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Mycobacterial and Nocardial Infections in the Compromised Host

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1. Introduction

Among the broad range of pathogenic and opportunistic microorganisms that can affect the immunologically impaired host are members of various mycobacterial and nocardial species. These organisms are often grouped together because of a common tinctorial property: both *Mycobacteria* and *Nocardia* spp. generally appear acid fast when stained with the traditional Ziehl-Neelson procedure or with modified acid-fast staining techniques. Despite this similarity, these organisms behave quite differently in biologic, clinical, and therapeutic terms, and as a result they require separate discussion here.

2. Mycobacteria

2.1. Classification and Microbiology

Tuberculosis is an ancient disease; unmistakable skeletal stigmata of tuberculosis have been identified in Egyptian mummies, and clinical descriptions date back to the writings of Aristotle and Hippocrates. With the isolation and identification of *M. tuberculosis* by Koch in 1882, the etiology of tuberculosis became clear. In the succeeding years numerous other mycobacterial species were identified from cultures of soil and water as well as from animal and human sources. Although *M. bovis* was quickly recognized as an important human pathogen, the potential pathogenicity of the other nontuberculous, or atypical, mycobacteria was not recognized until 1951. Since the introduction of Runyon's classification system in 1959, our understanding of the nontuberculous mycobacteria has progressed greatly. Although the prevalence of tuberculosis in the United States has declined greatly since the turn of the century, *M. tuberculosis* remains by far the most important mycobacterial pathogen both for normal and for immunosuppressed hosts. However, the nontuberculous mycobacteria are assuming increased importance in the compromised host; some of these organisms are pathogens that can produce clinical illness in normal or impaired hosts, whereas others are true opportunists that affect only the immunocompromised. In addition, it is becoming increasingly clear that various mycobacteria can produce nosocomial infections that may pose special hazards to the impaired host.

All mycobacteria share certain common properties: they are obligate aerobic bacilli that are nonmotile and nonsporulating. A distinctive feature of the mycobacteria is their high cell wall lipid content, which approaches 50% of the cell wall by weight. As a result of this high lipid content, mycobacteria are impermeable to conventional bacteriologic stains but are resistant to decolorization with acid alcohol after staining with carbol fuscin. Because of their lipid-rich cell walls, mycobacteria are hydrophobic, tend to clump together, and are difficult to work with in

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the laboratory. However, mycobacteria are very resistant to physical stress and can be subjected to digestion and concentration procedures that would kill ordinary bacteria. Although this can be an advantage in the diagnostic laboratory, mycobacteria can also survive many commonly employed hospital disinfectants, thereby posing the risk of nosocomial infection. Another feature common to most mycobacteria is their requirement for special enriched media to grow in the laboratory; the rapid growers of Runyon's group IV are an exception in that they can grow on some ordinary laboratory media such as MacConkey agar. These group IV organisms are also exceptions to the final important property of the mycobacteria: their slow rate of growth. For example, the generation time of M. tuberculosis is 12–18 hr in contrast to the 20-min division time for many ordinary bacteria. This slow rate of growth has two major consequences: in the laboratory, it takes 3–8 weeks to isolate most mycobacterial species, and in clinical terms, most mycobacterial infections progress at a subacute to chronic pace.

The mycobacteria can be subdivided into common or medically more important species and into the atypical mycobacteria. Mycobacterium tuberculosis is recognized in the laboratory on the basis of its slow rate of growth (15–40 days), by its heaped-up, nonpigmented or buff-colored, colonial morphology, and on the basis of the niacin test. Mycobacterium tuberculosis is unique among the mycobacteria in that it produces niacin, and a simple colorimetric test for niacin thus permits rapid laboratory identification of M. tuberculosis.

Mycobacterium bovis closely resembles M. tuberculosis in the laboratory but is niacin negative. Like M. tuberculosis, most strains of M. bovis are sensitive to INH and other antituberculous drugs. Mycobacterium bovis was once an important human pathogen causing pulmonary infection, lymphadenitis, osteomyelitis, enteritis, and other infections clinically identical to tuberculosis. With the slaughter of tuberculin-positive cattle and with the pasteurization of milk, M. bovis has become a clinical rarity in the United States. For example, between 1954 and 1968, the Mayo Clinic treated 2080 patients with infection caused by M. tuberculosis but only six with disease caused by M. bovis.[1]

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of M. bovis that was selected by serial passage in the laboratory to serve as a vaccine against tuberculosis. Since its introduction in 1921, BCG has remained controversial; initially considered to be 80% effective in preventing tuberculosis,[2] more recent trials have failed to demonstrate efficacy.[3] BCG has little virulence for normal vaccines; it has been administered to an estimated 500 million people with fewer than 20 reported fatalities from disseminated BCG infection. However, BCG is now being administered in large doses to cancer patients as an immunologic adjuvant, and BCG infection in the compromised host is of growing concern.

Mycobacterium leprae is an uncommon pathogen in the United States, but leprosy remains an important problem in many parts of the world. Mycobacterium leprae has not been cultured in vitro, and relatively little is known about the organism. The most severe form of leprosy, lepromatous leprosy, results from a failure of cell-mediated immunity. Lepromatous leprosy has been reported in a renal transplant recipient.[4] However, leprosy is not a problem in the impaired host in the United States and is not considered further here.

The atypical mycobacteria, which are all niacin negative, were classified by Runyon into four groups based on their pigment production and rate of growth.[5]

Group I organisms produce pigmented colonies only when grown in the light and are hence called photochromogens. The most important member of group I is M. kansasii, which grows in 7–21 days, producing a yellow pigment in the light. Mycobacterium kansasii is an important cause of pulmonary disease, especially in urban areas of the midwest, and can disseminate in compromised hosts. Whereas most atypical mycobacteria are highly drug resistant, group I organisms are sensitive to most antituberculous drugs.

Group II organisms produce pigmented colonies whether grown in light or dark and are therefore called scotochromogens. These organisms also grow in 7–21 days and typically produce a yellow-orange pigment. The most important species is M. scrofulaceum, which causes cervical lymphadenitis in children.

Group III organisms are called nonchromogens because their colonies are nonpigmented. A member of this group, M. avium-intracellulare (formerly M. battey), is the most important of all the nontuber-

culous mycobacteria. *Mycobacterium avium-intracellulare* is most prevalent in rural areas of the southeast United States but is found in all regions of the country. *Mycobacterium avium-intracellulare* also grows in 7–21 days and is drug resistant. Pulmonary disease is the most common clinical manifestation of *M. avium-intracellulare* infection, but dissemination can occur occasionally both in normal and in impaired hosts. *M. avium-intracellulare* has been a particularly severe problem in patients with the acquired immunodeficiency disease (AIDS).

Group IV organisms are classified together as rapid growers because their colonies can be recognized in only 3–7 days. *Mycobacterium fortuitum* is the most important of the rapid growers, which are generally drug resistant. *Mycobacterium fortuitum* typically causes localized soft tissue abscesses but can disseminate in impaired hosts. Group IV organisms have been increasingly recognized as nosocomial pathogens.

2.2. Host Defenses

In order to understand which immunosuppressed patients are at greatest risk of mycobacterial infection, it is important to understand normal host-defense mechanisms against these organisms.[6] According to current immunologic dogma, the first step in immunity to tuberculosis involves the interaction of mycobacterial antigens with T lymphocytes. When exposed to tuberculoproteins, committed lymphocytes that recognize the antigen undergo blastogenesis, resulting in the establishment of a population of T lymphocytes sensitized to mycobacterial antigens. T lymphocytes are motile cells, and when further exposure to bacilli occurs, sensitized T cells will accumulate at the site of inflammation. The antigenetically stimulated lymphocyte in turn activates the host's macrophages,[7] probably by secreting soluble mediators (lymphokines) including chemotactic factor, migration inhibitory factor (MIF), macrophage activation factor (MAF), and others. The nodular accumulation of inflammatory cells that results is histologically recognizable as a granuloma. More importantly, the activated macrophages present in regions of granulomatous inflammation possess enhanced metabolic, phagocytic, and bactericidal potential. Tubercle bacilli are engulfed by

macrophages, and most of the bacteria are killed. However, a small number of bacilli are able to survive in a dormant state within host macrophages, and if immunity breaks down, clinical reactivation tuberculosis can result.

The implications for the immunosuppressed patient are clear: any process that interferes with the integrity of cell-mediated immunity increases the risk of dissemination of primary infection and of reactivation of latent mycobacterial infection. In clinical terms, the greatest potential risk is from human immunodeficiency virus (HIV) infection (as in AIDS) or prolonged corticosteroid therapy. Other settings in which cellular immunity may be impaired include Hodgkin disease and other neoplasia, debility and cachexia, old age, and treatment with antilymphocyte globulin, corticosteroids, and possibly with cytotoxic agents. By contrast, immunoglobulin deficiencies and granulocytopenia do not present a special risk for tuberculosis.

2.3. Skin Testing

Cell-mediated immunity to mycobacteria can be demonstrated clinically be means of delayed hypersensitivity skin testing. The tuberculin skin test is far more sensitive than the chest radiograph in detecting latent infection with *M. tuberculosis*. The Mantoux test using the intradermal injection of polysorbate 80-stabilized purified protein derivitive (PPD) is more reliable than multiple puncture tests such as the Tine test. Three strengths of PPD are available, the first strength containing 1 tuberculin unit (TU), the intermediate-strength 5 units, and the second strength 250 units. Intermediate-strength PPD is the standard test material. The tuberculin skin test should be interpreted at 48–72 hr after injection, and the diameter of induration rather than erythema determines the interpretation: 0–4 mm is a negative reaction; 5–9 mm is doubtful; and 10 mm or more is positive. First-strength PPD should be reserved for patients in whom a very strong reaction is anticipated; second-strength PPD should be reserved for individuals with negative reactions to a lower strength.

Skin testing can also be used to identify patients infected with nontuberculous mycobacteria. Whereas patients infected with *M. bovis* or BCG can be expected to react to intermediate PPD, patients in-

fected with atypical mycobacteria typically have negative or very weak reactions. However, antigens can be prepared from each group of atypical mycobacteria (group I: PPD-Y; group II: PPD-G: group III: PPD-B; group IV: PPD-F), and patients infected with organisms from each group can be expected to have positive skin tests with the group-specific antigen. Unfortunately, the atypical mycobacterial antigens are not currently available for clinical use. However, a positive second-strength (250 TU) PPD test in the face of a negative or doubtful intermediate-strength (5 TU) test is suggestive of infection with atypical mycobacteria and resultant cross sensitization to PPD.

Obviously, whereas a positive skin test demonstrates previous mycobacterial infection, it does not by itself prove active disease. Conversely, negative reactions have been demonstrated in up to 70% of patients with active tuberculosis. There are three potential explanations for negative skin tests. The first is technical failure of the skin test itself because of inactive antigens, improper injection, or faulty interpretation. Technical failures have become much less prevalent since the introduction of bioassayed, polysorbate 80-stabilized PPD products. The second reason for negatie skin tests in patients with proven infection is the presence of an underlying disease or treatment that impaires cellular immunity. Except for viral infections (which produce only transient anergy) and sarcoidosis (which is only rarely complicated by infection), the problems responsible for anergy are precisely those encountered in the immunosuppressed host: AIDS, steroid therapy, Hodgkin disease and other neoplasia, cachexia, and treatment with antilymophocyte globulin and possibly certain cytotoxic agents. Finally, a third group of patients with active tuberculosis will have negative skin tests without underlying immunosuppressive conditions precisely because of the overwhelming nature of the mycobacterial infection itself. Miliary tuberculosis is the best example of this phenomenon. These patients generally recover tuberculin reactivity during the course of antituberculous therapy.

If intermediate and second-strength tuberculin skin tests are negative in the immunosuppressed patient with suspect mycobacterial infection, it is important to test for anergy with streptokinase-streptodornase, Candida, or mumps antigens. Although some workers have suggested that in vitro lymphocyte transformation in response to PPD may be pre-served in patients with negative skin tests,[8] other groups have found that the in vitro tests correlate well with cutaneous reactivity, so they are not diagnostically helpful.[9] The mechanism of anergy in tuberculosis was not well understood until the studies of Ellner demonstrated the presence of suppressor cell activity in the peripheral blood mononuclear cells of patients with pulmonary tuberculosis and negative PPD skin tests.[10]

2.4. Pathogenesis

With the elimination of bovine tuberculosis in the United States, virtually all cases of tuberculosis are acquired through person-to-person transmission via the aerosol route. Patients with active pulmonary infection shed infected droplets into the air; because most infectious patients discharge relatively few organisms, there is a low risk of infection in casual contacts, and most secondary cases occur in household members, schoolmates, or other close contacts of the index case. Infectivity is greatest in patients with cavitary disease, with tuberculosis of the larynx, and with thin, watery sputum; shedding is further enhanced by coughing. Once airborne, infected particles can remain aloft for many hours; thus, adequate ventilation is of prime importance for control of tuberculosis, particularly in the hospital setting. After the droplets have settled onto environmental surfaces, however, they are essentially noninfectious, although they may still contain viable bacilli.

