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Tuberculosis in the AIDS Era

KENT A. SEPKOWITZ,[1,2]* JOHN RAFFALLI,[1] LEE RILEY,[3] TIMOTHY E. KIEHN,[1] AND DONALD ARMSTRONG[1,2]

Infectious Disease Service,[1] Memorial Sloan-Kettering Cancer Center, and Division of Infectious Diseases[2] and Division of International Medicine,[3] New York Hospital-Cornell Medical Center, New York, New York 10021

HISTORY

Tuberculosis has been described since at least the time of Hippocrates, who referred to it as "phthisis," connoting the wasting character of the disease. Aristotle correctly determined its contagious nature, observing that the consumptive has around him a "pernicious air" that is "disease-producing" (95, 140).

However, tuberculosis did not become a major public health problem until the Industrial Revolution, when cities became overcrowded and public health facilities became overwhelmed—ideal circumstances for the spread of tuberculosis (157). In the 18th and 19th centuries, tuberculosis was responsible for 25% of all adult deaths in European cities, a chilling commentary on the poor living conditions that prevailed (22).

* Corresponding author. Mailing address: Infectious Disease Service, 1275 York Ave., Box 288, Memorial Sloan-Kettering Cancer Center, New York, NY 10021. Phone: (212) 639-2441. Fax: (212) 717-3021.

Osler recognized the impact on tuberculosis rates of people living in close quarters: "Poverty and tuberculosis are everywhere associated, particularly in the large centers of population... Wherever the population is so crowded that the families live in one or two rooms the tuberculosis death-rate is fully double that of districts in which the families live in houses with four rooms and upward" (237).

Long before there were effective medications such as isoniazid (INH) or streptomycin, the incidence of tuberculosis decreased (76). Several public health measures led to this remarkable improvement: pasteurization of milk, thereby removing *Mycobacterium bovis*; improved housing and ventilation; and earlier diagnosis of tuberculosis with isolation of infectious cases.

With the introduction of the first tuberculosis agents, streptomycin in 1944, *p*-aminosalicylic acid (PAS) in 1946, and INH in 1952, control of tuberculosis seemed a possibility. Stories of miraculous cures became common, and Selman Waksman, who led the group that synthesized streptomycin, traveled around the world to meet people whose lives streptomycin had saved.

However, despite these drugs and the subsequent introduction of many additional effective antituberculosis agents, eradication of tuberculosis has remained elusive. Worldwide, tuberculosis still kills 3 million persons a year, making it the leading infectious cause of death. Even in countries such as the United States, where sufficient funds, physicians, hospitals, and medicines are available, there has been a resurgence of tuberculosis (18, 31, 41, 60, 108, 128, 131, 178, 251, 271, 310). This demonstrates that without firm resolve, control of diseases such as tuberculosis cannot be achieved (40).

In addition, there has been a coincident rise in cases of drug-resistant tuberculosis, the ultimate result of effective drugs ineffectively administered (118, 220, 290). In one report from Africa, 30% of cases in 1992 were resistant to all four first-line agents (276). Thus, the problem confronting physicians who cared for the tuberculous in the 19th century—the lack of effective medicines—may be reexperienced by the physicians of the 21st century. Containment of this growing problem is one of the great challenges in public health.

Two unique aspects of tuberculosis have continued to thwart eradication efforts. First, *Mycobacterium tuberculosis* requires 2 to 8 weeks to grow in culture, and, second, 6 to 12 months of treatment is required to cure the disease. The former problem results in numerous missed or delayed diagnoses, often allowing spread of infection, and the latter problem leads to high rates of patient noncompliance, which in turn contributes to the emergence of resistant strains and to further spread of the disease. It may well be that until courses of therapy are measured in weeks rather than months, tuberculosis will continue to be an ineradicable public health problem.

PATHOGENESIS AND NATURAL HISTORY

The tuberculin skin test (TST) is now done in a standardized fashion with purified protein derivative, a filtrate of cultured *M. tuberculosis* that is precipitated. This test has been the cornerstone upon which much of our understanding of the natural history of tuberculosis has been built. Koch, who is known for his identification of the tubercle bacillus (105), developed a glycerol-based suspension containing killed *M. tuberculosis* organisms and announced that a series of injections of this "brownish transparent fluid"—later called tuberculin—would cure tuberculosis (15). After a few years, the claim was discredited, a failure that haunted Koch for the remainder of his career. According to many, Sir Arthur Conan Doyle, the physician who created the Sherlock Holmes mysteries, was the first person to recognize the diagnostic value of the TST for the detection of latent infection (94). The TST is still used today to identify persons with tuberculosis infection (latent subclinical infection) or disease (overt clinical tuberculosis).

TABLE 1. Interaction of HIV infection and *M. tuberculosis* infection

Influence of HIV infection on *M. tuberculosis* infection
Higher rates of reactivation disease (7–10%/yr vs. 5–8%/lifetime)
Higher rates of acute disease (37%/6 mo vs. 5%/2 years)
Higher rates of skin anergy
Higher rates of extrapulmonary tuberculosis
Malabsorption of antituberculosis medications
Influence of *M. tuberculosis* infection on HIV infection
Activation of macrophages in response to *M. tuberculosis* infection may increase macrophage expression of HIV
More rapid progression to AIDS if latent *M. tuberculosis* is untreated

Studies done through the years have defined how efficiently tuberculosis is spread. In general, about 30% of persons who have sustained contact with an index case patient from whom a stained sputum smear contains acid-fast bacilli (AFB) (smear-positive sputum) will develop tuberculosis infection, reflected by a positive TST (144, 263, 264, 296). Persons in contact with an AFB sputum smear-negative patient have less than a 10% rate of new infection (76, 144).

Most commonly, tuberculosis infection remains latent. Such primary infections are presumably unremarkable "colds" or "flus" for which the person has sought no medical attention. Without prophylaxis, 8 to 10% of persons with tuberculosis infection will develop tuberculosis disease, 3 to 5% in the first 2 years (acute and early disease) and another 5% during the remainder of life, often at senescence (reactivation disease). These rates increase for human immunodeficiency virus (HIV)-infected persons with tuberculosis infection.

Until recently, it was thought that most adult tuberculosis was the result of reactivation (317, 318). However, by using restriction fragment length polymorphism analysis, high rates of acute primary disease, often occurring among HIV-positive individuals, have been found among adults. One survey found that 54% of cases among adults from a group of hospitals in New York City were due to acute primary disease (119). In addition, cases of exogenous reinfection have been reported, wherein persons with a well-documented previous episode of tuberculosis later develop a second acute episode, often from an outbreak-associated strain. These reinfections have occurred among veterans (267), family members (236), the homeless (228), and persons with HIV infection (164, 307). In one study, persons with a history of previous tuberculosis infection had a worse clinical outcome than persons infected with the same outbreak strain who had no history of tuberculosis (228).

Influence of HIV Infection on Pathogenesis

HIV infection currently affects over one million persons in the United States and up to 10 million worldwide. It exerts a pronounced influence on the natural history of tuberculosis in several ways (32); in addition, infection with *M. tuberculosis* appears to affect the course of HIV disease, as follows (Table 1). (i) Among persons latently infected with tuberculosis who become HIV infected, active tuberculosis develops at a rate of 7 to 10% per year rather than 8% per lifetime (9, 34, 285, 286).

(ii) Persons with HIV (regardless of $CD4^+$ cell counts) who are newly infected with *M. tuberculosis* progress to active tuberculosis at a rate as high as 37% in the first 6 months rather than 2 to 5% in the first 2 years (83, 88). (iii) HIV confers anergy upon a large number of persons with HIV infection, thus confounding TST interpretation (138, 221, 252, 286). the prevalence of anergy increases as the CD4 cell count decreases (181, 285, 286). In many areas where tuberculosis is endemic, prophylactic INH therapy is recommended for anergic persons with HIV infection (221, 286). (iv) HIV-infected persons may malabsorb drugs (29, 246), perhaps because of HIV-related enteropathy, which may further complicate the treatment of tuberculosis. In addition, immunocompetent persons who have undergone gastrectomy may, in the course of treatment for drug-susceptible tuberculosis, progress to drug-resistant tuberculosis because of malabsorption of drugs (340).

Tuberculosis may influence the natural history of HIV infection by activating macrophages that harbor HIV (333, 338). The result of activation is expression of HIV, rather than prolonged latency without expression of HIV. In one study, progression to AIDS occurred sooner among TST-positive persons not treated with INH than those treated with INH, even when tuberculosis was excluded as AIDS indicator disease (240). This suggests that treatment of latent tuberculosis can help preserve the immune function of HIV-infected individuals.

These influences have conspired to create an epidemic of tuberculosis within the HIV epidemic that is particularly threatening to the public health in areas such as Africa, where large numbers of individuals are dually infected with *M. tuberculosis* and HIV (87).

EPIDEMIOLOGY

About one-third of the world's population, or 1.8 billion people, have been infected with *M. tuberculosis*. Active disease develops in 8 to 10 million people per year, and tuberculosis is responsible for 3 million deaths per year, making it the leading infectious cause of death in the world, far surpassing measles (2 million deaths per year) and malaria (1 million). In addition, the World Health Organization and Centers for Disease Control and Prevention (CDC) calculate that tuberculosis is responsible for about 27% of the preventable deaths worldwide (192).

Such dramatically high morbidity and mortality rates are in contrast to the experience in the United States, even at the height of the problem. Beginning in the 1920s, annual rates of tuberculosis in the United States declined. In 1953, when official annual reporting began, there were 84,304 reported cases of tuberculosis; by 1984, reported cases had dropped to 22,255, a decrease of about 5% per year (62). However, in 1984 the trend reversed, and by 1988 the annual rate of tuberculosis in the United States began to rise. In 1990, nearly 26,000 cases, or about 10/100,000 persons, were reported. More disturbingly, in certain populations, case rates exceeded 300/100,000 (41, 62, 257).

There are several reasons for the increase in the incidence of tuberculosis: the deterioration of public health care facilities, the rise in the number of homeless persons and persons living in congregate settings, the continued influx of immigrants from countries where tuberculosis is endemic, and the emergence of the AIDS epidemic, which has placed a new and large group of patients at risk for tuberculosis (41).

It is particularly instructive to consider the lesson learned by dismantling the public health infrastructure in the 1970s and 1980s. As annual rates of tuberculosis dwindled, so too did public concern about tuberculosis as a public health threat. There followed a systematic taking apart of public health care facilities, making it increasingly difficult for persons with tuberculous infection or disease to be treated in an efficient, professional manner (341). Many infected patients therefore simply did not seek further care until they were in need of hospitalization.

The amount of money saved in the 1970s and 1980s by relaxing antituberculosis efforts in the public health care system is now dwarfed by the enormous expenditures required to manage the resultant problems. Treating the increased number of cases, creating safe hospitals and clinics, and confronting the growing problem of resistant tuberculosis are problems that might have been averted had proper attention been paid to tuberculosis in previous years. Hopefully, if current efforts result in better control of tuberculosis and decreasing annual incidence, the response will not once again be to decrease public health dollar support of tuberculosis treatment programs (268). Even now, only a fraction of requested dollars are approved by the Federal government. In 1994, $484 million was requested, of which only $111 million to $124 million is expected to be approved. Notably, implementation of the same program in 1989 (when no funds were allotted) was estimated to cost $36 million (156).

In the United States, the highest recent increases in the annual number of cases of tuberculosis occurred among Asian, black, and Hispanic persons, paralleling the high rates of HIV infection in these specific groups, while rates for non-Hispanic whites, American Indians, and Alaskan Natives have continued to decrease. Among age groups, the most striking rise was among persons aged 25 to 44, also reflecting the epidemiology of HIV infection. Significant increases were also noted among children, probably owing to the rise in the 25- to 44-year-old age group, who are persons of childbearing age (58, 62, 271). The only decrease in the number of cases of tuberculosis was in persons over the age of 65, a vestige of the era of better tuberculosis control.

Epidemiology of Drug-Resistant Tuberculosis

In addition to the rise in the number of cases of tuberculosis in the United States, the number and proportion of cases of drug-resistant tuberculosis have increased. Although high rates of resistant tuberculosis in developing countries have long been described, this is a relatively recent phenomenon in the United States (92), although two hospitals in the United States, Harbor General in Los Angeles, Calif. (27), and Kings County Hospital in Brooklyn, N.Y. (324), have reported that 16 to 22% of primary tuberculosis cases have been drug resistant for the past 25 years.

Resistance to antituberculous medications may be either primary or secondary. Primary resistance occurs when patients are infected with an already resistant strain of tuberculosis. Secondary resistance occurs when resistant mutations of an initially drug-susceptible infection emerge in the setting of incomplete compliance with therapy or incorrect selection of treatment.

In the United States, primary drug resistance was 1 to 2% in the 1950s and rose to about 3% over the next decade (92, 348). By the 1970s, primary drug resistance had increased to 8.6% (194). Some populations and areas of the country were found to have a much higher incidence of resistant disease. For example, rates of resistant disease as high as 50% among Asian wives of servicemen returning from Southeast Asia (44), 27% among the homeless in Texas (222), and 15 to 20% in some groups of Asian and Hispanic Americans (194) were found. A

national survey from the early 1980s found 7% primary resistance (47), while a later survey found 9% primary resistance and 23% secondary resistance (311).

Recent reports from New York City have documented a rate of resistance to at least one drug to be 28 to 33%, with rates of multidrug-resistant (MDR) tuberculosis at 14 to 19% (93, 118, 290). In addition, in three of the four most populous boroughs (counties) of New York, the prevalence of MDR tuberculosis has risen dramatically: from 0–3% in 1987 to 14–16% in 1991 (290).

Outside the United States, drug resistance remains a significant problem. In surveys done in the last 15 to 20 years, resistance rates to at least one commonly used agent ranged from 20 to 30% in India, Pakistan, and Central Haiti, while 11% of cases in Taiwan were resistant to both INH and streptomycin (189, 282). In Spain, 13% of cases were resistant to at least one antituberculosis drug, as were 9% of cases in France (189). The highest reported rate of resistant tuberculosis is from the Republic of Djibouti, Horn of Africa, where 36% of cases were resistant to all first-line drugs and 78% were resistant to at least two first-line drugs in 1992 (276).

Patients with cavitary tuberculosis or HIV infection and those born in a country where tuberculosis is endemic have an increased risk for developing drug-resistant tuberculosis (5, 19, 118, 273). Historically, it had been thought that most resistance occurred as a result of intermittent compliance by a specific patient over months to years or of incorrect physician-prescribing practices (secondary resistance) (205).

However, recent work has suggested that primary resistance accounts for a large number of drug-resistant adult cases, particularly among HIV-infected persons (119, 123, 164, 293, 307, 314). This has contributed to an improved understanding of how the current drastic rise in the incidence of resistant tuberculosis has occurred. A likely scenario is that several patients with already resistant tuberculosis had the opportunity, either in hospitals or in other congregate settings, to expose HIV-positive persons to tuberculosis. The exposed HIV-positive persons in turn progressed to active tuberculosis at high rates, each infected with the strain (and susceptibility profile) of the index case. Thus, the resistance pattern of the index case was amplified by a series of secondary cases, all with acute primary resistant disease. The decreases in rates of MDR tuberculosis that have been reported (187, 294) may therefore have as much to do with interruption of ongoing spread of primary disease as with long-term compliance by a group of patients.

TRANSMISSION

Tuberculosis is transmitted in three ways: (i) inhalation of infectious droplet nuclei containing *M. tuberculosis* bacteria; (ii) ingestion of contaminated material, usually milk; and (iii) direct inoculation, usually occurring among health care workers. The respiratory route accounts for the overwhelming number of cases worldwide, especially in countries that routinely pasteurize milk, thereby removing *M. bovis*, which is part of the "*M. tuberculosis* complex" and causes human tuberculosis.

Much has been learned about the transmission of tuberculosis as a result of a series of well-studied outbreaks. We will review some of the more instructive of these.

Tuberculosis Outbreaks in Hospitals

Many outbreaks of tuberculosis have occurred in hospitals, affecting health care workers and patients (4, 6, 46, 84, 106, 124, 266, 287, 347). Some of these are described below and in Table 2.

