REVIEWS OF INFECTIOUS DISEASES • VOL. 9, NUMBER 2 • MARCH-APRIL 1987
 0162-0886/87/0902-0004$02.00

Mycobacteria Other than *Mycobacterium tuberculosis:* Review of Microbiologic and Clinical Aspects

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The rate of isolation of mycobacteria other than *Mycobacterium tuberculosis* (MOTT) has increased over the past several years; in some areas the isolation rate for *Mycobacterium avium–Mycobacterium intracellulare* has surpassed that for *M. tuberculosis.* Simultaneously, the spectrum of clinical manifestations associated with the various species has widened. Outbreaks of disease due to *Mycobacterium chelonae* have occurred in renal dialysis patients. New species have been described: *Mycobacterium malmoense* is primarily a pulmonary pathogen, and *Mycobacterium haemophilum* has been recovered from cutaneous lesions in immunosuppressed patients. In addition, reports of disease due to species generally considered saprophytic have become more numerous. In this review, the epidemiologic, pathologic, and clinical features of the individual MOTT species are discussed. A brief summary of mycobacteria isolated at the Cleveland Clinic Foundation between 1982 and 1985 is also presented.

Mycobacteria other than *Mycobacterium tuberculosis* (MOTT) differ from *M. tuberculosis* in several respects. Person-to-person transmission generally does not occur with this group of organisms. MOTT species are ubiquitous in nature, and their pathogenic potential for humans varies; they may colonize an individual without causing invasive disease. Thus, in contrast to *M. tuberculosis*, which is always considered a pathogen when isolated, MOTT, when isolated, are not necessarily equated with disease. Furthermore, because of the pathogenicity of MOTT for humans, the existence of a predisposing condition frequently is required for tissue invasion to occur. For example, chronic pulmonary disease due to MOTT is frequently superimposed on previous parenchymal damage. Also, patients with malignancies and immunosuppression, in particular those with the acquired immunodeficiency syndrome (AIDS), are at increased risk of developing a wide spectrum of disease manifestations.

As the incidence of tuberculosis has declined in the United States over the past several years, the rate of isolation of MOTT has risen. Furthermore, several new species have been described. It is important, therefore, for clinicians to be aware of both the pathogenic potential of these organisms and the clinical syndromes with which they are associated.

The purpose of this review is twofold: first, to summarize data on all mycobacteria isolated at the Cleveland Clinic between April 1982 and October 1985 and, second, to discuss the epidemiologic, pathologic, and clinical features of the individual MOTT species described.

Cleveland Clinic Experience

All mycobacteria isolated at the Cleveland Clinic Foundation (CCF) between April 1982 and October 1985 are listed in table 1; during this period culture techniques were unchanged. The rates of isolation of individual species are similar to frequencies reported for the United States in 1980 [1]. At CCF in 1985, *Mycobacterium avium–Mycobacterium intracellulare* (MAI) was isolated from more patients than was *M. tuberculosis.* Slightly over one-half of the MAI isolates were from patients with AIDS. Sites from which the organisms were recovered, listed in table 2, are fairly typical. Three cases, however, are of particular interest: (*1*) a patient receiving chronic ambulatory peritoneal dialysis who developed *Mycobacterium fortuitum* peritonitis [2], (*2*) a patient with AIDS whose stool and rectal ulcer cultures yielded *Mycobacterium kansasii*, and (*3*) a patient who had undergone removal of an acoustic neuroma several months before being diagnosed as having meningitis due to *Mycobacterium terrae-triviale* (authors' unpublished observation).

Received for publication April 16, 1986, and in revised form July 24, 1986.

We thank Faith Cumberledge for her expert secretarial assistance in preparation of this manuscript.

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Table 1. Mycobacteria isolated from patients at the Cleveland Clinic Foundation from April 1982 to October 1985.

Mycobacterium species	No. of isolates in designated year*			
	1982	1983	1984	1985
tuberculosis	28 (9)	45 (15)	34 (15)	19 (8)
avium-intracellulare	21 (7)	15 (10)	24 (14)	16 (10)
gordonae	1 (1)	7 (6)	11 (11)	9 (8)
fortuitum	5 (3)	0 (0)	5 (3)	10 (3)
kansasii	0 (0)	3 (3)	5 (3)	5 (4)
scrofulaceum	0 (0)	4 (2)	1 (1)	0 (0)
terrae-triviale	3 (2)	2 (2)	1 (1)	0 (0)

* Data in parentheses are numbers of patients from whom organism was isolated.

Classification

The method of Runyon was one of the earliest used to classify MOTT [3]. He separated these organisms into four groups—I, photochromogens; II, scotochromogens; III, nonphotochromogens; and IV, rapid growers—on the basis of colony pigmentation and growth rate. There are limitations to Runyon's classification system, however. *M. kansasii* is most often photochromogenic, but occasional strains are nonpigmented or scotochromogenic. Not infrequently, strains of MAI are slightly pigmented, and these findings may be misinterpreted and the strains classified as scotochromogenic. *Mycobacterium szulgai* is scotochromogenic at 37°C but is photochromogenic at 25°C.

A more clinically relevant method of classification is one based on human pathogenicity, as shown in tables 3 and 4. MAI, *M. kansasii*, and *Mycobacterium fortuitum-chelonae* complex are most frequently associated with human disease. A discussion of the epidemiology, pathology, and clinical manifestations of each species follows.

Mycobacterium avium-Mycobacterium intracellulare

Animal disease caused by *M. avium* was described approximately one century ago, but the organism was not recognized as a human pathogen until 1943 [4]. Initially, *M. avium* and *M. intracellulare* were differentiated on the basis of their virulence in chickens and rabbits, but today, because the two species are so similar, most laboratories do not distinguish between them and report isolates of both species as "MAI."

MAI is a nonphotochromogen, although occasional strains may be lightly pigmented. It grows slowly, often requiring eight weeks of incubation. Colonies are smooth and either small, thin, and transparent or large, opaque, and domed; scattered rough colonies may appear. Growth is optimal at 37°C, is usually present at 25°C, and is variable at 45°C.

The MAI complex is composed of 28 separate serovars, which are determined by the seroagglutination testing originally described by Schaefer [5, 6]. The seroagglutination test is based on the presence of species- or type-specific antigens. Brennan et al. [7, 8] recently defined the structures of these glycopeptidolipid antigens and devised a sensitive, thin-layer chromatography (TLC) procedure as a

Table 2. Sites from which mycobacteria were isolated in patients at the Cleveland Clinic Foundation from April 1982 to October 1985.

Mycobacterium species	Total no. of isolates	Sites of isolation									
		Resp	Urine	LN	CNS	Perit	Blood	BM	Gastric	Stool	Other
tuberculosis	129	92	14	6	6	2	1	2			6*
avium-intracellulare	79	56	2	3			4	4	2	5	3†
kansasii	12	9	1							2	
fortuitum	20	7				8					5‡
gordonae	12	4	5						2		1§
scrofulaceum	4	2	2								
terrae-triviale	6	4			2						

NOTE. Resp = respiratory sources, including sputum, bronchoscopy specimens, and lung tissue; LN = lymph node; CNS = CSF and brain tissue; Perit = peritoneal; and BM = bone marrow.

* Includes one liver specimen and five wound specimens (site not specified).

† Includes one specimen each of semen, liver, and wound (site not specified).

‡ Includes one specimen each from clavicle and maxillary sinus and three from sternal wounds.

§ Skin specimen.