Although a single tubercle bacillus is theoretically capable of causing infection, it must first bypass the upper airway defense mechanisms and lodge in the pulmonary alveoli; airborne particles 5–10 μm in diameter are thus most likely to transmit infection. Initial infection usually occurs in the lower lung fields because of both gravity and the greater ventilation of the lung bases. Once in the alveoli, tubercle bacilli multiply slowly, and because these organisms do not secrete any enzymes or toxins, they initially provoke little inflammatory reaction in the nonimmune host. By about 3 weeks, however, a single organism can potentially have given rise to over a million progeny, and these bacilli will have invaded lymphatics and spread to the draining regional nodes. With further multiplication, bacilli invade the bloodstream and can spread hematogenously to any organ. Even at this stage, the great majority of patients are

completely asymptomatic, so that this truly is a silent bacillemia.[11] Although any tissue can be hematogenously seeded, organs with high blood flow tend to receive the most bacilli, and tissues with the highest Po_2 provide the most favorable environment for their multiplication; hence, the lung apices themselves are by far the most common repositories of organisms. Other frequently infected areas include the renal cortex, the vertebral column, and the metaphyseal ends of long bones.

By the time 6–8 weeks have passed, cell-mediated immunity is well established; the tuberculin skin test becomes positive at this time, but more importantly, granulomatous inflammation develops and contains the tubercle bacilli both in the lung and in regions of metastatic spread. As a result, most patients go on to healing of these initial tuberculous lesions, but if immunity is incomplete, progressive primary tuberculosis or even disseminated disease may develop. In patients who heal their primary lesions, the chest radiograph may be entirely normal or may show focal calcifications. The primary lower lobe lesion and its draining node may be recognized radiologically as the Ghon complex, whereas apical calcifications are termed Simon foci. It is essential to note, however, that healed or inactive granulomatous lesions contain small numbers of dormant but viable tubercle bacilli; inactive lesions can break down and result in reactivation infection.[12]

Reactivation of old tuberculous lesions occurs in no more than 3–5% of all infected individuals, with the remainder having positive skin tests but no clinical illness. At present, only 10% of all new tuberculosis diagnosed in this country result from primary infection, the great majority representing reactivation of latent endogenous infection. As many as one-fifth of patients with reactivation tuberculosis have histories of inadequately treated clinical tuberculosis. Reactivation is most likely to occur within the first few years after the initial infection or at times of lowered host resistance, such as in adolescence or during the postpartum period. However, reactivation can occur many decades after initial infection and, in fact, is now most common in the elderly. Not surprisingly, patients with tuberculosis tend to cluster in certain population groups, being more common in males, in the economically disadvantaged, in inner-city residents, and in members of certain minority groups. The majority of patients with active disease are above 50 years of age, and the proportion of

elderly patients appears to be increasing. Other population groups with a disproportionally high incidence of tuberculosis include immigrants, alcoholics, and patients with gastrectomies, neoplasia, and other debilitating diseases.

The atypical mycobacteria differ from M. tuberculosis in several important respects. First, whereas M. tuberculosis is highly adapted to humans and is spread by person-to-person transmission, the atypical mycobacteria live free in nature and spread from the environment to man. Person-to-person transmission of atypical mycobacteria does not occur; instead infection is acquired by inhalation of organisms from soil, by ingestion of organisms in milk or water, or by direct inoculation of organisms into the skin. Second, the atypical mycobacteria are much less virulent for man than is M. tuberculosis. Skin test surveys suggest that up to 40 million Americans have been infected with atypical mycobacteria, but only about one-third as many people have been infected with M. tuberculosis. However, because of the much greater virulence of M. tuberculosis and its greater potential for late reactivation, clinically active tuberculosis is much more common than atypical mycobacteriosis. About 25,000 new cases of mycobacterial infection are reported in the United States each year, but the atypical mycobacteria account for no more than 5% of this number.

Another clinically important difference between tuberculosis and the atypicals lies in the significance of a positive culture. Except for the occasional patient with very few organisms identified as a result of contaminated cultures,[13] the isolation of M. tuberculosis from a clinical specimen is sufficient to establish the diagnosis of active infection. Diagnosis of atypical mycobacterial infection is much more complex because these organisms can be present as saprophytes or even as laboratory contaminants. When dealing with immunosuppressed patients, the physician must maintain a particularly high index of suspicion about the significance of atypical mycobacteria. Clinical disease caused by an atypical mycobacterium should be suspected when the same species is repeatedly isolated from clinical specimens, when other potential pathogens are absent, and when the clinical, radiologic, and pathologic features are suggestive of atypical infection. Differential skin testing may be diagnostically helpful, but unfortunately many immunosuppressed patients are anergic. In all cases, the species of mycobacteria

TABLE 1. Relative Virulence of Certain Mycobacteria Encountered in Clinical Situations

Virulence	Organism (Runyon group)
Pathogens	M. tuberculosis
	M. bovis
	M. leprae
	M. ulcerans (I)
Usually pathogenic	M. marinum (balnei) (I)
	M. kansasii (I)
	M. avium-intracellulare (battey) (III)
Sometimes pathogenic	M. scrofulaceum (III)
	M. fortuitum (IV)
	M. chelonei (IV)
Usually nonpathogenic	Bacillus Calmette–Guérin
	M. gordonae (II)
Nonpathogenic or opportunistic	M. gastri (II)
	M. xenopi (III)
	M. terrae (III)
	M. smegmatis (IV)

isolated may provide important help since some species are much more likely to cause infection than are other low-virulence organisms. Table 1 classifies selected mycobacteria according to relative pathogenic potential. It must be remembered, however, that the compromised host is potentially vulnerable to organisms that are harmless for normal persons. Although diagnosis may be very difficult in these circumstances, it assumes great importance because of the final broad difference between tuberculosis and the atypicals: whereas most strains of M. tuberculosis are sensitive to many excellent chemotherapeutic agents, the atypical mycobacteria (except for group I) are generally drug resistant.

2.5. Epidemiology

These pathogenetic considerations are of particular importance in the case of the immunosuppressed host. In most cases, mycobacterial infection in the impaired host results from reactivation of latent endogenous infection. Although ordinary bacterial infections in these patients often originate from endogenous flora, mycobacterial infection differs in several respects. Vulnerability to reactivation can be predicted on the basis of a positive skin test (unless the patient is anergic), a history of previous tuberculosis, or radiographic evidence of old mycobac-

terial infection (Ghon complex, Simon focus). The potential for reactivation is life-long but is increased by factors that depress cellular immunity, such as corticosteroid therapy or cachexia. Thus, in addition to a careful history, physical examination, and chest radiograph, skin testing should be performed in all potentially immunosuppressed patients using PPD to determine tuberculin reactivity and one or more antigens to which most normal patients will react (streptokinase-streptodornase, Candida, or mumps) to test for anergy. This is particularly important because of the availability of chemoprophylaxis with isoniazid to prevent reactivation. The pros and cons of chemoprophylaxis are discussed in Section 2.7.

Although reactivation tuberculosis is the greatest risk in the immunocompromised patient, another epidemiologic factor has received insufficient attention: nosocomial infection. Many cases of tuberculosis are not recognized until late in the patient's hospitalization or even at postmortem; this is particularly true in the compromised host.[14] If patients with active pulmonary infection are not isolated appropriately, they may transmit disease to the hospitalized immunoimpaired patient. Finally, mycobacterial infection may even be iatrogenic—the problems of BCG infection and atypical mycobacterioses following surgery or dialysis will be discussed shortly.

Although these immunologic and pathophysiologic considerations provide many reasons why the immunosuppressed host should be more vulnerable to mycobacterial infection, the magnitude of this risk is far from clear. Indeed, with a few notable exceptions,[15] most major overviews of infection in the compromised host devote little attention to the mycobacteria.

Numerous case reports document the occurrance of significant mycobacterial infection in patients with neoplastic disease, but only a few large studies have examined this problem in detail. The association of pulmonary tuberculosis with carcinoma of the lung has long been known.[16] This relationship does not appear to be related to immunosuppression per se, since most of these lung cancer patients develop tuberculosis prior to antineoplastic therapy. In some persons, cachexia may impair host defenses. However, nonimmunologic factors such as smoking, alcohol intake, the occurrence of scar carcinomas in old inflammatory foci, and increased detection as a result of repeated chest radiographs prob-

ably account for this association. In fact, although miliary dissemination has occurred in lung cancer patients,[17] pulmonary infection is the rule. Moreover, infection in these individuals tends to behave in routine fashion, unlike the more serious processes encountered in compromised hosts. Pulmonary tuberculosis has also been reported in patients with mesotheliomas.[18]

In a study of cancer patients treated at Memorial Hospital in New York between 1950 and 1971, Kaplan et al.[19] detected 201 cases of active tuberculosis. Patients with lung cancer and lymphoproliferative disorders had the highest incidence of infection. An intermediate incidence was noted in patients with acute leukemias, head and neck malignancies, and stomach cancer. Patients with cancer of the breast, colon, and genitourinary tract had a significantly lower incidence of tuberculosis, but even in these cases, the incidence probably exceeded the risk of active tuberculosis in patients without tumors. In most cases, tuberculosis appeared to result from reactivation of old infection. Patients treated with corticosteroids, radiation, or chemotherapy had more severe forms of tuberculosis. As a group, these patients fared poorly with an overall mortality by tuberculosis of 17%. The prognosis was particularly poor in patients with lymphomas, who had a 48% mortality.

In a study of mycobacterial infections in cancer patients from the M. D. Anderson Hospital in Texas, 59 infections were discovered over a 5-year period.[20] Interestingly, 51% of these infections were caused by nontuberculosis mycobacteria, with *M. kansasii* and *M. fortuitum* being the most important. The geographic distribution of patients may account for the high incidence of atypical mycobacterial infections. The overall incidence of mycobacterial infections was about three times greater than the incidence in the general population of Texas. The median age of these 59 patients was 60 years; even when age adjustments were taken into account, the cancer patients had an incidence of mycobacterial infection about 50% higher than the general population. The most common malignancies in these patients were carcinomas of the head and neck and of the lung. Lymphoma and leukemia were also frequent. Neutropenia did not appear to be a significant factor in these infections, whereas chemotherapy did seem to predispose to infection, especially in the patients

with atypical mycobacterioses. In 80% of these cases, infection was confined to the lungs. Only three patients had miliary infection, and in all, the responsible organism was *M. tuberculosis*. Thirty-one of these 59 patients died, but most did not have autopsies, and it is unclear whether mortality was attributable to mycobacterial infection, the malignancy itself, or other processes. The authors of this study felt that infection was controlled in most patients who were diagnosed early enough to receive adequate antituberculous chemotherapy.

Although these studies of mycobacterial infection and malignancy derive from cancer hospitals, similar findings have been reported in a general hospital population.[21] The prevalence of mycobacterial infection was six times greater in patients with cancer than in the general hospital population. Lung cancer was the most common neoplasm in patients with mycobacterial infection, with hematologic malignancies ranking second. Many patients were receiving chemotherapy when the infection was diagnosed. Only 37% of patients with tuberculosis and cancer had positive tuberculin tests, whereas 70% of the infected patients without tumors were reactors. Nontuberculous mycobacteria were responsible for 27% of the infections, with *M. avium-intracellulare* and *M. kansasii* of equal importance.

Despite these studies, the precise incidence of tuberculosis in cancer patients is unknown. For example, a group of experienced investigators at the National Institutes of Health have not experienced an increased frequency of tuberculosis in patients with leukemia and lymphoma, although they do recognize the problem of disseminated infection in conjunction with chemotherapy.[22] By contrast, studies by the Atomic Bomb Casualty Commission in Hiroshima found an increased incidence of active tuberculosis in patients with chronic myelogenous leukemia and myelofibrosis but not in cases of acute leukemia or lymphoma.[23] The problem of disseminated mycobacterial infection in patients with aplastic anemia and leukemia has received a great deal of attention because of the controversies regarding the causal relationship between the infection and the hematologic abnormalities. This issue is discussed in Section 2.6.

These studies emphasize the importance of a high index of suspicion of tuberculosis in patients with malignant disease. In addition, it is important to remember that tuberculosis itself can present with

clinical features which mimic cancer in patients without malignancies.[24] Most often, a tuberculous pulmonary lesion may be radiologically misinterpreted as lung cancer; similarly, tubercular lymphadinitis may be clinically misdiagnosed as lymphoma. Biopsy and culture should establish the correct diagnosis in these cases. Although corticosteroids are frequently cited as the factor most likely to be responsible for the reactivation of tuberculosis in immunosuppressed patients, the actual risk of tuberculosis in steroid-treated patients is unknown. In pharmacologic doses, corticosteroids, suppress inflammation and cause lymphocytopenia and monocytopenia. The direct effects of steroids on lymphocyte function are unclear, but adverse effects on monocyte–macrophage function have been recognized.[25] One result of the daily administration of prednisone is suppression of the delayed hypersensitivity skin test; about 2 weeks of steroid therapy will produce anergy in most patients.[26] By contrast, alternate-day prednisone therapy does not suppress delayed hypersensitivity.[27]

Because steroids suppress cell-mediated immunity, it is logical to expect that they should predispose to the reaction of tuberculosis in previously infected patients. Indeed, the American Thoracic Society recommends the administration of INH to tuberculin-positive patients who require steroid therapy.[28] By contrast, Schatz et al.[29] do not recommend INH prophylaxis because of their failure to detect active tuberculosis in 132 steroid-treated asthmatic patients. However, only 28% of their patients had positive 5-TU tuberculin skin tests, 59% were on alternate-day steroid schedules, and the mean prednisone dose in the patients receiving daily therapy was only 16 mg. Thus, it is far from clear that these patients were truly immunosuppressed, and the conclusions of this study are not necessarily applicable to patients receiving daily prednisone for the treatment of malignancies, transplantation, or inflammatory disease. The same qualifications apply to two large British studies of long-term corticosteroid therapy.[30,31] Although only one case of tuberculosis developed in a total of 786 steroid-treated patients, the great majority of these patients were on low-dose (≤ 10 mg prednisolone/day) or intermittent therapy, and the tuberculin status of the study population was not defined.