TABLE 2. Hospital outbreaks of tuberculosis

Duration of exposure	No. of people exposed	No. (%) of skin test conversions	Conclusions	Reference
29 days	158	30 (19%)	Presence of MAI can confound diagnosis of tuberculosis in AIDS patients	249
4 h	129	23 (17.8%)	Rare patients are hyperinfectious	147
6 mo	56	9 (16%)	Undiagnosed tuberculosis is a risk for health care workers	182
2 wk	442	68 (15%)	Nonpulmonary tuberculosis can be infectious	167

In 1992, an AIDS patient admitted with fever and cough was diagnosed with both *Pneumocystis carinii* pneumonia and *Mycobacterium avium-intracellulare* (MAI) infection (249). Because two diagnoses had been already been secured, tuberculosis was not suspected. Sputum smears for AFB had been negative, and the *M. tuberculosis* in culture was initially overgrown by MAI. After tuberculosis was diagnosed, contact tracing revealed that 19 (20%) of 93 hospital workers, 11 (17%) of 65 hospice workers, and 5 (45%) of 11 visitors had converted to a positive TST. This episode underscores the fact that AIDS patients may have several concurrent diagnoses, as well as the particular problems encountered when a patient has concurrent MAI and tuberculosis.

An intubated patient with cavitary tuberculosis spent 4 h in an emergency room (147). His copious pulmonary secretions required frequent, vigorous suctioning via the endotracheal tube. Contact tracing revealed that 15 (12%) of 129 emergency room staff converted to a positive TST including 5 persons who developed tuberculosis.

An elderly patient with metastatic small cell carcinoma of the lung and a chronically abnormal chest radiograph was treated with chemotherapy and corticosteroids (182). Four years earlier, he had been found to have a positive TST but was not treated. During his admission to the hospital, his chest radiograph appeared worse and he developed a productive cough, necessitating vigorous pulmonary suctioning. He died 6 months after admission to the hospital. At autopsy, disseminated tuberculosis was found. Contact tracing revealed that 8 (14.5%) of 55 exposed employees had converted to a positive TST.

The particular risk of performing bronchoscopy and intubation was demonstrated by Malasky et al. (206), who compared the incidence of TST conversions among infectious disease fellows and pulmonary fellows. They found a higher conversion rate among the pulmonary fellows (11% compared with 2.4%).

Extrapulmonary tuberculosis may also be infectious (117, 167). A recent outbreak involved a patient with a draining tuberculous thigh abscess that was frequently irrigated, aerosolizing *M. tuberculosis* (167). Although it was well known by the health care workers caring for the patient that the abscess drainage was teeming with *M. tuberculosis*, no special precautions were taken, because the patient did not have pulmonary tuberculosis. However, 55 (12%) of 442 hospital employees converted to a positive TST, and nine cases of tuberculosis occurred. Proximity to the index patient's room correlated with an increased rate of tuberculin positivity.

Transmission of tuberculosis (but not simultaneous transmission of HIV) from a needle stick has been described, a rare instance of transmission of blood-borne *M. tuberculosis* (196). In this case, a nurse sustained a superficial laceration from a needle. The source patient had advanced HIV infection and tuberculosis. Five weeks later, the nurse noted abscess formation at the laceration site and developed fever and local adenopathy. Cultures of the lymph node biopsy specimen grew *M. tuberculosis*. The authors noted that cutaneous infection has resulted from ear piercing, tattooing, circumcision, injections, and mouth-to-mouth resuscitation (196). Among pathologists, the so-called "prosector's wart" of primary cutaneous tuberculosis occurs as a result of inadvertent inoculation during postmortem examination. Among laboratory workers, tuberculosis is the sixth most common occupationally acquired disease (72, 141, 298).

Since 1990, the CDC has investigated several institutional outbreaks of MDR tuberculosis in hospitals (25, 52, 79, 91, 104, 115, 180, 241, 253). Much of our current understanding of the natural history, clinical presentation, treatment, and outcome of MDR tuberculosis in persons with AIDS has been learned from this series of outbreaks, which have affected hundreds of persons. In addition to the HIV-infected patients, an outbreak has been described among renal transplant patients (179).

Common to each outbreak has been the failure to isolate patients early. This possibly occurred because HIV-infected persons with tuberculosis often have atypical clinical presentations. In addition, as noted above, HIV-infected persons progress to active tuberculosis at unusually high rates. Therefore, although many persons may have become infected during these outbreaks, those who were HIV infected were the most likely to progress to active disease. In the coming years, the hundreds of immunocompetent persons who were infected with MDR tuberculosis during these outbreaks will remain at risk for reactivation of their now latent infection. The impact of this series of outbreaks will therefore be felt for the next 40 to 50 years.

Tuberculosis Outbreaks in Congregate Housing and Prisons

Congregate housing (8, 55, 63, 83, 208, 228, 232, 260, 283, 320, 334), including housing for the homeless, and prisons (26, 33, 57, 59, 127, 242, 309, 319) have features particularly conducive to the spread of tuberculosis. In a study of 169 homeless men in New York City in 1990 (334), Torres et al. found that 63 (67%) of 94 were TST positive. HIV infection was shown to be a significant risk factor for progression to active disease: 27 (26%) of 105 HIV-positive men developed tuberculosis, as opposed to 3 (5%) of 64 HIV-negative men. Development of tuberculosis was correlated with the duration of time spent in the shelter but not with risk factor for HIV or stage of HIV disease.

In early 1991, a tuberculosis outbreak occurred in a residential facility for HIV-infected individuals (83). Of 30 persons, 11 (37%) developed active tuberculosis with a strain that shared a restriction fragment length polymorphism pattern in common with the index case. In addition, four other HIV-positive persons had documented TST conversions. This outbreak demonstrated the startlingly high rates of development of active disease that may occur among HIV-positive persons.

Persons in prisons have been known for many years to have high rates of *M. tuberculosis* infection and disease (319). A report on prisoners in New York State compared rates of tuberculosis in the 1970s and the 1980s (33) and found a rise from 15 cases per 100,000 in the 1970s to 105 cases per 100,000 in the 1980s. Inmates with a history of intravenous drug use were at highest risk. In this study, all tested prisoners with tuberculosis were HIV positive. Intravenous drug users with HIV infection were found to be at highest risk for developing tuberculosis. The rising number of tuberculosis cases in prison paralleled the increasing numbers of incarcerated persons with AIDS. This led the authors to deduce that HIV infection predisposed persons to the development of active tuberculosis.

A follow-up study demonstrated that long incarcerations and multiple incarcerations were risk factors for development of tuberculosis (26). In addition, because the risk of developing active tuberculosis was four times greater among inmates assigned to methadone detoxification programs, full evaluations including TST and chest radiography, with sputum examination when indicated, are now performed before assignment to the detoxification units. Inmates are also educated on the importance and ramifications of taking antituberculous therapy.

TABLE 3. Risk factors for the development of active tuberculosis among persons infected with *M. tuberculosis*[a]

Risk factor	Increased risk (fold) compared with persons with no known risk factor
AIDS	170
HIV positive	113
Other immunocompromising conditions[b]	4–16
Recentness of infection (≤2 yr)	15
Age of contact (≤5 and ≥60 yr)	2–5

[a] Modified from reference 56.
[b] Includes diabetes mellitus, renal failure, carcinoma of the head and neck, and iatrogenic immunosuppression.

Tuberculosis Outbreaks in Other Settings

While the spread of tuberculosis most commonly has been found in hospitals and residences, there have been reports of tuberculosis outbreaks in the community (49, 51, 54, 54a), schools (21, 85, 272, 278), the workplace (125, 215, 223), ships (150, 166), and choirs (21, 102, 335). The risk of transmission on airplanes appears low (24). In 1965, Edith Lincoln summarized the world literature pertaining to outbreaks, recounting features of 109 different epidemics (201).

CLINICAL PRESENTATION

Active tuberculosis may develop in two settings: first, persons with latent infection may, under certain conditions, reactivate and develop clinical disease. This classically has been described with immune senescence but also may occur as a result of immunosuppressive therapy, HIV infection, or other immunocompromising conditions. In many persons, no obvious cause of immunocompromise is apparent. Second, acute infection may progress immediately to active disease, especially among infants and HIV-infected persons. The calculated risk of developing active disease according to underlying condition is shown in Table 3.

Normal Host

The protean manifestations of tuberculosis have been well appreciated for centuries. Although the classic consumptive suffering from progressive pulmonary disease, fever, productive cough, and/or hemoptysis, with an abnormal chest radiograph, is familiar, also well known is the difficulty in diagnosing extrapulmonary and even pulmonary tuberculosis. Many physicians have experienced the humbling call from the microbi-

ology laboratory, weeks after a certain patient has been discharged, informing them of a culture growing *M. tuberculosis*. The dermatologic, hematologic, neurologic, gastrointestinal, urologic, and other manifestations of tuberculosis have filled many textbooks, and each presentation cannot be covered in this review. It should be sufficient to say that in the 1990s, as in the 1890s, any puzzling multisystem disease may turn out to be tuberculosis. This is well documented by the continued prevalence of tuberculosis as the final diagnosis in 5 to 10% of cases of fever of unknown origin reported over the last 40 years (191, 197, 248).

Influence of HIV Infection on Clinical Presentation

As difficult as tuberculosis can be to diagnose in immunocompetent persons (188) and in patients with cancer (183, 258), its manifestations among the HIV infected are even more subtle and less specific. Because of this, many cases are diagnosed late or not at all (195), resulting in persons remaining infectious longer and thereby potentially spreading tuberculosis to hospital staff and other patients. Numerous articles and reviews examining different aspects of the interrelationship between AIDS and tuberculosis have been published (13, 20, 48, 64, 65, 67, 116, 145, 155, 203, 219, 238, 254, 256, 291, 306, 328).

Overall, persons with higher $CD4^+$ cell counts often present in "classic" fashion whereas persons with low $CD4^+$ cell counts are more likely to present atypically (181): brain abscess (30), meningitis (28), bacteremia (280), skin lesions (316), breast abscess (151), and visceral abscess (204) have been described. Some "atypical" presentations are in fact typical presentations of primary disease and, as such, are well known to pediatricians (308).

The sputum smears of approximately 50% of HIV-infected patients with pulmonary tuberculosis are negative by acid-fast stain, a rate possibly higher than that encountered in HIV-negative patients (284). There is debate whether bronchoscopy increases the incidence of positive smear and culture (23, 214).

Extrapulmonary tuberculosis is seen commonly in patients with HIV-associated tuberculosis (292, 305). Such patients should be placed in respiratory isolation pending evaluation of sputum specimens, since many have concurrent pulmonary infection, even in the absence of respiratory symptoms. In addition, extrapulmonary tuberculosis may be infectious (167).

Patients with HIV infection and pulmonary tuberculosis may present with an atypical chest radiograph (114, 224, 255, 295). Lobar infiltrates with or without hilar adenopathy or diffuse infiltrates resembling the interstitial pattern seen in *P. carinii* pneumonia are seen. The chest radiograph is normal in up to 10 to 20% of patients with AIDS (295), whereas cavitary disease is much less common, possibly reflecting the overall immune dysfunction of patients with advanced HIV infection.

The symptoms of tuberculosis in this population are particularly nonspecific. Signs and symptoms such as fever, weight loss, and fatigue may be due to tuberculosis but also may be due to MAI infection, lymphoma, AIDS-wasting syndrome, cytomegalovirus infection, or other diseases (289). Because of this and because of the contagious nature of tuberculosis, the treating physicians may be uncertain about when to institute a trial of anti-tuberculosis therapy in a patient with AIDS who has nonspecific but significant constitutional symptoms. Such decisions should be guided by the prevalence of tuberculosis in a given community, any special risks for tuberculosis that a specific patient might have, and the results of various tests. The contribution of liver biopsy (262) and bone marrow biopsy (231) in such cases has been disappointing.

LABORATORY DIAGNOSIS

In the past, the mycobacteriology laboratory has had to rely on diagnostic methods that often do not rapidly give a definitive diagnosis of tuberculosis or rapidly determine the antimicrobial susceptibility pattern of the organism. Conventional methods include the acid-fast stain, culture, and biochemical tests for detecting and identifying *M. tuberculosis*. An agar proportion method has been the standard for drug susceptibility testing. However, the resurgence of tuberculosis and an increase in the recovery of single-drug-resistant and MDR strains of *M. tuberculosis* have coincided with the development of rapid laboratory methods. New tests include amplification methods and probes that aid in rapidly detecting and identifying *M. tuberculosis* and a radiometric method that rapidly detects organisms in culture and the resistance of an isolate to primary drugs. The new methods, when applied directly to clinical specimens or actively growing cultures, may dramatically reduce the time to diagnosis of infection (185).

Conventional Laboratory Methods for Diagnosing Tuberculosis

Acid-fast stain. Smears for AFB can be prepared directly from clinical material or from concentrated specimens and can give an early indication of mycobacterial infection. The more sensitive concentrated smear is prepared from specimens that have been digested with a mucolytic agent (e.g., *N*-acetyl-L-cysteine) to free AFB from proteinaceous material and have been decontaminated with sodium hydroxide to kill non-acid-fast organisms. The fluorochrome fluorescent stain (auramine-rhodamine) has replaced the basic fuchsin stain (Ziehl-Neelsen or Kinyoun) as the preferred acid-fast stain (315). The fluorochrome stain is as sensitive and specific as the basic fuchsin stains, and the slide can be rapidly scanned by low-power microscopy. Approximately 75% of state public health laboratories now use the fluorochrome stain (154).

The sensitivity and specificity of acid-fast stains are not optimal, however. Approximately 10^4 bacilli per ml of specimen are required for a positive result; therefore, smear-negative, culture-positive results often occur (134). Culture of specimens from nonpulmonary sites may be useful in increasing the sensitivity (190). Also, specificity is compromised since positive results indicate only that AFB are present. Mycobacterial species are not distinguished by microscopy, and more than one species of mycobacteria may be present.

Culture. Despite recent improvements, the sensitivity of culture is also not optimal. During specimen digestion, all mycobacteria may not be released from proteinaceous material by the mucolytic agent, thus decreasing the inoculum size; also, the decontaminating agent used to kill non-acid-fast organisms may kill some of the mycobacteria, thus further decreasing the inoculum size. For culture, most laboratories use a combination of liquid and solid media, either individually or in a single-component system, incubated at 37°C for 6 to 8 weeks in an atmosphere of 10% CO_2 and 90% air. Liquid media include Middlebrook 7H9 and BACTEC radiometric 12B broth (Becton-Dickinson Diagnostic Instrument Systems, Sparks, Md.), and solid media include Lowenstein-Jensen egg-based medium and Middlebrook 7H10, 7H11, and selective 7H11 agar (132).

The BACTEC radiometric broth system has been an important addition to culture methods. The system uses Middlebrook 7H12 broth with [^{14}C]palmitic acid, and growth of mycobacteria is detected by an instrument that measures radiolabeled CO_2 which is released when the organism metabolizes the palmitic acid. The system includes a decontaminating solution (PANTA), containing polymyxin B, amphotericin

B, nalidixic acid, trimethoprim, and azlocillin, and a growth factor, polyoxyethylene stearate (POES). In an early evaluation of smear-positive specimens, the BACTEC system detected *M. tuberculosis* in an average of 8.3 days compared with 19.4 days for conventional agar or egg-based media. The sensitivity of the BACTEC system was 96.4%, compared with 91.3% for conventional media (275).

The Septi-Chek AFB system (Becton-Dickinson Microbiology Systems, Cockeysville, Md.) is a biphasic single-bottle system that combines a paddle containing 7H11, modified egg-based, and chocolate solid media with a bottle containing 20 ml of 7H9 broth and an internal CO_2 source. Solutions with antimicrobial agents and growth factors are also provided. In two studies, Septi-Chek was as sensitive as BACTEC for the recovery of *M. tuberculosis* (95.7 and 95.9% for Septi-Chek compared with 93.3 and 95.0% for BACTEC) but the organisms were detected later by Septi-Chek (21.8 and 19.1 days with Septi-Chek versus 18.5 and 13.4 days with BACTEC) (1, 176).