Table 3. *Mycobacterium* species other than *Mycobacterium tuberculosis* that are potentially pathogenic in humans.

avium-intracellulare
kansasii
fortuitum-chelonae complex
scrofulaceum
xenopi
szulgai
malmoense
simiae
marinum
ulcerans
haemophilum

means of determining serotype. TLC is an especially useful method for identifying strains that autoagglutinate and the occasional rough colony variants [9]. Serotyping is important primarily from an epidemiologic point of view, and it may also help to assess the pathogenicity of an MAI isolate [10].

In 1980, MAI was second only to *M. tuberculosis* as the most frequently isolated species of mycobacteria in the United States [1]. Rates of isolation were highest along the Gulf Coast, the Pacific coast, and in the north-central region. Although MAI causes disease in some animals, including poultry, swine, and monkeys, environmental organisms are thought to be the most important source of disease and infection in humans [11]. Soil, house dust, water, dried plants, and bedding are among the environmental sources from which MAI has been isolated. Gruft et al. [12] examined water and air samples collected along the east coast of the United States for mycobacteria. *M. avium-intracellulare-scrofulaceum* (MAIS) was recovered from 25% of 520 water samples, taken primarily from estuaries in South Carolina, Georgia, and the Gulf states. It is of interest that only *M. intracellulare* was isolated from air samples, a finding that the authors postulated could explain the greater predilection of *M. intracellulare* than *M. scrofulaceum* for the lungs. Meissner and Falkinham [13] studied the plasmid profiles of clinical and environmental isolates of MAIS. Plasmids were found in 56% of clinical and 75% of aerosol isolates but in only 5% of soil, 7% of dust, <6% of sediment, and 25% of water isolates, a finding that suggests aerosols are a likely source of human infection.

Table 4. Saprophytic *Mycobacterium* species that rarely cause disease in humans.

Growth rate, species
Slow
gordonae
asiaticum
terrae-triviale
gastri
nonchromogenicum
paratuberculosis (?)
Intermediate, *flavescens*
Rapid
thermoresistibile
smegmatis
vaccae
parafortuitum complex
phlei

MAI is commonly found in the environment and is generally of low pathogenicity; these organisms may colonize an individual without causing subsequent disease. This possibility makes the interpretation of culture results difficult, especially cultures of sputum and other specimens from the respiratory tract. Factors that favor a diagnosis of disease are compatible roentgenographic changes, such as pulmonary infiltrates or cavitation; repeated isolation of multiple colonies of the same species of mycobacteria; or isolation of the mycobacteria from a closed lesion [14]. One group of investigators has suggested even more stringent criteria [15]. For cavitary disease, they advocate that sputum should be repeatedly positive for two or more weeks after the start of chemotherapy in order for a diagnosis to be validated. When chest roentgenograms show infiltration only, these authors recommend bronchial hygiene therapy initially; then, if the number of colonies does not decrease within one month or if sputum does not convert to negative within two to four months, they consider that invasive disease is present.

Pulmonary disease due to MAI varies in its clinical presentation and course. The typical patient is a middle-aged white male with preexisting lung disease, such as chronic bronchitis and emphysema, healed tuberculosis, bronchiectasis, or pneumoconiosis—especially silicosis. Individuals without a primary lung disorder are occasionally affected. Clinical presentation is similar to that of tuberculosis: cough with sputum production, fatigue, weight loss, fever, night sweats, and, less often, hemoptysis. Occasionally, patients are asymptomatic. Asymptomatic patients may or may not develop progressive disease. Symptomatic disease, on the other hand, nearly always progresses and can be fatal unless adequately

treated [15–17]. Chest film findings vary. Most frequently, thin-walled cavities are observed. Less commonly, infiltrates or solitary nodules occur.

In 1984, Horsburgh et al. reviewed 37 non-AIDS patients with disseminated MAI infection [18]. Twenty of the 37 patients were immunocompromised, most as a result of adrenocorticosteroid therapy. All age groups were represented. The group of newborns to 10-year-olds had the greatest number of patients but the least number of compromised hosts. The most frequently observed clinical symptoms were fever, weight loss, and bone pain. Physical findings included fever, lymphadenopathy, hepatosplenomegaly, and a variety of skin lesions. Laboratory studies were nonspecific. Many patients had hematologic abnormalities. Chest films and bone scans or bone surveys, if done, often showed abnormalities. MAI was isolated from many sites; bone marrow, sputum or lung tissue, bone, liver, and lymph nodes were those most commonly culture-positive.

Recently, disseminated MAI infection has become a serious problem in patients with AIDS [19–26]. Because patients with AIDS are usually infected with several different organisms, it is difficult to discern signs and symptoms that are specific to MAI infection. Many of these patients have gastrointestinal symptoms [23, 24], and some appear to be septic [19–22]. In the latter group, MAI can often be isolated from blood. At autopsy, involvement of lung, spleen, and lymph nodes has been documented histologically or culturally in essentially all of these patients and in many other organs in some patients [19].

MAI can be cultured from lymph nodes of patients with cervical lymphadenitis, a condition commonest in children [27–29] but also found in adults [29]. In some areas MAI is more frequently the causative agent than *M. scrofulaceum* [29, 30]. Other manifestations of MAI infection include granulomatous synovitis [31], genitourinary tract disease [32, 33], cutaneous lesions [34], deep infections of the hand [35], osteomyelitis [27], meningitis [27], and colonic ulcers [27, 36]. Disseminated disease initially presenting as panniculitis has also been described [37].

Histopathologically, MAI lesions are variable. Samples of lymph nodes from patients with localized cervical lymphadenitis frequently show caseating granulomas with acid-fast bacilli (AFB), changes indistinguishable from those found in tuberculosis. A spectrum of findings can be observed in lung tissue, including caseating granulomas [38], interstitial fibrosis with organizing pneumonia, or necrotizing granulomatous vasculitis (a finding similar to that in Wegener's granulomatosis) [39]. In a recent review of the pathology observed in 11 cases of disseminated MAI disease, the authors concluded that these changes can be distinguished from those seen in tuberculosis [40]. Granulomas similar to those found in tuberculosis were present in liver and spleen; skin, bone, bronchus, and some lymph nodes, on the other hand, demonstrated necrotizing acute and chronic inflammation with histiocytes but with no definite granulomas. The histologic description of tissue from patients with AIDS with disseminated disease may be similar to that described above [25, 31, 37], or there may be aggregates of foamy macrophages, which, when seen in the small intestine, resemble those in Whipple's disease [23, 24]. But in contrast to the macrophages seen in Whipple's disease, these macrophages contain numerous intracellular AFB.

Results of treating infection due to MAI are less satisfactory than those of treating infections due to other mycobacterial species, because MAI demonstrates in vitro resistance to many of the antituberculosis drugs. The protocol selected depends on clinical presentation. Complete surgical excision without chemotherapy is considered adequate for the patient whose immune status is normal who presents with either localized lymphadenitis [11, 30] or a solitary well-circumscribed pulmonary nodule (detected on chest film) which, after resection for diagnostic purposes, demonstrates granulomata histologically and MAI on culture [11].

Various authors have suggested different medical and/or surgical treatment regimens for MAI pulmonary disease [11, 16, 17, 30]. In a recent National Consensus Conference on Tuberculosis, the Committee on *M. intracellulare* Disease made several recommendations [11]. (*1*) In asymptomatic patients with noncavitary disease and inconsistent culture results, bronchial hygiene, observation, and follow-up are indicated. Chemotherapy is begun only when disease progresses. (*2*) Patients who have radiologically demonstrated moderately advanced disease and moderate but stable respiratory symptoms should receive isoniazid, ethambutol, and rifampin for 18 to 24 months plus streptomycin for the first two to three months. In a patient with adequate cardiopulmonary reserve and localized disease, however, chemotherapy followed by surgical resection may offer a

better prognosis. (*3*) Patients with progressive symptoms, marginal pulmonary reserve, and advanced roentgenographic findings should receive intensive chemotherapy utilizing five to six drugs.

