These lesions may ulcerate with time. The pattern shown here is referred to as "sporotrichoid" because it resembles the grouping of lesions seen in sporotrichosis.

Course, Treatment, Prognosis, and Prevention

Single skin papules may heal spontaneously in 6 to 36 months; however, some infections have persisted for more than 45 years,[45] which makes initiation of therapy a reasonable approach. In the past, since this organism is resistant to some antituberculous drugs, local destruction of small areas of involvement was carried out by surgical excision, cryotherapy, curettage, or radiation. Fortunately, over the past 15 years, treatment with oral tetracycline (2 g/d) and, more recently, minocycline or doxycycline (200 mg/d) for 2 to 4 months has been quite effective in most cases.[46] Oral trimethoprim-sulfamethoxazole administered twice daily, or rifampin (600 mg) with ethambutol (15 mg/kg) administered daily for 3 months, or both, have also been successful therapy in resistant cases.[22] Rarely, cutaneous dissemination occurs in immunocompetent patients[42,47] and, on occasion, dissemination of infection may be associated with the administration of systemic corticosteroids.[48] Similarly, intralesional steroid injection may produce enlargement or exacerbation or both of the lesion (Figure 16-8). Dissemination or more severe and widespread cutaneous infection may occur in immunocompromised patients with *M marinum*.[48]

Preventive measures include adequate chlorination of swimming pools, protection of traumatized skin from contaminated water, and reduction of skin trauma in those exposed to natural water sources or fish tanks. For example, in the Chesa-

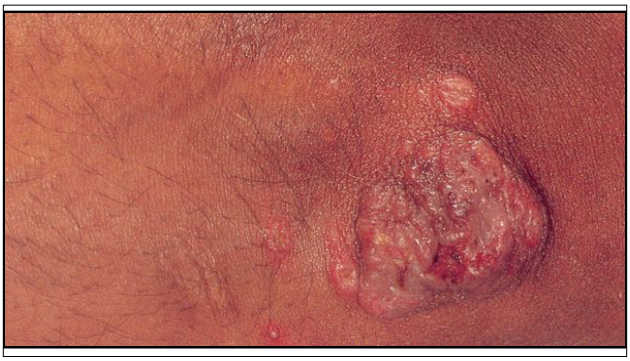

Fig. 16-8. Plaque of *Mycobacterium marinum* infection on the elbow. The original lesion began as a verrucous plaque resembling psoriasis and initially was injected with intralesional steroid by an unsuspecting civilian healthcare provider. Photograph: Courtesy of Commander S. J. Walker, Medical Corps, US Navy, Naval Hospital, San Diego, Calif.

peake Bay area, many commercial fishermen and watermen wear thick gloves while working with fish or crabs. If salt-water wounds occur, meticulous wound care, with thorough irrigation, should be performed. Severe or multiple wounds may benefit from a short prophylactic 3- to 5-day course of oral tetracycline or minocycline.[49] Infection with *M marinum* frequently produces persistent positive cross-reactivity with tuberculin skin testing; this, however, is not a reliable diagnostic modality but should be kept in mind when PPD skin testing is done on patients who work in or around marine industries.[7]

Mycobacterium kansasii Disease (Group I, Photochromogen)

Epidemiology

M kansasii, also known as the yellow bacillus of Buhler and Pollak, and as the orange bacillus, is worldwide in distribution but is especially prevalent in temperate-climate areas such as the midwestern and southwestern United States. This organism is commonly found in tap water and in both wild and domestic animals such as cattle and pigs. Pulmonary infections are most common and are probably caused by inhalation of aerosolized organisms; skin infections are much less common. Skin infection was reported in 1965,[16] with only nine additional cases reported as of 1987.[12] Cutaneous involvement may occur in normal or previously traumatized skin, and is commonly seen in patients with immunodeficiency.

Diagnostic Features

The infection incubation time of *M kansasii* is from 15 days to several months. Clinical manifestations include red-to-violaceous indurated papules or plaques; pustular, ulcerated, crusted, or verrucous papules or nodules; cellulitis; abscesses; joint pain including arthritis, synovitis, and bursitis; cervical adenopathy; and a sporotrichoid adenopathy of an involved extremity (see Figure 16-6).

The clinical differential diagnosis includes pyogenic abscess, cellulitis, and sporotrichosis, as well as the other mycobacterioses. Exhibit 16-3 not only presents the variety of diseases that can have a sporotrichoid pattern of lymphatic spread but also directs the reader to the most noteworthy description of this clinical presentation.

Histopathology. Histopathology can show acute and chronic inflammation alone, or tuberculoid or epithelioid granulomas with large, cross-barred, acid-fast bacilli in about 10% of all cases.[50]

Laboratory Features. Cultures grow best on Lowenstein-Jensen medium at 37°C after 10 to 20 days (see Table 16-2), and produce yellow-orange pigment containing beta carotene crystals after exposure to bright light (see Figure 16-3). There are no reliable, routine, specific skin tests or serologic tests available.

Course, Treatment, Prognosis, and Prevention

Pulmonary *M kansasii* disease is apparently self-healing, as evidenced by research studies with prepared PPD-like material showing positive skin tests in about 50% of the healthy adult population of the United States.[50] In the few skin infections reported, untreated infections lasting up to 22 years have been seen.[16] For skin infection, successful therapy has included daily isoniazid (300 mg) plus rifampin (600 mg), with ethambutol (15 mg/kg for 18–24 mo), with streptomycin added (1 g/d for 2 wk, then twice weekly for 3 mo).[22] The addition of transfer factor to the treatment regimen has been helpful in successfully treating immunocompromised patients.[51] Oral therapy with minocycline (200 mg/d) has also been successful,[52] as has surgical excision of localized cervical adenitis.[29] There are no preventive measures known.