Blood culture systems used primarily for detection of MAI bacteremia also recover *M. tuberculosis*. The Isolator lytic system (Wampole Laboratories, Cranbury, N.J.) can be used to quantitate mycobacteremia. Lysed blood from the Isolator collection tube is inoculated onto agar plates (e.g., 7H11); the colonies that develop can be counted; and the number of CFU per milliliter of blood can be calculated. Quantitative changes can be used to monitor the effect of antimycobacterial therapy. Radiometric 13A broth blood culture bottles can be used as part of the BACTEC TB system. The Isolator and BACTEC systems were shown to be approximately equal in sensitivity and time to detection of mycobacteremia (186, 343).

Identification. Until recently, identification of *M. tuberculosis* from positive cultures depended on biochemical tests for the production of niacin, catalase, and nitrate reductase after test media were incubated for 2 to 3 weeks. More-rapid identification was made available with the BACTEC NAP test. The NAP compound, *p*-nitro-α-acetylamino-β-hydroxypropiophenone, selectively inhibits the *M. tuberculosis* complex group of mycobacteria. The test is performed on actively growing organisms, including those from a positive BACTEC bottle, and is completed in 5 days. The test results correlate well with other identification methods (299).

Cultures of mycobacteria can also be identified with DNA probes on the basis of the principle that complementary nucleic acid strands bind to form stable double-stranded (hybrid) complexes. Methods in which whole chromosomal DNA probes or DNA probes that detect a complementary sequence on the 16S rRNA are used are highly specific. The AccuProbe system (GenProbe, San Diego, Calif.) uses a DNA probe labeled with an acridinium ester directed at the rRNA of the mycobacterium. After the mixture of probe and organism is briefly incubated, unhybridized probe is chemically degraded, and the esterified acridinium on the hybridized probe is hydrolyzed by the addition of an alkaline hydrogen peroxide solution, resulting in the production of visible light, which is measured with a luminometer. The AccuProbe *M. tuberculosis* probe was shown to be 100% specific for the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, and *M. africanum*), but the probes have a detection limit of approximately 10^6 CFU/ml and hence require actively growing cultures for use (137).

Cultures of *M. tuberculosis* containing at least 10^7 mycobacteria can be identified by reverse-phase high-performance liquid chromatography (HPLC). Most species of mycobacteria have unique patterns of mycolic acid esters. A sample of the organism is prepared, saponified overnight, and analyzed by an instrument with a detector linked to a computer that stores data from control organisms (43). The equipment is rather expensive, but sample preparation is inexpensive. HPLC is used primarily by reference laboratories.

Laboratories can now use a combination of new culture and identification procedures to shorten the time required for diagnosing tuberculosis. For example, culture-positive broth from the BACTEC bottle has been concentrated by centrifugation and the pellet has been used as a source of organisms for identification by the Gen-Probe TB DNA probe. Organisms were usually detected and identified within 2 weeks of culture inoculation (109, 110). Approximately 75% of state public health laboratories now use a combination of nucleic acid probes, HPLC, and the NAP test for rapid identification of *M. tuberculosis* in culture (154).

PCR

Definitive laboratory diagnosis of tuberculosis relies on the production of a sufficient number of mycobacteria or amount of product that can be identified. Accumulation of the slowly growing organism by culture takes several days or weeks. Methods that shorten the accumulation time to hours by rapidly amplifying nucleic acids of the organism with the use of primers are being developed (279). Primers used in the amplification process can be either species specific or genus specific. Once amplified, the characteristic nucleic acids of mycobacteria can be rapidly identified. Assays in which PCR (297) is used for amplification with species-specific primers for *M. tuberculosis* are the most thoroughly studied of the new techniques.

Species-specific primers. PCR is part of the diagnostic process in which mycobacterial DNA in a clinical sample is extracted, amplified, and identified. The double-stranded target DNA of the organism is first denatured by heating. The optimal temperature of denaturation is determined empirically and depends on several factors, including the guanine-cytosine content of the DNA fragment. Next, a pair of oligonucleotide primers is annealed to the complementary (usually 5′) ends of each of the target single strands. These primers determine the specificity of the reaction. Several sets of primers have been constructed to detect *M. tuberculosis*. For example, primers have been designed to detect single-copy genetic elements encoding proteins such as the conserved mycobacterial 65-kDa heat shock protein (36, 239) or repetitive insertion sequences, such as IS*6110* (IS*986*) (107, 153, 332), which are specific to and repeated 1 to 20 times in the chromosome of members of the *M. tuberculosis* complex. The enzyme polymerase then catalyzes the extension of the new DNA strand with the target single strand as a template. This cycle is repeated 20 to 40 times. Thus, a single copy of the DNA fragment is amplified to approximately 10^6 copies in about 30 cycles in 2 to 3 h. The amplified product is then detected and identified. In one detection method, the DNA is resolved by agarose gel electrophoresis and stained with an ethidium bromide stain, and the product is visualized by UV transillumination (149). Since the molecular weight of the amplified product is known, electrophoresis adds to the specificity of the reaction. In another detection method, amplified DNA is bound to a nylon or nitrocellulose membrane matrix (dot or slot blot) and the product is hybridized with a probe that is complementary to an internal region of the amplified product (149).

The sensitivity of the PCR assay for *M. tuberculosis* varies from approximately 50 to 100%, and the specificity is uniformly high at 95 to 100%. A recent seven-laboratory blinded study (234) confirms earlier observations (35, 80, 107, 239, 297, 342) that there is considerable laboratory-to-laboratory variability in the sensitivity and specificity of the PCR assay for detecting *M. tuberculosis* in clinical specimens. PCR sensitivity is depen-

dent on the DNA extraction procedure, cycling parameters, and methods used to detect and identify the amplified DNA product. Because of their waxy coat, *M. tuberculosis* bacilli are quite resistant to simple disruption procedures. The detection limit of purified DNA by PCR has been reported to be as low as 1 fg (equivalent to one-fifth of an organism), but in clinical specimens such as sputum, the detection limit has varied from 100 to 1,000 organisms (149, 153). Sensitivity can be enhanced by extraction procedures that involve protease digestion, phenol-chloroform extraction, and ethanol precipitation of the extracted DNA; however, these laborious procedures may not be conducive to use in the busy clinical laboratory. A simpler preparation method, in which samples are heated in lysis buffer containing nonionic detergents, is less sensitive (297).

Sensitivity is also affected by the method used to detect and identify the amplified DNA product. Most research laboratories now use a hybridization procedure with probe identification. The sensitivity of the reaction is dependent on the type of reporter signal complexed to the probe. A probe labeled with ^{32}P produces the most sensitive reaction; however, because of disposal problems, routine use of radioisotopes in the clinical laboratory is being discouraged. Recent reports suggest that enzyme-conjugated probes, including those labeled with alkaline phosphatase, digoxigenin, or biotin and detected by colorimetric (297, 342) or chemiluminescent (233) methods, are at least as sensitive as the ethidium bromide stain method.

The sensitivity of the PCR assay can also be improved by subjecting the amplified DNA product to a second PCR assay with a second set of primers designed to amplify an internal segment (nested PCR) (250). This method is more laborious and may be unsuitable for routine use in the clinical laboratory. Recently, a simpler one-tube nested PCR test was described (342).

Genus-specific primers. A clinical specimen may contain *M. tuberculosis* and/or other mycobacteria. Therefore, there are advantages to using genus-specific primers in the amplification step of PCR. The amplified product could then be identified with species-specific probes. Recently, laboratories have used combinations of *Mycobacterium*-specific primers for amplification, and the amplified product has been hybridized with specific probes (329) or analyzed by RFLP (259, 330). In one study, restriction fragment profiles of known organisms were normalized to a fixed distance and the similarity of patterns were calculated by using a computer-aided comparison program. Patterns of unknown organisms could be compared with this database for identification (259).

Fingerprinting. Products of the PCR assay have a variety of uses. The repetitive DNA elements present in *M. tuberculosis* have been used as strain-specific markers, and the information has been used in epidemiologic studies of tuberculosis (146). Strains can be identified, or fingerprinted, by growing the organisms, extracting the DNA, digesting the DNA with restriction enzymes, and blotting and probing for the repetitive element. Data from fingerprints can be compared by computer-aided analysis. Rapid strain identification will be very valuable in providing insight into global transmission of tuberculosis, studying outbreak investigations of MDR strains, and answering questions of reactivation versus reinfection disease. Recommendations for a standard fingerprinting method have recently been made (336).

PCR in the clinical laboratory. At present there are no commercial kits that have been evaluated and licensed by the Food and Drug Administration available for PCR detection of *M. tuberculosis* in clinical laboratories. In addition to improvements needed in the sensitivity and specificity of the system, other practical considerations include the following. (i) What combination of genus and species primers and probes will be used, and in what order? (ii) What conventional stain and culture methods can be replaced? (iii) How will the antimicrobial susceptibility pattern of the organism be determined? (iv) How will mixed mycobacterial infections be detected? (v) Can these new procedures be used in developing countries, where tuberculosis is a major problem and conventional biochemical and radiometric methods are not easily implemented? (vi) Are there other amplification methods that are more practical for the diagnostic laboratory? (vii) What is the level of service laboratory that will use these new procedures?

Antimicrobial Susceptibility Tests

Most laboratories use either the agar-based proportion method or the broth-based radiometric method for antimicrobial susceptibility testing of *M. tuberculosis* obtained either directly from acid-fast positive specimens or indirectly from positive cultures. Results of the indirect test are available in 2 to 3 weeks for the agar method and in 5 days for the broth method. Surprisingly, 80% of state public health laboratories still use the slower agar method (154).

Proportion method. With the proportion method (229), various concentrations of antimicrobial solutions or antimicrobial disks are incorporated into quadrants of 7H10 agar plates. Standardized dilutions of the organisms are inoculated onto the agar medium. The plates are incubated at 37°C and examined for colonies after 2 and 3 weeks. Growth on drug-containing media that represents more than 1% of the colonies that develop on drug-free media defines resistance. Both first- and second-line drugs have been tested by this method.

Radiometric method. In the radiometric method (168), various concentrations of the organism and antimicrobial agents are inoculated into BACTEC 12B broth bottles. Each day for 5 days, growth, as indicated by an increasing growth index reading in the drug-containing bottles, is compared with growth, indicated in the same way, in a control bottle. Continued growth in a bottle containing drug indicates resistance, while a declining or leveling rate of growth indicates susceptibility. Commercially available reagents are available for using the BACTEC method to test strains of *M. tuberculosis* for susceptibility to INH, streptomycin, rifampin, ethambutol, and pyrazinamide (PZA).

New methods. New and innovative methods for rapid drug testing are being developed. In one method, mycobacteria were infected with specific reporter phages expressing the firefly luciferase gene (177). Light production was dependent on phage infection, expression of the luciferase gene, and the level of cellular ATP. Signals could be detected within minutes after infection of virulent *M. tuberculosis* isolates with reporter phages. When organisms were exposed to drugs to which they were susceptible, the light was extinguished. Light was produced from a strain resistant to that drug.

Recommendations

Patients suspected of having active tuberculosis should have early laboratory documentation by rapid performance of acid-fast stained smears, culture and identification, and drug susceptibility testing. Federal and state health agencies, including the CDC (331) and New York State (228), have made the following recommendations, among others, regarding the diagnostic laboratory. (i) Good communication should be encouraged between the clinician and the laboratory regarding proper specimen selection and rapid transport of the specimen to the laboratory within 24 h. (ii) Fluorescence microscopy should be used for reading smears for AFB. (iii) Concentrated

specimens should be inoculated immediately to liquid and solid media, and media should be inspected weekly or more often as specified by the manufacturer. (iv) As soon as mycobacterial growth is detected, identification should be conducted by using probes, NAP methodology, and/or mycolic acid analysis. (v) All initial isolates of *M. tuberculosis* should be tested for susceptibility to INH, rifampin, streptomycin, ethambutol, and PZA in a BACTEC or similar system. Susceptibility tests for second-line agents are usually conducted at reference laboratories. The drugs tested may include amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, PAS, and rifabutin. (vi) The decision to perform drug susceptibility studies on later isolates should be based on the patient's response to therapy. Susceptibility testing should be repeated if the patient remains culture positive at 3 months. (vii) All results of AFB-positive smears, positive cultures, and results of susceptibility studies should be reported within 24 h, preferably immediately, to the clinician. The appropriate public health agency should also be notified of results mandated to be reported to that agency. (viii) The laboratory should maintain up-to-date records and review laboratory procedures and facilities to guarantee the safety of personnel.

TREATMENT OF TUBERCULOSIS

When streptomycin first was introduced, miraculous "cures" of severely ill persons were described. Almost immediately thereafter, however, a new and unexpected problem emerged—many patients suffered relapses of tuberculosis, this time with streptomycin-resistant strains (210, 265, 346). Studies demonstrated that *M. tuberculosis* developed resistance to streptomycin within 3 months of therapy (265, 346).

Fortunately, the efficacy of combination therapy was soon demonstrated. When a second drug, PAS, which had been recently introduced, was added, the emergence of resistant strains was delayed and in most cases prevented (211). With the introduction of INH a few years later, initial treatment with INH and streptomycin proved even more effective at preventing the emergence of drug-resistant disease. Some physicians used all three available medicines—INH, PAS, and streptomycin—to gain further leverage against the potential emergence of resistant disease (212). Since that time, standard practice has been to treat with an initial three- or four-drug regimen, with modifications made on the basis of susceptibility results.

Medications

First-line therapy. Five medications are "first-line therapy": INH, rifampin, PZA, ethambutol, and streptomycin (126, 130) because of their activity and favorable toxicity profile. Dose schedules depend on the site of disease, but, in general, only meningitis, osteomyelitis, and miliary tuberculosis need protracted courses of therapy (18, 213). Treatment of disease at other extrapulmonary sites, such as lymph nodes (39) and pleura (97), follows the recommendations for pulmonary tuberculosis, which is routinely treated for 6 months (98).

INH has been the mainstay of therapy since its introduction in 1953. The usual dose is 300 mg daily. The most common side effect is liver toxicity, which correlates with increasing age and dose and is generally reversible with cessation of the drug. Rare fatal cases of fulminant hepatitis have been described, particularly among postpartum women (148). Most fatal cases occurred when persons continued to take the drug despite developing symptoms of liver disease. Rapid acetylators metabolize INH more quickly and so rapidly accumulate a hepatotoxic metabolite, increasing the frequency of adverse reactions (216). The frequency of another common side effect, peripheral neuropathy, is reduced with coadministration of vitamin B_6 (pyridoxine) at 50 mg daily. Arthralgia may develop, particularly among the elderly, and other patients may develop a lupus-like syndrome, including a positive antinuclear antibody test.

Rifampin, discovered in 1966, is an equally potent agent for tuberculosis. The usual dose is 600 mg daily. Like INH, rifampin is hepatotoxic. More importantly, it induces hepatic microsomal enzymes, thereby affecting the metabolism of many medications. Methadone, birth control pills, coumadin, dapsone, and many antiseizure medications are only some of the medicines that may require dose adjustment (generally an increase) and heightened vigilance during rifampin therapy. Most patients develop an orange discoloration of the urine, which some clinicians use as a means of gauging patient compliance and absorption. INH and rifampin appear to have additive, rather than synergistic, hepatotoxicity (323).

PZA has been increasingly used in recent years. The usual dose is 25 mg/kg once daily. Only recently has standardized in vitro susceptibility testing been developed. Because of its excellent activity, regimens containing PZA may be given for as briefly as 6 months. It is hepatotoxic and causes hyperuricemia. Unless gout or renal failure from hyperuricemia develops, most clinicians continue to administer PZA, despite a high (up to 12- to 15-mg/dl) uric acid level. The uric acid level, if elevated, may provide indirect evidence that a given patient is compliant with medicines.

Ethambutol is bacteriostatic at doses of 15 mg/kg/day (the usual dose) and may be bactericidal at 25 mg/kg/day (81). At the lower dose, the feared toxicity of optic neuritis is rarely encountered. Regular screening of color vision may disclose early visual disturbances. Renal failure increases the risk of optic neuritis.

Streptomycin was the first drug introduced for the treatment of *M. tuberculosis*. Currently, its use is limited by the need to deliver the medicine intramuscularly, although some hospitals use intravenous administration (245). Like other aminoglycosides, streptomycin causes ototoxicity and renal dysfunction. Other active aminoglycosides include amikacin and kanamycin (209). When available, streptomycin is the preferred aminoglycoside.

Second-line therapy. The second-line agents are seldom used except in areas with high rates of drug resistance (173) or, as with thiacetazone, because of the low cost of the drug. Shortages of some second-line agents have been described (244).