Therapy for extrapulmonary disease varies according to the patient's immune status and the extent of disease. For immunocompetent patients with localized cutaneous or soft-tissue infection, arthritis, or osteomyelitis, drainage or debridement in addition to chemotherapy with three to four drugs is advocated [11]. Immunocompromised patients or those with disseminated disease require a more aggressive regimen [11, 18]. Rifampin, streptomycin, ethambutol, and ethionamide plus second-line drugs, such as cycloserine or kanamycin, have been suggested. Disagreement exists concerning the use of isoniazid.

In addition to these conventional antituberculous drugs, two other agents have recently been investigated [11, 41]. Clofazimine, an antileprosy agent taken up by epithelium, bone marrow, and the reticuloendothelial system, shows promise in the treatment of non-AIDS patients. Ansamycin, a spiropiperidyl rifamycin, has, in studies focused primarily on patients with AIDS, demonstrated greater in vitro activity against MAI than did rifampin. At present, however, ansamycin is considered a research drug, and its use is restricted to patients with life-threatening disease due to MAI. The administration of neither clofazimine nor ansamycin has resulted in sustained remission of infection in patients with AIDS, despite the in vitro activity of these drugs. Attempts to restore immune capacity in immunocompromised patients are critically important. Recommended guidelines for duration of therapy in patients with extrapulmonary disease range from 24 to 36 months [11, 18].

Mycobacterium scrofulaceum

M. scrofulaceum was named following the publication by Prissick and Masson of reports of mycobacterial cervical lymphadenitis in children in 1956 [42]. Colonies of *M. scrofulaceum* are buttery in consistency, smooth, and globoid. Pigmentation varies from light yellow to deep orange and may darken on prolonged exposure to light. Growth occurs at 25°C, 31°C, and 37°C in four to six weeks. Organisms have been isolated from raw milk and other dairy products, pooled oysters, soil, and water [30]. Antigenic similarities exist between *M. scrofulaceum* and MAI, and occasional isolates identified biochemically as *M. scrofulaceum* are serotyped as MAI and vice versa. For this reason some authors classify MAI and *M. scrofulaceum* together as the MAIS complex.

The disease most commonly associated with *M. scrofulaceum* is cervical lymphadenitis in children [27, 43–45]. Most cases occur in children one to five years old. Usually unilateral and involving nodes located not far from the mandible and high in the neck, this disease may affect other nodes as well. In general these children appear healthy. They do not have constitutional symptoms, and they complain of minimal, if any, pain or tenderness in the involved area. In a relatively short time the nodes soften, rupture, and drain, although occasionally the disease process may remain stationary and then regress, healing by fibrosis and calcification. When peripheral nodes are infected, pathogenesis is assumed to have been triggered by trauma to the extremities. In contrast, when cervical nodes are infected, most frequently no portal of entry can be unequivocally documented, although circumstantial evidence suggests that the infection originates in the mouth and throat [30].

Children with lymphadenitis represent the one group of patients in whom differential skin testing may be of diagnostic value. Test antigens other than those prepared from *M. tuberculosis* (PPD-S) include PPD-A (*M. avium*), PPD-B (MAI), PPD-G (*M. scrofulaceum*), PPD-Y (*M. kansasii*), and PPD-F (*M. fortuitum*). In the United States these antigens used to be prepared by the Centers for Disease Control (CDC, Atlanta). Reasons why they are no longer available include the lack of standardization of the antigens and the resultant difficulty in evaluating the observed skin reactions. Appropriate interpretation of skin test results is further complicated because, due to the ubiquity of these organisms in the environment, many adults have been sensitized to one or more MOTT species, and therefore correlation of skin test reaction with disease is problematic. Children, on the other hand, have not had sufficient time to become sensitized, and several investigators have found that, in children with lymphadenitis, dual testing with PPD-S and PPD-B makes it possible to differentiate between tuberculous and nontuberculous disease [43, 46–49]. Furthermore, because this distinction helps guide patient management, the authors have suggested that PPD-B be made available again.

Extranodal manifestations include pulmonary dis-

ease [50, 51], disseminated disease [52, 53], and rare cases of conjunctivitis, osteomyelitis [27], meningitis [54], and granulomatous hepatitis [55].

Histopathologic examination of involved lymph nodes does not help distinguish disease due to *M. scrofulaceum* from that due to tuberculosis. In both, granulomatous inflammation with Langhans' giant cells, various degrees of caseation, and the presence of AFB often are observed. In the one reported case of granulomatous hepatitis, microscopic examination of a liver biopsy specimen revealed multiple, discrete, noncaseating granulomas [55]—again, nondiagnostic features.

Treatment depends on the clinical syndrome. For cervical lymphadenitis, Taha et al. recommend excision of the involved lymph nodes (when possible) without the administration of antituberculosis medications [44]. They found that only incision and drainage or biopsy resulted in the development of a draining sinus or recurrent disease within a few months, despite the use of antituberculosis drugs. Other investigators, likewise, have found surgery to be the mainstay of therapy [48, 49]. For other forms of disease, however, surgery is not a viable option, and antituberculosis drugs must be given. In general, *M. scrofulaceum* demonstrates in vitro resistance to isoniazid, streptomycin, ethambutol, and *p*-aminosalicylic acid (PAS). Inconsistent results have been observed with rifampin, and in one case the organism was susceptible to cycloserine and erythromycin. Because disease other than cervical lymphadenitis is seen infrequently, no large series exists that evaluates optimal drug therapy. The patient with granulomatous hepatitis, however, showed clinical improvement after treatment with isoniazid, streptomycin, and cycloserine [55].

Mycobacterium kansasii

M. kansasii was first described as the "yellow bacillus" in 1953 by Buhler and Pollak [56]. Nearly all strains of *M. kansasii* are photochromogenic; a rare strain is nonpigmented or scotochromogenic. Colonies usually are rough, and after prolonged exposure to light, red β-carotene crystals typically appear [57]. Acid-fast stained smears of *M. kansasii* characteristically demonstrate large cross-barred bacilli.

M. kansasii accounted for only 3% of mycobacteria isolated in the United States in 1980 [1]. California, Texas, Louisiana, Illinois, and Florida reported isolation of *M. kansasii* most frequently. Recent studies have shown a decline in the incidence of *M. kansasii* disease [58]. Although the organism has occasionally been cultured from samples of water in various parts of the world, its natural reservoir remains unknown [30].

The most common *M. kansasii* infection is chronic pulmonary disease, which resembles that caused by MAI except that fewer patients have preexisting lung disease and the response to chemotherapy is much better [15, 58–61]. In a review of 187 cases [59], the male-to-female ratio was 4:1, and 80% of the patients were white. Ages ranged from 18 to 93 years, with a median age of 50 years. Chest films showed involvement of the upper lobe in nearly all cases; one or more cavities were present in 96% of cases and were thin-walled in 33%. Scarring was seen in two-thirds of cases, and 63% of patients had endobronchial spread. Pleural effusions and lymphadenopathy were rare.