Mycobacterium szulgai Disease (Group I, Photochromogen/Scotochromogen)

Epidemiology

M szulgai, first recognized in 1972, is a rare pathogen with fewer than 20 total cases reported—of which most have been chronic pulmonary disease in middle-aged men with fewer than 6 cases involving skin or soft tissue.[13] Apparently, this organism is distributed worldwide with no known natural reservoirs. The incidence of disease reported in 1983 in the United States was 0.01/100,000.[41]

Diagnostic Features

M szulgai has an array of manifestations. Red, tender nodules on the extremities, trunk, or neck may become fluctuant and drain spontaneously.[53,54] Some of these lesions have manifestations of underlying osteomyelitis or bursitis with or without accompanying pulmonary disease. Disease has been seen in immunocompromised and immunocompetent patients. The differential diagnosis includes all the causes for carbuncle, cellulitis, subcutaneous pyogenic abscess, olecranon bursitis, and tenosynovitis.

Histopathology. Histopathology is that of a histiocytic granuloma with multinuclear giant cells without caseation necrosis. The presence of acid-fast bacilli within the granuloma is variable.

Laboratory Features. Culture characteristics are both interesting and confusing: this organism is a photochromogen, with yellow-orange pigment production (see Figure 16-3) only after light exposure, when grown at 25°C; but it is also a scotochromogen, producing yellow pigment when grown in the dark at 37°C. Colonies appear at 2 to 4 weeks, with slower growth at the lower temperature.

Course, Therapy, Prognosis, and Prevention

Apparently *M szulgai* disease is progressive, especially in immunocompromised patients and, therefore, deserves treatment when it occurs. In a prednisone-immunosuppressed patient,[53] effective therapy was achieved with oral administration of isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (1,200 mg/d for 24 mo); the prednisone was discontinued over a 3-week period at the beginning of this therapy. Since prolonged treatment of this organism is required, it must be distinguished from the usually more-responsive infections with *M tuberculosis* and other atypical mycobacteria.

EXHIBIT 16-3

SKIN INFECTIONS WITH SPOROTRICHOID LYMPHATIC SPREAD

- Sporotrichosis[1]
- Nocardiosis[1]
- Atypical mycobacteria
  - *M marinum*[2,3]
  - *M kansasii*[2,4]
  - *M scrofulaceum*[5,6]
  - *M chelonae*[7]
  - *M avium–intracellulare*[8]
  - *M gordonae*[9,10]
- Tuberculosis[1]
- Tularemia[1]
- Syphilis[1]
- Yaws[1]
- Scopulariopsis (blochi)[1]

The following are the most significant descriptions of the clinical presentations of these organisms:

1. Moschella SL. Diseases of the mononuclear phagocytic system (the so-called reticuloendothelial system). In: Moschella SL, Hurley HJ, eds. *Dermatology*. Vol 1, 2nd ed. Philadelphia, Pa: WB Saunders; 1985: 890–999.
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There are no suggested preventive measures at present.

Mycobacterium scrofulaceum Disease (Group II, Scotochromogen)

Epidemiology

In 1956, *M scrofulaceum*, also called the Gause strain of mycobacteria, was named because of its scrofula-like involvement of the cervical lymph nodes in children. Most cases involving this organism still occur in the cervical nodes of children between 1 and 5 years of age, with rare occurrence in adults. Distribution is worldwide in soil, tap water, raw milk, dairy products, and other products of the environment such as oysters.[13] The route of infection has not been firmly established; however, oral, oropharyngeal, and hematogenous pathways are suspected circumstantially. The estimated overall incidence of all *M scrofulaceum* disease in the United States was 0.07/100,000 in 1987.[41] Due to similar antigenicity with *M avium–intracellulare*, *M scrofulaceum* is sometimes classified as part of a *M avium–intracellulare–scrofulaceum* (MAIS) complex. An additional organism that causes ulcerative skin lesions and shares some biochemical characteristics with both species is classified as *M avium–intracellulare–scrofulaceum* intermediate.[55]

Diagnostic Features

Clinically, *M scrofulaceum* disease usually occurs in healthy-appearing children and, rarely, in adults as unilateral cervical adenopathy high in the neck, with minimal pain or tenderness.[13] Occasionally, the involved nodes may remain stationary for perhaps weeks to months[13,56,57] and then regress, leaving residual fibrosis and calcification. More commonly, the nodes progress to softening with eventual rupture and drainage. This organism also occasionally appears as scattered, multiple, subcutaneous abscesses and in a sporotrichoid pattern (see Figure 16-7).[58] Other manifestations of disease caused by this organism include pulmonary disease, disseminated disease, conjunctivitis, osteomyelitis, meningitis, and granulomatous hepatitis.

In adults, the differential diagnosis includes those entities that produce an expanding neck mass such as infectious adenitis, dermopathic reactive lymphadenitis, lymphoproliferative malignancy, metastatic node, cat-scratch fever, mononucleosis, salivary gland infection or duct stone, subcutaneous or peritonsillar abscess, tuberculosis, or mumps. In children, the differential includes the causes of cervical lymphadenitis such as cat-scratch fever, infectious adenitis, hematological malignancy, reactionary inflammatory nodes, deep abscess, or mononucleosis. The other skin lesions of *M scrofulaceum* resemble pyogenic abscesses or sporotrichosis (see Exhibit 16-3).

Histopathology. The histopathological appearance is essentially the same as that of tuberculosis with varying degrees of caseation necrosis, granulomatous inflammation, and acid-fast bacilli.

Laboratory Features. Culture on Lowenstein-Jensen medium produces buttery, smooth, yellow-orange colonies in 2 to 4 weeks with the best growth at 37°C and slow growth at 24°C, 32°C, and 35°C (see Figure 16-3). The colony pigmentation occurs even when grown in the dark (scotochromogen) and then continues to darken to a deeper orange with prolonged exposure to light. No reliable, diagnostic, skin-test procedure is presently available for routine testing; and PPD skin testing may be reactive or nonreactive.