The fluoroquinolones, such as ciprofloxacin (184), ofloxacin (193), and its L-isomer, levofloxacin, are active in vitro and are being actively investigated (135, 344) for their uses against mycobacteria. The usual dose of ofloxacin is 400 to 800 mg/day. Ciprofloxacin is usually used in doses of 500 to 750 mg twice daily. Fever, rash, agitation, and gastrointestinal disturbance are the most common side effects.

Cycloserine commonly causes central nervous system side effects ranging from somnolence to irritability and seizure. Addition of quinolones may increase the rate of serious central nervous system side effects (345). The usual dose is 500 to 750 mg/day. Pyridoxine (vitamin B_6) administration may decrease some central nervous system side effects.

Capreomycin is an injectable polypeptide that causes otic and renal toxicity. It is given at 1 g daily intramuscularly, although there is growing experience with intravenous dosing that suggests that this route is also safe.

TABLE 4. Rate of sterilization of culture according to treatment regimen[a]

Regimen[b]	No. of patients	% Culture negative by mo:			
		1	2	3	5
SHRZ (6 mo)	146	38	77	97	100
EHRZ (6 mo)	141	35	77	99	100
EHR (9 mo)	157	29	64	88	100

[a] Reprinted from reference 143 with permission of the publisher.
[b] S, streptomycin; H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol.

Ethionamide causes gastrointestinal upset. The usual dose is 500 to 750 mg/day, beginning at 250 mg and increasing slowly, according to patient tolerance.

PAS can cause hepatitis, fluid retention due to an obligate sodium load, and profound gastrointestinal upset. The usual dose is 8 to 12 g/day.

Thiacetazone is not available in the United States because of relatively poor efficacy and the high rate of severe skin reactions, but it is used in many countries in Africa. The dose of thiacetazone is 150 mg/day. Initial 2-month therapy with INH, streptomycin, and thiacetazone followed by an additional 10 months with INH and thiacetazone costs less than $50 in many countries and is effective. Persons with HIV infection have a particularly high rate of severe, adverse reactions to thiacetazone (247).

Rifabutin is a rifamycin similar to rifampin. Most experts do not use rifabutin if a mycobacterial strain is resistant to rifampin, even if in vitro tests show that rifabutin may be active. However, levels of rifabutin in serum are 7 to 10 times lower than those achieved with rifampin, and this may be insufficient (243). The usual treatment dose is 600 mg daily, which has been associated with development of uveitis in some patients and is not recommended.

Clofazimine, an active anti-leprosy drug, has been given rarely to patients with tuberculosis. The usual dose is 100 to 200 mg/day. It may cause gastrointestinal disturbance as well as a bronze discoloration to the skin.

The macrolides, including azithromycin and clarithromycin, which show excellent activity against many nontuberculous mycobacteria, are not active against *M. tuberculosis* (135). Amoxicillin-clavulanic acid was suggested in an early report to be active (225), although some experts do not recommend its use (173).

Therapeutic Regimens

The current regimen for the treatment of pulmonary tuberculosis evolved over many years and is based on dozens of clinical trials involving thousands of patients worldwide (142). Trials conducted in Africa (7, 100, 101), Hong Kong (159–162), Singapore (300–303), other Asian countries (16, 86, 200, 207), the United States (2, 70, 73, 304, 312, 313), Europe (37, 38, 45, 349), and South America (112) have all contributed to current recommendations (11, 12). Mitchison and Nunn reviewed features of 12 trials headed by the British Medical Research Council and involving over 8,000 patients (218). Not all trials demonstrate identical results, and not all results are readily explained. However, the strength of the current recommendation of a 6-month regimen for pulmonary tuberculosis with a susceptible organism is well appreciated after a review of the numerous trials (143) and subsequent commentaries (121, 122, 175) (Table 4). The current standard is 2 months of INH, rifampin, PZA, and ethambutol followed by 4 months of INH and rifampin ("4 for 2 and 2 for 4") (11, 12). Doses are calculated according to body weight (see the ranges above).

Space does not permit an exhaustive discussion of each, although the references include many trials. We will review four key studies that have led to the current recommendation.

The effectiveness of PZA in allowing a 6-month course of combined therapy was established by the Hong Kong Chest Service and the British Medical Research Council (159). They reported a 5-year follow-up of 792 patients with drug-susceptible tuberculosis treated with one of five different supervised 6-month regimens: (i) thrice-weekly INH-RIF-SM-ETA (RIF is rifampin, SM is streptomycin, and ETA is ethambutol), (ii) thrice-weekly INH-RIF-PZA-SM, (iii) thrice-weekly INH-RIF-PZA-ETA, (iv) daily INH-RIF-PZA-ETA, or (v) thrice-weekly INH-RIF-ETA-SM. Patients receiving PZA-containing regimens had a significantly lower initial relapse rates at 2 years (9 [1.4%] of 626 versus 13 [7.8%] of 166). This advantage extended out to 5 years of follow-up: relapse occurred in 3.4% of patients receiving PZA, in contrast to 10.4% receiving the non-PZA regimens. In addition, patients in the PZA group had better cure rates when the organism was resistant to INH, streptomycin, or both.

The Singapore Tuberculosis Service along with the British Medical Research Council established that streptomycin was no longer essential in initial therapy. In a 1988 report (302), three directly supervised 6-month regimens were evaluated. Patients received either (i) daily INH-RIF-PZA-SM for 2 months and then thrice-weekly INH-RIF for 4 months, (ii) daily INH-RIF-PZA-SM for 1 month and then thrice-weekly INH-RIF for 5 months, or (iii) daily INH-RIF-PZA for 2 months and then thrice-weekly INH-RIF for 4 months. Relapse rates after 5 years were similar for all regimens: only 7 (2.4%) of 297 patients with drug-susceptible strains relapsed. This study demonstrated that streptomycin in the initial phase of disease did not confer benefit when the strain was susceptible to all first-line agents. Also, a thrice-weekly dosage schedule for the continuation phase was effective in this study. Advantages to thrice-weekly dosing are less expense and better ability to supervise all doses to ensure compliance.

In 1990, the U.S. Public Health Service evaluated short-course chemotherapy (6 versus 9 months) for pulmonary tuberculosis (73). After 96 weeks, relapse rates were the same: 3.5% in the 6-month group versus 2.8% in the 9-month group. Compliance was worse in the 9-month group, and on the basis of this study, a 6-month course of INH-RIF-PZA for 2 months followed by INH-RIF for an additional 4 months was recommended for uncomplicated susceptible pulmonary tuberculosis.

In an effort to further ensure compliance and decrease the cost of therapy, the U.S. Public Health Service next devised a 62-dose, twice-weekly 6-month regimen, tested on consecutive new cases of both pulmonary and extrapulmonary tuberculosis (70). Of 125 patients, only 2 relapsed, 6 and 56 months after completing therapy. Thirteen patients were lost to follow-up, and 4 persons died of unrelated causes. During treatment, 17% of patients had twofold or greater elevations of aspartate aminotransferase levels and 27% of patients had ≥1.5-fold elevations of alkaline phosphatase levels in blood. Over half of the patients were alcoholics. Excluded patients included the elderly, persons with HIV infection, those with a history of resistant tuberculosis, or those with significant underlying liver or kidney disease. This trial demonstrated that a short-course, fully supervised, intermittent-dose regimen was effective, cheap, and likely to be complied with.

The duration of therapy for patients with HIV and susceptible tuberculosis is unclear. Some reports suggest that stan-

dard 6-month courses of therapy are adequate (158), while others report failures of standard 6-month regimens (99, 152, 247, 327) or have suggested longer therapy (171). Recent reports describing exogenous reinfection raise the possibility that some patients who had been considered as having relapsed were in fact exogenously reinfected (82). The crucial issue of duration of therapy is currently undergoing a large clinical trial under the auspices of the National Institutes of Allergy and Infectious Disease, Division of AIDS.

Patients with Negative-Stained Sputum Smears

In many series, the rate of AFB smear-negative tuberculosis approaches 50%. In addition, many patients with a syndrome suggestive of tuberculosis may have negative cultures, referred to as culture-negative tuberculosis.

In 1989, the Hong Kong Chest Service addressed the problem of patients with negative sputum smears (either culture negative or culture positive) who have clinical tuberculosis (162). Smear-negative patients are presumed to have a small organism load, and therefore shorter courses of therapy were studied: patients were treated with one of three regimens: daily INH-RIF-SM-PZA for 3 months or thrice-weekly INH-RIF-SM-PZA for 3 or 4 months. Data at 5 years revealed a combined relapse rate for the 3-month regimens at 7% (unacceptably high). In the 4-month group, an acceptable relapse rate of 4% was observed. Therefore, the Hong Kong Chest Service advocates treating all sputum smear-negative patients (regardless of culture results) with 4 months of thrice-weekly INH-RIF-SM-PZA.

In 1989, the Arkansas Department of Health published their experience with 4-month treatment regimens in 452 patients with smear- and culture-negative tuberculosis (96). They administered shortened antituberculous regimens when sputum cultures were negative but tuberculosis was the likeliest diagnosis clinically. Treatment was started before culture results were final in anticipation of a 9-month course; however, when three cultures were negative, therapy was discontinued at 4 months. Patients received Rifamate (combination capsule of 300 mg of INH and 600 mg of rifampin) for 1 month and were then changed to twice-weekly therapy (900 mg of INH with 600 mg of rifampin). Twenty-eight percent (126 of 452) showed clinical or radiographic response to treatment. Follow-up of 414 patients who completed 4 months of therapy revealed only 5 relapses (1.2%), 3 among responders and 2 among nonresponders. All patients who relapsed had drug-susceptible organisms.

Directly Observed Therapy

Treatment noncompliance, the major cause of secondary resistance of tuberculosis, is common, with at least 20% of patients who start antituberculous regimens failing to complete the course within 12 months (3, 14, 136, 326). Many tricks to improve compliance have been tried (68). One method to ensure patient compliance is with directly observed therapy (DOT), wherein an observer dispenses medicine and then watches a specific patient take the pills. This method is easiest when patients keep scheduled clinic visits. However, field workers may be asked to keep track of the whereabouts of 15 to 20 patients who cannot or will not come to the clinic. The whereabouts of these patients may be difficult to ascertain, and patients are occasionally found in drug "shooting galleries" or other dangerous places. Delivery of medication to tuberculous patients under these circumstances requires a dedicated and organized staff, as well as generous financial backing. Inducements such as money, food, or subway tokens may increase the likelihood of patient compliance (174).

Weis et al. (339) showed that DOT was more effective than traditional unsupervised therapy. Of 407 patients on traditional therapy, 85 (21%) relapsed on therapy (25 [6%] had MDR organisms), while only 32 (5.5%) of 581 on DOT relapsed. No patients with relapses who were treated on the DOT regimen had drug-resistant organisms on repeat cultures (339).

In a DOT program in Denver, Colo., fewer than 10% of patients were lost to follow-up (174). In a cost analysis, Iseman et al. determined that there is not a significant cost difference between running a DOT program and having patients take self-administered regimens (174). However, when one takes into account the decreased costs from better infection control and less disease spread when compliance is improved, the cost benefit of DOT is apparent. The savings from eliminating development of new drug resistance more than compensates for the operating costs needed to oversee such a program. In 1988, the estimated cost of an intermittently administered DOT program for tuberculosis was about $400 per patient (174). This included the cost of a salary and benefits for a registered nurse, the medications, and laboratory costs. This regimen was found to be less expensive than a daily, self-administered regimen as well.

The exponential cost of treatment failure is well exemplified by the following. In 1990, a man was hospitalized several times for the treatment of tuberculosis (51). He took medications while in the hospital but never after discharge. He developed MDR tuberculosis and subsequently infected nine family members, who also developed resistant tuberculosis. The cost of the care of these 10 patients was $950,433.

Resistant Tuberculosis: Overview

Patient noncompliance, acute infection with already resistant strains, and 40 years of ineffective administration of effective medicines have conspired to create a growing number of persons with resistant tuberculosis. Therapy of resistant tuberculosis is slower, more toxic, and more expensive than therapy of susceptible disease, with lower cure rates and an increased likelihood that the patient will remain infectious for an extended period (90, 165, 173, 199, 311). Research to identify genes coding for different antibiotic resistances appears promising and may lead to diagnostic and therapeutic innovations (325, 350).

Current CDC recommendations are for persons with suspected tuberculosis to receive at least four drugs initially, including three drugs to which the patient's organism is likely to be susceptible. The best "empirical therapy" for patients with possible resistant disease cannot be generalized, since resistance patterns vary from hospital to hospital and city to city. Also, the added toxicity of a broadened five-, six-, or seven-drug initial therapy must be considered.

In general, there are two key drugs in the treatment of tuberculosis: INH and rifampin. Susceptibility to both allows 6- to 9-month regimens (218); susceptibility to rifampin but not INH allows 9- to 12-month regimens; and susceptibility to INH but not rifampin allows 12- to 18-month effective regimens (218). However, when an isolate is resistant to both INH and rifampin, the outcome is uncertain. Maintenance of susceptibility to at least one of these two agents is therefore central to the control and cure of tuberculosis.

Resistant tuberculosis in HIV-negative patients. A recent report from National Jewish Hospital in Denver provided a sobering reminder of how difficult it can be to cure MDR

tuberculosis, even in the best of circumstances (129). In this study, the outcome of 171 persons with MDR tuberculosis from 1973 to 1983 was reported. The patients had previously received a median of six drugs, were resistant to a median of six drugs, and had received therapy for a median of 6 years.

Analysis revealed that only one-half of the patients were cured medically; an additional one-fourth were surgically cured; while one-fourth were treatment failures. Surgery has been shown to be a viable alternative in some patients (129, 170, 261).

Resistant tuberculosis in HIV-positive patients. Because of the particular susceptibility of HIV-infected persons for development of active tuberculosis, acute resistant primary tuberculosis (primary resistance) is increasingly common among persons with HIV infection. Initial reports of patients with MDR tuberculosis and AIDS described extremely high mortality rates, with most patients dying within 1 to 3 months (114). A report of 62 patients with MDR tuberculosis and 55 patients with susceptible or single-drug-resistant tuberculosis found that patients with MDR tuberculosis were more likely to have pulmonary and extrapulmonary active disease simultaneously (114). Patients with MDR tuberculosis were eight times more likely to have AIDS and less likely to have presented with a productive cough or lymphadenopathy. Differences on chest radiographs were subtle and could not be used to predict whether a given patient was likely to have MDR tuberculosis. Only 7% of patients with MDR tuberculosis achieved a durable sputum culture conversion to negative. Of 25 patients who received at least 2 months of effective antituberculous therapy, only 2 had three consecutive negative cultures (114). Additionally, the mean time to the first of three negative cultures was 9 months. The other 23 patients had intermittently or persistently positive sputum cultures.

Survival data in this study found a much worse prognosis for patients with MDR tuberculosis and AIDS: 1.5-month survival for patients with MDR tuberculosis and AIDS; 14.8-month survival for patients with MDR tuberculosis who were HIV negative; 14.3-month survival for patients with susceptible or single-drug-resistant tuberculosis and HIV infection; and 17.9-month survival for patients with susceptible or single-drug-resistant tuberculosis without HIV infection. This report suggests that the severe immune defect of AIDS patients may be central to the drastically high mortality rates. Others have reported similarly dismal results (42, 53, 118).

Against these data are results from two hospitals in New York City (103, 202). Because outbreaks of MDR tuberculosis had occurred at these hospitals, broadened initial empirical regimens were given to patients with suspected resistant disease. In one study, patients with MDR tuberculosis who had received at least two drugs to which their isolate was ultimately found to be susceptible had better survival rates than those who received less than two active drugs (13 of 21 [62%] versus 4 of 12 [33%]) (103). An update of these data extended the observation and described a clear survival advantage to those who had received at least three agents to which their isolate was ultimately found to be susceptible.

At another outbreak hospital, the ultimate outcome of patients treated with a five- to six-drug regimen was described (202). Of 12 patients studied, 7 were alive a median of 5 months after diagnosis. Median survival for the remaining five patients was 6 to 7 months. The median $CD4^+$ cell count in this group was 50 (range, 0 to 160), indicating that patients were severely immunocompromised.