Manifestations of extrapulmonary disease due to *M. kansasii* are diverse. Cervical lymphadenitis is seen predominantly in children from the urban Midwest and Southwest [30, 62]. Cutaneous disease may resemble pyogenic abscesses [63], cellulitis [64], or sporotrichosis [65]. Musculoskeletal-system involvement may present as carpal tunnel syndrome [35], synovitis [31, 66], arthritis [67], tendonitis and fasciitis [68], or osteomyelitis [69]. Patients with either cutaneous or musculoskeletal involvement may or may not have an associated predisposing condition, such as trauma, rheumatoid arthritis, or immunosuppression. Disseminated disease, on the other hand, generally affects patients with impaired cellular immunity [70, 71]. The majority of reported cases, both adult and pediatric, have occurred in males. Characteristic signs are fever, constitutional symptoms, pulmonary manifestations, hepatosplenomegaly, and hematologic abnormalities, especially leukopenia or pancytopenia. Lymphadenopathy, diffuse bone involvement, skin lesions, genitourinary involvement, and gastrointestinal involvement occur less frequently. Cases of isolated genitourinary tract disease have been described [72, 73]. One case of pericarditis has been reported [74]. We recently isolated *M. kansasii* from stool of two patients with AIDS (authors' unpublished data).

Histologic findings from examination of biopsied or resected tissues are not diagnostic. With *M. kansasii*, as with MAI, lung and lymph-node specimens often demonstrate caseating granulomas positive for AFB [30, 62]. Noncaseating granulomas have been

observed in synovial tissue [31, 66]. Skin lesions may show granulomas with areas of necrosis or collections of acute and chronic inflammatory cells without well-formed granulomas [63–65]. AFB may or may not be seen.

Most strains of *M. kansasii* are susceptible in vitro to rifampin and only slightly resistant to isoniazid, ethambutol, and streptomycin. Patients with both pulmonary and extrapulmonary disease generally are treated with two or more antituberculosis drugs, one of which is rifampin [58, 61, 75]. Pulmonary disease typically responds well to therapy, but relapses can occur, and rare cases of death due to progression of the disease have been reported. Surgical treatment of pulmonary disease, although rarely indicated, may be of benefit in the following specific cases: (*1*) localized disease with persistent cavitation in which the organism has not been eradicated from sputum after a six-month follow-up period, (*2*) acquired drug resistance resulting from poor compliance, and (*3*) severe drug intolerance [55]. Excluding disseminated disease, for which the prognosis is uncertain despite adequate therapy [71], the outcome of extrapulmonary disease with appropriate treatment is favorable.

Mycobacterium fortuitum-chelonae Complex

Human pathogens included in this group are *M. fortuitum* and *M. chelonae*. *M. fortuitum*, which has also been referred to as *Mycobacterium ranae* in the literature, was first described and named in 1938, but its name did not become official until 1972 [76]. Several different names for *M. chelonae* have appeared in the literature: *Mycobacterium friedmannii*, *Mycobacterium abscessus*, *Mycobacterium runyonii*, and *Mycobacterium borstelense*.

Both species grow on routine bacteriologic media, as well as on media used specifically for mycobacteria, in seven days or less at temperatures ranging from 25°C to 40°C. Colonies may be smooth, rough, or a mixture of both and are nonphotochromogenic. There are three biovariants of *M. fortuitum:* biovariant *fortuitum*, biovariant *peregrinum*, and an unnamed biovariant designated "third group." There are also three subspecies of *M. chelonae:* subspecies *chelonae*, subspecies *abscessus*, and an unnamed subspecies known as *M. chelonae*-like organisms. *M. fortuitum* has been isolated from water, soil, and dust; yet whether *M. chelonae* has such a diverse habitat is uncertain [77, 78].

Clinical manifestations of infection with these organisms include disseminated disease, cutaneous lesions, postsurgical infections, pulmonary disease, and a gamut of miscellaneous infections. Patients with disseminated disease have no primary source of infection. They present with multiple, recurrent abscesses of the skin and soft tissue located most commonly on the extremities [79, 80]. Patients may or may not be systemically ill, and in those who are ill, organisms can be isolated from many sources, including blood. All reported cases have occurred in adults, most of whom were immunocompromised.

Primary cutaneous disease is seen in all age groups. Manifestations include localized cellulitis, frequently with draining abscesses, or individual nodules that are minimally tender [79, 81–83]. Patients generally have an intact immune system, and most give a history of penetrating injury with possible soil or water contamination. Outbreaks due to *M. chelonae* have occurred after administration of diphtheria-pertussis-tetanus-polio vaccine and after histamine injections. The time interval between injury and clinical onset ranges from three weeks to 12 months, and most commonly is four to six weeks. Osteomyelitis occasionally complicates cutaneous disease, especially when puncture wounds to the feet are present [79].

Postoperative infections generally develop three weeks to three months after surgery [79]. Implicated procedures include median sternotomy, augmentation mammaplasty, and procedures involving insertion of a percutaneous catheter. Outbreaks of postsurgical infection following sternotomy have been reported (North Carolina, 1976 [84]; Colorado, 1976 [84]; Hungary, 1977 [85]; Texas, 1981 [79]). Patients present with failure of the wound to heal or with breakdown of a healed wound, with drainage of serous, watery fluid; usually they have few systemic symptoms [86].

In many cases chronic pulmonary disease is indistinguishable from disease due to MAI or *M. kansasii* [87, 88]. In one series, however, cavitation was seen in only three of 24 patients [79]. In addition, an association between achalasia and pulmonary disease due to the *M. fortuitum-chelonae* complex has been reported [89].

Endocarditis with prosthetic valve involvement usually becomes manifest four to 12 weeks after surgery; patients present with fever, the characteristic cutaneous and embolic phenomena, and multiple positive blood cultures. In one series all four patients died, despite valve replacement [79]. A different form

of cardiac-valve infection occurred in 1977 after the placement of porcine heterograft valves (Hancock Laboratories, Anaheim, Calif.) that were contaminated with *M. chelonae* [90]. Although none of the patients who received a contaminated valve developed clinical endocarditis, one patient developed a pericardial effusion and one, an aortic root abscess; neither of these infections was fatal.

Other entities associated with the rapidly growing mycobacteria include keratitis and corneal ulceration, both subsequent to traumatic injury [91, 92]. Cervical lymphadenitis may occur in any age group, and occasionally the patient's history includes recent dental extraction [79]. Outbreaks of disease in patients undergoing renal dialysis have been reported. In one such outbreak peritonitis due to contaminated water developed in patients receiving intermittent peritoneal dialysis [93]. In a second outbreak a variety of *M. chelonae* infections occurred, including bacteremia, disseminated disease, and soft tissue infections, in patients receiving hemodialysis as a result of the use of hemodialyzers contaminated during processing [94]. Meningitis, hepatitis, synovitis, and epidural abscess are rarely observed [79, 81].

Histologic examination of lesions produced by these organisms often demonstrates a biphasic pattern [79]. Polymorphonuclear leukocytes (PMNs) are seen in direct association with granulomatous inflammation. Although necrosis is invariably present, caseation necrosis is minimal. Foreign body and/or Langhans' giant cells frequently are observed. AFB are seen in fewer than one-third of cases, but when present, they tend to be located extracellularly in clumps within aggregates of PMNs. Unlike the other mycobacteria, these organisms do not stain with auramine-rhodamine, which is used for fluorescence microscopy. Foamy macrophages are often seen in lung tissue, a pattern simulating that in lipoid pneumonia. Lipid-laden macrophages may also be found in biopsy specimens from other sites.

Clinical outcome is generally good, with the exception of prosthetic-valve endocarditis, which has been uniformly fatal. Deaths in patients with disease other than endocarditis are often due to unrelated underlying medical conditions. Approximately 10%–20% of cutaneous infections resolve spontaneously over an average period of eight months. In many cases, however, infections persist for longer periods, and because serious disease can result in death, treatment is recommended [95]. Abscesses and significant deep infections should be incised, drained, and packed open; cathethers and prosthetic devices should be removed, and chemotherapy should be given. *M. fortuitum* and *M. chelonae* are resistant to conventional antituberculosis drugs but do respond to other antimicrobial agents. Recommended therapy for serious infections includes amikacin plus cefoxitin for a minimum of two to six weeks followed by administration of one of the active oral agents – sulfonamide, tetracycline, or erythromycin – depending on results of in vitro susceptibility studies. A few of the newer antimicrobial agents, such as imipenem and various cephamycins [96], have demonstrated good in vitro activity, and one patient treated here has received treatment with ciprofloxacin [2]. The suggested duration of therapy is four to six weeks after wound healing is complete.