Although the incidence of tuberculosis in steroid-treated patients is unknown, the occurrence of this problem is well documented. Sohn and Lakshminaryan have reported 14 episodes of reactivation tuberculosis associated with corticosteroid therapy.[32] Most of these patients had underlying diseases with immunosuppressive effects, and four were receiving cytotoxic agents as well. Fever was absent in ten cases, suggesting that steroids can mask the symptoms of tuberculosis, making diagnosis difficult. Five patients had disseminated infection, but the response to chemotherapy was good. Because the population at risk was undefined, this study cannot estimate the incidence of tuberculosis in steroid-treated patients, and the authors quite properly refrain from firm recommendations as to the value of INH prophylaxis in steroid-treated patients.

Unfortunately, the incidence of tuberculosis in transplant recipients has not been fully defined. A number of case reports document pulmonary infection,[33,34] extrapulmonary infection,[35,36] and disseminated disease[35,37] caused by *M. tuberculosis*[37,38] and nontuberculous mycobacteria[39–42] in these patients. However, mycobacterial infections are uncommon in transplant recipients. For example, only three of 400 transplant recipients in Denver developed tuberculosis over a 10-year period,[37] and in Minneapolis there were only three cases in 845 recipients over a period of 12 years.[35]

Whereas the risk of tuberculosis in transplant recipients cannot be fully defined, Lichtenstein and MacGregor[43] estimated that it is at least 480 cases per 100,000 as compared with a tuberculosis rate of 131 per 100,000 in the general population. This study includes a number of interesting observations. Of the 47 renal transplant recipients with mycobacterial infection reported from various centers, 20 (43%) had disseminated disease and 16 (38%) had atypical mycobacteria. In two cases, tuberculin-negative recipients developed tuberculosis after receiving kidneys from tuberculin-positive donors, suggesting that infection may arise from reactivation of tubercle bacilli in the transplanted kidney.

Tuberculosis has also been reported in dialysis patients. Five cases of active tuberculosis were noted in one study of 136 dialysis patients;[44] none of the infected patients was receiving immunosuppressive therapy, and only one was a diabetic. The diagnosis of tuberculosis in these patients was difficult because of atypical features and concomitant uremic symptoms. The incidence of tuberculosis in this small

group of patients is at least 15 times greater than in the general population and should raise the question of person-to-person transmission within the dialysis unit itself. The possibility of nosocomial infection was considered unlikely by Pradhan et al.,[44] but detailed epidemiologic data are not presented. Other dialysis centers have not reported a high incidence of tuberculosis, and the relevance of this single outbreak to other dialysis and transplant patients is unclear. However, nosocomial outbreaks of *M. chelonei* have been reported at several dialysis centers.[45,46] Clinical vigilance is mandatory, and the possibility of mycobacterial infection must be considered in transplant or dialysis patients with undiagnosed infections. In addition, routine PPD skin testing has been recommended for transplant recipients.[43,47,48] The administration of prophylactic INH to tuberculin-positive patients[43,48,49] has also been suggested but is controversial (see Section 2.7).

2.6. Clinical Features

Even in normal hosts, mycobacterial infections can produce an extremely diverse spectrum of clinical presentations, ranging from subtle disorders to overwhelming disease. In the immunocompromised host, this clinical spectrum is further expanded because, on the one hand, steroids and other medications may suppress fever and other symptoms, whereas, on the other hand, the immunosuppressed state may predispose to unusually fulminant infections. In addition, symptoms of the patient's underlying disorder may confuse the clinical presentation. Finally, the nontuberculous mycobacteria are more often pathogens in these patients, and in some cases patients may be simultaneously infected with mycobacteria and other organisms.

Because of this wide range of clinical presentations, it seems prudent first to review the usual features of tuberculosis and then to examine the unusual problems unique to impaired hosts, concentrating especially on disseminated infection and marrow involvement and on BCG and atypical mycobacteria.

2.6.1. Pulmonary Tuberculosis

2.6.1a. Primary Infection. More than 90% of patients are entirely asymptomatic at the time of primary infection and can be identified only through conversion of the tuberculin skin test from negative to positive. Most of these patients have normal chest radiographs, but fibrocalcific stigmata of old primary infection are radiographically demonstrable in others. In the past, primary infection occurred almost entirely in childhood, but as the incidence of tuberculosis has declined, primary tuberculosis is also seen in adults. Among symptomatic patients, four broad syndromes can be identified.[50] Most common is a picture not unlike atypical pneumonia with fever and nonproductive cough. Chest radiographs may show unilateral lower lobe patchy parenchymal infiltrates and/or paratracheal or hilar adenopathy. Although such patients should receive full antituberculous chemotherapy when diagnosed, most will go on to resolution of disease even without treatment.

The same is true for patients presenting with the second syndrome, tuberculous pleurisy with effusion. These individuals often have high fever, cough, and pleuritic chest pain and may be dyspneic. Chest radiographs reveal unilateral pleural effusions often without identifiable parenchymal lesions. The diagnosis should be suspected if there is a recent history of exposure to tuberculosis. Except in anergic patients, the tuberculin skin test is almost always strongly positive. Because cultures of sputum and/or gastric washings are positive in only about 30% of these patients, diagnosis depends on examination of the pleural fluid or on percutaneous needle biopsy of the pleura. Although primary tuberculous pleuritis will resolve spontaneously in most cases, up to 60% of these patients develop reactivation tuberculosis, so combined chemotherapy is indicated in all patients. Surgery is almost never needed, and complications are rare.

The third major syndrome of primary tuberculosis is direct progression to upper lobe disease. Finally, patients may develop extrapulmonary tuberculosis as a progression of primary infection. This was previously seen most commonly in young children who presented with cervical adenitis, miliary tuberculosis, or tuberculous meningitis but is now quite rare. Immunosuppressed patients may be at increased risk of miliary dissemination. In addition to these major manifestations, patients with primary tuberculosis may develop a variety of syndromes including erythema nodosum and other hypersensitivity reactions.

2.6.1b. Reactivation (Postprimary) Tuberculosis.

This is the most common clinical form of tuberculosis and is seen most often in the elderly or debilitated patient. Symptoms usually begin insidiously and progress over a period of many weeks or months prior to diagnosis. Constitutional symptoms are often prominent including anorexia, weight loss, and night sweats. Most patients have low-grade fevers, but higher temperatures and even chills may be seen occasionally when the disease progresses more rapidly. Immunosuppressed patients are at greater risk of rapidly progressive pulmonary involvement. For example, nine of the 201 cancer patients with tuberculosis reported by Kaplan et al.[19] developed tuberculous pneumonia, which was uniformly fatal. One of these patients progressed from an inactive Ghon complex to fulminant tuberculous pneumonia, respiratory failure, and death in 6 days. Even in normal hosts, miliary tuberculosis can on rare occasion present with rapidly progressive diffuse interstitial infiltrates causing adult respiratory distress syndrome (ARDS).[51] Hence, although a subacute to chronic presentation is much more common, tuberculosis must also be considered in the differential diagnosis of rapidly progressive alveolar or interstitial infiltrates in the immunocompromised patient.

Most patients with postprimary tuberculosis present with pulmonary symptoms including cough and sputum production. Dyspnea is relatively uncommon in the absence of underlying chronic lung disease. A frequent complaint is hemoptysis, often in the form of bright red streaks of blood caused by bronchial irritation. Although physical examination is usually nondiagnostic, chest radiographs are highly suggestive of the diagnosis. Typical features include infiltration in the posterior–apical pulmonary segments, which may be unilateral or bilateral, progressing to frank cavitation. Apical lordotic views, chest tomography, and CT scans may be helpful in documenting cavitary disease. In occasional patients, the lower lung fields may be involved with postprimary tuberculosis, and in rare instances the chest radiograph may appear normal.[52,53]

The tuberculin skin test is positive in about 80% of patients with reactivation tuberculosis; patients with advanced disease are often malnourished and anergic. The diagnosis of pulmonary tuberculosis can be confirmed in most individuals by examination of the sputum. If patients are not able to produce sputum spontaneously, attempts should be made to induce sputum with the aid of pulmonary physiotherapy, IPPB, and mucolytic agents. Bronchoscopy may be necessary to obtain appropriate specimens. Although cultures are necessary for a positive diagnosis and are more sensitive than smears, sputum specimens should be examined microscopically either by the traditional Ziehl-Neelson acid-fast stain or by the newer Truant fluorescent stain. Sputum or bronchoscopic washings should be examined both directly and after concentration by centrifugation and digestion. Carefully collected individual specimens are preferred to a 24-hr pool of sputum and saliva. Cultures of first morning fasting gastric aspirates are also helpful. Because gastric acid is toxic to mycobacteria, the collection bottles should contain a buffer such as sodium bicarbonate. Smears of gastric juice are misleading because of the potential presence of saprophytic mycobacteria and should not be performed.

With combined chemotherapy, the prognosis of pulmonary tuberculosis is excellent. Without therapy, devastating complications may occur. Massive hemoptysis is one such complication. The vessels in the walls of tuberculous cavities are usually thrombosed and do not bleed, but if a pulmonary artery branch is patent, erosion into the vessel can produce a Rasmussen aneurysm and massive hemoptysis. Another complication is bronchogenic spread of infection to other pulmonary segments. In extreme cases, this can result in massive tuberculous pneumonia with hypoxia and an acute lethal course despite chemotherapy. Other complications of pulmonary tuberculosis include direct spread of infection to the pleural space, resulting in a bronchopleural fistula or tuberculous empyema, or to the upper airway, resulting in tuberculous laryngitis. Swallowed organisms can produce tuberculous enteritis. Tuberculous pericarditis may result from direct extension of an adjacent pulmonary focus. In other patients, late fibrosis may produce bronchial obstruction and/or mediastinal fibrosis. Bronchial obstruction may also be caused by extrinsic compression because of tuberculous lymphadenitis; such patients may develop secondary bacterial pneumonias. Still another complication of pulmonary tuberculosis is hematogenous dissemination with simultaneous extrapulmonary disease. Finally, the syndrome of inappropriate ADH

is a not infrequent metabolic complication of pulmonary tuberculosis. Anemia is common in patients with advanced or longstanding disease. Diffuse hyperglobulinemia and elevated erythrocyte sedimentation rates are also common but nonspecific. Secondary amyloidosis is rare.

Illustrative Case 1: Pulmonary Tuberculosis

This 21-year-old woman was hospitalized in 1979 for neurologic reevaluation. She had been well until 1974 when she noted stumbling and right leg weakness. Over the next year she developed slurred speech, nystagmus, an obvious right-sided hemiparesis. She was hospitalized for study. Skull radiographs, a brain scan, and an EEG were unremarkable, but a pneumoencephalogram disclosed a mass lesion in the floor of the fourth ventricle with compression of the prepontine space. The CSF was normal. Her chest radiograph, hemogram, and liver-function tests were normal. A tuberculin skin test was not performed. She was considered to have a malignant brain stem tumor and was treated with 6000 rad and started on dexamethasone.

Over the ensuing 4 years, she remained on monthly CCNU injections. Several months prior to admission, she noted increased right leg weakness, and corticosteroid therapy was reinstituted. On presentation she was a frail, wasted dysarthic young woman with a right hemiparesis. She did not have a cushingoid habitus. She was afebrile and had no respiratory or constitutional symptoms. There was no history of exposure to tuberculosis.

The neurologic workup revealed a cystic brain stem lesion that subsequently proved to be a benign cyst. However, a routine admission chest radiograph revealed a cavitating lesion in the superior segment of the right lower lobe (Fig. 1). No sputum was available for examination. Her laboratory studies revealed a mild anemia with a normal white count and differential, a slightly elevated alkaline phosphatase and 5'-nucleotidase, and mild hyperglobulinemia. Intermediate strength (5 TU) PPD and SK–SD skin tests were negative.

Because of the peripheral location of the lesion, she underwent a percutaneous lung biopsy rather than a bronchoscopy. Cytological examination revealed only inflammatory cells, and smears for acid-fast bacilli, bacteria, and fungi were negative. Following the biopsy, she developed a 20% right pneumothorax that failed to resolve. Corticosteroids were discontinued. She became febrile to 103°F (39.4°C) and developed a mild nonproductive cough. After 6 weeks of incubation, her lung biopsy cultures became positive for *M. tuberculosis*. Therapy with INH, etham-
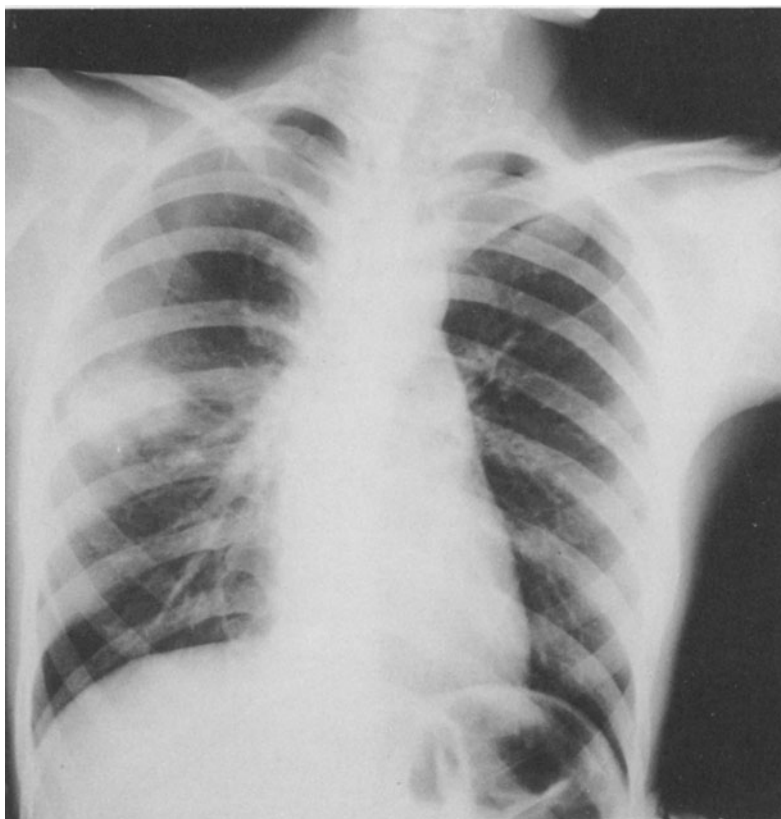

FIGURE 1. Chest radiograph from Illustrative Case 1 demonstrating a cavity lesion in the superior segment of the right lower lobe.

butol, and streptomycin was instituted. Within 5 days she became afebrile, and her cough had ceased. After 3 weeks of therapy, the pneumothorax resolved, and the infiltrate was appreciably smaller. After 6 weeks, streptomycin was dicontinued, and she has continued to do well on INH and ethambutol.