These two reports suggest that a severe immune defect may not necessarily be responsible for high mortality rates of MDR tuberculosis; rather, the studies demonstrate that untreated MDR tuberculosis is a rapidly fatal disease in patients with AIDS. In the early studies, resistant tuberculosis was not anticipated; therefore, almost no patients who were subsequently found to have MDR tuberculosis had received effective therapy for their disease. The last two studies show that a response can be obtained no matter how severe the immune defect and suggest that a key determinant in survival for patients with MDR tuberculosis and AIDS is prompt selection of an effective regimen.

The selection of specific empirical regimens will necessarily depend on the local pattern of susceptibility at a given medical center (173). One regimen used in New York City to treat persons suspected to have an increasingly common strain resistant to seven drugs includes INH, rifampin, PZA, ofloxacin, cycloserine, and capreomycin.

While five- to six-drug empirical regimens do appear superior when given in the correct setting, a great deal of additional study must be undertaken before a specific regimen can be recommended. First, initiating a six-drug regimen, often with several toxic second-line agents, to patients with AIDS, who are often already receiving several other medicines, can complicate an already complicated clinical picture. Management of common toxicities such as rash, fever, or hepatitis is particularly difficult, since it is seldom obvious which is the provocative agent.

In addition, the impact of administering a relatively toxic six-drug regimen as empirical therapy to patients who may have a susceptible *M. tuberculosis* strain, or may not have tuberculosis at all, must be considered. Although some factors increase the risk of resistant tuberculosis, many patients with resistant disease have no discernible risk factors; conversely, many persons with several risk factors turn out to have susceptible tuberculosis. Until rapid tests to identify resistant tuberculosis are developed, recommendations concerning empirical regimens will have to be determined by hospital-based infectious-disease and pulmonary specialists.

Finally, the ultimate disposition of patients with AIDS who survive with MDR tuberculosis must also be considered in the public health context. Many of these patients remain intermittently smear and culture positive after 12 to 18 months of therapy, despite clinical signs of response such as defervescence, weight gain, and normalization of the chest radiograph. Therefore, returning them to their previous residence, which may be a home with HIV-infected family members, congregate housing, or prison, may be unwise. As a result, such patients may remain hospitalized indefinitely, which can be extremely demoralizing and expensive.

PROPHYLAXIS

Soon after demonstration of the activity of INH in clinical tuberculosis, a series of trials examining its efficacy as prophylaxis were performed (78, 113, 235, 337). Initial groups studied included an assortment of persons with a positive tuberculin test, including many with abnormal chest radiographs and some with a history of treated tuberculosis (74, 77, 169). In addition, many persons were enrolled who were subsequently found to have microbiologically proven tuberculosis. Despite the heterogeneity of populations studied, the results have remained remarkably constant. About 65% fewer persons who received INH daily for 1 year developed tuberculosis than did patients who did not receive INH, and the protective effect lasted for as long as 19 years (75).

Because of compliance problems and the risk of INH-induced hepatitis, courses of INH chemoprophylaxis shorter than 1 year have been studied. In one trial of 28,000 persons

TABLE 5. Results of INH prophylaxis trials[a]

Regimen (wk)	No. of persons	No. of cases	5-yr incidence[b]	% Reduction
Placebo	6,990	97	14.3	0
INH (12)	6,956	76	11.3	21
INH (24)	6,995	34	5	65
INH (52)	6,919	24	3.6	75

[a] Reprinted from reference 169 with permission of the publisher.
[b] Incidence is defined as the number of culture-positive persons per 1,000 persons at risk.

with a positive TST and an abnormal chest radiograph, four treatment groups were examined: (i) placebo; (ii) 12 weeks of INH; (iii) 24 weeks of INH; and (iv) 52 weeks of INH (159) (Table 5). The results at 5 years demonstrated that 12, 24, and 52 weeks of therapy reduced cases of active disease by 21%, 65%, and 75%, respectively. In addition, the group treated for 24 weeks had fewer cases of INH-induced hepatitis than the group treated for 52 weeks. However, when the "completer-compliers"—persons who took at least 80% of their pills—were analyzed, the 52-week group had a 93% reduction in cases compared with a 69% reduction for the 24-week group (Table 6). In addition, among the completer-compliers in the 24-week group, a trend toward an increasing number of cases in the fourth and fifth years was evident, whereas persons who received 52 weeks of INH maintained a durable and low annual rate of tuberculosis for the entire 5 years.

Subsequent analysis of additional trials suggested that the risk-benefit ratio of 24-week therapy, as well as a higher likelihood of compliance, continued to favor its use (50, 52). Clinical trials of 2-month therapy with rifampin and PZA are in progress (198). For HIV-infected persons, a course of 52 weeks is currently recommended.

The prevalence of positive TSTs in a given population has not been closely studied recently, but it ranges from 12% in New York City Board of Education employees (270) to 32% in members of an alcohol unit (120) and 40% in new employees at a New York City hospital (288).

TST

Despite the simple principles of INH prophylaxis, much controversy (281, 322) and confusion continue to surround just who should receive treatment (52). Much of the confusion derives from a blurring of the distinction between documented TST converters and newly identified TST-positive persons who have not previously been tested. In general, all persons with a documented conversion (increase in induration of more than 10 mm if <35 years old and 15 mm if ≥35 years old), should receive prophylaxis. Persons with a reactive tuberculin and no history of a TST should routinely receive prophylaxis if younger than 35 years. Persons older than 35 who are positive on an initial test should receive prophylaxis if they have an underlying medical illness, such as HIV or other immunocompromising conditions (Table 3).

An additional area of confusion surrounds the definition of a positive reaction. First, only induration, not erythema, is measured. Second, the influence of previous *M. bovis* BCG vaccination on adult TSTs remains unsettled (213a).

The exact size of a positive test is an additional source of confusion. Persons at high risk for development of active disease, such as HIV-infected persons and recent contacts of infected persons, are considered positive with only 5 mm of induration. Persons who are either from areas where tuberculosis is endemic or at increased risk for progression to active disease because of medical illness (such as dialysis) are considered positive with 10 mm of induration. For all others, 15 mm of induration is considered positive. The CDC will issue updated guidelines in a forthcoming document (61).

The booster phenomenon describes the anamnestic response that occurs when persons who are latently infected with *M. tuberculosis* are given serial purified protein derivative skin tests. A certain percentage of such persons, generally the elderly, will have an initially negative response, despite being latently infected; on subsequent tests given 1 week to 1 year later, the skin test is positive because of the booster effect. Because of this phenomenon, two-step skin testing is recommended for persons being tested for the first time (10, 277). In this scheme, two skin tests are administered 1 week apart.

TABLE 6. Results of INH prophylaxis trials—Completer-Compliers[a]

Regimen (wk)	No. of persons	No. of cases	5-yr incidence[b]	% Reduction
Placebo	5,616	83	15.0	0
INH (12)	6,039	61	10.4	31
INH (24)	5,437	25	4.7	69
INH (52)	4,543	5	1.1	93

[a] Reprinted from reference 169 with permission of the publisher.
[b] Incidence is defined as the number of culture-positive persons per 1,000 persons at risk.

Prophylaxis in Persons Exposed to Resistant Tuberculosis

In patients newly infected with strains of *M. tuberculosis* resistant to INH but susceptible to rifampin, rifampin prophylaxis may be effective while INH is not (111). However, if the exposure is to an MDR strain, treatment options are limited, and no studies have been completed to evaluate efficacy. Drug susceptibility results from the source case are the primary consideration in selecting preventive therapy (56, 217). If neither INH nor rifampin can be used, preventive therapy should include at least two drugs to which the index isolate is susceptible. Alternative drugs for preventive therapy include PZA, ethambutol, and a quinolone such as ciprofloxacin. The suggested duration of preventive therapy of resistant tuberculosis is 6 to 12 months. The CDC has suggested that persons with a high likelihood of infection with a strain resistant to both INH and rifampin might benefit from PZA-quinolone therapy (56). Health care workers who have tried this regimen, however, have had a high rate of dose-limiting toxicity (163).

BCG Vaccination

Although it has not been given routinely in the United States, vaccination with BCG has been used for more than 50 years in most other parts of the world. Giving a vaccine to millions of persons to prevent a common disease would seem to allow a clear assessment of the efficacy of the intervention. However, despite analyses and meta-analyses, there is still no clear consensus as to the relative efficacy of the vaccine (17, 69, 269).

The vaccine was developed in the early 1900s from a strain of *M. bovis*, and properties of immunogenicity without pathogenicity were selected for. However, because of great variation in stock quality, in the health of the recipients, and in the ability of a given country to deliver the vaccine and record the vaccination, debate continues. A recent meta-analysis of the published literature demonstrated that, on average, BCG reduces the risk of tuberculosis by about 50% (71). Protection

was observed across many populations, study designs, and forms of tuberculosis. Protection against tuberculous death, meningitis, and disseminated disease was higher than that observed for total cases of tuberculosis. Given this study and other results, continued calls have been sounded for BCG vaccination among health care workers (139), but the debate is unsettled. Central to the discussion is whether a vaccine that is only 50% effective is sufficiently effective to warrant loss of the TST as a marker of new infection, since BCG-vaccinated persons predictably become TST positive (71).

INFECTION CONTROL ISSUES

Because of the threat of nosocomial tuberculosis to patients and health care workers, development of guidelines to ensure safety has become an important and actively debated issue (66, 133). Current recommendations (56, 61, 89, 230) include placement of any person with suspected tuberculosis into respiratory isolation. Rooms with negative ventilation and at least six air exchanges per hour are considered optimal. In addition, use of an effective respirator (personal protective device) by health care workers is recommended, as is the use of high-efficiency particulate air (HEPA) filtration, which is capable of filtering AFB from the air. The use of germicidal UV light (172, 226, 227, 274), although possibly useful, has not been as strongly advocated. Persons who work in high-risk areas such as bronchoscopy suites may benefit from an even higher level of protection. Annual tuberculin screening for hospital employees is recommended (321). The high cost of implementing these recommendations versus the need to protect workers make this particular issue particularly difficult to settle.

FUTURE CONCERNS

As the 21st century approaches, it is ironic that we are again confronted with the quintessential 19th century disease: tuberculosis. Application of modern technology may contribute to better understanding of the pathogenesis of infection and disease, more rapid diagnosis and identification of resistant strains, and newer treatments, including novel chemotherapeutic agents and immune system modulators. In addition, candidate vaccines may be developed and tested.

However, faith that such advances will "solve the problem" of tuberculosis is ill founded. In the U.S., tuberculosis is a disease of the poor and the already sick. Its treatment continues to be measured in months rather than days or weeks. Successful control of tuberculosis in the 1990s, therefore, depends less on advances in molecular diagnostics or cytokine-based therapies than on the nonglamorous work of identifying and treating thousands of patients with hundreds of thousands of pills.

The ultimate control of tuberculosis rests on development of much shorter courses of therapy, vastly improved diagnostic methods, and an unprecedented cooperation among medical facilities, public health agencies, and governmental organizations. Given the difficulty of realizing these goals, it seems inevitable that tuberculosis will remain a major public health problem for years to come.

REFERENCES

1. **Abe, C., S. Hosojima, Y. Fukasawa, Y. Kazumi, M. Takahashi, K. Hirano, and T. Mori.** 1992. Comparison of MB-Check, BACTEC, and egg-based media for recovery of mycobacteria. J. Clin. Microbiol. **30:**878–881.
2. **Acocella, G., and J. Angel.** 1986. Short-course chemotherapy of pulmonary tuberculosis: a new approach to drug dosage in the initial intensive phase. Am. Rev. Respir. Dis. **134:**1283–1286.
3. **Addington, W.** 1979. Patient compliance: the most serious problem in control of tuberculosis in the United States. Chest **76**(Suppl.)**:**741–743.
4. **Adler, J., and G. Di Ferdinando.** 1991. Tuberculosis transmission among health care workers. N. Y. State J. Med. **91:**89–90. (Commentary.)
5. **Aitken, M. L., R. Sparks, K. Anderson, and R. K. Albert.** 1984. Predictors of drug-resistant *Mycobacterium tuberculosis*. Am. Rev. Respir. Dis. **130:** 831–833.
6. **Albert, M. E., and M. E. Levison.** 1965. An epidemic of tuberculosis in medical school. N. Engl. J. Med. **272:**718–721.
7. **Algerian Working Group/British Medical Research Council Cooperative Study.** 1984. Controlled clinical trial comparing a 6-month and a 12-month regimen in the treatment of pulmonary tuberculosis in the Algerian Sahara. Am. Rev. Respir. Dis. **129:**921–928.
8. **Alland, D., K. Brudney, R. McAdam, G. Kalcut, J. Dobkin, B. Jacobs, and B. R. Bloom.** 1992. An outbreak of tuberculosis in a New York City men's shelter, abstr. 47D, p. 47. *In* Program and abstracts of the First World Congress on Tuberculosis.
9. **Allen, S., J. Batungwanayo, K. Kerlikowske, A. R. Lifson, W. Wolf, R. Granich, H. Taelman, P. van de Perre, A. Serufilira, J. Bogaerts, G. Slutkin, and P. Hopewell.** 1992. Two-year incidence of tuberculosis in cohorts of HIV-infected and uninfected urban Rwandan women. Am. Rev. Respir. Dis. **146:**1439–1444.
10. **Alvarez, S., D. R. Kasprzyk, and M. Freundl.** 1987. Two-stage skin testing for tuberculosis in a domiciliary population. Am. Rev. Respir. Dis. **136:** 1193–1196.
11. **American Thoracic Society.** 1994. Treatment of tuberculosis and tuberculosis infection in adults and children. Am. J. Respir. Crit. Care Med. **149:**1359–1374.
12. **American Thoracic Society/Centers for Disease Control.** 1986. Treatment of tuberculosis and tuberculosis infection in adults and children. Am. Rev. Respir. Dis. **134:**355–363.
13. **American Thoracic Society/Centers for Disease Control.** 1987. Mycobacterioses and the acquired immunodeficiency syndrome. Am. Rev. Respir. Dis. **136:**492–496.
14. **Annas, G.** 1993. Control of tuberculosis—the law and the public's health. Legal issues in medicine. N. Engl. J. Med. **328:**585–588.
15. **Ayvasian, L. F.** 1993. History of tuberculosis, p. 1–20. *In* L. B. Reichman and E. S. Hershfeld (ed.), Tuberculosis: a comprehensive international approach. Marcel Dekker, Inc., New York.
16. **Aziz, A., M. Ishaq, N. Jaffer, R. Akhwand, and A. Bhatti.** 1986. Clinical trial of two short-course (6-month) regimens and a standard regimen (12-month) chemotherapy in retreatment of pulmonary tuberculosis in Pakistan. Am. Rev. Respir. Dis. **134:**1056–1061.
17. **Barclay, W.** 1983. BCG: an effective immunizing agent. JAMA **249:**2376. (Letter.)
18. **Barnes, P., and S. Barrows.** 1993. Tuberculosis in the 1990s. Ann. Intern. Med. **119:**400–410.
19. **Barnes, P. F.** 1987. The influence of epidemiologic factors on drug resistance rates in tuberculosis. Am. Rev. Respir. Dis. **136:**325–328.
20. **Barnes, P. F., A. B. Bloch, P. T. Davidson, and D. E. Snider.** 1991. Tuberculosis in patients with human immunodeficiency virus infection. N. Engl. J. Med. **324:**1644–1650.
21. **Bates, J., W. Potts, and M. Lewis.** 1965. Epidemiology of primary tuberculosis in an industrial school. N. Engl. J. Med. **272:**714–717.
22. **Bates, J. H., and W. W. Stead.** 1993. The history of tuberculosis as a global epidemic. Med. Clin. North Am. **77:**1205–1217.
23. **Baughman, R. P., M. N. Dohn, R. G. Loudon, and P. T. Frame.** 1991. Bronchoscopy with bronchoalveolar lavage in tuberculosis and fungal infections. Chest **99:**92–97.
24. **Baxter, T.** 1993. Low infectivity of tuberculosis. Lancet **342:**371. (Letter.)
25. **Beck-Sague, C., S. W. Dooley, M. D. Hutton, J. Otten, A. Breeden, J. T. Crawford, A. E. Pitchenik, C. Woodley, G. Cauthen, and W. R. Jarvis.** 1992. Hospital outbreak of multidrug-resistant *Mycobacterium tuberculosis* infections: factors in transmission to staff and HIV-infected patients. JAMA **268:**1280–1286.
26. **Bellin, E., D. Fletcher, and S. Safyer.** 1993. Association of tuberculosis infection with increased time in or admission to the New York City jail system. JAMA **269:**2228–2231.
27. **Ben-Dov, I., and G. R. Mason.** 1987. Drug-resistant tuberculosis in a Southern California hospital, trends from 1969 to 1984. Am. Rev. Respir. Dis. **135:**1307–1310.
28. **Berenguer, J., S. Moreno, and F. Laguna.** 1992. Tuberculous meningitis in patients infected with the human immunodeficiency virus. N. Engl. J. Med. **326:**668–672.
29. **Berning, S. E., G. A. Huitt, M. D. Iseman, and C. A. Peloquin.** 1992. Malabsorption of antituberculosis medications by a patient with AIDS. N. Engl. J. Med. **327:**1817–1818. (Letter.)
30. **Bishberg, E., G. Sunderman, L. B. Reichman, and R. Kapila.** 1986. Central nervous system tuberculosis and the acquired immunodeficiency syndrome and its related complex. Ann. Intern. Med. **105:**210–213.
31. **Bloom, B. R., and C. J. L. Murray.** 1992. Tuberculosis: commentary on a reemergent killer. Science **257:**1055–1064.
32. **Braun, M., T. Cote, and C. Rabkin.** 1993. Trends in death with tuberculosis during the AIDS era. JAMA **269:**2865–2868.