Mycobacterium xenopi

First isolated from a toad and described in 1957 [98], *M. xenopi* was not recognized as having pathogenicity in humans until 1965 [30]. The organism is a scotochromogen, producing a yellow pigment that varies in intensity. Growth is optimal at 42°C–43°C but occurs at 37°C after prolonged incubation. Colonies are smooth and on cornmeal agar may demonstrate filamentous extensions [57]. Acid-fast stained smears show long, slender cells, tapered at both ends with a palisading arrangement.

Mycobacterium xenopi has been cultured frequently from both hot- and cold-water taps [98, 99]. It has also been recovered from hot-water generators and storage tanks of various hospitals, and in some cases has caused nosocomial disease [100]. Birds have been considered a possible natural reservoir in Great Britain, where the organism has been found more often in coastal than in inland areas. In a study examining mycobacteria cultured from tonsils, *M. xenopi* accounted for 60% of isolates [101].

Several reports of infection due to *M. xenopi* have appeared in the literature. The majority of cases have been of pulmonary disease, and most reports have been from Europe and Great Britain. In the United States, *M. xenopi* accounted for only 0.2% of mycobacterial isolates reported to the CDC in 1980 [1]. Half of these isolates came from Connecticut, Wisconsin, and California.

Pulmonary disease due to *M. xenopi* has been reported only in adults and affects males more fre-

quently than females [100–107]. The mean age of those affected is ~56–62 years, with a range of 23–84 years. Most patients have either preexisting lung disease or another predisposing condition, such as extrapulmonary malignancy, alcoholism, or diabetes mellitus. The disease may be chronic, subacute, or acute. Clinical symptoms are indistinguishable from those due to MAI or *M. kansasii*. Manifestations seen on roentgenograms of the chest are variable, including nodular or mass lesions, single or multiple cavities, multifocal nodular densities, apical shadowing, consolidation, and fibrosis.

Extrapulmonary infection has involved bone, lymph node, epididymis, a sinus tract, and a prosthetic temporomandibular joint [30]. In addition, three cases of disseminated disease have been described [108–110], two of which were in patients with AIDS [110, 111].

Little has been written concerning the histologic findings associated with *M. xenopi*. Isolated reports have described nonspecific granulation tissue together with epithelioid macrophages, Langhans' giant cells, and caseating granulomas positive for AFB.

Results of both in vitro susceptibility testing and treatment of *M. xenopi* infection have been inconsistent. Some authors have found isolates to be sensitive or only slightly resistant to isoniazid, ethambutol, streptomycin, and rifampin and have claimed that patients treated with a combination of these drugs have a good prognosis for cure [100]. In contrast, Banks et al. [102] observed more resistance to the above antituberculosis agents but uniform susceptibility to cycloserine and ethionamide when tested. In their experience, long-term response to chemotherapy was unpredictable. Relapses were not infrequent, and response to retreatment was poor. In their study, occasional patients underwent resection and most were cured. They therefore suggest that surgery may play a role in the treatment of those patients who are able to safely undergo surgical management.

Mycobacterium szulgai

M. szulgai was first recognized in 1972 [111]. Colonies appear after ~14 days of incubation and demonstrate unique pigmentation. When grown at 37°C, they are scotochromogenic, but at 25°C they are photochromogenic. Although the organism has worldwide distribution, its natural reservoir is not known.

Fewer than 20 cases of human disease due to *M. szulgai* have been reported. Most have been chronic pulmonary disease [112, 113], which occurs predominantly in middle-aged men. Chest films frequently show cavitary lesions. Clinical symptomatology is indistinguishable from that of disease due to MAI or *M. kansasii*. Extrapulmonary disease is uncommon. Infection of the olecranon bursa occurred in two patients, one after repeated trauma and the other after a cortisone injection [30]. Extensive cutaneous infections have been reported in two patients; both were receiving corticosteroids [114, 115], and one patient developed osteomyelitis [109]. There has been one case of tenosynovitis with carpal tunnel syndrome in a florist [116], one case of cervical lymphadenitis in a child, and one report of disseminated disease [117]. In the latter case, *M. szulgai* was isolated from 28 specimens of bone, skin lesions, and sputum of a previously healthy young man after recovery from a *Salmonella paratyphi* D infection.

Microscopically, lesions due to *M. szulgai* show granulation tissue consisting of lymphocytes, plasma cells, and histiocytes. In most cases granulomas composed of histiocytes and multinuclear giant cells but without caseation necrosis are also observed. Occasionally PMNs are seen. The presence of AFB is variable.

Although *M. szulgai* is slightly more resistant than *M. tuberculosis* to most antituberculosis drugs, in many cases the infection has responded to a three-drug regimen consisting of rifampin, isoniazid, and ethambutol, with streptomycin, capreomycin, or viomycin serving as a fourth or substitute drug.

Mycobacterium malmoense

M. malmoense was reported as a new species in 1977 by Schröder and Juhlin [118]. The organism grows as dysgonic, smooth, colorless colonies at temperatures ranging from 22°C to 37°C. At 37°C growth is generally apparent after ~18 days; however, incubation for up to 12 weeks may occasionally be required. Exposure to light does not alter colony pigmentation. Acid-fast stains reveal rods that are coccoid to short to moderately long and that stain positively by the gram method, although they lack crossbands. The natural reservoir of these organisms is unknown.

Patients infected with *M. malmoense* generally present with chronic pulmonary disease. Most cases have occurred in middle-aged men with previously documented pneumoconiosis [119, 120]. The organ-

ism has been recovered from sputum, gastric lavage, bronchial secretions, and lung tissue of patients with pulmonary disease. Two cases of cervical lymphadenitis in children have also been described [120]. The majority of reported cases have come from England, Wales, and Sweden. Isolation of *M. malmoense* has been reported from various parts of this country, but only one well-documented case has been reported in the United States [119]. Although little has been written describing the histopathologic characteristics of lesions, the results of histologic examination of cervical adenitis were described in one study as "typically that of a tuberculous infection" [119].

The antimicrobial susceptibility patterns of various isolates of *M. malmoense* have varied. The original organisms studied were uniformly susceptible to ethionamide, ethambutol, kanamycin, and cycloserine and resistant to other antimycobacterial drugs, including isoniazid, streptomycin, rifampin, PAS, and capreomycin. The isolate reported from the United States, however, was susceptible to rifampin, streptomycin, and capreomycin as well as to ethionamide and ethambutol [119]. Regardless of in vitro susceptibility results, however, treatment of disease has generally not been satisfactory. Some patients have died, some have developed progressive disease, others have remained clinically stable with positive cultures, and a few have improved clinically, including those with cervical adenitis. More intensive study is necessary before recommendations on effective treatment can be made.

Mycobacterium simiae

M. simiae was first isolated from monkeys imported to Hungary from India by Karassova et al. in 1965 [121] and was named in 1969 by Weiszfeiler et al. [122]. In 1971, Valdivia et al. [123] isolated from the sputum of patients with either pulmonary tuberculosis or other respiratory diseases a niacin-positive strain of *Mycobacterium* belonging to Runyon group III for which they proposed the name *Mycobacterium habana*. Studies have since shown *M. simiae* and *M. habana* to be the same species [124, 125].