Course, Treatment, Prognosis, and Prevention

M scrofulaceum disease usually progresses; therefore, therapy is recommended. Surgical excision of the affected lymph node has been successful in patients who have limited cervical adenitis; however, incision and drainage alone may result in chronic draining sinuses and recurrence despite concomitant drug therapy.[13] Successful drug therapy has included oral rifampin (600 mg/d) plus isoniazid (300 mg/d) for 9 months despite in vitro resistance.[58] There are no effective preventive measures yet established.

Mycobacterium xenopi Disease (Group II, Scotochromogen)

Epidemiology

M xenopi, also called the hot-water bacillus and *M littorale*, was first isolated in 1957 and recognized as a pathogen in 1965. This organism has been found in both cold and hot water systems.[6] Remarkably, it has been recovered from hot water generators and storage tanks of several hospitals, where it was linked to pulmonary disease.[13] It has been recovered from bird droppings and, considering the fact that it has been isolated commonly from the coastal areas of England, Europe, and the United States, sea birds are considered possible reservoirs.[6,13] In the southeastern part of England, *M*

xenopi is reported[22] to be the most common atypical mycobacterium recovered in the laboratory since 1977. Interestingly, *M xenopi* is common among the atypical organisms isolated incidentally from tonsils. Although not yet isolated from water mains, the organism may enter hospital hot-water tanks in small numbers via the water system and multiply at its optimum growth temperature of 43°C to 45°C. Infection may then occur by aerosolization and absorption via the respiratory tract.[22] Not a common pathogen, its incidence in the United States is estimated as 0.01/100,000[41]; most occurrences appear as pulmonary disease in patients with preexisting lung disease or other debilitating systemic disease.[13]

Diagnostic Features

Immunocompromised patients with *M xenopi* disease may have cutaneous involvement when they have underlying bone or soft tissue involvement such as epididymitis, osteomyelitis, lymphadenitis, arthritis, or sinus tract.[13] The rare occurrence of disseminated disease is usually found in AIDS patients. The differential diagnosis of skin manifestations includes all causes related to the underlying disease process, and pulmonary disease is clinically identical to infections with *M kansasii* and *M avium–intracellulare*.

Histopathology. Histopathology is nonspecific with collections of epithelioid macrophages, Langhans'-type giant cells, and acid-fast bacilli within caseating granulomas.[13]

Laboratory Features. In culture, this organism is a scotochromogen, producing yellow pigment in the absence of light (see Figure 16-3), and growing best at the relatively warm temperature of 42°C to 43°C after 3 to 4 weeks. This is the temperature of hot-water holding tanks where this organism has been isolated, giving rise to the name hot-water bacillus.

Course, Treatment, Prognosis, and Prevention

Infection by *M xenopi* is opportunistic in immunocompromised patients and should be treated when it occurs. Response to therapy has been inconsistent; however, some success has been obtained with combinations of isoniazid, rifampin, ethambutol, and streptomycin with uniform susceptibility to cycloserine and ethionamide.[13] Preventive measures might include culturing hospital hot-water systems in facilities that serve immunocompromised patients, thus ensuring an uncontaminated hot-water source for drinking, bathing, hydrotherapy, and wound cleansing.

Mycobacterium gordonae Disease (Group II, Scotochromogen)

Epidemiology

M gordonae is variously known as the water bacillus, the tap-water bacillus, the tap-water scoto-chromogen, and *M aquae*. Rare extrapulmonary postoperative infections have been reported since the early 1970s[28,59] but the first cutaneous infection was not reported until 1984,[60] and by 1987, only three cases had been reported.[28,61] This organism has been one of the most common contaminant saprophytes isolated in the laboratory (sometimes approaching 15% of all mycobacterial isolates) and has been found in water, mud, water supplies, swimming pools, and in soil where it has been shown to multiply.[13,27,28] Some wild animals may be reservoirs, since *M gordonae* strains have been recovered from the lymph nodes of wild armadillos in Louisiana.[61] An interesting case report from Belgium involved a patient who developed cutaneous infection with *M gordonae* several months after being bitten by a rat while collecting frogs in a pond. Although the animal bite may have been the source of infection, it may also merely have been the mode of organism inoculation from another environmental source such as water or soil.[61]

Diagnostic Features

Cutaneous *M gordonae* infection occurs as small tender, red-blue papulonodules 0.5 to 1.5 cm in diameter with mamillated or ulcerated surfaces and with or without proximal lymphangitic spread in a sporotrichoid pattern,[61] as was seen in the first reported skin infections by this organism (see Figure 16-7).[60] Occurring after inoculation from a penetrating wound, infection may produce spreading, diffuse inflammation, with the wound discharging serosanguineous material. The patient can have localized lymphadenitis but systemic signs of toxicity: fever, chills, malaise, nausea, and vomiting.[28] The clinical differential diagnosis includes sporotrichoid diseases (see Exhibit 16-3), other mycobacterioses (especially *M marinum* or *M kansasii*), pyogenic infection, sarcoidosis, and other infectious granulomas.

Histopathology. Histopathology reveals large histiocytes, multinucleated giant cells, acute and chronic inflammation, and a few of the acid-fast

bacilli sometimes described as "plump rods." The inflammatory elements may be intermixed with areas of fibrosis.[60]

Laboratory Features. This organism produces yellow-orange colonies even when grown in the dark, thus it is a scotochromogen (see Figure 16-3). The optimum growth temperature is 37°C. The required time for colonies to grow varies from 4 to 8 weeks, with some colonies not seen for 24 weeks on Lowenstein-Jensen medium (see Table 16-2). Culture growth is reported to have been enhanced by decontamination with sodium hydroxide and by using modified Ogawa medium at pH 6 (versus the usual Lowenstein-Jensen medium at pH 7).[61] Both tine and Mantonx PPD skin testing with 10 tuberculin units have been reported positive at greater than 5 mm induration at 48 hours.[28]

Course, Treatment, Prognosis, and Prevention

Therapy has included oral rifampin (300 mg/d) alone for 6 months, or trimethoprim/sulfamethoxazole (320 mg/1600 mg) administered twice daily with ethambutol (800 mg/d), both given for 24 months, with cycloserine (250 mg/d) added during the first 9 months.[28,61] Antibiotic disc susceptibility testing may be useful in guiding therapy of resistant cases of this infection. In two reported cases,[28,61] all lesions cleared without recurrence within the treatment periods. In the initial report of skin infection by *M gordonae*,[60] the investigator warns that this organism should not always be assumed to be a harmless contaminant if isolated from clinical specimens. At the present time, no specific preventive measures are recommended.