33. **Braun, M., B. Truman, B. Maguire, G. DiFerdinando, G. Wormser, R. Broaddus, and D. Morse.** 1989. Increasing incidence of tuberculosis in a prison inmate population—association with HIV infection. JAMA **261:**393–397.
34. **Braun, M. M., N. Badi, R. W. Ryder, E. Baende, Y. Mukadi, M. Nsuami, B. Matela, J.-C. Willame, M. Kaboto, and W. Heyward.** 1991. A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire. Am. Rev. Respir. Dis. **143:**501–504.
35. **Brisson-Noel, A., C. Aznar, C. Chureau, S. Nguyen, C. Pierre, M. Bartoli, R. Bonett, G. Pialoux, B. Gicquel, and G. Garrique.** 1991. Diagnosis of tuberculosis by DNA amplification in clinical practice evaluation. Lancet **ii:**363–366.
36. **Brisson-Noel, A., B. Gicquel, D. Lecossier, V. Levy-Frebault, X. Nassif, and A. J. Hance.** 1989. Rapid diagnosis of tuberculosis by amplification of mycobacterial DNA in clinical samples. Lancet **ii:**1069–1071.
37. **British Thoracic and Tuberculosis Association.** 1976. Short-course chemotherapy in pulmonary tuberculosis: a controlled trial. Lancet **ii:**1102–1104.
38. **British Thoracic Society.** 1984. A controlled trial of 6 months chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. Br. J. Dis. Chest **78:**330–336.
39. **British Thoracic Society Research Committee.** 1985. Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. Br. Med. J. **290:**1106–1108.
40. **Brudney, K., and J. Dobkin.** 1991. A tale of two cities: tuberculosis control in Nicaragua and New York City. Semin. Respir. Infect. **6:**261–272.
41. **Brudney, K., and J. Dobkin.** 1992. Resurgent tuberculosis in New York City: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. Am. Rev. Respir. Dis. **144:**745–749.
42. **Busillo, C., K. Lassnau, V. Sanjana, S. Soumakis, M. Davidson, M. Mullen, and W. Talavera.** 1992. Multidrug resistant *Mycobacterium tuberculosis* in patients with human immunodeficiency virus infection. Chest **102:**797–801.
43. **Butler, W. R., and J. O. Kilburn.** 1988. Identification of major slowly growing pathogenic mycobacteria and *Mycobacterium gordonae* by high-performance liquid chromatography of their mycolic acids. J. Clin. Microbiol. **26:**50–53.
44. **Byrd, R. B., D. E. Fisk, R. A. Roethe, J. N. Glover, L. D. Wooster, and N. J. Wilder.** 1979. Tuberculosis in oriental immigrants: a study in military dependents. Chest **76:**136–139.
45. **Castelo, A., J. Jardian, S. Goihman, A. Kalckman, M. Dalboni, E. Da Silva, and R. Haynes.** 1989. Comparison of daily and twice weekly regimens to treat pulmonary tuberculosis. Lancet **ii:**1173–1176.
46. **Catanzaro, A.** 1982. Nosocomial tuberculosis. Am. Rev. Respir. Dis. **125:** 559–562.
47. **Centers for Disease Control.** 1983. Primary resistance to antituberculosis drugs—United States. Morbid. Mortal. Weekly Rep. **32:**521–523.
48. **Centers for Disease Control.** 1987. Diagnosis and management of mycobacterial infection and disease in persons with human immunodeficiency virus infection. Ann. Intern. Med. **106:**254–256.
49. **Centers for Disease Control.** 1987. Outbreak of multidrug-resistant tuberculosis—North Carolina. Morbid. Mortal. Weekly Rep. **35:**785–787.
50. **Centers for Disease Control.** 1989. A strategic plan for the elimination of tuberculosis in the United States. Morbid. Mortal. Weekly Rep. **38**(S-3)**:**1–25.
51. **Centers for Disease Control.** 1990. Outbreak of multidrug-resistant tuberculosis—Texas, California, and Pennsylvania. Morbid. Mortal. Weekly Rep. **39:**369–372.
52. **Centers for Disease Control.** 1990. The use of preventative therapy for tuberculosis infection in the United States: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET). Morbid. Mortal. Weekly Rep. **39:**369–372.
53. **Centers for Disease Control.** 1991. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons—Florida and New York. Morbid. Mortal. Weekly Rep. **40:**585–591.
54. **Centers for Disease Control.** 1991. Tuberculosis outbreak on Standing Rock Sioux Reservation—North Dakota and South Dakota, 1987–1990. Morbid. Mortal. Weekly Rep. **40:**204–207.

54a. **Centers for Disease Control.** 1991. Tuberculosis transmission along the U.S.-Mexican border—1990. Morbid. Mortal. Weekly Rep. **40:**373–375.

55. **Centers for Disease Control.** 1991. Transmission of multidrug-resistant tuberculosis from an HIV-positive client in a residential substance-abuse treatment facility—Michigan. Morbid. Mortal. Weekly Rep. **40:**129–131.
56. **Centers for Disease Control.** 1992. National action plan to combat multidrug-resistant tuberculosis. Morbid. Mortal. Weekly Rep. **41**(RR-11)**:**1–71.
57. **Centers for Disease Control.** 1992. Transmission of multidrug-resistant tuberculosis among immunocompromised persons in a correctional system—New York. Morbid. Mortal. Weekly Rep. **41:**507–509.
58. **Centers for Disease Control.** 1992. Tuberculosis morbidity in the United States: final data. Morbid. Mortal. Weekly Rep. **41:**240.
59. **Centers for Disease Control.** 1993. Probable transmission of multidrug-resistant tuberculosis in a correctional facility—California. Morbid. Mortal. Weekly Rep. **42:**48–51.
60. **Centers for Disease Control.** 1993. Tuberculosis—Western Europe, 1974–1991. Morbid. Mortal. Weekly Rep. **42:**628–631.
61. **Centers for Disease Control.** 1993. Draft guidelines for preventing the transmission of tuberculosis in healthcare facilities, 2nd ed. Fed. Regist. **58:**52810–52854.
62. **Centers for Disease Control. Advisory Council for the Elimination of Tuberculosis.** 1992. Prevention and control of tuberculosis in U.S. communities with at-risk minority populations. Morbid. Mortal. Weekly Rep. **41**(RR-5)**:**1–11.
63. **Centers for Disease Control. Advisory Council for the Elimination of Tuberculosis.** 1992. Prevention and control of tuberculosis among homeless persons. Morbid. Mortal. Weekly Rep. **41**(RR-5)**:**13–23.
64. **Chaisson, R. E., G. F. Schecter, C. P. Theuer, G. W. Rutherford, D. F. Echenberg, and P. C. Hopewell.** 1987. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. Am. Rev. Respir. Dis. **136:**570–574.
65. **Chaisson, R. E., and G. Slutkin.** 1989. Tuberculosis and human immunodeficiency virus infection. J. Infect. Dis. **159:**96–100.
66. **Charney, W., J. Fisher, and C. Ishida.** 1991. The inefficiency of surgical masks for protection against droplet nuclei tuberculosis. J. Occup. Med. **33:**943–944. (Letter.)
67. **Chawla, P., P. Klatter, S. Kamholz, A. Pollack, and A. Heurich.** 1992. Drug-resistant tuberculosis in an urban population including patients at risk for human immunodeficiency virus infection. Am. Rev. Respir. Dis. **146:** 280–284.
68. **Cheung, R., J. Dickins, P. Nicholson, A. Thomas, A. Hillas, H. Smith, H. Larson, A. Deshmukh, R. Dobbs, and S. Dobbs.** 1988. Compliance with anti-tuberculous therapy: a field trial of a pill-box with a concealed electronic recording device. Eur. J. Clin. Pharmacol. **35:**401–407.
69. **Clemens, J., J. Chuong, and A. Feinstein.** 1983. The BCG controversy: a methodological and statistical reappraisal. JAMA **249:**2362–2369.
70. **Cohn, D., B. Catlin, and K. Peterson.** 1990. A 62 dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. Ann. Intern. Med. **112:**407–415.
71. **Colditz, G., T. Brewer, C. Berkey, M. Wilson, E. Burdick, H. Fineberg, and F. Mosteller.** 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. JAMA **271:**698–702.
72. **Collins, H. C.** 1988. Laboratory-acquired infections, 2nd ed. Butterworth & Co. Ltd., London.
73. **Combs, D., R. O'Brien, and L. Geiter.** 1990. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability; the report of final results. Ann. Intern. Med. **112:**397–406.
74. **Comstock, G. W.** 1962. Isoniazid prophylaxis in an undeveloped area. Am. Rev. Respir. Dis. **86:**810–822.
75. **Comstock, G. W., C. Baum, and D. E. Snider.** 1979. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the Bethel isoniazid studies. Am. Rev. Respir. Dis. **119:**827–830.
76. **Comstock, G. W., and G. M. Cauthen.** 1993. Epidemiology of tuberculosis, p. 23–48. *In* L. B. Reichman and E. S. Hershfeld (ed.), Tuberculosis: a comprehensive international approach. Marcel Dekker, Inc., New York.
77. **Comstock, G. W., S. H. Ferebee, and L. M. Hammes.** 1967. A controlled trial of community-side isoniazid prophylaxis in Alaska. Am. Rev. Respir. Dis. **95:**935–943.
78. **Comstock, G. W., V. T. Liversay, and S. F. Woolpert.** 1974. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am. J. Epidemiol. **99:**131–138.
79. **Coronado, V. G., C. M. Beck-Sague, M. D. Hutton, B. J. Davis, P. Nicholas, C. Villareal, C. L. Woodley, J. Kilburn, J. T. Crawford, T. R. Freiden, R. Sinkowitz, and W. Jarvis.** 1993. Transmission of multidrug-resistant *Mycobacterium tuberculosis* among persons with human immunodeficiency virus infection at an urban hospital: epidemiologic and restriction fragment length polymorphism analysis. J. Infect. Dis. **168:**1052–1055.
80. **Cousins, D. V., S. D. Wilton, B. R. Francis, and B. L. Gow.** 1992. Use of polymerase chain reaction for rapid diagnosis of tuberculosis. J. Clin. Microbiol. **30:**255–258.
81. **Croule, A. J., J. A. Sbarbaro, F. N. Judson, and M. H. May.** 1985. The effect of ethambutol on tubercle bacilli within cultured human macrophages. Am. Rev. Respir. Dis. **132:**742–745.
82. **Daley, C. L.** 1993. Tuberculosis recurrence in Africa: true relapse or reinfection. Lancet **342:**756–757.
83. **Daley, C. L., P. M. Small, G. F. Schecter, G. K. Schoolnik, R. A. McAdam, W. R. Jacobs, and P. C. Hopewell.** 1992. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment length polymorphisms. N. Engl. J. Med. **326:**231–235.
84. **Daniels, M., F. Ridehalgh, V. H. Springett, and I. M. Hall.** 1948. Tuberculosis in young adults: report on the Prophit Tuberculosis Survey, 1936–1944. H. K. Lewis and Co., Ltd., London.
85. **Darney, P., and N. Clenny.** 1971. Tuberculosis outbreak in an Alabama high school. JAMA **216:**2117–2118.
86. **Datta, M., M. P. Radhamani, R. Selvaraj, C. Paramasivan, B. Gopalan, C. Sudeendra, and R. Prabhakar.** 1993. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tu-