Comment. Unfortunately, this young woman had received radiotherapy, chemotherapy, and corticosteroids for what eventually proved to be nonmalignant disease. Cutaneous anergy reflected the immunocompromised state that resulted from drug therapy and cachexia. Of interest was the fact that she was entirely free of both pulmonary symptoms and fever despite a large cavitary lesion; corticosteroids have been reported to mask the symptoms of tuberculosis in some patients, and this patient became febrile only when steroids were discontinued. This case demonstrates several points about the diagnosis of pulmonary tuberculosis when no sputum is available: invasive procedures such as lung biopsy or bronchoscopy may be necessary; cultures may be positive even when smears are negative; and persistent pneumothorax can complicate percutaneous lung biopsy in tuberculosis. Although many compromised hosts with tuberculosis fare poorly, this patient did very well, in part because it was possible to discontinue immunosuppressive therapy.

2.6.2. Extrapulmonary Tuberculosis

Approximately 10% of all newly recognized cases of tuberculosis in the United States are extrapulmonary; although the frequency of pulmonary tuberculosis is declining, the incidence of extrapulmonary disease is remaining relatively constant.[54] Although the clinical features of extrapulmonary tuberculosis vary widely, certain generalizations may be useful. Past history is not a reliable guide to the diagnosis of extrapulmonary tuberculosis; only about 25% of patients have a past history of tuberculosis, but virtually all of these have been inadequately treated. Except in children, there is typically a long latent period between the first episode of infection and the extrapulmonary presentation. Approximately 50% of patients with extrapulmonary tuberculosis have entirely normal chest radiographs; most of the others have stigmata of old inactive pulmonary disease, and a minority have coexisting active pulmonary infection. Although all organ systems can be involved with extrapulmonary disease, either singly or in various combinations, the most commonly involved areas are the genitourinary tract, the musculoskeletal system, and the lymph nodes.

Although generalizations are subject to many exceptions, I think it is clinically useful to divide extrapulmonary tuberculosis into three large categories. The first is subacute, progressive, life-threatening disease. These patients are generally febrile and have prominent constitutional symptoms suggestive of infection. The tuberculin skin test may be negative in up to 20% because of the severity of the illness itself. Without therapy, they experience a progressive, downhill course with an extremely high mortality rate, often in a matter of weeks. Important examples of this fulminating type of extrapulmonary tuberculosis are miliary tuberculosis,[55,56] tuberculous meningitis,[57–59] and tuberculosis of the pericardium[60,61] and great vessels. Disseminated mycobacterial infection is a particular problem in immunosuppressed patients and is discussed separately (see Section 2.6.3).

The second category of extrapulmonary tuberculosis may be thought of as tuberculosis of the large serosal surfaces. These patients too have prominent constitutional symptoms including fever in almost all cases. As a rule, however, the tuberculin skin test is positive, the clinical course is longer, and the prognosis with or without therapy is better. Examples in this category include tuberculous pleuritis[62] and peritonitis.[63]

The third and most common type of extrapulmonary tuberculosis is infection of individual organ systems. These patients are most often afebrile and can be entirely free of constitutional complaints. Their illness typically pursues a very indolent course characterized by local organ dysfunction and eventually destruction rather than by progressive general decline. In fact, the differential diagnosis in these individuals more often suggests neoplastic disease then infection. Unless cellular immunity is depressed, the tuberculin skin test is positive in almost all of these patients. Clinical syndromes in this category include genitourinary tuberculosis,[64] tuberculous arthritis,[65] and osteomyelitis,[66] tuberculous lymphadenitis,[67] and many others. Although all these syndromes can occur in the immunocompromised patient, they are uncommon. Moreover, although the diagnostic features of these syndromes are diverse, they are not characteristically different in the impaired host; hence, these problems will not be considered in detail here.

Illustrative Case 2: Extrapulmonary (Meningeal) Tuberculosis

This 9-year-old girl was hospitalized because of fever and lethargy. Eighteen months earlier she was found to have Hodgkin disease, nodular sclerosing stage IIIB. A complete remission had

been induced and maintained with chlorambucil, vincristine, procarbazine, and prednisone. Twelve days prior to admission, she developed fevers to 102°F (38.9°C) and generalized headache. Seven days before admission she developed vomiting. Over the ensuing week, she remained febrile and became progressively lethargic. There was no history of exposure to tuberculosis.

At the time of admission, she was drowsy but arousable and oriented. Aside from mild nuchal rigidity and a temperature of 103.2°F, her physical examination was normal. Laboratory studies included a Hct of 34% and a WBC count of 2700/mm³ with 64% polys, 16% lymphocytes, and 20% monocytes. The platelets appeared normal on smear. The chest radiograph was normal, as was the urinalysis. Blood chemistries including liver function tests were normal. Blood and urine cultures were negative. Intermediate-strength PPD and *Candida* skin tests were negative.

On the day of admission, a lumbar puncture revealed clear CSF under a pressure of 240 cm H_2O. The CSF contained six RBCs and 336 WBCs/mm³, of which 97% were lymphocytes. The CSF protein was 116 mg/dl, and the sugar was 24 mg/dl with a simultaneous blood sugar of 96 mg/dl. Gram stain, AFB stain, and India ink preparations of the CSF were negative, as were cytologic examinations and a latex agglutination test for cryptococcal polysaccharide. No therapy was instituted. However, 48 hr later, the patient was more lethargic and was found to have bilateral sixth nerve palsies. Cultures of CSF for bacteria were negative. Therapy with INH, rifampin, and ethambutol was instituted. By the fifth day of treatment, she became afebrile, and her headache, stiff neck, and sixth nerve palsies resolved over the next 8–10 days. Cerebrospinal fluid cultures grew *M. tuberculosis*. The patient was maintained on all three drugs for 3 months and on INH and ethambutol for an additional 2 years. She remained free of tuberculosis, but her Hodgkin disease has relapsed.

Comment. This child was clearly immunosuppressed as a result of Hodgkin disease and its chemotherapy. Like so many patients with extrapulmonary tuberculosis, she had neither a history of exposure to tuberculosis nor an abnormal chest radiograph. Her case illustrates the typical clinical features of tuberculous meningitis. This is the most rapidly progressive form of tuberculosis, and the history of fever, headache, and irritability progressing to lethargy and cranial nerve palsies over a period of about 3 weeks is highly characteristic. The CSF findings of a moderate lymphocytic pleiocytosis, low sugar, and elevated protein are also typical. This case also demonstrates that CSF cultures are more sensitive than acid-fast stains in the diagnosis of meningeal tuberculosis. Finally, her physicians proceeded appropriately in rapidly excluding bacterial, fungal, and neoplastic meningitis and in instituting antituberculous chemotherapy long before cultures became positive. Isoniazid, ethambutol, and rifampin all penetrate the CSF, and this girl's response to triple therapy was excellent.

2.6.3. Disseminated Mycobacterial Infection and Hematologic Abnormalities

The problem of disseminated mycobacterial infection in patients with hematologic abnormalities is of particular interest. The Atomic Bomb Casualty Commission found an increased incidence of tuberculosis in patients with chronic myelogenous leuke-

mia and myelofibrosis but not in patients with acute leukemia or lymphoma.[23] A more recent clinical series[68] found a 4.6% incidence of tuberculosis among 130 patients with hematologic diseases but only a 0.2% incidence among 13,930 patients without marrow disorders admitted to the same hospital during the same 18-month period. However, in a much larger autopsy series surveying 27,104 cases postmortem between 1925 and 1952, Lowther[69] found no evidence of an increased incidence of tuberculosis in leukemics.

If the risk of tuberculosis in patients with leukemia is unsettled, there is even more controversy about the significance of hematologic abnormalities in patients with tuberculosis. Most patients with miliary tuberculosis have some abnormality of the hemogram, which often includes anemia and which may include leukopenia, leukocytosis, and monocytosis.[70] In occasional patients, a dramatic leukemoid reaction can accompany miliary tuberculosis. However, in all these situations, the hematologic findings revert to normal during the course of effective antituberculous therapy.

In addition to these patients, numerous case reports describe the occurrence of either a frankly leukemic blood picture or of severe pancytopenia resembling aplastic anemia in patients with disseminated mycobacterial disease. On the basis of these reports, tuberculosis has sometimes been considered a "treatable" cause of leukemia or aplastic anemia. The careful study conducted by Glasser et al.[70] casts serious doubt on this proposition. From among 3507 tuberculosis patients, they studied 40 with miliary disease. Thirty-five had hematologic abnormalities, including anemia in 63% and leukopenia in 32%. Only three patients had a bacteriologic cure without full return to normal of the hematologic abnormalities, and of these patients with persistent abnormalities, one had clear-cut chronic lymphocytic leukemia, and two had only mild anemia. However, none of these patients had blood pictures resembling myeloproliferative disorders or aplastic anemia. In sharp contrast, this same study also identified 24 patients with leukemia, lymphoma, myeloma, or aplastic anemia and tuberculosis. None of these patients demonstrated hematologic recovery as a result of antituberculous therapy.

In reviewing the reported cases of leukemia or pancytopenia in patients with tuberculosis. Glasser et al.[70] point out that the vast majority of these cases

have been fatal and that none of these patients has had documented marrow recovery as a result of anti-microbial therapy alone. They conclude that tuberculosis does not cause these severe marrow abnormalities but that patients with primary hematologic abnormalities may be unusually susceptible to disseminated and rapidly fatal mycobacterial infection because of their immunologic impairments. More recently, a patient with severe pancytopenia who survived miliary tuberculosis was reported.[71] However, although the patient was said to be "perfectly well" following therapy, no post-treatment hematologic data are presented. An additional patient with disseminated *M. kansasii* infection and pancytopenia recovered clinically and had recovery of normal marrow function after therapy.[72] Even granting marrow recovery in these patients, tuberculosis must be exceedingly rare as a bona fide cause of pancytopenia or of a truly leukemic blood picture.

Patients with leukemia or pancytopenia in whom mycobacterial infections develop may manifest either of two unique features of their infection. First is the occurrence of disseminated infection with atypical mycobacteria. Of 59 cancer patients with mycobacterial infection at M. D. Anderson, 51% were infected with nontuberculous mycobacteria.[20] Although none of these patients had disseminated disease, numerous case reports document the occurrence of disseminated atypical mycobacterial infection in patients with leukemia[73-80] or pancytopenia.[81-84] In many of these patients, *M. kansasii, M. avium-intracellulare*, or *M. chelonei* was the causative organism. Not surprisingly, these cases have almost all been fatal.

The second striking feature of tuberculous infection in patients with leukemia is the severity of the infection. In a postmortem series, Oswald[85] found that although tuberculosis was not more common in patients dying of leukemia than in those dying of other causes, there was a clear propensity for miliary dissemination in the leukemic patients. Among 262 patients dying with leukemia, 16 had inactive pulmonary tuberculosis, only three had active pulmonary infection, but 10 had miliary disease. Moreover, these infections were clinically fulminant, and many cases had a destructive pathologic picture of nonreactive tuberculosis. In nonreactive tuberculosis, lesions are more common in nodes and visceral organs and less common in the lungs and meninges than in ordinary miliary tuberculosis. The lesions themselves consist of areas of tissue necrosis teeming with acid-fast bacilli; there is little evidence of granuloma formation, although a polymorphonuclear exudate may be seen.[85,86] It seems clear that the immunologic deficiency of these patients impairs granuloma formation, thus allowing unchecked multiplication of bacilli and overwhelming infection in a situation analogous to lepromatous leprosy. Although nonreactive tuberculosis is rare, the diagnosis must be considered in leukemic or other immunosuppressed patients with overwhelming infection. In practical terms, it must be remembered that the absence of miliary lung lesions does not rule out disseminated mycobacterial infection and that even if biopsy specimens show only necrosis and acute inflammation without granulomas, acid-fast stains and mycobacterial cultures can still provide vital diagnostic information.

Illustrative Case 3: Occult Miliary Tuberculosis

This 65-year-old Polish-born gentleman was hospitalized in July 1969 because of recurrent fever. There was no history of exposure to tuberculosis at any time. He had been entirely well except for head trauma sustained in an auto accident 3 years earlier. His only medications were phenytion (Dilantin) and phenobarbital. Three weeks before admission, he first experienced fevers to 104°F that recurred nightly. He admitted to rigors, drenching sweats, anorexia, and a 14-lb (6.4 kg) weight loss, but he denied other symptoms.