Mycobacterium avium–intracellulare Complex Disease (Group III, Nonchromogen)

Epidemiology

The *M avium–intracellulare* complex is known by a variety of synonyms including Battey bacillus (specifically *M intracellulare*) and *M avium* complex (MAC). As its name suggests, *M avium* was first known as a pathogen of chickens, and has been recognized as such since 1868. In 1943, the organism was recognized as a human pulmonary pathogen; however, in 1953, a separate but closely related organism without pathogenicity for chickens was isolated. Later in 1957, this organism was found to be pathogenic in several inpatients of the Battey State Tuberculosis Hospital in Rome, Georgia, and was named the Battey bacillus.[33] This organism was later speciated as *M intracellulare*, but it is so similar to *M avium* that for human pathogenicity the two can be combined into one complex. With an incidence of about 3.2/100,000 population, approximately one third that of tuberculosis, *M avium–intracellulare* complex became second only to *M tuberculosis* in total numbers of mycobacterial isolates in the United States by 1980 (see Table 16-1).[27] In the United States, this organism is found most often in rural areas of the southeastern part of the country. This complex is of interest to dermatologists because of its rare involvement of skin and lymphatics and because of its rising incidence in AIDS patients.

M avium–intracellulare complex has been found in soil, salt and fresh water, house dust, animal feed, dried plants, and bedding; however, the highest number of isolates are found in aerosol samples. This suggests a likely route for pulmonary infection. Although *M avium–intracellulare* complex is a cause of disease in such animals as poultry, pigs, and monkeys, these are not thought to be sources of human infection.[13] This species of atypical mycobacteria is discussed in the AIDS section of this chapter.

Diagnostic Features

In otherwise healthy patients, *M avium–intracellulare* complex may be isolated from sputum without being the cause of disease. Disease that is manifest is usually expressed as pulmonary infection in middle-aged white males with preexisting lung disease. In AIDS patients, the presence of *M avium–intracellulare* is an ominous sign, especially if it is found in the urinary or pulmonary tract. Dissemination of disease is usually seen in patients who are immunocompromised secondary to systemic steroid therapy or AIDS. Primary skin lesions are very rare and their presence strongly suggests immune compromise in any affected patient. Clinical manifestations of skin involvement include red-bordered plaques or crusted ulcerations, which range from limited numbers of lesions to spreading, extensive lesions. With dissemination of disease, multiple granulomas, pustules, ulcerations, and generalized adenopathy have been reported.[29] Other dermatologic manifestations include cervical adenitis in children or adults, subcutaneous nodules, sporotrichoid spread (see Figure 16-7), panniculitis, fascitis, and synovitis.[62] The differential diagnosis can include all reactive, malignant,

and infectious causes of the above underlying diseases, as well as any chronic granulomatous or sporotrichoid disease (see Exhibit 16-3).

Histopathology. Histopathologically, skin and lymph nodes show either caseating or noncaseating granulomas with acid-fast bacilli either within or outside of giant cells. In AIDS patients, foamy macrophages containing many intracellular acid-fast bacilli may be seen.

Laboratory Features. Culture on Lowenstein-Jensen medium produces nonpigmented colonies in the dark or light at 37°C within 2 to 3 weeks (see Table 16-2).

Course, Treatment, Prognosis, and Prevention

In immunocompetent adult patients with localized disease, surgical debridement plus oral rifampin (600 mg/d); ethambutol (25 mg/kg/d for 2 mo, then decreased to 15 mg/kg/d); isoniazid (300 mg/d); and ethionamide or streptomycin (administered for several months beyond clearing) are usually recommended. An effective role for isoniazid has not been clearly established. In children with cervical adenitis, recommended treatment is local excision for primary involvement and limited recurrence.[22] Treatment of disseminated disease in immunocompromised patients is not yet specific; however, the above adult-disease regimens with the addition or substitution of amikacin and clofazimine may offer potential therapeutic advantages. Prevention lies in reducing or preventing the causes of immunosuppression in the involved patient. At present, the true impact of disseminated *M avium* complex disease on the survival of AIDS patients is not certain, but projections appear gloomy.[22,40]

Mycobacterium ulcerans Disease (Group III, Nonchromogen)

Epidemiology

As previously discussed, the *M ulcerans* organism was formerly also known as *M buruli*[6]; the disease is likewise known by several synonyms: Buruli ulcer (in the Buruli District of Uganda), Kakerifu ulcer (in Zaire), Bairnsdale ulcer or Searls' ulcer (in Australia), and Kumusi ulcer (in New Guinea).

Although large cutaneous ulcers had been described in Uganda in 1897 and mycobacterial skin ulcers had been recognized in 1937 in Bairnsdale, Australia, not until 1948 was *M ulcerans* first described in patients from Bairnsdale.[5,20,63] Later, in 1964, multiple cases of ulcerations, with isolation of an organism named *M buruli*, occurred in the Buruli District of Uganda.[6] Subsequently, this organism was shown to be *M ulcerans*. This infection occurs almost exclusively in tropical or subtropical climates in areas of lush vegetation or marshy terrain, with thousands of endemic cases in Uganda and Zaire and hundreds of cases in New Guinea and Australia, making it the largest cause of atypical mycobacterial skin disease worldwide. Although the disease is not endemic in the United States, military physicians should be aware that infection can be brought in from more tropical climates. Until 1984, when it was first isolated in koalas,[20] this organism had never been isolated outside the human body; and although it has been hypothesized[63] that *M ulcerans* resides in soil as a contaminant or on foliage as a commensal and is transmitted via injury from the environment, transmission from animals to humans has not been demonstrated.