Although *M. simiae* is a photochromogen, pigment production often requires prolonged exposure to light; even then production may be weak. In addition to being found in monkeys, the organism has been recovered from water taken from taps in hospitals.

The few recorded cases of disease due to *M. simiae* include chronic pulmonary disease [126, 127], osteomyelitis [128], and disseminated disease with renal involvement [128]. In the latter case both *M. kansasii* and *M. simiae* were recovered from urine and bone marrow. Histologic reports included granulomas with Langhans' giant cells, caseation necrosis, and AFB present in lung and kidney tissue; vertebral tissue showed only a minimal chronic inflammatory infiltrate in addition to degenerating cartilage and necrotic bony sequestra.

Susceptibility studies have been relatively consistent. *M. simiae* isolates have demonstrated in vitro resistance to all antituberculosis drugs except ethionamide and cycloserine. Because so few cases of disease have been reported, no recommendation concerning the optimal approach to therapy can be made. Disease has been stabilized following treatment with isoniazid, ethambutol, and rifampin; however, in some cases, excretion of the organism continued.

Mycobacterium marinum

M. marinum was first described and named in 1926 by Aronson [129], who was investigating disease of salt-water fish, but it was not implicated in human infections until 1951 [130]. *M. marinum* has also been referred to as *Mycobacterium platypoecilus* and *Mycobacterium balnei*, but it has subsequently been proven that all are of the same species.

A photochromogen, *M. marinum* has an optimal growth temperature of 31°C–33°C. Colonies appear in eight to 14 days. In most instances colonies are slightly wrinkled and shiny, but they may be smooth and hemispherical or, rarely, rough and dry.

Characteristically, cutaneous disease, acquired as the result of trauma to skin while in contact with contaminated nonchlorinated fresh or salt water, is associated with *M. marinum* infection. Disease can develop both after trauma unassociated with water contact or after contact with water in the absence of preceding trauma. The typical presentation is a single papulonodular lesion confined to one extremity, most commonly involving the elbow, knee, foot, toe, or finger [131–133]. The lesion usually appears two to three weeks after inoculation and, with time, may become verrucous or ulcerated. A second variety resembles cutaneous sporotrichosis. In this form there is abscess formation at the inoculation site, followed by the development of a series of secondary nodules that progress centrally along the lym-

phatics. Reports of disseminated cutaneous lesions in immunocompromised patients have also appeared, though they are rare [134, 135].

Extracutaneous manifestations include synovitis, most commonly involving the hands and rarely the knees; infections of the deep structures of the hands; osteomyelitis [136]; and laryngeal lesions [137].

The histologic appearance of skin lesions is somewhat dependent on the age of the lesions. Very early a central collection of PMNs surrounded by a zone of histiocytes appears. As lesions age, the inflammatory infiltrate changes. Lesions of less than six months' duration consist mainly of lymphocytes and epithelioid cells. Langhans' giant cells are occasionally present, and foci of fibrinoid necrosis may be observed. Caseous necrosis, however, is not seen. Lesions present for more than six months demonstrate nonspecific focal aggregates of lymphocytes in the dermis, often surrounding blood vessels or skin appendages. Sites other than skin show similar findings. In the majority of cases acid-fast stains are unrevealing. When organisms are observed, they are generally located within histiocytes, are longer and broader than *M. tuberculosis*, and often show cross-banding.

Treatment depends on the presentation of disease. Single cutaneous lesions often resolve spontaneously in three months to three years, whereas the sporotrichoid form may persist for prolonged periods. Occasionally discomfort is severe enough to warrant treatment. Methods of localized treatment include curettage, electrodesiccation, freezing, excision followed by skin grafting, irradiation, intralesional steroid injection, local heat, and incision and drainage. For unresponsive or disseminated skin disease or deep infections, systemic therapy is indicated. In vitro, most strains are susceptible to rifampin and ethambutol, resistant to isoniazid, and moderately resistant to streptomycin. Other antimicrobial agents demonstrating good in vitro activity include amikacin and kanamycin and, to a lesser degree, tetracycline, doxycycline, and minocycline [138].

Mycobacterium ulcerans

Alsop and Searls first recognized disease due to *M. ulcerans* as a clinical entity in Bairnsdale, Australia, in the 1930s [139]. Cutaneous ulcers in two patients in Uganda, described by Sir Albert Cook in 1897, probably represent the same disease [140]. Areas of endemic disease have been identified in Zaire, Uganda, Nigeria, Ghana, Cameroon, Malaysia, New Guinea, Guyana, Mexico, and at least three separate areas in Australia. These foci occur on three continents in latitudes 25° north to 38° south in both tropical and temperate climates. Neither the natural reservoir of the organism nor the usual route of transmission to humans has been identified.

Colonies of *M. ulcerans* resemble those of *M. tuberculosis:* they are rough, hydrophobic, nonpigmented and have the ability to form cords. The organism has a very slow growth rate, growing optimally at 33°C and poorly or not at all at 37°C and 25°C.

Various eponyms for disease due to *M. ulcerans* have appeared in the literature. Among these are Bairnsdale ulcer, from the area where it was first recognized in Australia, and Buruli ulcer or Buruli disease after the area of Uganda reporting the most cases. Because the natural reservoir and mode of transmission are unknown, the incubation period has not been accurately determined. Studies in endemic areas suggest that although the usual period is six to 12 weeks it may be as short as two weeks. Children five to eight years old are most frequently affected. In Australia, however, the mean age of 29 patients was 28.6 years, and a third were 40 years of age or older. The male-to-female ratio is ~1.3:1 in all endemic areas.

Clinically, disease begins as a "boil" or subcutaneous lump on an exposed area which may itch but is usually painless. The leg is the site involved most frequently, with lesions occurring on the left side more often than on the right. Occasionally, there is a preceding history of trauma. In most instances a single lesion is present, but multiple lesions have been reported, though rarely, from Australia [139].

After several weeks, the initial lump breaks down, revealing a shallow ulcer with a necrotic base and edges that resemble and have the consistency of an orange peel. The condition becomes indolent over a period of weeks to months, with prominent involvement of the subcutaneous tissue. Satellite nodules and ulcers may develop. Lymph node enlargement usually is not present, and patients remain afebrile and without systemic symptoms unless secondary bacterial infection occurs. Histologic examination of acute lesions reveals necrosis and edema, especially of adipose tissue, with an inflammatory infiltrate of lymphocytes, plasma cells, and macrophages. Unless there is a coexisting bacterial infection, PMNs are not observed. Occasional gi-

ant cells may be seen, but caseating granulomas have not been reported. AFB occur in large clusters in necrotic areas.

Surgical treatment is required. For early lesions excision and primary closure is appropriate. For large ulcerated areas, however, radical excision followed by skin grafting is recommended. Although chemotherapy alone is ineffective, less extensive surgery combined with chemotherapy has been reported [139]. The most appropriate regimen appears to be streptomycin and dapsone with or without ethambutol for at least two weeks after healing appears complete.

Mycobacterium haemophilum

M. haemophilum was first described and named by Sompolinsky et al. in 1978 [141], although it is very likely that noncultivable AFB recognized in skin ulcers in 1972 [142] and 1974 [143] represented this species. The organism is unique among mycobacteria in that hemoglobin or hemin is required for growth [141]. Appropriate media for culture include chocolate agar, 5% sheep-blood Columbia agar, Mueller-Hinton agar with Fildes supplement, and Lowenstein-Jensen medium containing 2% ferric ammonium citrate. Growth is stimulated in the presence of 10% CO_2. Reports concerning the optimal growth temperature are inconsistent: 20°C, 28°C, and 32°C have all been suggested. There is agreement, however, that little, if any, growth occurs at 37°C, even after prolonged incubation, a characteristic similar to that of *M. marinum* and *M. ulcerans*. The period required for isolation also varies, ranging from 10 days to six or eight weeks. Individual colonies are nonpigmented, both before and after exposure to light, and predominantly rough, with smooth variants frequently occurring. Acid-fast staining reveals straight, uniformly staining rods, which are not stainable by the gram method. The natural habitat of the organism is unknown.