At the time of hospitalization he was an elderly, wasted, ▾chronically ill man with a temperature of 104.6°F. His fundi were normal, and his neck was supple. His lungs were clear. A soft systolic ejection murmur was audible at the cardiac apex. There was no hepatosplenomegaly or lymphadenopathy. His admission laboratory studies included a Hct of 24%, a white WBC count of 1900/mm^3 with 65% polys, 1% bands, 27% lymphocytes, 2% monocytes, and 5% eosinophils, and a platelet count of 69,000/mm^3. The ESR was 69 mm/hr. The urine was normal, as were the blood chemistries apart from an alkaline phosphatase of 8.7 BU (normal <4.5), an SGOT of 52 units (normal <40). Multiple cultures of blood and urine were negative. The chest radiograph was normal.

In the hospital he had daily fevers, reaching 107°F on one occasion. He grew progressively weaker. An IVP, a barium enema, and a UGI series were normal. Tuberculin skin tests with both 5 and 250 TU were negative, as were SK–SD and mumps skin tests. On the sixth hospital day, a bone marrow biopsy was performed, revealing reticulum cell sarcoma but no granulomas. Before therapy could be instituted, he was found dead in bed on the ninth hospital day. At autopsy, the patient was found to have

reticulum cell sarcoma of the marrow, spleen, and paraaortic nodes. In addition, there were multiple noncaseating granulomas in the liver (Fig. 2) and caseating granulomas in the marrow, spleen, and mediastinal lymph nodes but not in the lung. Acid-fast smears were negative, but cultures grew *M. tuberculosis.*

Comment. This case is unusual in that the patient was found to have a lymphoproliferative disease and miliary tuberculosis simultaneously. His fever, chills, weight loss, and pancytopenia could have been caused by the tumor, the tuberculosis, or both. He demonstrated cutaneous anergy, and his immunosuppressed state was probably caused by widespread lymphoma and cachexia.

This case demonstrates a number of features of miliary tuberculosis in the immunosuppressed patient. This diagnosis was not considered because of the normal chest radiograph, yet up to 10% of patients with miliary tuberculosis have normal chest radiographs. Moreover, the involvement of liver, spleen, and nodes without pulmonary lesions appears to be more common in the immunosuppressed patient. This man had well-formed gran-

ulomas rather than the necrosis with acute inflammation sometimes seen in immunosuppressed hosts with fulminating nonreactive tuberculosis. This case also demonstrates that granulomas can be missed on marrow biopsy because of sampling error and that hepatic granulomas in tuberculosis are frequently noncaseating. Finally, he illustrates the difficulty of determining whether pancytomenia is related to tuberculosis, tumor, or both. The cause of this man's death was not determined, but even if chemotherapy had been instituted, the prognosis would have been very poor.

Illustrative Case 4: Disseminated Nontuberculous Mycobacteriosis

This 48-year-old man was hospitalized in 1977 because of spiking fevers. Two years earlier, a splenectomy and bone marrow biopsy were performed because of profound fatigue and severe
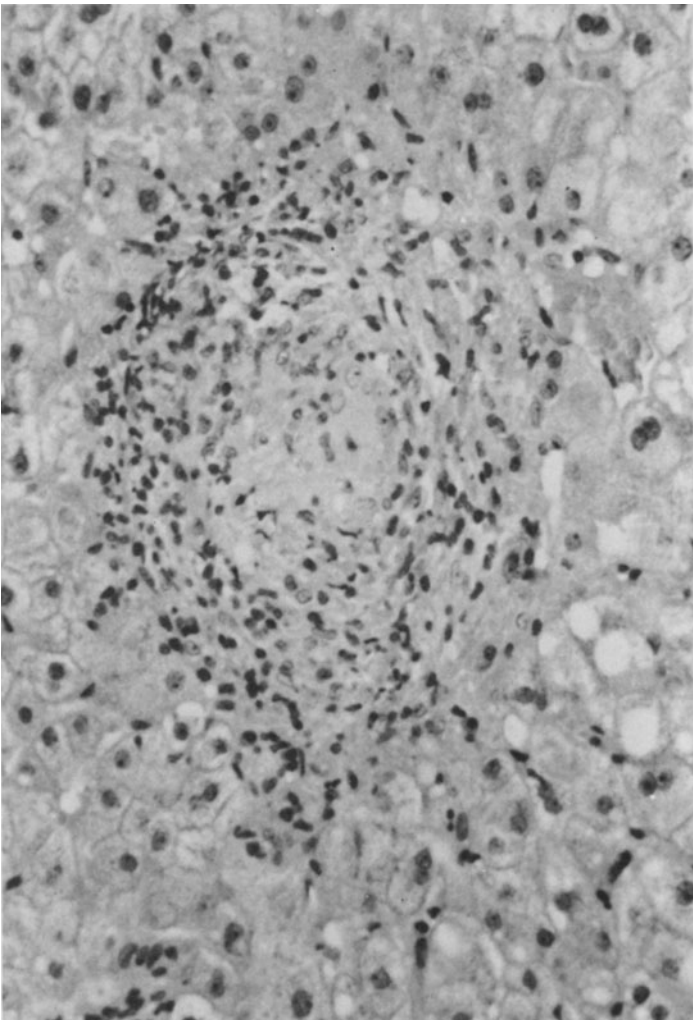

FIGURE 2. Liver biopsy from Illustrative Case 3 demonstrating granulomatous inflammation without caseation.

pancytopenia. He was found to have a malignant lymphoma of the poorly differentiated lymphocytic type. He responded symptomatically to transfusions, prednisone, and cyclophosphamide. Although there was no history of exposure to tuberculosis, his chest roentgenogram showed a calcified granuloma in the apical posterior segment of the left upper lobe. An intermediate-strength PPD administered prior to therapy was positive. Insoniazid was not prescribed.

Four months prior to admission, pancytopenia recurred. His peripheral blood contained more than 50% mononuclear cells, many of which had hairy cytoplasmic borders. Cyclophosphamide and prednisone were reinstituted. He improved symptomatically, but 3 months later a temperature of 104.8°F as well as rigors and sweats developed. He was hospitalized elsewhere. His physical examination was normal apart from fever. His chest radiograph showed hilar adenopathy. Multiple blood and urine cultures were negative. Therapy with oxacillin, gentamicin, INH, ethambutol, prednisone, and indomethocin failed to control the fever, and he was transferred to the Massachusetts General Hospital.

On admission, he was febrile to 103.4°F (39.7°C). He appeared acutely and chronically ill, and examination disclosed a cushingoid habitus, pallor, hepatomegaly, and mild confusion. The Het was 35%, the platelets 137,000/mm^3, and the WBC count 1700/mm^3 with 30% polys, 19% bands, 6% eosinophils, and 2% metamyelocytes. The urinalysis was normal, and the chest radiograph was unchanged. Blood chemistries included an SGOT that was elevated to 86 units and an alkaline phosphatase that was elevated to 17.7 Bodansky units. Cultures of blood and urine remained sterile. An attempted bone marrow aspiration yielded only a few mononuclear cells. However, a liver biopsy revealed multiple noncaseating granulomas. Acid-fast stains were negative, but culture grew *M. avium-intracellulare* resistant to all antituberculous agents. The patient was treated with numerous medications including, at various times, INH, ethambutol, rifampin, streptomycin, pyrazinamide, and cycloserine. Nevertheless, his condition deteriorated with ongoing fevers, wasting, progressive hepatic dysfunction, and finally diffuse pulmonary infiltrates. He died 4 months later. Permission for an autopsy was denied.

Comment. This patient demonstrates many of the features of disseminated mycobacterial infection that were evident in the preceding case. The major difference is that this patient was infected with a group III atypical mycobacteria that were highly resistant to chemotherapeutic agents. Disseminated infection with such organisms is rare in immunologically intact hosts but carries a grave prognosis in the impaired host. Although the diagnosis was made promptly in this case, therapy was ineffective, and the patient died of overwhelming *M. avium-intracellulare* infection.

2.6.4. Bacillus Calmette-Guérin Vaccine in Immunocompromised Patients

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of *M. bovis* that was introduced into clinical use in 1921. BCG remains controversial with estimates of its efficacy in providing protection against tuberculosis ranging from zero to 80%.[2,3,87]

Because of the low incidence of new tuberculous infection in the United States, BCG is not currently recommended for routine use.

Hundreds of millions of doses of BCG have been administered around the world. BCG is extremely safe when given intradermally to normal patients in doses recommended for the prevention of tuberculosis. Local reactions such as ulceration at the vaccination site and lymphadenitis are uncommon and are generally self-limited; BCG osteomyelitis is rare, and disseminated BCG infection is very rare.[2,87] Because most of these serious reactions have occurred in immunosuppressed patients, BCG should not be administered for the prevention of tuberculosis to patients with lymphoma, leukemia, or widespread cancer or to those receiving immunosuppressive drugs or radiotherapy.[2]

Over the past few years, however, BCG has been studied extensively as an immunotherapeutic agent in patients with melanoma, leukemia, lymphoma, and other malignancies.[88] The administration of BCG to cancer patients differs from the use of BCG as a vaccine against tuberculosis in several important respects.[89] Cancer patients are often given repeated doses of BCG, sometimes at intervals as short as 5 days. Extremely large doses may be given; in some protocols, organisms are injected directly into vascular tumor masses rather than into normal skin. Finally, the patients themselves are often immunosuppressed because of advanced malignancy, chemotherapy, or both.

Not surprisingly, cancer patients receiving BCG immunotherapy have experienced a variety of adverse reactions to the injection of viable mycobacteria. These complications can be divided into two broad categories. In immunocompetent patients, repeated injections can lead to hypersensitivity reactions, including local erythema and induration, regional lymphadenopathy, and constitutional reactions, including fever and even anaphylaxis and fatal shock with disseminated intravascular coagulation (DIC).[88] By contrast, in immunosuppressed patients, complications can be related to the unchecked spread of mycobacteria. These complications have been most pronounced following intratumor injection of BCG. Symptoms may include fever, chills, and an influenzalike syndrome in as many as 64% of patients receiving intralesional BCG.[90,91] Abnormal liver

function tests are common in this setting, and hepatic dysfunction can be severe and persistent. Disseminated BCG infection can be documented by finding granulomas in the liver and bone marrow. BCG is sensitive to INH and to most other antituberculous agents. However, although some groups have found chemotherapy efficacious in the control of disseminated BCGosis in immunosuppressed patients,[90,91] others have been disappointed by the results of INH therapy.[91]

Another reported complication of BCG immunotherapy is the occurrence of radiographically evident pulmonary granulomas that mimic recurrent metastatic cancer.[90,105] These have occurred even after intradermal administration of BCG by the multiple-puncture technique. Although these patients are as a rule asymptomatic, the lesions can be clinically important if they are radiographically mistaken for malignancies.

In summary, BCG should not be given to immunosuppressed patients for the prevention of tuberculosis. When BCG is administered for the experimental immunotherapy of malignancies, both local and systemic reactions can occur. In immunocompetent patients, hypersensitivity reactions can range from local inflammation to life-threatening anaphylaxis. In immunosuppressed patients, disseminated BCGosis may occur with fever and hepatic dysfunction reflecting granulomatous lesions in liver, bone marrow, and lung. Pulmonary granulomas may be mistaken for tumor. Systemic BCG infections are generally seen in patients receiving intralesional injections. Although most patients recover spontaneously, morbidity can be prolonged. Antituberculous chemotherapy is indicated, but results have been variable.

2.6.5. Mycobacterial Infections in AIDS

Mycobacteria are among the many infectious agents that can cause serious disease in patients with AIDS (see Chapter 15). Both pathogenic (*M. tuberculosis*) and opportunistic (*M. avium-intracellulare* and other atypical forms) mycobacterial species can cause disease in these patients. Dissemination is the rule and the response to chemotherapy is generally poor; other infections are present simultaneously in most cases.

Tuberculosis was diagnosed in 27 of 45 Haitians with AIDS in Florida (92). In 22 (81%) of these patients, tuberculosis was discovered 1–17 months before the diagnosis of AIDS was established. Nineteen (70%) of these patients had extrapulmonary tuberculosis. Only one of these Haitians with AIDS had disseminated *M. avium-intracellulare* infection. Unfortunately, follow-up date were available in only a few of these patients, but all 10 patients with pulmonary tuberculosis who could be evaluated responded favorably to antituberculous chemotherapy, which included INH and rifampin in all cases.

In non-Haitians with AIDS, infection with *M. avium-intracellulare* appears to be more common than infection with *M. tuberculosis,* and the response to chemotherapy is much less favorable.[93-97] Disseminated infection is common, with organisms frequently present in the lungs, liver, spleen, and lymph nodes. Despite the presence of many mycobacteria in macrophages, well-formed granulomas are typically absent; this lepromatous histology reflects the profound impairment of cell-mediated immunity in these patients and explains their inability to contain the infection. Patients with AIDS may also exhibit an impaired humoral (antibody) response to *M. avium-intracellulare.*[98] When the newer blood culture techniques are utilized (65b), a high-grade *M. avium-intracellulare* bacillium can be demonstrated in many patients with AIDS.[99,100] Intestinal infection can often be documented by stool or colonic biopsy cultures.[101] *M. avium-intracellulare* may contribute to diarrhea in these patients. It is not known whether the GI tract is the portal of infection in these patients or whether the intestinal infection is a manifestation of dissemined infection from a pulmonary source.

Although multiple antituberculous drugs are used in these patients, the response to therapy is usually poor: cultures typically remain positive and clinical and radiographic evidence of atypical mycobacterial infection progresses. Because neoplasia and multiple viral, parasitic, bacterial, and fungal infections often coexist with mycobacterial infection in patients with AIDS, it is often difficult to determine how much the mycobacteria per se contributes to any patient's demise.