Diagnostic Features

Almost all *M ulcerans* lesions occur on extremities. They probably begin as injuries or insect bites that do not heal but instead become indurated, with eventual necrosis and spreading ulceration. Otherwise, the skin lesion appears as a single, firm, sometimes itchy, papule that becomes more indurated and fluctuant over several weeks and then breaks

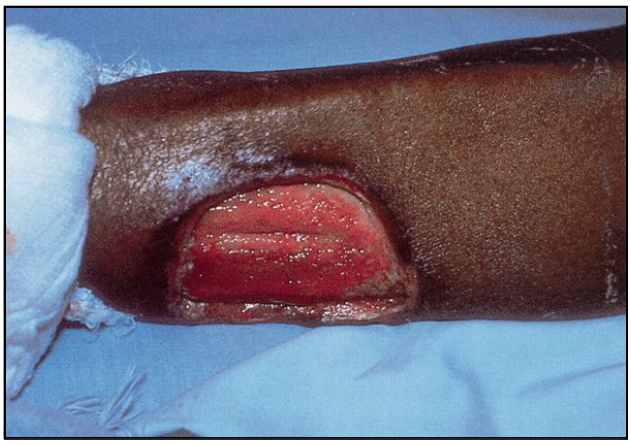

Fig. 16-9. The ulceration of this patient's lower leg is due to *Mycobacterium ulcerans* infection. Note the characteristic undermined borders. The lesion is surprisingly asymptomatic.

down into a spreading, punched-out ulceration with classically undermined edges (Figure 16-9). Multiple ulcers do appear, but have been reported in only a few cases.[64] There is little pain or tenderness associated with the ulceration and the skin just beyond the involved border appears perfectly normal without physical signs, systemic symptoms, or lymphangitic involvement. The ulceration usually extends only down to muscle, with rare bony involvement (probably due to the organism's preference for cooler growing conditions not usually found in warm, viable muscle). It has been hypothesized[63] that infection usually occurs on an extremity where the subcutaneous tissue temperature is lower than core temperature, thus fostering growth of this organism. In addition, if the organism is inoculated into the skin during the hotter months, it may remain dormant in the skin until a prolonged cooling period occurs, then exacerbate with development of ulcerations. According to some experts,[63,65] this disease should be considered in any patient who presents with a relatively painless, chronic, progressive skin ulcer on an extremity in a tropical area where it is endemic. Indeed, in West Africa, where hundreds of cases have been seen, Buruli ulcer is a reliable clinical diagnosis.

Differential diagnosis should include infected insect bite, pyoderma gangrenosum, brown recluse spider bite, deep fungal infection, tuberculosis, suppurative panniculitis, or self-inflicted injury.

Histopathology. Histopathology shows coagulation necrosis, septate panniculitis, without caseation necrosis, but with granulation tissue and giant cells towards the periphery. Smears and biopsy material from the necrotic areas almost always reveal acid-fast bacilli; however, material at the edge of the ulceration will usually be negative for organisms and positive for plasma cells—some with strikingly polynuclear features. In early skin lesions, large, spherical clumps of many acid-fast organisms can be found extracellularly in the deeper parts of necrosed, coagulated tissue.[10] In recurrent or chronic disease, acid-fast organisms may be sparse or difficult to find. A toxin produced by the organism is suspected as the necrolytic factor that allows progression of this necrolytic process.[66]

Laboratory Features. Cultures on Lowenstein-Jensen medium produce nonpigmented colonies at 32°C to 33°C after 6 to 12 weeks, a relatively long incubation time (see Table 16-2). At culture temperatures of 25°C, and above 35°C, growth may be very slow or completely absent. Tuberculin skin tests are sometimes positive but not to a reliable degree.

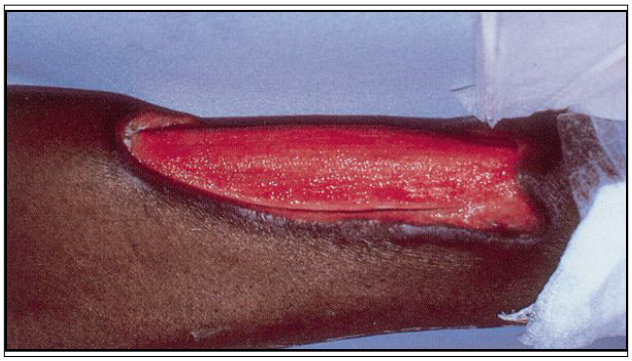

Fig. 16-10. The large, spreading skin ulceration of this patient's lower shin is due to infection with *Mycobacterium ulcerans*. Almost all Buruli ulcers occur on the extremities and, if untreated, tend to progress slowly in size.

Course, Treatment, Prognosis, and Prevention

If untreated, ulcerations tend to progress over months to years to involve large areas (Figure 16-10), sometimes involving an entire extremity, before healing with residual scarring, deformity, and lymphedema. Some rare cases have required amputation.[67] Small lesions respond to simple surgical curettage and heal by granulation.[63] In addition, heat application to 40°C to the involved area has been helpful in some cases.[67] The mainstay of therapy is surgical excision of the entire area with primary closure or skin grafting. Drug therapy consisting of dapsone and streptomycin with or without ethambutol for a few weeks beyond complete healing is not successful alone, but may be a helpful adjunct in more limited surgical treatment.[13] Other antituberculous drugs have not shown any consistent efficacy; however, some response has been seen with trimethoprim-sulfamethoxazole followed by rifampin and minocycline.[62]

Preventive measures are aimed at avoiding trauma or protecting traumatized extremities from environmental contact in endemic areas. Bacille bilié de Calmette-Guérin (BCG) vaccination may be somewhat protective for about 6 months.[67]

Mycobacterium haemophilum Disease (Group III, Nonchromogen)

Epidemiology

Since its first description in 1978, most of the dozen reported clinical cases of infection with *Mycobacterium haemophilum* have been from Austra-

lia or Israel. Almost all of these cases occurred in patients with lymphoma or renal transplants, many of whom were lymphopenic.[13,68] Organism sources and natural reservoirs are unknown at present.