berculosis programme. Tubercle Lung Dis. **74:**180–186.
87. **DeCock, K. M., B. Soro, I. M. Coulibaly, and S. B. Lucas.** 1992. Tuberculosis and HIV infection in Sub-Saharan Africa. JAMA **268:**1581–1587.
88. **Di Perri, G., M. C. Danzi, G. DeChecci, S. Pizzighella, M. Solbrati, M. Cruciani, R. Luzzati, M. Molena, R. Mazzi, E. Concia, and D. Bassetti.** 1989. Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet **ii:**1502–1504.
89. **Dooley, S., K. Castro, M. D. Hutton, R. Mullan, J. Polder, and D. E. Snider.** 1990. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. Morbid. Mortal. Weekly Rep. **39**(RR-17)**:**1–29.
90. **Dooley, S., W. Jarvis, W. Martone, and D. Snider.** 1992. Multidrug-resistant tuberculosis. Ann. Intern. Med. **117:**257–259. (Editorial.)
91. **Dooley, S. W., M. E. Villarino, M. Lawrence, L. Salinas, S. Amil, J. V. Rullan, W. R. Jarvis, A. B. Bloch, and G. M. Cauthen.** 1992. Nosocomial transmission of tuberculosis in a hospital unit for HIV-infected patients. JAMA **267:**2632–2635.
92. **Doster, B. D., G. J. Casas, and D. E. Snider.** 1976. A continuing survey of primary drug resistance in tuberculosis, 1961 to 1968. Am. Rev. Respir. Dis. **113:**419–425.
93. **Driver, C. R., T. R. Frieden, A. B. Bloch, and I. M. Onorato.** 1993. Drug resistance among tuberculosis (TB) cases, New York City, 1991–1992. Am. Rev. Respir. Dis. **147:**A121. (Abstract.)
94. **Dubos, R., and J. Dubos.** 1952. The white plague: tuberculosis, man and society, p. 105–107. Little, Brown & Co., Boston.
95. **Dufault, P.** 1941. Tuberculous infection among nurses and medical students in sanatoriums and general hospitals. N. Engl. J. Med. **224:**711–715.
96. **Dutt, A., D. Moers, and W. W. Stead.** 1989. Smear- and culture-negative pulmonary tuberculosis: four-month short-course chemotherapy. Am. Rev. Respir. Dis. **139:**867–870.
97. **Dutt, A., D. Moers, and W. W. Stead.** 1992. Tuberculous pleural effusion: 6-month therapy with isoniazid and rifampin. Am. Rev. Respir. Dis. **145:** 1429–1432.
98. **Dutt, A. K., D. Moers, and W. W. Stead.** 1986. Short-course chemotherapy for extrapulmonary tuberculosis. Nine years' experience. Ann. Intern. Med. **104:**7–12.
99. **Dylewski, J., and L. Thibert.** 1990. Failure of tuberculosis chemotherapy in a human immunodeficiency virus-infected patient. J. Infect. Dis. **162:**778–779. (Letter.)
100. **East African/British Medical Research Council.** 1972. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet **i:**1079–1085.
101. **East and Central African/British Medical Research Council Fifth Collaborative Study.** 1986. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis: final report. Tubercle **67:**5–15.
102. **Editors.** 1965. New twist on TB spread. Med. World News **6:**54.
103. **Edlin, B. R., L. S. Attoe, M. H. Grieco, J. Williams, N. Schneider, and M. E. Gilligan.** 1993. Recognition and treatment of primary multidrug-resistant tuberculosis (MDRTB) in HIV-infected patients, abstr. WS-BO9-6, p. 52. *In* Program and abstracts of the 9th International Conference on AIDS 1993.
104. **Edlin, B. R., J. I. Tokars, M. H. Grieco, J. T. Crawford, J. Williams, E. M. Sardillo, K. R. Ong, J. O. Kilburn, S. W. Dooley, K. G. Castro, W. R. Jarvis, and S. D. Holmberg.** 1992. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. **326:**1514–1521.
105. **Edwards, P. Q., and L. B. Edwards.** 1960. Story of the tuberculin test. Am. Rev. Respir. Dis. **81**(Suppl.)**:**1–47.
106. **Ehrenkranz, N. J., and J. L. Kicklighter.** 1972. Tuberculosis outbreak in a general hospital: evidence for airborne spread of infection. Ann. Intern. Med. **77:**377–382.
107. **Eisenach, K. D., M. D. Cave, J. H. Bates, and J. T. Crawford.** 1990. Polymerase chain reaction amplification of a repetitive DNA sequence specific for *Mycobacterium tuberculosis*. J. Infect. Dis. **161:**977–981.
108. **Ellner, J. J., A. R. Hinman, S. W. Dooley, M. Fischl, K. A. Sepkowitz, M. J. Goldberger, T. M. Shinnick, M. D. Iseman, and W. R. Jacobs.** 1993. Infectious Disease Society of America symposium: tuberculosis—emerging problems and promise. J. Infect. Dis. **168:**537–551.
109. **Ellner, P. D., T. E. Kiehn, R. Cammarata, and M. Hosmer.** 1988. Rapid detection and identification of pathogenic mycobacteria by combining radiometric and nucleic acid probe methods. J. Clin. Microbiol. **26:**1349–1352.
110. **Evans, K. D., A. S. Nakasone, P. A. Sutherland, L. M. De La Maza, and E. M. Peterson.** 1992. Identification of *Mycobacterium tuberculosis* and *Mycobacterium avium-M. intracellulare* directly from primary BACTEC cultures by using acridinium-ester-labeled DNA probes. J. Clin. Microbiol. **30:**2427–2431.
111. **Fairshter, R. D., G. P. Randazzo, J. Garlin, and A. F. Wilson.** 1975. Failure of isoniazid prophylaxis after exposure to isoniazid-resistant tuberculosis. Am. Rev. Respir. Dis. **112:**37–43.
112. **Farga, V., P. Valenzuela, F. Mendoza, E. Torres, I. Icekson, M. Grinspun, M. Fernandez, A. Corradini, M. Martinez, and J. Velasco.** 1983. Trials in Chile. Bull. Int. Union Tuberc. **58:**102–107.
113. **Ferebee, S. H.** 1970. Controlled chemoprophylaxis trials in tuberculosis: a general review. Adv. Tuberc. Res. **17:**28–106.
114. **Fischl, M. A., G. L. Daikos, R. B. Uttamchandani, R. B. Poblete, J. N. Moreno, R. R. Reyes, A. M. Boota, L. M. Thompson, T. J. Cleary, S. A. Oldham, M. J. Saldana, and S. Lai.** 1992. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug-resistant bacilli. Ann. Intern. Med. **117:**184–190.
115. **Fischl, M. A., R. B. Uttamhandani, G. L. Daikos, R. B. Poblete, J. N. Moreno, R. R. Reyes, A. M. Boota, L. M. Thompson, T. J. Cleary, and S. Lai.** 1992. An outbreak of tuberculosis caused by multiple-drug-resistant tubercle bacilli among patients with HIV infection. Ann. Intern. Med. **117:**177–183.
116. **FitzGerald, J. M., S. Grzybowski, and E. A. Aleen.** 1991. The impact of human immunodeficiency virus infection on tuberculosis and its control. Chest **100:**191–200.
117. **Frampton, M. W.** 1992. An outbreak of tuberculosis among hospital personnel caring for a patient with a skin ulcer. Ann. Intern. Med. **117:**312–313.
118. **Frieden, T. R., T. Sterling, A. Pablos-Mendez, J. O. Kilburn, G. M. Cauthen, and S. W. Dooley.** 1993. The emergence of drug-resistant tuberculosis in New York City. N. Engl. J. Med. **328:**521–526.
119. **Friedman, C. R., L. Riley, B. Kreiswirth, W. D. Johnson, S. Manoach, K. Sathianathan, and M. Y. Stoeckle.** 1994. Molecular epidemiology of tuberculosis in New York City, abstr. C-342, p. 550. *In* Abstracts of the 94th General Meeting of the American Society for Microbiology 1994. American Society for Microbiology, Washington, D.C.
120. **Friedman, L. N., G. M. Sullivan, R. P. Bevilaqua, and R. Lascos.** 1987. Tuberculosis screening in alcoholics and drug addicts. Am. Rev. Respir. Dis. **136:**1188–1192.
121. **Gangadharam, P.** 1987. Short-course chemotherapy of pulmonary tuberculosis: a new approach to drug dosage in the initial intensive phase. Am. Rev. Respir. Dis. **136:**1518. (Letter.)
122. **Geiter, L., and R. O'Brien.** 1987. Short course chemotherapy of pulmonary tuberculosis. Am. Rev. Respir. Dis. **135:**1215. (Letter.)
123. **Genewein, A., A. Telenti, C. Bernasconi, C. Mordasini, S. Weiss, A. Maurer, H. Rieder, K. Schopfer, and T. Bodmer.** 1993. Molecular approach to identifying route of transmission of tuberculosis in the community. Lancet **342:**841–844.
124. **George, R. H., P. R. Gully, O. M. Gill, J. A. Innes, S. S. Bakshi, and M. Connolly.** 1986. An outbreak of tuberculosis in a children's hospital. J. Hosp. Infect. **8:**129–142.
125. **Gibbs, J., J. Grange, J. Swanson Beck, E. Jawad, R. Potts, and G. Bothamley.** 1991. Early delayed hypersensitivity responses in tuberculin skin tests after heavy occupational exposure to tuberculosis. J. Clin. Pathol. **44:**919–923.
126. **Gilman, A. G.** 1990. Antimicrobial agents, p. 1061–1162. *In* A. G. Gilman (ed.), The pharmacologic basis of therapeutics. Pergamon Press, New York.
127. **Glaser, J. B., and R. B. Greifinger.** 1993. Correctional health care: a public health opportunity. Ann. Intern. Med. **118:**139–145.
128. **Glassroth, J.** 1992. Tuberculosis in the United States: looking for a silver lining among the clouds. Am. Rev. Respir. Dis. **146:**278–279.
129. **Goble, M. J., M. D. Iseman, L. A. Madsen, D. Waite, L. Ackerson, and R. C. Horsburgh.** 1993. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N. Engl. J. Med. **328:**527–532.
130. **Goldberger, M. J.** 1988. Antituberculous agents. Med. Clin. North Am. **72:**661–668.
131. **Goldsmith, M.** 1990. Forgotten (almost) but not gone, tuberculosis suddenly looms large on domestic scene. JAMA **264:**165–166. (Letter.)
132. **Good, R. C., and T. D. Mastro.** 1989. The modern mycobacteriology laboratory. How it can help the clinician. Clin. Chest Med. **10:**315–322.
133. **Gordin, F.** 1992. Tuberculosis control. JAMA **267:**2649–2650. (Editorial.)
134. **Gordin, F., and G. Slutkin.** 1990. The validity of acid-fast smears in the diagnosis of tuberculosis. Arch. Pathol. Lab. Med. **114:**1025–1027.
135. **Gorzynski, E. A., S. I. Gutman, and W. Allen.** 1989. Comparative antimycobacterial activities of difloxacin, temafloxacin, enoxacin, perfloxacin, reference floroquinolones, and a new macrolide clarithromycin. Antimicrob. Agents Chemother. **33:**591–592.
136. **Gostin, L.** 1993. Controlling the resurgent tuberculosis epidemic. JAMA **269:**255–261.
137. **Goto, M., S. Oka, K. Okuzumi, S. Kimura, and K. Shimada.** 1991. Evaluation of acridinium-ester-labeled DNA probes for identification of *Mycobacterium tuberculosis* and *Mycobacterium avium-Mycobacterium intracellulare* complex in culture. J. Clin. Microbiol. **29:**2473–2476.
138. **Graham, N. M., K. E. Nelson, L. Solomon, M. Bonds, R. T. Rizzo, J. Scavotto, J. Astembrowski, and D. Vlahov.** 1992. Prevalence of tuberculin positivity and skin test anergy in HIV-1 seropositive and -seronegative intravenous drug users. JAMA **267:**369–373.
139. **Greenberg, P. D., K. G. Lax, and C. B. Schecter.** 1991. Tuberculosis in house staff. Am. Rev. Respir. Dis. **143:**490–495.
140. **Grigg, E.** 1958. The arcana of tuberculosis. Am. Rev. Tuberc. Pulm. Dis. **78:**151–603.

141. **Grist, N. R., and J. A. N. Emslie.** 1991. Infections in British clinical laboratories, 1988–1989. J. Clin. Pathol. **44:**667–669.
142. **Grosset, J.** 1980. Bacteriologic basis of short-course chemotherapy for tuberculosis. Clin. Chest Med. **1:**231–241.
143. **Grosset, J. H.** 1989. Present status of chemotherapy for tuberculosis. Rev. Infect. Dis. **11**(S)**:**S347–S352.
144. **Grzybowski, S., G. D. Barnett, and K. Stylbo.** 1975. Contacts of cases of active pulmonary tuberculosis. Bull. Int. Union Tuberc. **50:**90–106.
145. **Haas, D., and R. Des Prez.** 1994. Tuberculosis and acquired immunodeficiency syndrome: a historical perspective on recent developments. Am. J. Med. **96:**439–450.
146. **Haas, W. H., W. R. Butler, C. L. Woodley, and J. T. Crawford.** 1993. Mixed-linker polymerase chain reaction: a new method for rapid fingerprinting of isolates of the *Mycobacterium tuberculosis* complex. J. Clin. Microbiol. **31:**1293–1298.
147. **Haley, C., R. McDonald, L. Rossi, W. Jones, R. Haley, and J. Luby.** 1989. Tuberculosis epidemic among hospital personnel. Infect. Control Hosp. Epidemiol. **10:**204–210.
148. **Hamadeh, M. A., and J. Glassroth.** 1992. Tuberculosis and pregnancy. Chest **101:**114–120.
149. **Hance, A. J., B. Crandchamp, V. Levy-Frebault, D. Lecossier, J. Rauzier, D. Bocart, and B. Gicquel.** 1989. Detection and identification of mycobacteria by amplification of mycobacterial DNA. Mol. Microbiol. **3:**843–849.
150. **Hardy, M., and H. Schmidck.** 1968. Epidemiology of tuberculosis aboard a ship. JAMA **203:**175–179.
151. **Haststein, M., and H. L. Leaf.** 1992. Tuberculosis of the breast as a presenting manifestation of AIDS. Clin. Infect. Dis. **15:**692–693.
152. **Hawken, M., P. Nunn, S. Gathua, R. Brindle, P. Godfrey-Faussett, W. Githui, J. Odhiambo, B. Batchelor, C. Gilks, J. Morris, and K. McAdam.** 1993. Increased recurrence of tuberculosis in HIV-1 infected patients in Kenya. Lancet **342:**332–337.
153. **Hermans, P. W. M., A. R. J. Schuitema, D. V. Soolingen, C. P. H. J. Verstynen, E. M. Bik, J. E. R. Thole, A. H. J. Kolk, and J. D. A. van Embden.** 1990. Specific detection of *Mycobacterium tuberculosis* complex strains by polymerase chain reaction. J. Clin. Microbiol. **28:**1204–1213.
154. **Heubner, R. E., R. C. Good, and J. I. Tokars.** 1993. Current practices in mycobacteriology: results of a survey of state public health laboratories. J. Clin. Microbiol. **31:**771–775.
155. **Hewlett, D., F. Duncanson, V. Jagadha, J. Lieberman, T. Lenox, and G. Wormser.** 1988. Lymphadenopathy in an inner-city population consisting principally of intravenous drug abusers with suspected acquired immunodeficiency syndrome. Am. Rev. Respir. Dis. **137:**1275–1279.
156. **Hilts, P. J.** 1993. Rise of TB linked to a U.S. failure; government did not supply funds needed to combat disease, report says. New York Times, October 8, p. A23.
157. **Holmberg, S. D.** 1990. The rise of tuberculosis in America before 1820. Am. Rev. Respir. Dis. **142:**1228–1232.
158. **Holt, E., M. Cantave, M. Johnson, H. C. Clermont, J. Atkinson, and R. E. Chaisson.** 1993. Efficacy of supervised, intermittent, short course therapy of tuberculosis in Haiti, abstr. WS-B09-4, p. 52. *In* Program and abstracts of the 9th International Conference on AIDS 1993.
159. **Hong Kong Chest Service/British Medical Research Council.** 1987. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Am. Rev. Respir. Dis. **136:**1339–1342.
160. **Hong Kong Chest Service/British Medical Research Council.** 1991. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Am. Rev. Respir. Dis. **143:**700–706.
161. **Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council.** 1984. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis: results at 60 months. Am. Rev. Respir. Dis. **130:**23–28.
162. **Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council.** 1989. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Am. Rev. Respir. Dis. **139:**871–876.
163. **Horn, D., D. Hewlett, C. Alfalla, and S. Peterson.** 1994. Limited tolerance of ofloxacin and pyrazinamide prophylaxis against tuberculosis. N. Engl. J. Med. **330:**1241. (Letter.)
164. **Horn, D. L., D. Hewlett, W. Haas, W. Butler, C. Alfalla, E. Tan, A. Levine, A. Nayak, and S. Opal.** 1994. Superinfection with rifampin-isoniazid-streptomycin-ethambutol (RISE)-resistant tuberculosis in three patients with AIDS: confirmation by polymerase chain reaction fingerprinting. Ann. Intern. Med. **121:**115–116.
165. **Horsfall, P. A. L.** 1972. Treatment of resistant pulmonary tuberculosis in Hong Kong with regimens of second-line drugs. Tubercle **53:**166–173.
166. **Houk, V., J. Baker, K. Sorensen, and D. Kent.** 1968. The epidemiology of tuberculosis in a closed environment. Arch. Environ. Health **16:**26–35.
167. **Hutton, M., W. W. Stead, G. Cauthen, A. Bloch, and W. Ewing.** 1990. Nosocomial transmission of tuberculosis associated with a draining abscess. J. Infect. Dis. **161:**286–295.
168. **Inderlied, C. B.** 1991. Antimycobacterial agents: in vitro susceptibility testing, spectrums of activity, mechanisms of action and resistance, and assays for activity in biological fluids, p. 134–197. *In* V. Lorian (ed.), Antibiotics in laboratory medicine, 3rd ed. The Williams & Wilkins Co., Baltimore.
169. **International Union Against Tuberculosis, Committee on Prophylaxis.** 1982. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull. W.H.O. **60:**555–564.
170. **Iseman, M., L. Madsen, M. Goble, and M. Pomerantz.** 1990. Surgical intervention in the treatment of pulmonary disease caused by drug-resistant *Mycobacterium tuberculosis*. Am. Rev. Respir. Dis. **141:**623–625.
171. **Iseman, M. D.** 1987. Is standard chemotherapy adequate in tuberculosis patients infected with the HIV? Am. Rev. Respir. Dis. **136:**1326.
172. **Iseman, M. D.** 1992. A leap of faith: what can we do to curtail intrainstitutional transmission of tuberculosis? Ann. Intern. Med. **117:**251–253.
173. **Iseman, M. D.** 1993. Treatment of multidrug-resistant tuberculosis. N. Engl. J. Med. **329:**784–791.
174. **Iseman, M. D., D. Cohn, and J. Sbarbaro.** 1993. Directly observed treatment of tuberculosis—we can't afford not to try it. N. Engl. J. Med. **328:**576–578.
175. **Iseman, M. D., and J. Sbarbaro.** 1991. Short-course chemotherapy of tuberculosis. Am. Rev. Respir. Dis. **143:**697–698. (Editorial.)
176. **Isenberg, H. D., R. F. D'Amato, L. Heifets, P. R. Murray, M. Scardamaglia, M. C. Jacobs, P. Alperstein, and A. Niles.** 1991. Collaborative feasibility study of a biphasic system (Roche Septi-Chek AFB) for rapid detection and isolation of mycobacteria. J. Clin. Microbiol. **29:**1719–1722.
177. **Jacobs, W. R., Jr., R. G. Barletta, R. Udani, J. Chan, G. Kalkut, G. Sosne, T. Kieser, G. J. Sarkis, G. F. Hatfull, and B. R. Bloom.** 1993. Rapid assessment of drug susceptibilities of *Mycobacterium tuberculosis* by means of luciferase reporter phages. Science **260:**819–821.
178. **Jereb, J., G. D. Kelly, S. W. Dooley, G. M. Cauthen, and D. E. Snider.** 1991. Tuberculosis morbidity in the United States: final data, 1990. Morbid. Mortal. Weekly Rep. **40**(SS-3)**:**23–27.
179. **Jereb, J. A., D. R. Burwen, S. W. Dooley, W. H. Haas, J. T. Crawford, L. J. Geiter, M. B. Edmond, J. N. Dowling, R. Shapiro, A. W. Pasculle, S. L. Shanahan, and W. R. Jarvis.** 1993. Nosocomial outbreak of tuberculosis in a renal transplant unit: application of a new technique for restriction fragment length polymorphism analysis of *Mycobacterium tuberculosis* isolates. J. Infect. Dis. **168:**1219–1224.
180. **Jereb, J. A., S. W. Dooley, R. Klevens, M. Pearson, T. Frieden, B. Davis, P. Rivera, V. Sharp, C. Woodley, J. Crawford, J. Kilburn, W. Jarvis, and G. Cauthen.** 1992. Nosocomial transmission of multidrug-resistant tuberculosis to health care workers, New York City, abstr. 51A, p. 51. *In* Program and abstracts of the 1992 World Congress on Tuberculosis.
181. **Jones, B. E., S. M. M. Young, D. Antoniskis, P. T. Davidson, F. Kramer, and P. F. Barnes.** 1993. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am. Rev. Respir. Dis. **148:**1292–1297.
182. **Kantor, H., R. Poblete, and S. Pusateri.** 1988. Nosocomial transmission of tuberculosis from unsuspected disease. Am. J. Med. **84:**833–838.
183. **Kaplan, M., D. Armstrong, and P. Rosen.** 1974. Tuberculosis complicating neoplastic disease: a review of 201 cases. Cancer **33:**850–858.
184. **Kennedy, N., R. Fox, G. M. Kisyombe, A. O. S. Saruini, L. O. Uiso, A. R. C. Ramsay, F. I. Ngowi, and S. H. Gillespie.** 1993. Early bactericidal and sterilizing activities of ciprofloxacin in pulmonary tuberculosis. Am. Rev. Respir. Dis. **148:**1547–1551.
185. **Kiehn, T. E.** 1993. The diagnostic mycobacteriology laboratory of the 1990s. Clin. Infect. Dis. **17**(Suppl. 2)**:**S447–S454.
186. **Kiehn, T. E., and R. Cammarata.** 1988. Comparative recoveries of *Mycobacterium avium-M. intracellulare* from Isolator lysis-centrifugation and BACTEC 13A blood culture systems. J. Clin. Microbiol. **26:**760–761.
187. **Kin, S. J., and Y. P. Hong.** 1992. Drug resistance of *Mycobacterium tuberculosis* in Korea. Tubercle Lung Dis. **73:**219–224.
188. **Kissner, D. G.** 1987. Tuberculosis. Missed opportunities. Arch. Intern. Med. **147:**2037–2040.
189. **Kleeberg, H., and M. Oliver.** 1984. A world atlas of initial drug resistance, rev 2nd ed. Tuberculosis Research Institute of the South African Medical Research Council (MRC), Pretoria, South Africa.
190. **Klotz, S., and R. Penn.** 1987. Acid-fast staining of urine and gastric contents is an excellent indicator of mycobacterial disease. Am. Rev. Respir. Dis. **136:**1197–1198.
191. **Knockaert, D. C., L. J. Vanneste, S. B. Vanneste, and H. J. Bobbaers.** 1992. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. Arch. Intern. Med. **152:**51–55.
192. **Kochi, A.** 1991. The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercle **72:**1–6.
193. **Kohno, S., H. Koga, M. Kaku, S. Maesaki, and K. Hara.** 1992. Prospective comparative study of ofloxacin or ethambutol for the treatment of pulmonary tuberculosis. Chest **102:**1815–1818.
194. **Kopanoff, D. E., J. O. Kilburn, J. L. Glassroth, D. Snider, L. Farer, and R. Good.** 1978. A continuing survey of primary drug resistance in the United States: March 1975 to November 1977. Am. Rev. Respir. Dis. **118:**835–842.