M. xenopi was isolated from the lung and liver of a patient with AIDS; cultures became negative on INH, rifampin, and pyrazinamide.[102]

Illustrative Case 5: Disseminated *M. Avium-intracellulare* in AIDS

This 38-year-old homosexual man developed cervical lymphadenopathy in December 1982. In February 1983, he noted weight loss, generalized lymphadenopathy, and oral candidiasis. Two months later, he was hospitalized with *Pneumocystis* pneumonia; a rash developed during therapy with trimethoprim–sulfamethoxazole, but the patient responded to pentamidine. Cutaneous Kaposi sarcoma developed in May 1983. Esophageal herpes simplex infection was documented by biopsy that same month, and ocular changes consistent with CMV infection developed shortly thereafter.

In July 1983, pancytopenia developed. A bone marrow biopsy revealed numerous acid-fast bacilli but no granulomas. Sputum smears revealed acid-fast bacilli, but the chest radiograph was clear. Sputum, blood, bone marrow, and stool cultures grew *M. avium-intracellulare*. The patient was treated with ansamycin, clofazamine, cycloserine, and isoniazid, which was discontinued after sensitivity testing revealed that the organisms were INH resistant.

Despite continued antituberculous therapy, blood, sputum, and stool cultures remained positive for *M. avium-intracellulare*. Diarrhea, profound weight loss, progressive lymphodenopathy, and hepatosplenomegaly were noted. Cutaneous lesions of Kaposi sarcoma progressed and nodular pulmonary lesions developed. By January 1984 the patient weighed only 66 lb (30 kg). A rapidly progressive encephalopathy developed, and the patient died.

Autopsy findings included Kaposi sarcoma of skin and lung, disseminated CMV, and diffuse encephalitis without organisms. The spleen and many lymph nodes were massively infiltrated with foamy macrophages laden with acid-fast bacilli. Similar macrophages were present in periportal areas of the liver, in the small bowel lamina propria, and in the subcutaneous fat. The bone marrow and lungs contained acid-fast bacilli. No granulomas were identified in any organ. Postmortem cultures were positive for *M. avium-intracellulare*.

Comment. In only 13 months, this young man lost 100 lb (45 kg). *Pneumocystis* pneumonia, oral candidiasis, esophageal herpes infection, and disseminated CMV were all important problems, but the dominant infection was disseminated *M. avium-intracellulare*. Despite ansamysin, clofazimine, and cycloserine, the infection progressed relentlessly. Kaposi sarcoma and AIDS encephalopathy combined with *M. avium-intracellulare* to cause death. Autopsy confirmed an enormous mycobacterial burden with a total absence of an appropriate granulomatous response, a situation reminiscent of lepromatous leprosy. When disseminated *M. avium-intracellulare* first becaue evident, the patient had a normal chest radiograph despite positive sputum smears and cultures. In 12% of patients with AIDS, chest radiographs are normal despite positive sputum cultures. The most common radiographic abnormality in this setting is hilar or mediastinal adenopathy (59%); localized infiltrates in the lower lung fields occur in 29%, but upper lobe infiltrates occur in only 18%.[103]

2.7. Management of Mycobacterial Infections

The chemotherapy of tuberculosis in both normal and immunocompromised hosts involve two very different issues: isoniazid prophylaxis of patients who have been exposed to tuberculosis but are free of active disease, and combined chemotherapy of patients with active infection. Paradoxically, although there are many more patients who may be considered for chemoprophylaxis than there are patients with active tuberculosis, the guidelines for INH prophylaxis are more controversial than are the recommendations for chemotherapy. This is particularly true in the immunosuppressed host.

2.7.1. Chemoprophylaxis

The question of chemoprophylaxis is raised most commonly in patients with positive tuberculin skin tests. Except in patients who have received chemotherapy, a positive skin test implies the presence of a few dormant but viable tubercle bacilli that have the potential for reactivation. The overall risk of reactivation in patients with positive skin tests has been estimated at 3–5%. Although the risk of reactivation is always present, it is greatest within the first few years of initial infection, in childhood, in adolescence, and in patients who have had previous clinical tuberculosis but who have been inadequately treated by present standards.

In a sense, then, patients with positive tuberculin skin tests serve as their own reservoir for future clinical disease. It has been demonstrated that the administration of isoniazid (INH) daily for 1 year reduces the risk of subsequent tuberculosis by up to 80%.

A recent European study of 28,000 tuberculin-positive adults with fibrotic pulmonary lesions demonstrated that 52 weeks of INH chemoprophylaxis reduces the incidence of tuberculosis by 75%; a 24-week regimen produced a 65% reduction. The rate of hepatitis was only 0.5% among INH recipients as compared with 0.1% in placebo recipients.[104]

However, INH has its own potential toxicities and should therefore be used selectively. The major concern in the use of INH is its hepatotoxicity. This is quite rare below age 20 and occurs in no more than 0.3% between the ages of 20 and 34. On the other hand, among patients older than 50, up to 2.3% may develop INH hepatotoxicity. Based on the risk of reactivation and the risks of INH toxicity, risk–benefit ratios can be calculated to help select patients for INH chemoprophylaxis. Those who have converted a

tuberculin skin test from negative to positive within 2 years should be considered for chemoprophylaxis. In addition, close contacts of patients with active pulmonary tuberculosis should be considered for INH therapy on epidemiologic grounds, particularly if they are children or adolescents. Older patients who have recovered from clinical tuberculosis but who have never received chemotherapy should be worked up to exclude active disease; if none is demonstrated, these persons too may benefit from INH. Finally, it can be argued that all persons below age 35 should be skin tested at the time of routine medical evaluations and that INH should be administered to positive reactors. The prevalence rate of positive reactions among 6-year-olds is now about 0.2% and among adolescents about 0.7%. Thus, a positive reaction in a young patient may indicate recent exposure. Additional arguments for the use of INH in young patients include the fact that the drug is well tolerated in this age group and that without chemoprophylaxis the risk of reactivation would persist for the life span of the individual.[106]

The question of chemoprophylaxis in the immunosuppressed patient is considerably more complex because of the lack of data in many critical areas. On the simplest level, the tuberculin skin test may be negative because of anergy in these patients. If possible, tuberculin skin testing should be performed prior to the institution of immunosuppressive therapy. When this is not possible, control skin tests should be applied at the same time as PPD is injected. If anergy is present, the immunosuppressed patient must still be considered at risk for reactivation tuberculosis if there is a history of previous PPD positivity, of close exposure to tuberculosis, or of previous clinical tuberculosis. Even if these are absent, the chest radiograph should be carefully reviewed for abnormalities compatible with previous tuberculous infection such as a Gohn complex, pleural abnormalities, or apical calcifications. Patients with these radiologic findings must also be considered at risk.

It is important to screen all immunosuppressed patients for previous tuberculosis exposure with skin tests, a detailed history, and chest radiographs. Patients with positive findings should be followed closely, and tuberculosis should be accorded a prominent position in the differential diagnosis of infectious processes in those patients, even if the features are atypical.

But apart from maintaining a high index of suspicion, can the clinician offer more to the immunosuppressed patient with previous tuberculosis exposure? Unfortunately, the data required to answer this question are incomplete. Although the immunosuppressed state is classically considered a predisposing factor to tuberculosis, the magnitude of the risk is unknown (see Section 2.5), and estimates run the gamut from a slight risk[28] to a major risk.[107] Moreover, the efficacy of INH in reducing this risk has not been studied comprehensively. On theoretical grounds, immunosuppression per se should not interfere with the action of INH, but tuberculosis has been reported in immunosuppressed patients receiving prophylactic INH.[32] In addition, if INH is to be administered, it is unknown whether 1 year of therapy is sufficient or if the drug should be given throughout the period of immunosuppression. Finally, concern has been voiced that INH may have a greater toxic potential in immunosuppressed patients. Although this point has not been demonstrated, it is clear that the interpretation of abnormal liver function tests in immunosuppressed patients is much more difficult because they are often receiving other potentially hepatotoxic drugs and because transfusions, dialysis, and organ transplantation increase the risk of viral hepatitis and CMV infection.[108–110]

Recommendations on the use of INH prophylaxis in the immunocompromised patient vary widely, with some groups advocating daily therapy as long as the immunologically impaired state exists,[107] others suggesting a year of therapy,[106,108] and still others advocating close clinical observation without therapy.[29] In view of the many unknowns, individualized decisions would seem preferable to blanket recommendations.

Factors favoring the use of INH in immunosuppressed patients would include recent tuberculin conversion, young age, previously active tuberculosis that had not been treated with appropriate drugs, normal liver function tests, and the absence of concurrent hepatotoxins, including both drugs and alcohol. Reliable patients who will cooperate with close follow-up and who can recognize symptoms of INH hepatitis are also better candidates for INH prophylaxis, as are patients who are clearly immunosuprssed but who are expected to survive their underlying disease for prolonged periods. The duration of

therapy should also be individualized: 12 months of continuous daily INH should be the goal, but in the absence of toxicity, it is reasonable to continue treatment for longer periods if the patient remains immunosuppressed.

If INH chemoprophylaxis is recommended, the potential risks and benefits of INH should be explained. Patients who accept chemoprophylaxis should be instructed to discontinue the medication and report to the physician if adverse effects are noted, including skin rash, fever, symptoms of peripheral neuritis, or symptoms of hepatitis including fatigue, anorexia, abdominal distress, or jaundice.

The American Thoracic Society[106] does not recommend routine SGOT determinations in patients who are reliable and who are able to comply with these directions. However, immunosuppressed patients are much more complex and generally require close medical surveillance on other grounds, so periodic SGOT determinations would seem reasonable. The problem with SGOT determinations is that 10–20% of patients receiving INH can be expected to develop mild transient elevations in SGOT that will return to normal even during continued therapy and are of no clinical significance. Although precise data are lacking, a reasonable approach is to routinely determine the SGOT at monthly intervals for at least the first 3 months of therapy. In symptomatic patients with elevated SGOTs, the drug should be discontinued and LFTs monitored. In asymptomatic patients with mild elevations of SGOT (perhaps up to three times normal), the drug can be continued, but the patient should be monitored weekly. If the SGOT fails to return to normal in 3–4 weeks, it seems prudent to discontinue INH. On the other hand, even if a patient is asymptomatic, a single more substantial elevation of SGOT, perhaps above 200 units, may be grounds to discontinue the agent. Again, it must be emphasized that these are "rules of thumb" rather than precise guidelines.

2.7.2. Chemotherapy

The chemotherapy of active tuberculosis[111,112] is different from other antimicrobial programs and should proceed according to five basic principles. The first is the use of multiple drugs to prevent the emergence of drug-resistant organisms. A second principle of chemotherapy is that in treatment failures, drugs should be changed in combination rather than singly; in such cases, drug sensitivity testing is mandatory. A third principle is that single daily dosages of drugs are preferred. The fourth principle is that prolonged chemotherapy is necessary. Standard regimens have employed multiple drugs for periods of 18–24 months. With combinations of newer agents, shorter regimens of 6–9 months have been found equally effective in normal hosts. No matter what regimen is chosen, it is important to follow patients closely to ensure compliance and to monitor drug efficacy and toxicity. For normal hosts, the currently recommended antituberculous regimens are so effective that following the conclusion of treatment, relapse is unlikely, and it is unnecessary to keep patients under prolonged surveillance. By contrast, immunosuppressed patients should be followed after therapy.

Finally, most patients with tuberculosis should be hospitalized for the initial phases of therapy. As little as 2 weeks of combined therapy will greatly decrease the infectiousness of patients with pulmonary tuberculosis, although a few mycobacteria may still be present on sputum smears or cultures. Hence, short-term admission to general hospitals is preferred, with early home care in patients who are reliable and clinically stable. Patients with extrapulmonary tuberculosis are much less infectious and can sometimes be managed entirely as outpatients if their clinical status permits. Immunocompromised patients may be sicker and may respond less rapidly to therapy, necessitating more prolonged hospitalization.

2.7.3. First-Line Antituberculous Agents

2.7.3a. Isoniazid. Introduced into clinical use during the early 1950s, Isoniazid remains the single most important antituberculous drug. INH is bactericidal against *M. tuberculosis*. Of importance also is the excellent tissue penetration of this small water-soluble molecule; the distribution of INH includes the CNS, tuberculous abscesses, and intracellular sites. The major metabolism of INH is by hepatic acetylation, with metabolites then excreted by the kidneys. Although metabolites are excreted by the kidney, it is not necessary to modify INH doses except in advanced renal failure. Isoniazid is available both orally and parenterally. The usual dose is 5

mg/kg body weight, which averages 300 mg/day for the adult. For initial therapy of life-threatening disease, doses of 10–15 mg/kg per day may be used. The major toxicities of INH include the following:

1. Neurologic toxicity ranging from peripheral neuropathy (prevented by administration of pyridoxine, 50 mg/day) to much less common manifestations including encephalopathies, seizures, optic neuritis, and personality changes.
2. Hypersensitivity reactions including fever, rash, and rheumatic syndromes with or without positive antinuclear antibodies (ANA) and lupus erythematosus preps.
3. Hepatitis including serious clinical hepatitis in less than 2%, but a transient clinically insignificant rise in SGOT in 10–20%.

Isoniazid is an inexpensive drug. We recommend the administration of pyridoxine in a daily dose of 50 mg to patients receiving INH.