Diagnostic Features

The skin lesions usually occur in multiple locations on the extremities and occasionally on the trunk, with red-to-violaceous papules that gradually enlarge to become tender, crusted, ulcerated nodules or abscesses and fistulas draining purulent material.[13,39] Rarely, patients may have bony involvement or, in children, cervical adenitis may be present.[68] The clinical differential includes pyogenic abscesses, other mycobacterioses, metastatic disease, osteomyelitis, and all the causes of cervical adenitis in children.

Histopathology. Histopathology reveals granulomatous panniculitis with a polymorphous infiltrate, occasional Langhans'-type giant cells, and usually no caseation necrosis. Straight, uniformly staining, acid-fast bacilli are frequently present singly or in small clusters, and often intracellularly.[13] Biopsy material tissue imprints frequently reveal acid-fast organisms.[68]

Laboratory Features. *M haemophilum's* most unique feature is its requirement for hemoglobin or hemin for growth on culture media. This requirement can be fulfilled with the use of chocolate agar, 5% sheep-blood agar, Mueller-Hinton agar with Fildes supplement, or most commonly, Lowenstein-Jensen medium with 2% ferric ammonium citrate.[13] Nonpigmented colonies are produced in 2 to 4 weeks, with growth definitely stimulated by the addition of 10% carbon dioxide. The optimum growth temperature is not yet established but appears to be about 30°C, especially on subculture (see Table 16-2). Intermediate and second-strength tuberculin PPD skin testing have been negative in patients tested thus far.[68]

Course, Treatment, Prognosis, and Prevention

It is possible that some patients may recover with improvement in their immune status; however, improvement has been seen after only a few weeks of isoniazid and rifampin.[68] Other reports record resistance to isoniazid.[13] Although not usually a cause of death, *M haemophilum* infection does produce considerable morbidity before healing spontaneously after months to years. Prognosis and preventive measures have not been formulated.

Mycobacterium malmöense Disease (Group III, Nonchromogen)

Epidemiology

Since the mycobacterium was first isolated in 1977 in Malmö, Sweden, only a few cases of *M malmöense* pulmonary or cervical-nodal infections in children had been reported until 1990, when the first case of cutaneous infection was reported from Ireland.[21] One earlier case report, in 1989, was that of an insulin-dependent diabetic who had a cold abscess of the hand, the infection in which may have been stimulated or possibly introduced when hydrocortisone was injected into a nodule that was assumed to be a ganglion cyst.[69] Most of the previous noncutaneous cases were reported from relatively small areas of Wales, England, and Sweden, and a rare case was reported from both Australia and the United States. Natural sources and possible reservoirs for this organism are not known.

Diagnostic Features

A patient with *M malmöense* disease presented with cervical adenitis; 6 months later, the patient developed tender, red, dermal nodules scattered on the extremities and trunk.[21] The differential diagnosis can include any condition manifesting as a tender dermal nodule or as cervical adenitis.

Histopathology. Histopathology has shown epithelioid granulomas, a few Langhans'-type giant cells, with caseation necrosis and variable numbers of acid-fast bacilli.[21,69]

Laboratory Features. Nonpigmented colonies grow in the dark or light in 2 to 12 weeks, with the shorter times required when pyruvate-containing media are used. Optimum temperatures for colony growth range from 24°C to 37°C, with growth usually in about 3 weeks at 37°C (see Table 16-2). Occasionally, cultures may require up to 12 weeks for growth. Acid-fast stains of colony material reveal coccoid, short, or moderately long acid-fast organisms.

Course, Treatment, Prognosis, and Prevention

The true course of this infection is not yet clear. Complete healing of skin lesions has occurred with cycloserine (750 mg/d) and ethambutol (1,200 mg/d) administered for 2 months. After 9 months,

medication was stopped, with the patient remaining free of disease for more than 5 years.[21] Preventive measures are not yet established.

Mycobacterium fortuitum–chelonae Complex Disease (Group IV, Rapid Growers)

M fortuitum is also known as *M ranae*; *M minetti*; *M fortuitum* biovariant *fortuitum*; biovariant *peregrinum*; and third biovariant complex, containing at least three subgroups. *M chelonae* is also known as *M chelonei*, *M friedmannii*, *M abscessus*, *M runyonii*, and *M borstelense*; and as two subspecies: *M chelonae* (*abscessus*) and *M chelonae* (*chelonae*).

Epidemiology

First found as a pathogen in frogs in 1905 and named *M ranae* in 1923, *M fortuitum* was rediscovered as a human pathogen and named by da Costa Cruz in 1938.[9] *M chelonae* was isolated by Friedman in 1903 from the lung of a diseased sea turtle (*Chelona corticata*).[30] Although *M fortuitum* (with five subgroups) and *M chelonae* (with two subspecies) are separate species of the genus *Mycobacterium*, their very similar clinical manifestations and culture characteristics allow them to be grouped together for discussion of clinical skin disease. There are subtle differences between the two species in their noncutaneous disease incidence (more than 90% of the lung disease is due to *M chelonae*), in some drug susceptibilities, and in DNA homology.[70] These organisms are distributed worldwide in soil, water supplies, tap water, surgical basins, hemodialysis equipment, hydrotherapy pools, gentian violet solution, and even in laboratory distilled water containers.[30] Some disease has been seen in animals such as rodents and amphibians, but transmission to humans apparently does not occur. Overall incidence in the United States in 1980 was about 0.2/100,000.[27]