Only 10 cases of *M. haemophilum* infection have been reported, most of them from Australia. The organism has been isolated from skin lesions of immunosuppressed adults, many of whom were lymphopenic [144–146], and it also was cultured from the submandibular lymph node of an infant [147]. Skin lesions are generally multiple and most commonly involve the extremities, but they are occasionally found on the face, abdominal wall, and in the gluteal and breast regions. Clinical presentation is that of nodules, ulcers, or painful swellings that increase in size and may develop into abscesses and open fistulas, draining purulent material.

Microscopically, small areas of necrosis in the lower dermis, surrounded by a polymorphous inflammatory infiltrate and occasional Langhans' giant cells, are seen in skin biopsy specimens. Caseation necrosis is not a prominent feature, if it is observed at all. AFB are frequently present, either singly or in small clusters and often intracellularly.

There are discrepancies in the literature concerning results of in vitro susceptibility studies, which in some instances can be attributed to the type of media used to perform the tests. In most reports *M. haemophilum* has been resistant to isoniazid, streptomycin, and ethambutol but susceptible to either rifampin and/or PAS. Tetracyclines and trimethoprim-sulfamethoxazole have shown variable in vitro activity. Despite in vitro results, patients have been treated with rifampin, isoniazid, and ethambutol, often in conjunction with surgical debridement. Lesions do heal, but only after a prolonged period of months to years. Because of this, some authors have questioned the beneficial role of drug treatment, suggesting that recovery may depend to a large degree on improvement of the patient's immunologic status [146].

Rarely Pathogenic Mycobacteria

Mycobacterium gordonae is the most commonly isolated saprophyte and one of the most frequently encountered mycobacteria in the laboratory. *M. gordonae* can be recovered from soil and water, and has been referred to as *M. aquae* or the tap-water bacillus. The organism is a scotochromogen, with smooth orange colonies appearing after four to eight weeks of incubation at either 25°C or 37°C. *M. gordonae* is commonly isolated from gastric washings and bronchial secretions and, in most cases, is considered a nonpathogen. Rarely, however, *M. gordonae* can cause disease. Reports in the literature include meningitis in a hydrocephalic infant with ventriculoatrial and ventriculoperitoneal shunts [148], hepatoperitoneal disease [149], infection of a prosthetic aortic valve [150], and cutaneous lesions of the hand [151]. There have also been two cases of possible, but unproven, pulmonary involvement [38].

The histologic description of lesions is variable. Caseating or noncaseating granulomas may be seen.

Skin lesions have shown acute and chronic inflammation with scattered histiocytes and giant cells. Although AFB have been infrequently observed, in one report they were described as "relatively plump rods" and "not morphologically typical of *M. tuberculosis*" [148].

In vitro susceptibility studies have shown *M. gordonae* to be resistant to isoniazid, streptomycin, and PAS but susceptible to rifampin and ethambutol. Treatment of the few patients has varied. Where foreign devices were involved, their removal was necessary. Chemotherapy has included long-term isoniazid and ethambutol in the patient with meningitis [148] and isoniazid, rifampin, and ethambutol in the patients with aortic valve and hepatoperitoneal involvement [149, 150]. All three demonstrated clinical recovery. The patient with skin lesions refused treatment, and after one year nodules had regressed in size but were still present [151].

Mycobacterium asiaticum, first isolated from healthy monkeys in 1965 by Karassova et al. [121], was named and described as a new species by Weiszfeiler in 1971 [152]. *M. asiaticum*, a photochromogen, grows at 25°C and 37°C but not at 45°C. The natural habitat is unknown. Although four isolates were reported from Florida in 1980 [1], details of the cases were not provided. Two cases of pulmonary disease have been reported from Australia, however [153]. Both patients had cavitary lesions; one had preexisting lung disease. Both strains showed in vitro susceptibility to cycloserine and ethionamide; were resistant to isoniazid, rifampin, and PAS; and demonstrated variable results with ethambutol and streptomycin. One patient was treated with rifampin and ethambutol for two years, but disease progressed and sputum cultures remained positive. The second patient received only short-term therapy with rifampin, ethambutol, capreomycin, and pyrazinamide; the result of this therapy was that disease was stable for two years and eight months.

Mycobacterium thermoresistibile is a rapidly growing (seven days) *Mycobacterium* that has the unique ability to grow at 52°C. Colonies may be smooth or rough; initially they are yellowish-orange but become brown with age. Growth occurs at 25°C, 37°C, and 45°C but is better at the two higher temperatures. The organism has been isolated from soil. Only one case of disease caused by *M. thermoresistibile* in humans has been reported [154]. The organism was cultured repeatedly from sputum, from a bronchoscopy specimen, and from lung tissue of an immunocompetent middle-aged woman with cough, fever, weight loss, and cavitary lesions seen on chest films. Lung tissue revealed microabscesses and granulomas with Langhans' giant cells. In vitro the organism was resistant to isoniazid, PAS, and ethionamide; susceptible to ethambutol and rifampin; and moderately susceptible to streptomycin. The patient showed clinical and radiologic improvement after receiving rifampin, ethambutol, and streptomycin.

Mycobacterium terrae-triviale complex includes *M. terrae* and *M. triviale*. *M. terrae* was first isolated in 1950 by Richmond and Cummings from the washings of a radish—hence the name "radish bacillus" [155]. It has subsequently been cultured from soil and various other vegetables. Both species grow slowly at 25°C and 37°C. Colonies of *M. terrae* are intermediate in roughness; those of *M. triviale* are rough. Both are nonphotochromogens. Few cases of pathogenicity in humans have been reported. Kestle et al. [156] reported that five of 48 isolates were clinically significant but provided no details. Case reports have included septic arthritis due to *M. triviale* in an infant [157], synovitis and osteomyelitis due to *M. terrae* in a young man with Fanconi's pancytopenia [158], and a possible case of disseminated *M. terrae* in a young woman who had previously had miliary tuberculosis [160]. Caseating granulomas were found in tissues that were examined. Susceptibility patterns of isolated organisms have differed. The two patients with bone and/or joint disease showed clinical improvement with surgery and antituberculosis medications.

Mycobacterium nonchromogenicum, a nonphotochromogen, and *Mycobacterium flavescens*, a scotochromogen, have each been rarely implicated as pulmonary pathogens. Three cases of primary lung disease due to *M. nonchromogenicum* have been reported [160]. All occurred in men 26–57 years old who were in occupations known to predispose to lung damage. All isolates were resistant to streptomycin, isoniazid, PAS, ethionamide, rifampin, and cycloserine but susceptible to ethambutol. One patient died from cor pulmonale despite treatment with ethambutol, isoniazid, and kanamycin. The other two received rifampin, streptomycin, and isoniazid; cavitary lesions resolved, as shown on chest film, and sputum samples became culture-negative.

The one case of human disease caused by *M. flavescens* was in an elderly man with a history of metastatic melanoma who presented with dys-

pnea, cough, weight loss, and night sweats; chest roentgenograms revealed cavitation in the left lobe [161]. Bronchoscopy and bronchial washings yielded pure cultures of *M. flavescens* sensitive to rifampin and resistant to streptomycin, PAS, ethambutol, and isoniazid. Treatment with ethambutol, rifampin, and isoniazid resulted in clinical improvement and negative cultures of sputum; chest roentgenographic findings remained unchanged after six months.