2.7.3b. Rifampin. Rifampin is the newest of the major antituberculous agents; it rivals INH in efficacy. Rifampin is bactericidal against *M. tuberculosis*. Rifampin is a large fat-soluble molecule that achieves excellent tissue penetration, including the CNS. The drug is excreted by the liver; modification of dosage is not required in renal failure but may be necessary in patients with hepatic insufficiency. Although rifampin is available parenterally in Europe, only an oral preparation has been approved in the United States. Unlike INH and ethambutol, rifampin is actually a broad-spectrum antimicrobial agent, acting against some atypical mycobacteria, *M. leprae,* many bacteria (including staphylococci, meningococci, and various gram-negative bacilli), trachoma agents, and some viruses. The average dose in adults is 600 mg/day administered in a single dose. Patients should be cautioned to expect orange discoloration of urine, sweat, tears, and saliva, which is of no clinical significance. Toxicities include hypersensitivity reactions such as fever, rash, or eosinophilia, hematologic toxicities such as thrombocytopenia, leukopenia, and hemolytic anemia, and hepatitis, including elevated SGOTs in up to 10%. Drug interactions occur, so that rifampin antagonizes the effect of warfarin, oral contraceptives, and methadone. High-dose rifampin should never be used in intermittent therapy because toxic reactions, including hemolytic anemia, thrombocytopenia, and renal failure, occur frequently. Rifampin is an expensive drug.

2.7.4. Second-Line Antituberculous Agents

2.7.4a. Ethambutol. Ethambutol was introduced clinically in the United States in 1967 and represented a major advance in antituberculous chemotherapy. Ethambutol penetrates tissues well, including the CNS when the meninges are inflamed. A disadvantage of ethambutol is that it is only bacteriostatic against *M. tuberculosis.* The drug is excreted by the kidneys. Although a modification of drug dosage is required in patients with renal failure, a nomogram to calculate dosage is not available; serum ethambutol levels (available through the manufacturer) should be monitored in patients with renal failure who require the drug. Ethambutol is available only in an oral preparation. Many authorities recommend initial therapy with 25 mg/kg body weight per day for the first 6–8 weeks of therapy and then reduced doses of 15 mg/kg body weight per day for the remainder of the course. Good results have also been obtained with use of the lower dose throughout therapy. The major toxicities of ethambutol include hypersensitivity reactions, such as fever and rash and optic neuritis, which is dose related and is usually manifested first by a loss of color vision. Less common side effects include neuritis, GI intolerance, headache, and hyperuricemia. The cost of ethambutol is moderate.

2.7.4b. Streptomycin. Streptomycin was the first effective antituberculous agent and remains a useful member of the therapeutic arsenal. Like other aminoglycosides, streptomycin has only a fair tissue distribution, being inactive at an acid pH or in an anaerobic milieu and penetrating the CSF very poorly. The excretion of streptomycin is via the kidneys, and dosage should be reduced in patients with renal failure. Streptomycin must be given parenterally. The average adult dose is 1 g/day for the first 2–8 weeks of therapy followed by 1 g twice a week. Major toxicities include hypersensitivity reactions and eighth nerve toxicity, especially to the vestibular division, resulting in vertigo. The cost of streptomycin is moderate, averaging about $1.00 per day.

Streptomycin is active against a variety of organisms in addition to *M. tuberculosis,* although many gram-negative bacilli have now become resistant because of the widespread use of this drug over many years.

Pyrazinamide. One of the older antituberculous agents, pyrazinamide is receiving renewed attention because of its bactericidal action against dormant intracellular *M. tuberculosis* organisms. Pyrazinamide is well absorbed from the GI tract and achieves therapeutic serum levels and good tissue penetration. Metabolism and excretion are by both hepatic and renal routes. The average dosage of pyrazinamide is 20–35 mg/kg per day (3-g maximum) divided into three doses. Side effects include hyperuricemia and hypersensitivity reactions; hepatic toxicity may occur in 3–15%, which may cause confusion in patients who are also taking other drugs with hepatotoxic potential, including INH and rifampin.

2.7.5. Third-Line Antituberculous Agents

In addition to the five major drugs, five other agents are available in the United States for the treatment of tuberculosis. Three of these are administered orally including *p*-aminosalicylic acid (PAS), ethionamide, and cycloserine. For many years, PAS was considered a first-line drug, but its relatively weak tuberculostatic action and the very high incidence of GI intolerance have now relegated this drug to alternate status. Two other drugs are available parenterally including kanamycin, and capreomycin, both of which are pharmacologically similar to streptomycin. The third-line drugs tend to be both less effective and more toxic than the standard agents but occasionally are of critical importance in treating patients with drug-resistant tuberculosis or atypical mycobacterial infection or in patients who cannot tolerate the standard drugs.

2.7.6. Antituberculous Regimens

Many combinations of antituberculous agents are effective in the treatment of tuberculosis, and many different regimens have been advocated. For the chemoprophylaxis of tuberculin convertors or selected tuberculin reactors, isoniazid is the only drug that can be recommended. For patients with active tuberculosis ranging from minimal infection to moderately advanced pulmonary or extrapulmonary disease, two-drug therapy is efficacious.

Most authorities now recommend the use of INH and rifampin in these circumstances. Ethambutol may be substituted for rifampin if hepatotoxicity is a concern and if the patient does not have advanced tuberculosis; in immunologically impaired hosts, however, the concomitant use of INH and rifampin would seem preferable, and a third drug may even be advisable. In patients with advanced pulmonary tuberculosis, tuberculous meningitis, mililary tuberculosis, or tuberculous pericarditis, triple therapy with INH, rifampin, and ethambutol is advisable; ethambutol can be discontinued after 2–3 months if clinical improvement has occurred. Streptomycin or pyrazinamide may be substituted for one or more of these drugs in patients who are intolerant to the first-line drugs. The treatment of resistant organisms may requite other drug combinations.

Standard chemotherapy of tuberculosis requires daily administration of drugs for 18–24 months. In addition to these standard regimens, new approaches to the treatment of tuberculosis include short course[113,114] and intermittent[115] drug regimens. Although these programs can be very useful for normal hosts, they cannot be recommended for the immunocompromised patient with tuberculosis.

2.7.7. Ancillary Therapeutic Modalities

The availability of excellent chemotherapeutic agents has greatly reduced the role of surgery in the treatment of tuberculosis. In general, drugs are now used to erradicate infection per se, whereas surgery may be helpful occasionally to treat complications or to repair or remove damaged tissues. Corticosteroids are useful only in selected situations such as patients with tuberculous meningitis complicated by hydrocephalus or CSF block and possibly patients with tuberculous pericarditis. Elaborate programs of rest and diet have no place in the treatment of tuberculosis.

2.7.8. Atypical Mycobacteria

The treatment of atypical mycobacterial infections is often extremely difficult.[5] Whereas *M. kansasii* and *M. marinum* are sensitive to the usual anti-

tuberculous drugs, most other nontuberculous my-cobacteria are highly drug resistant. Sensitivity testing is mandatory, and complex multidrug regimens are often needed. However, even these programs often fail, and surgical extirpation of localized disease may be necessary. The prognosis of disseminated atypical mycobacterial infection in the immunosuppressed host is extremely poor. Ansamycin, a compound related to rifampin, has shown promise in the treatment of *M. avium-intracellulare,* and is available on a compassionate investigational new drug basis from the Centers for Disease Control (404/329-3670). Clofazimine, an antileprosy drug, is also being studied in *M. avium-intracellulare* infections. Rapidly growing mycobacteria (Runyon group IV) may be susceptible to various antibiotics; amikacin, doxycycline, and sulfonamides have been used for *M. fortuitum,* and amikacin and cefoxitin have been used for *M. chelonei.*

3. Nocardia

Like many other opportunistic infections, nocardiosis has increased in prominence over the years from a medical curiosity to an important illness. Between the description of the causitive organism in 1888 and a review of nocardiosis in 1960,[116] only 174 cases were reported in the world's literature. By contrast, it has recently been estimated that as many as 500–1000 cases of nocardiosis occur in the United States annually.[118] It is not clear whether this apparent increase reflects more accurate recognition and reporting of this hard-to-diagnose infection or if the expanded population of immunosuppressed patients has contributed to a true increase in the incidence of nocardiosis. It is clear that an aggressive approach to the diagnosis of nocardiosis is vitally important, because the results of chemotherapy have been very encouraging even in the compromised host.

3.1. Classification and Microbiology

Nocardia species are often misclassified as fungi because of their branched, filamentous, hyphaelike morphology or as mycobacteria because of their acid fastness. In fact, the nocardias are true bacteria; unlike the fungi, they are prokaryotic (i.e.,

have no nuclear membrane), they lack cytoplasmic organelles, they are small (usually <1 μm in diameter), their cell walls contain muramic acid peptides characteristic of bacteria, and their cell membranes lack the sterols characteristic of fungi.

Three species of nocardia are clinically important. Of these, *N. asteroides* is by far the most important, accounting for at least 85% of the cases of pulmonary and disseminated nocardiosis[117] and for the great majority of nocardial infections in immunocompromised hosts. Although *N. caviae* and *N. brasiliensis* can cause identical clinical illnesses, the latter is most commonly encountered as the cause of chronic subcutaneous suppuration in tropical and semitropical regions. *N. brasiliensis* can cause pulmonary and disseminated disease in immunocompromised patients in the United States.[118] These three species of *Nocardia* are morphologically identical, and speciation can be difficult.

Nocardia appear as slender, filamentous, branching organisms that may fragment into coccobacillary forms. They stain gram positive, often in an irregular or beaded fashion. *Nocardia* are acid fast but are less resistant to decolorization than are the mycobacteria. Hence, they are best visualized with a modification of the Ziehl–Neelsen method, in which 1% sulfuric acid is substituted for acid alcohol as the decolorizing agent.[119] *Nocardia* may also be visualized in tissue with methenamine–silver stain, but they are not visible with hematoxylin and eosin or with periodic acid-Schiff (PAS) stains.

Nocardia can be grown in the laboratory on a variety of media, including the blood agar and thioglycollate broth generally used for bacteria, the Sabouraud agar generally used for fungi, and the Lowenstein–Jensen medium generally used for mycobacteria. These organisms grow aerobically, but their growth is slow: 3–5 days are often required to identify colonies, and final identification of *Nocardia* species can take 3 weeks or longer. Because of this, it is most important for the clinician to alert the laboratory when *Nocardia* is suspected, so that cultures will be held longer and scrutinized with particular care. Nocardial colonies may be orange pigmented or chalky white and have a characteristic wrinkled texture.

The nocardias are morphologically similar to the actinomyces, to which they are closely related. Actinomyces tend to be less acid fast and to form

sulfur granules in tissues.[119] Actinomyces are unlike *Nocardia* in that they are commonly present as part of the normal human flora, they cause infections primarily in the normal host, and they are sensitive to penicillin. Laboratory differentiation is easy because the actinomyces are anaerobes, whereas the nocardias grow aerobically.

3.2. Epidemiology and Pathogenesis

Nocardiosis is a worldwide infection. Although the pulmonary and disseminated forms of the infection do not demonstrate any geographic concentration, the third type of nocardiosis is much more common in Central and South America. This process is a chronic granulomatous infection of the skin and of the subcutaneous tissue of the feet, called maduromycosis or mycetoma. Sinus tracts are commonly present, and this is the only form of nocardiosis in which sulfur granules (generally characteristic of actinomycosis) may be present in the purulent drainage. In some cases, bone may be involved. Maduromycosis is caused by direct inoculation of *N. brasiliensis* into the skin. Because this process is not characteristic of immunosuppressed patients, it is omitted from further consideration here.

The epidemiology of pulmonary and disseminated nocardiosis is not well understood. Nocardial species can be cultured from soil and decaying vegetable matter. It is presumed that they enter the body by inhalation of aerosolized organisms, but most patients do not have a history of soil or dust exposure. Person-to-person transmission is unknown. Cases may cluster together in hospitalized patients, and *N. asteroides* has been isolated from the air and dust in a renal transplant unit in which four cases of nocardiosis occurred,[120] but nosocomial infection has not been documented.

Males outnumber females with nocardiosis at a rate of about 2 : 1.[121] Patients of all ages have been infected. Serious underlying diseases are present in 50%[121] to 85%[117] of patients with nocardiosis. The most important predisposing conditions are those producing systemic immunosuppression, including leukemia, lymphoma, organ transplantation, and corticosteroid therapy. Nocardiosis can occur in patients with AIDS.[122] In the Stanford experience, heart transplant recipients were at unusually high

risk, a nocardiosis developed in 21 of 160 patients.[123] In other patients, nocardiosis is superimposed on underlying pulmonary diseases, including COLD, tuberculosis, and pulmonary alveolar proteinosis. Diabetes has also been cited as a predisposing factor. In occasional patients, trauma or chronic inflammatory diseases have been incriminated, but in up to 50% of patients with nocardiosis, no primary disorder can be identified.

The host response to *Nocardia* has not been well defined. Pathologically, an acute inflammatory response is present, often with areas of necrosis or even abscess formation. Although this picture is reminiscent of a pyogenic process, it has been suggested that cell-mediated immunity is important in host defense against nocardias.[124] Further studies will be required to clarify this issue.