Diagnostic Features

Most *M fortuitum–chelonae* complex infections follow trauma or surgery (especially cardiovascular surgery, intravenous catheter placement, and injections) and manifest themselves, about 3 to 4 weeks after the initiating event, as tender, red, indurated areas or as an inflamed or cold abscess, any of which may break down and drain.[29] Occasionally, firm, red-brown, nontender, subcutaneous nodules arise at scattered sites in the skin as a result of dissemination from prior surgery or trauma sites.[17,71] The infection sometimes does not arise until several months or even years after the causative surgical procedure. Rarely, infection may follow blunt trauma: in one case,[72] infection developed in the hip where, 2 months before, the patient had been kicked by a horse. These organisms may also cause solitary draining cervical lymphadenopathy (Figure 16-11), postoperative endocarditis, osteomyelitis, and chronic pulmonary disease. A sporotrichoid pattern of lymphangitic spread has been seen with *M chelonae* infection (see Figure 16-7).[46]

The differential diagnosis includes all causes of postoperative wound infections and injection ab-

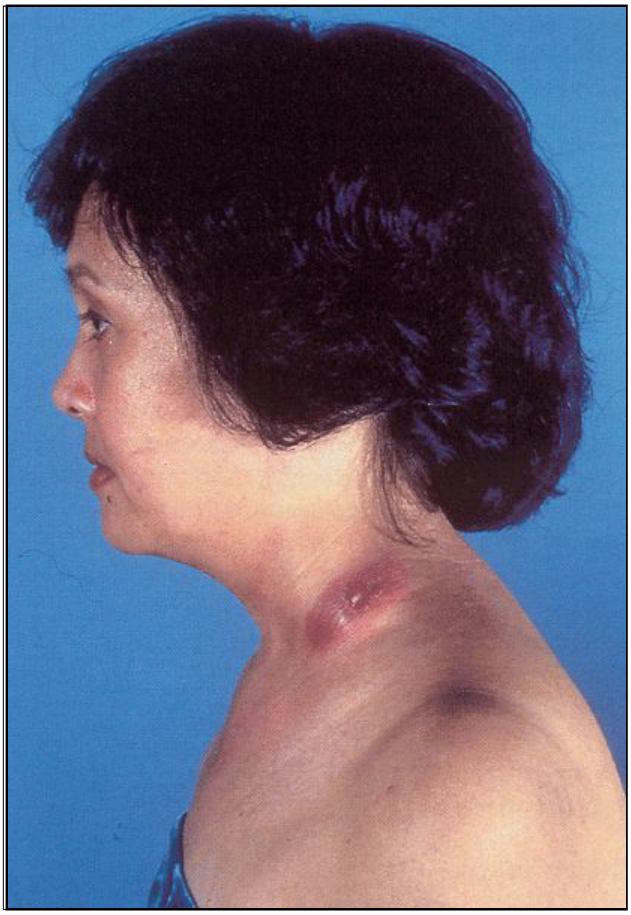

Fig. 16-11. The solitary draining cervical lymphadenitis was due to *Mycobacterium chelonae* infection in this patient. Other patients may exhibit sporotrichoid patterns of subcutaneous nodules due to lymphatic spread up an extremity, or widespread scattered papulonodules from hematogenous dissemination. Photograph: Courtesy of Captain E. C. Oldfield, Medical Corps, US Navy, Naval Hospital, San Diego, Calif.

scesses. In disseminated disease with bacterial embolization and scattered skin lesions with lymphatic involvement, the differential includes tuberculosis and all metastatic diseases including lymphoma. Sporotrichoid diseases should also be included in the differential (see Exhibit 16-3).

Histopathology. Histopathology shows polymorphonuclear cells with granulomatous inflammation, necrosis, giant cells, rare caseation, and, in about one third of the cases, acid-fast bacilli.[13] In addition, the *M fortuitum–chelonae* complex is the one type of mycobacteria that does not stain well with the auramine-rhodamine fluorochrome staining technique.

Laboratory Features. Cultures grow in 3 to 5 days on routine culture media and Lowenstein-Jensen medium at 24°C to 37°C without pigment production, in darkness or light (see Table 16-2). Old tuberculin skin testing may be weakly positive.

Course, Treatment, Prognosis, and Prevention

M fortuitum–chelonae complex infections tend to persist, with only a 10% to 20% remission rate for cutaneous infections, and a mortality rate of 10% to 20% with disseminated disease.[30] Fortunately, all localized diseases caused by *M fortuitum–chelonae* complex organisms appear to be responsive to surgical excision, with or without (depending upon the severity and extent of disease) systemic treatment with doxycycline, amikacin, and ciprofloxacin. Some infections that are secondary to wound contamination or injection may be prevented by (*a*) using only sterile surgical equipment, syringes, and needles and (*b*) adhering to strict aseptic technique during surgical procedures, especially those procedures involving deep body cavities or prolonged tissue exposure.

Mycobacterium smegmatis Disease (Group IV, Rapid Growers)

Epidemiology

M smegmatis was the second type of mycobacterium to be described following its discovery in syphilitic chancres and gummas in 1884. Later, it was found in chancres and in smegma (normal genital secretions) and was subsequently named *M smegmatis*.[73] This organism has been grown from soil and is known to occur in water and hospital dust.[24] This latter fact may account for the occurrence of some of the first isolations of this organism from postoperative wound infections, mostly from cardiac bypass surgery, which occurred beginning in 1980. These cutaneous infections were first recognized and reported in 1988.[73] Remarkably, none of the organisms isolated from infections in these reported cases came from the male genital tract or from urine isolates. Distribution of *M smegmatis* is probably worldwide but thus far reports of disease have come only from the United States and Australia. This may be in part due to the failure of laboratories to consider this organism as a pathogen when it is isolated from patient specimens. Disease has been seen in cats as panniculitis (following injury) and in cattle as bovine mastitis.