Mycobacterium paratuberculosis is the causative agent of paratuberculosis or Johne's disease. Johne's disease occurs throughout the world and primarily affects cattle, although sheep, goats, and other ruminants are susceptible [162]. Infected animals have nonresponsive, chronic or intermittent diarrhea and intermittent fever. Although remissions occur, the disease is inevitably fatal.

Mycobacterium paratuberculosis is a gram-positive, facultative AFB, measuring 0.5 μm × 1.5 μm. The organism is dependent on exogenous mycobactin, an iron-chelating agent produced by all mycobacteria, for in vitro growth. Colonies, which develop in four to eight weeks, are small, white, glistening, and rough-smooth; however, occasional strains producing yellow-to-orange pigments have been recovered.

Recently, Chiodini et al. [163] isolated an AFB from resected terminal-ileum samples of three patients with Crohn's disease. Primary colonies, which developed after three, five, and 18 months of incubation, measured 0.5–1.0 mm and were white, irregularly shaped, mucoid, and rough. No pigment was produced. Optimal growth occurred at 37°C and was significantly enhanced on media supplemented with mycobactin J (the mycobactin extracted from *M. paratuberculosis*). Biochemical profiles of all three strains were identical. The characteristics of this *Mycobacterium* did not conform to any of the presently recognized *Mycobacterium* species but most closely resembled *M. paratuberculosis*.

Animal and immunologic studies suggested that this *Mycobacterium* species could play a role in some cases of Crohn's disease. Oral inoculation of a seven-day-old goat with one of the above three strains (strain Linda) of *Mycobacterium* species did not produce clinical disease during a five-month observation period; however, the goat did develop both humoral and cell-mediated immunologic responses in two to three weeks, and autopsy revealed granulomatous disease of the distal small intestine and regional lymph nodes [164]. Culture of one of the lymph nodes grew a *Mycobacterium* species with characteristics identical to those of the inoculum. Thayer et al. [165] examined sera from patients with Crohn's disease and found a statistically significant increase in antibody titer to *M. paratuberculosis* when these values were compared with those of healthy controls.

Although these data are suggestive of a possible relation between Crohn's disease and a *Mycobacterium* species, the small number of isolates and the prolonged incubation period in one case (18 months) indicate the need for confirmation of this work by other investigators. In addition, the mycobactin-dependent species of mycobacteria isolated from these patients have not been taxonomically characterized. Further studies are necessary to determine whether this *Mycobacterium* represents a new species or whether it is a biovariant or subspecies of *M. paratuberculosis*.

Summary

The incidence of tuberculosis in this country has decreased over the past few decades; coincidentally infections caused by other species of mycobacteria have increased. During this period new species have been described. The clinical manifestations of MOTT infections are diverse. Clinical manifestations associated with MOTT species pathogenic for humans are summarized in table 5. Infrequently, cases of genitourinary tract involvement, meningitis, keratitis and corneal ulceration, and hepatitis may also occur.

Specific patient populations are often at risk for disease. In general, immunocompromised patients are at increased risk for the development of any one of the various clinical manifestations. This is especially true for disseminated disease, which occurs predominantly in immunosuppressed hosts. Disseminated MAI infection, however, is seen in infants and young children with intact immune systems. Chronic pulmonary disease most frequently affects patients with preexisting pulmonary damage, such as chronic obstructive lung disease, pneumoconiosis, healed tuberculosis, or carcinoma. Skin and soft tissue infections are often preceded by trauma.

Histopathologic study of resected or biopsied tissue, though not diagnostic, may provide important clues to indicate that one of the MOTT species is involved. The histologic findings of pulmonary disease and lymphadenitis most commonly resemble changes classically associated with tuberculosis. Fre-

Table 5. Mycobacteria other than *Mycobacterium tuberculosis* that are associated with clinical disease.

Species	Associated diseases [reference(s)]		Therapy [reference(s)]	
	Frequent	Infrequent	Surgery*	Drugs†
avium-intracellulare	Pulmonary [15–17], dissemination [9–17], lymphadenitis [27–29]	Skin, soft tissue [34, 35, 37], musculoskeletal [21, 27]	± [11, 30]	Rif, Str, Etmb, Etn, Cyc, Clf, Ans [11]
kansasii	Pulmonary [58–60]	Dissemination [70, 71], lymphadenitis [30, 62], skin, soft tissue [63–65], musculoskeletal [35, 66–69]	±	Rif, Inh, Etmb, Str
scrofulaceum	Lymphadenitis [27, 43–45]	Pulmonary [50, 51], dissemination [72, 75]	+ [44]	Inh, Str, Cyc [55]
fortuitum-chelonae	Skin, soft tissue [79–83], musculoskeletal [79, 84–86]	Pulmonary [79, 87, 88], lymphadenitis [79], dissemination [79, 80]	+ [95]	Amik, Cfx, Sulf, Tet, Eryth [95]
xenopi	Pulmonary [100–107]	Dissemination [108–110]	± [102]	Inh, Etmb, Str, Rif [100]
szulgai	Pulmonary [112, 113]	Musculoskeletal [114–116], dissemination [117]	–	Rif, Inh, Etmb
malmoense	Pulmonary [119, 120]	Lymphadenitis [120]	± [120]	?Rif, Str, Etn, Cpr, Etmb [119]
simiae	Pulmonary [126, 127]	Osteomyelitis [128], dissemination [128]	–	?Inh, Etmb, Rif
marinum	Skin, soft tissue [131–135], musculoskeletal [136]		±	Rif, Etmb, Tet [138]
ulcerans	Skin, soft tissue [139]		+ [139]	Str, Dap, Etmb [139]
haemophilum	Skin, soft tissue [142–146]	Lymphadenitis [147]	± [146]	Rif, Inh, Etmb [146]

* + = usually necessary; ± = may be necessary; – = usually not necessary.

† Rif = rifampin; Str = streptomycin; Etmb = ethambutol; Etn = ethionamide; Cyc = cycloserine; Clf = clofazamine; Ans = ansamycin; Inh = isoniazid; Amik = amikacin; Cfx = cefoxitin; Sulf = sulfonamide; Tet = tetracycline; Eryth = erythromycin; Cpr = capreomycin; Dap = dapsone. Drugs are used in various combinations, as specified in the references.

quently, however, rather than the caseating granulomas typical of tuberculosis, a mixture of acute and chronic inflammation, often with microabscess formation, with or without a component of noncaseating granulomas, is seen. AFB may be present, despite the paucity or complete absence of granuloma formation, a factor that emphasizes the importance of special stains. Furthermore, the morphology of the bacilli may suggest a particular species, especially *M. kansasii*. In patients with disseminated MAI infections, particularly in those with AIDS, aggregates of foamy macrophages with many intracytoplasmic AFB are frequently observed. When the small intestine is involved, this pattern simulates that of Whipple's disease.

Optimal therapy depends on the organism isolated and the disease process involved. Lymphadenitis generally responds to surgery alone. Cutaneous lesions due to *M. marinum* or *M. ulcerans* may also require surgery. *M. kansasii* is generally susceptible to antituberculosis drugs, and therefore disease caused by that organism, with the exception of dissemination, generally responds well to chemotherapy. Infection with *M. szulgai* also responds to appropriate antituberculosis medications. The response of *M. xenopi*, however, is unpredictable. *M. fortuitum* and *M. chelonae* are resistant to antituberculosis drugs, but respond to various antibacterial agents. MAI infections are extremely resistant, requiring multiple-drug therapy. The new agents clofazimine and ansamycin may prove beneficial. More experience with infections due to *M. simiae*, *M. malmoense*, and *M. haemophilum* is necessary before recommendations concerning treatment can be made.

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