3.3. Clinical Features and Diagnosis

The clinical picture of nocardiosis is extremely variable, ranging from inapparent infection to fulminating pulmonary and systemic disease. With the exception of primary cutaneous infection,[125] the lung is the portal of entry in most cases. *Nocardia* is not part of the normal human flora, and these organisms are uncommon as laboratory contaminants.[126] Because of this, the finding of a positive sputum culture is generally considered highly suggestive of active pulmonary infection. However, in Mayo Clinic experience with 25 cases of nocardiosis, nine had positive sputum cultures with negative chest radiographs; although these patients did not receive antimicrobial therapy, they remained free of clinical infection.[127] Hence, simple colonization or subclinical infection clearly represents one pole of the clinical spectrum of pulmonary nocardiosis. Moreover, in a review of nocardiosis in 22 patients, Young et al.[128] reported nine cases in which fever and respiratory symptoms were present but chest radiographs were negative. Despite multiple positive cultures for *Nocardia,* therapy was withheld. All nine patients recovered, suggesting that *Nocardia* can produce self-limited infection of the respiratory tract. *Nocardia* is also a rare cause of upper respiratory tract infection, including one interesting case of chronic sinusitis presenting as fever of unknown origin.[129]

Despite these milder presentations, most patients with nocardiosis present with symptomatic pul-

monary and/or systemic disease. Here, too, the clinical and radiologic features are extremely variable.[130] Nocardiosis can produce solitary lung nodules, localized pneumonitis, or lung abscesses that may be single or multiple. A micronodular or miliary pattern is less common. Direct extension to the pleura or, rarely, the pericardium,[131] may occur. Although in many patients these infections are insidious in onset and indolent in progression, in some cases nocardiosis can produce an acute necrotizing pneumonia.[132] Not surprisingly, clinical findings vary widely from low-grade fever and cough to spiking fevers and chills, copious production of purulent or even bloody sputum, chest discomfort, and respiratory embarrassment. Malaise and weakness are often present, and weight loss can be prominent in chronic nocardiosis.

Hematogenous spread of infection is common in nocardiosis. The lungs are the initial site of infection in almost all patients, but in about 25%, the pulmonary focus is subclinical or has healed, so that it cannot be detected at the time of clinical presentation. The most frequent site of metastatic infection is the CNS. About 25% of all patients with nocardiosis develop CNS infection; brain abscess is the most common manifestation of metastatic nocardiosis.[121] The second most common type of extrapulmonary nocardiosis is infection of skin and subcutaneous tissues. On rare occasions, these soft tissue lesions can cause extensive local damage. But even in milder cases, subcutaneous abscesses can be very important clues to the diagnosis of nocardiosis because of their accessibility for biopsy and culture.[123] Virtually any other organ can be hematogenously seeded in the course of nocardiosis, including the eyes, the liver, spleen, lymph nodes, kidneys, bones, and joints.

The diverse clinical features of nocardiosis often make diagnosis difficult. This is particularly true in the immunosuppressed host, both because of the expanded differential diagnosis in these patients and because nocardiosis can develop simultaneously or in sequence with other pulmonary and systemic infections. An aggressive approach to the diagnosis of nocardiosis is mandatory because the prognosis without treatment is dismal, whereas with antimicrobial agents, the outlook is favorable.

Despite the prominence of pulmonary lesions, sputum smears and cultures will yield the diagnosis of nocardiosis in fewer than 30% of cases.[121] As a result, invasive studies are necessary in most cases, including procedures such as transtracheal aspiration, bronchoscopy with biopsy, bronchial brushings, and percutaneous or surgical lung biopsies. The choice of procedure depends on the type and location of the lesions, on the patient's ability to tolerate the studies, and on the expertise available at each institution. Interestingly, paratracheal abscesses have complicated transtracheal aspiration procedures in some patients with nocardiosis.[127] In the case of nocardial brain abscesses, scans and angiograms disclose nonspecific mass lesions. The CSF in such cases may be normal or may show a modest elevation of pressure and protein with a normal sugar and a mild lymphocytic pleiocytosis. Unless pulmonary lesions are present, cranitomy is generally required for diagnosis. If subcutaneous lesions are present, they provide excellent material for diagnostic studies. On rare occasions, positive blood cultures can lead to the diagnosis of nocardiosis.[133-135] In all cases, specimens should be examined by both Gram and modified acid-fast stains, and cultures should be examined closely for at least 5–7 days because of the slow rate of growth of this organism. Unfortunately, serologic and skin tests are not reliable for diagnosis.

Illustrative Case 6: Pulmonary Nocardiosis

This 41-year-old woman was hospitalized in 1978 because of cough and chest pain. Six months earlier, she had received a cadaver renal allograft, and she had been maintained on azathropine and prednisone. Five days before admission, a nonproductive cough and right-sided pleuritic chest pain had developed. She denied fever, chills, dyspnea, and hemoptysis.

On examination, she was a cushingoid woman in moderate distress. She was afebrile, and her lungs were normal to examination. She had no lymphadenopathy, and there were no lesions of the skin or subcutaneous tissues. She was neurologically intact. Laboratory studies included a Hct of 26% and a WBC count of 11,400/mm³ with 77% polys, 11% bands, 5% lymphocytes, 2% myelocytes, and 5% metamyelocytes. The BUN was 26 mg/dl, the creatinine 1.8 mg/dl, and the blood sugar 83 mg/dl. The results of liver function tests and arterial blood gas determinations were normal. The chest radiograph demonstrated a 4-cm rounded density in the periphery of the right middle lobe. Tomograms did not disclose either cavitation or calcification.

A needle aspiration biopsy of the pulmonary lesion was performed; the material obtained contained many polys, but no organisms were visualized on Gram stain, fungal wet mounts, and acid-fast stain. After 5 days of incubation, aerobic and anaerobic cultures were negative, and an open lung biopsy was performed. A

3-cm area of bronchopneumonia was found, with sheets of polys and areas of necrosis with abscess formation. Gram stain revealed slendor, filamentous, branching gram-positive organisms (Fig. 3) that were acid fast when stained with the modified Ziehl–Neelson method. Culture grew *N. asteroides*. The patient was treated with high-dose sulfisoxazole for 6 months and did well.

Comment. This case illustrates the need for an aggressive approach to the diagnosis of pulmonary infection in the immunosuppressed host. In this case, nocardiosis presented as pleuritic pain and a solitary lung nodule. In other patients, fever and productive cough dominate clinically, and rapid deterioration may occur. Radiographic findings are variable, including multiple nodules, necrotizing lesions, or both. Probably because of early diagnosis and vigorous therapy, there were no signs of hematogenous dissemination, and she responded well to treatment.

Illustrative Case 7: Nocardial Brain Abscess

This 79-year-old woman was hospitalized because of weakness and ataxia. Six years earlier, generalized lymphadenopathy had developed and she was found to have chronic lymphocytic leukemia. She was treated with prednisone and, in addition, received several courses of chlorambucil. She remained well until 2 days before admission when she developed weakness and loss of balance. She denied headache and fever.

On examination, she was afebrile and nontoxic. She was found to have cushiongoid facies, mild lymphodenopathy, and hepatosplenomegaly. The neurologic examination revealed proximal muscle weakness, a broad-based waddling gait, and absent
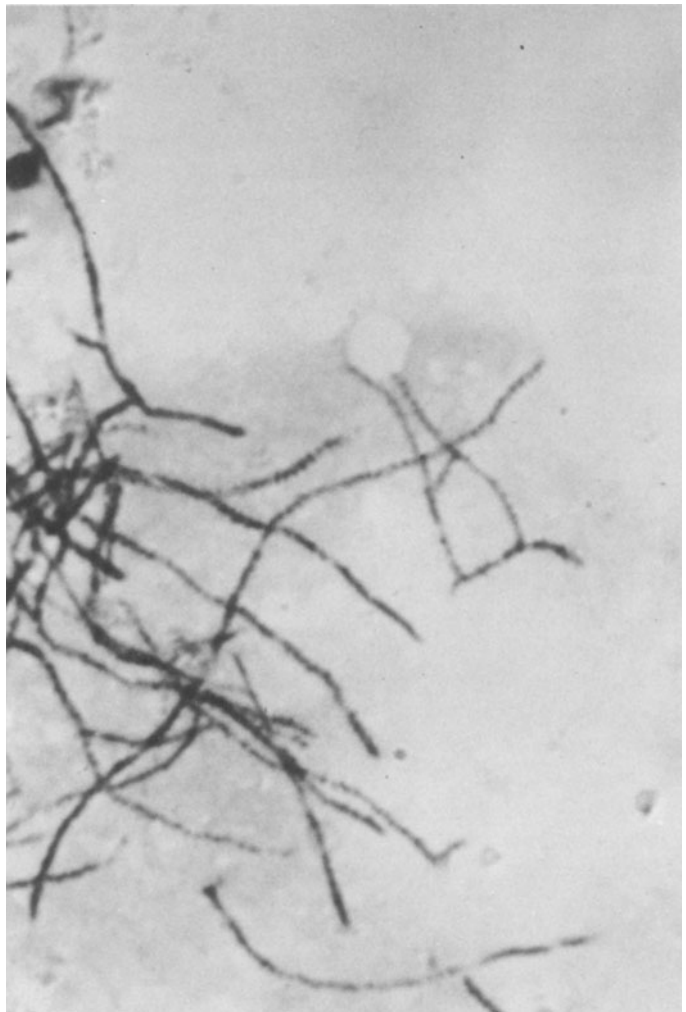

FIGURE 3. Gram stain of lung biopsy specimen from Illustrative Case 6 demonstrating the presence of slender, filamentous, branching gram-positive organisms.

ankle jerks bilaterally. Laboratory studies included a Hct of 30% and a WBC count of 19,000/mm³ with 9% polys, 88% lympho-cytes, 2% atypical lymphocytes, and 1% moncytes. Blood chem-istries, including liver function tests, were normal. The chest radi-ograph revealed a patchy right lower lobe infiltrate, which had resolved when another film was obtained 4 days later.

Over the next 4 days, her gait deteriorated, and she developed incoordination of the arms and legs, an intention tremor, and mild dysmetria. Computed tomographic (CT) scan of the skull per-formed with contrast material disclosed a mass with surrounding edema and contrst enhancement. At craniotomy, a thick-walled abscess was found and excised. Histologically, acute inflamma-tion was present. Gram stain revealed only rare short gram-positive bacillary forms that appeared weakly acid fast when stained with the modified Ziehl–Neelson technique. She was treat-ed with high-dose steroids and intravenous sulfisoxazole and pen-icillin. Penicillin was omitted on the third postoperative day when cultures revealed organisms subsequently identified as *N. as-teroides*. The patient was slowly improving neurologically, when she sustained a myocardial infarction and died on the sixth postop-erative day.

Comment. This elderly woman was immunosuppressed by virtue of chronic lymphocytic leukemia and prolonged prednisone therapy. She presented with a progressive neurologic illness and was found to have a nocardial brain abscess. The correct diagnosis was suspected on Gram stain even though only fragmented coc-cobacillary forms were seen. Her disease undoubtedly originated with hematogenous spread of infection from the lung to the brain. She had no pulmonary symptoms, but in retrospect, a transient pulmonary infiltrate had been present. The CNS is the most com-mon site of extrapulmonary nocardiosis. In patients who do not have concurrent pulmonary nocardiosis, cranitomy is required for diagnosis. This patient was treated appropriately with surgical excision of the lesion and intravenously administered sulfasox-izole, but she died of unrelated causes.

3.4. Therapy

Without therapy, nocardiosis is almost invari-ably fatal in the immunocompromised host. The overall survival rate at present is 58%[121] but, since these statistics include patients diagnosed late in their illness or even at autopsy, the results of early diag-nosis and vigorous therapy should be more favorable. Adverse prognostic features include immunosup-pression, acute onset of symptoms, dissemination of infection, and CNS involvement.

Sulfonamides have been the traditional treat-ment of choice for nocardiosis. High doses are re-quired. Sulfisoxazole may be administered in a total daily dose of 6–10 g given in divided doses every 6 hr. In very sick patients, the drug should be adminis-tered intravenously, but as improvement occurs, the oral route may be used instead. Serum sulfonamide

levels should be measured, and the drug dosage should be adjusted to achieve peak serum levels of 12–15 mg/dl. Other sulfonamides such as sul-fadiazine or triple sulfonamides are also acceptable, but serum sulfa assays must be performed for the specific agent chosen.

The optimal duration of therapy for nocardiosis has not been established. However, relapses follow-ing cessation of treatment have been observed fre-quently, indicating the need for prolonged therapy. Antimicrobial agents should be administered for at least 6–8 weeks following clinical recovery, and many authorities suggest continuing treatment for 6–12 months.

A number of alternate antimicrobial regimens are now under study as a result of improved tech-niques for in vitro drug susceptibility testing.[136,137] Trimethoprim–sulfamethoxazole combinations are very active in some assays[136,137] but are less active in other test systems.[136,138] Only small numbers of pa-tients have been treated with this combination,[139–141] but the results have been favorable; there have been no direct trials comparing trimethaprim–sul-famethoxazole with sulfonamides alone. Mino-cycline is active against the great majority of nocar-dial strains, and favorable results have been achieved with minocycline, 600 mg/day.[142,143] Combination therapy with ampicillin and erythromycin[142] was ef-fective in a transplant patient who could not tolerate sulfonamides. Other antibiotics including amikacin are active against *Nocardia* in vitro,[135,136] but clinical experience with these drugs is scant.[144]

Although nocardial lung abscesses will gener-ally resolve with antimicrobial therapy alone, brain abscesses require surgical excision as well. Similar-ly, other focal purulent infections may require sur-gical drainage in addition to medical therapy.

3.5. Infection Caused by Related Organisms

Immunocompromised hosts have repeatedly demonstrated their ability to contract infections with opportunistic organisms even before the micro-biology of these organisms is well defined. The rho-docrous taxon is an incompletely defined genus of organisms that lies intermediate between group IV mycobacteria (rapid growers) and *Nocardia* species. Aerobic partially acid-fast members of the rho-dochrous taxon are rare causes of pulmonary and

disseminated infection in impaired hosts.[145] Optimal therapy of these infections has not been defined.

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