Diagnostic Features

Almost always occurring after surgery, trauma, or invasive procedures, *M smegmatis* infections appear as either (*a*) cellulitis with redness, swelling, pain, tenderness, and heat or (*b*) draining, red, swollen areas around wounds, from trauma or surgical procedures including placement of intravenous catheters. The differential diagnosis includes any cause of posttraumatic or postoperative wound infection.

Histopathology. Histopathology is nonspecific, with the following findings: necrosis; presence of epithelioid cells; a mixed inflammatory infiltrate of giant cells, polymorphonuclear cells, and plasma cells; and variable short, coccoid-to–moderately long acid-fast bacilli.

Laboratory Features. Cultures grow best on Middlebrook 7H10 agar, with less growth on Lowenstein-Jensen medium, at 43°C to 45°C and always in less than 7 days. The colonies are buff-colored at 7 days but some develop yellow-orange color after 2 weeks' growth in the dark, with some intensification of the color on exposure to light. A notable characteristic is the ability of this organism to grow on special MacConkey agar without crystal violet. Isolates closely resemble *M fortuitum* in the laboratory because both mycobacteria are rapid growers and have similar-appearing colonies; however, *M smegmatis* is distinguished by a negative 3-day arylsulfatase test, a low semiquantitative catalase test, and colony growth at 45°C (see Table 16-2).[73]

Course, Treatment, Prognosis, and Prevention

Infections with this organism produce chronic draining wounds and abscesses; however, they are

reported to respond well to combinations of doxycycline, trimethoprim-sulfamethoxazole, ciprofloxacin, and amikacin.[72] Preventive measures may be aimed at ensuring the adequacy of air filtration and the strict use of only sterile water and its containers in operating rooms.[24]

ATYPICAL MYCOBACTERIAL INFECTIONS IN ACQUIRED IMMUNODEFICIENCY SYNDROME

Like other opportunistic infections, atypical mycobacterial infections have a much more severe and fulminant course in patients with AIDS than in immunocompetent patients. The most common atypical mycobacterial infection seen in AIDS patients is *M avium–intracellulare* complex disease.[74,75] This may be due to the depression of monocyte and T lymphocyte function in AIDS patients, an important host defense specifically against *M avium–intracellulare* complex and *M tuberculosis*, another increasingly frequent infection in patients with AIDS. In one series,[40] approximately 30% of AIDS patients harbored *M avium–intracellulare* complex while alive, and 52% at autopsy. The researchers also reported that the mere presence of *M avium–intracellulare* complex in urine or respiratory secretions is a sign that dissemination is impending: within 1 to 9 months. Once dissemination occurs, treatment has been unsatisfactory, with poor responses to the usually effective treatment regimens and progression of disease to a uniformly fatal outcome with a mean survival time of about 3 months.[40]

The new macrolides clarithromycin and azithromycin have shown promise in the treatment of disseminated *M avium–intracellulare* complex disease in patients with AIDS.[76] In the treatment of disseminated *M avium–intracellulare* complex disease, clinical trials with high-dose clarithromycin show 98% bacteriological cure initially but with a 25% failure rate by 6 months of treatment.[77] Azithromycin substantially reduced *M avium–intracellulare* complex bacteremia to 7% of the untreated level in 30 days of treatment of 21 patients.[78] In vitro studies[79] of the susceptibility of *M fortuitum–chelonae* to the macrolides clarithromycin, azithromycin, and roxithromycin suggest the clinical usefulness of these agents against atypical mycobacterial infections due to this organism. An earlier report[80] describes a patient with AIDS who had 25 months free of *M avium–intracellulare* complex disease following multiple drug therapy with amikacin, clofazimine, rifampin, ethambutol, and ciprofloxacin. With this regimen, four other patients had favorable clinical and microbiologic responses for up to 1 year.[80]

Like they do in other immunosuppressed patients (ie, those who have had renal transplants; have been treated with corticosteroids; or who have autoimmune disease, leukemia, or lymphoma), atypical mycobacterial infections have more flagrant manifestations in AIDS patients, with the production of large lesions or extensive involvement. Individual skin lesions may reveal large numbers of acid-fast organisms on biopsy, or even on stained tissue smears of the skin lesion. If a tissue smear reveals acid-fast bacilli, specific mention should be made to suspect *M haemophilum*, a very rare cause of skin infection, and to include hemin- or ferric ammonium citrate–enriched media in culturing for this acid-fast organism.[74]

In addition, atypical mycobacteria that are currently classified as saprophytic may, in the future, become true opportunistic pathogens in the population of patients with AIDS. Vigilance should be exercised to rule out atypical mycobacterial infection if a patient with AIDS develops adenopathy or unusual fulminant skin lesions.

It is apparent that, should a patient manifest fulminant, widespread, or disseminated involvement from any atypical mycobacterial infection, especially *M avium–intracellulare* complex, the physician must suspect an immunocompromised status and pursue the diagnosis. In any patient, in fact, even the presence of an atypical mycobacterial infection should raise some suspicion of transient or early immunosuppression.

SUMMARY

The varied and diverse group of cutaneous mycobacterial infections arise from a combination of the low innate pathogenicity of the organisms and opportune exposures of the hosts. The virulence of the particular organism, individual host susceptibility, and the timing and degree of exposure all play crucial roles in the acquisition, progression, and duration of the specific

disease produced. Although they are classified together in the same genus of bacteria, the various atypical mycobacteria have widely varying clinical manifestations, culture characteristics, histologies, and responses to therapy. These very diversities, however, help to define the specific organism involved and the spectrum of disease produced in immunocompetent and immunocompromised patients.

The incidence of these diseases in the military has been negligible in the past. Medical officers should be aware of them, however, especially as the population of immunocompromised individuals continues to increase.

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