195. **Kramer, F., T. Modilevsky, A. R. Waliany, J. M. Leedom, and P. F. Barnes.** 1990. Delayed diagnosis of tuberculosis in patients with human immunodeficiency virus infection. Am. J. Med. **89:**451–456.
196. **Kramer, F., S. A. Sasse, J. C. Simms, and J. M. Leedom.** 1993. Primary cutaneous tuberculosis after a needlestick injury from a patient with AIDS and undiagnosed tuberculosis. Ann. Intern. Med. **119:**594–595.
197. **Larson, E. B., H. J. Featherstone, and R. G. Petersdorf.** 1982. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. Medicine (Baltimore) **61:**269–292.
198. **Lecoeur, H. F., C. Truffot-Pernot, and J. H. Grosset.** 1989. Experimental short course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am. Rev. Respir. Dis. **140:**1189–1193.
199. **Levy, S.** 1993. Confronting multidrug resistance. JAMA **269:**1840–1842.
200. **Lin, T., J. Suo, C. Lee, J. Lee, and S. Yang.** 1987. Short-course chemotherapy of pulmonary tuberculosis in pneumoconiotic patients. Am. Rev. Respir. Dis. **136:**808–810.
201. **Lincoln, E.** 1965. Epidemics of tuberculosis. Adv. Tuberc. Res. **14:**152–201.
202. **Lockhart, B., V. Sharp, K. Squires, A. Chopra, and K. Sepkowitz.** 1993. Improved outcome of MDR-TB in patients receiving a five or more drug initial therapy, abstr. PO-B07-1163, p. 329. *In* Program and abstracts 9th International Conference on AIDS 1993.
203. **Louie, E., L. B. Rice, and R. S. Holzman.** 1987. Tuberculosis in non-Haitian patients with acquired immunodeficiency syndrome. Chest **90:**542–545.
204. **Lupatkin, H., N. Brau, P. Flomenberg, and M. S. Simberkoff.** 1992. Tuberculous abscess in patients with AIDS. Clin. Infect. Dis. **14:**1040–1044.
205. **Mahmoudi, A., and M. D. Iseman.** 1993. Pitfalls in the care of patients with tuberculosis. JAMA **270:**65–68.
206. **Malasky, C., T. Jordan, F. Potulski, and L. Reichman.** 1990. Occupational tuberculous infections among pulmonary physicians in training. Am. Rev. Respir. Dis. **142:**505–507.
207. **Manalo, F., F. Tan, J. Sbarbaro, and M. D. Iseman.** 1990. Community-based short-course treatment of pulmonary tuberculosis in a developing nation. Am. Rev. Respir. Dis. **142:**1301–1305.
208. **McAdam, J. M., P. W. Brickner, L. L. Scharer, J. A. Crocco, and A. E. Duff.** 1990. The spectrum of tuberculosis in a New York City men's shelter clinic (1982–1988). Chest **97:**798–805.
209. **McClatchy, J. K., S. W. Kane, P. R. Davidson, and T. S. Moulding.** 1977. Cross-resistance in *M. tuberculosis* to kanamycin, capreomycin and viomycin. Tubercle **58:**29–34.
210. **Medical Research Council.** 1948. Streptomycin treatment of pulmonary tuberculosis. Medical Research Council investigation. Br. Med. J. **2:**769–782.
211. **Medical Research Council.** 1950. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. Medical Research Council investigation. Br. Med. J. **2:**1073–1086.
212. **Medical Research Council—Tuberculosis Chemotherapy Trials Committee.** 1962. Long-term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavitation. Tubercle **43:**201–267.
213. **Medical Research Council Working Party on Tuberculosis of the Spine.** 1986. A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. Tubercle **67:**243–259.
213a. **Menzies, R., B. Vissandjee, I. Rocher, and Y. St. Germain.** 1994. The booster effect in two-step tuberculin testing among young adults in Montreal. Ann. Intern. Med. **120:**190–198.
214. **Merrick, S., J. Walsh, K. A. Sepkowitz, and J. Jacobs.** 1993. Does induced sputum or bronchoscopy increase yield in the diagnosis of tuberculosis? abstr. PO-B07-1222, p. 339. *In* Program and abstracts of the 9th International Conference on AIDS 1993.
215. **Michu, B., K. Gensheimer, G. Bogden, J. Horan, G. Andrews, A. Bloch, and W. Shaffner.** 1992. Tuberculosis outbreak in a shipyard, abstr. 554, p. 203. *In* Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents on Chemotherapy. American Society for Microbiology, Washington, D.C.
216. **Mitchell, J., H. Zimmerman, K. Ishak, U. Thorgeirsson, J. Timbrell, W. Snodgrass, and S. Nelson.** 1976. Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. Ann. Intern. Med. **84:**181–192.
217. **Mitchison, D.** 1990. Pyrazinamide in the chemoprophylaxis of tuberculosis. Am. Rev. Respir. Dis. **142:**1467. (Letter.)
218. **Mitchison, D., and A. Nunn.** 1986. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am. Rev. Respir. Dis. **133:**423–430.
219. **Modilevsky, T., F. Sattler, and P. Barnes.** 1989. Mycobacterial disease in patients with human immunodeficiency virus infection. Arch. Intern. Med. **149:**2201–2205.
220. **Monno, L., G. Angarano, S. Carbonara, S. Coppola, D. Costa, M. Quarto, and G. Pastore.** 1991. Emergence of drug-resistant *Mycobacterium tuberculosis* in HIV-infected patients. Lancet **337:**852. (Letter.)
221. **Moreno, S., J. Baraia-Etxaburu, E. Bouza, F. Parras, M. Perez-Tascon, P. Miralles, T. Vicente, J. C. Alberdi, J. Cosin, and D. Lopez-Gay.** 1993. Risk for developing tuberculosis among anergic patients infected with HIV. Ann. Intern. Med. **119:**194–198.
222. **Morris, J., and C. McAllister.** 1992. Homeless individuals and drug-resistant tuberculosis in South Texas. Chest **102:**802–804.
223. **Mosher, C., J. Derebery, B. Young, and R. Adams.** 1987. Unusually aggressive transmission of tuberculosis in a factory. J. Occup. Med. **29:**29–31.
224. **Mukadi, Y., J. H. Perriens, M. E. St. Louis, C. Brown, J. Prignot, J. Willame, F. Pouthier, M. Kaboto, R. Ryder, F. Portaels, and P. Piot.** 1993. Spectrum of immunodeficiency in HIV-1 infected patients with pulmonary tuberculosis in Zaire. Lancet **342:**143–146.
225. **Nadler, F., J. Berger, J. Nord, R. Cofsky, and M. Saxena.** 1991. Amoxicillin-clavulanic acid for treating drug-resistant *Mycobacterium tuberculosis*. Chest **99:**1025–1026.
226. **Nardell, E.** 1990. Dodging droplet nuclei. Am. Rev. Respir. Dis. **142:**501–503.
227. **Nardell, E., J. Keegan, S. Cheney, and S. Etkind.** 1991. Airborne infection: theoretical limits of protection achievable by building ventilation. Am. Rev. Respir. Dis. **144:**302–306.
228. **Nardell, E., B. McInnis, B. Thomas, and S. Weidhaas.** 1986. Exogenous reinfection with tuberculosis in a shelter for the homeless. N. Engl. J. Med. **315:**1570–1575.
229. **National Committee for Clinical Laboratory Standards.** 1990. Antimycobacterial susceptibility testing. Document M24-P. National Committee for Clinical Laboratory Standards, Villanova, Pa.
230. **New York State Department of Health.** 1992. Control of tuberculosis in hospitals. Series 92-7. Health Facilities Series H-7. New York State Department of Health, Albany.
231. **Nichols, L., B. Florentine, W. Lewis, F. Sattler, M. U. Rarick, and R. K. Brynes.** 1991. Bone marrow examination for the diagnosis of mycobacterial and fungal infections in the acquired immunodeficiency syndrome. Arch. Pathol. Lab. Med. **115:**1125–1132.
232. **Nolan, C. M., A. M. Elarth, H. Barr, A. M. Saeed, and D. R. Risser.** 1991. An outbreak of tuberculosis in a shelter for homeless men. A description of its evolution and control. Am. Rev. Respir. Dis. **143:**257–261.
233. **Nolte, F. S., B. Metchock, J. E. McGowan, Jr., A. Edwards, O. Okwumabua, C. Thurmond, P. S. Mitchell, B. Plikaytis, and T. Shinnick.** 1993. Direct detection of *Mycobacterium tuberculosis* in sputum by polymerase chain reaction and DNA hybridization. J. Clin. Microbiol. **31:**1777–1782.
234. **Noordhoek, G. T., A. H. J. Kolk, G. Bjune, D. Catty, J. W. Dale, P. E. M. Fine, P. Godfrey-Faussett, S. Cho, T. Shinnick, S. B. Svenson, S. Wilson, and J. D. A. van Embden.** 1994. Sensitivity and specificity of PCR for detection of *Mycobacterium tuberculosis*: a blind comparison study among seven laboratories. J. Clin. Microbiol. **32:**277–284.
235. **Ormerod, L.** 1987. Reduced incidence of tuberculosis by prophylactic chemotherapy in subjects showing strong reactions to tuberculin testing. Arch. Dis. Child. **62:**1005–1008.
236. **Ormerod, P., and C. Skinner.** 1980. Reinfection tuberculosis: two cases in the family of a patient with drug-resistant disease. Thorax **35:**56–59.
237. **Osler, W.** 1909. Historical sketch, p. 3–10. *In* A. Klebs (ed.), Tuberculosis, a treatise by American authors on its etiology, pathology, frequency, semeiology, diagnosis, prognosis, prevention and treatment. D. Appleton and Co., New York.
238. **Pablos-Mendez, A., M. Raviglione, and R. Battan.** 1990. Drug-resistant tuberculosis in AIDS. Chest **97:**511–512. (Letter.)
239. **Pao, C. C., T. S. B. Yen, J. B. You, J. S. Maa, E. H. Fiss, and C. H. Chang.** 1990. Detection and identification of *Mycobacterium tuberculosis* by DNA amplification. J. Clin. Microbiol. **28:**1877–1880.
240. **Pape, J. W., S. S. Simone, J. L. Ho, A. Hafner, and W. D. Johnson.** 1993. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet **342:**268–272.
241. **Pearson, M. L., J. A. Jareb, T. R. Frieden, J. T. Crawford, B. J. Davis, S. W. Dooley, and W. Jarvis.** 1992. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*. Ann. Intern. Med. **117:**191–196.
242. **Pelletier, A. R., G. T. DiFerdinando, A. J. Greenberg, D. Sosin, W. Jones, A. Bloch, and C Woodley.** 1993. Tuberculosis in a correctional facility. Arch. Intern. Med. **153:**2692–2695.
243. **Peloquin, C., and S. Berning.** 1994. Infection caused by *Mycobacterium tuberculosis*. Ann. Pharmacother. **28:**72–84.
244. **Peloquin, C. A.** 1992. Shortages of antimycobacterial drugs. N. Engl. J. Med. **326:**714. (Letter.)
245. **Peloquin, C. A., and S. E. Berning.** 1993. Comment: intravenous streptomycin. Ann. Pharmacol. **27:**1546–1547.
246. **Peloquin, C. A., A. A. MacPhee, and S. E. Berning.** 1993. Malabsorption of antimycobacterial medications. N. Engl. J. Med. **329:**1122–1123. (Letter.)
247. **Perriens, J., R. Colebunders, C. Darahunga, J. Willame, J. Jeugman, M. Kaboto, Y. Mukadi, P. Pauwels, R. Ryder, J. Prignot, and P. Piot.** 1991. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive patients compared with HIV seronegative patients with pulmonary tuberculosis treated with standard therapy in Zaire. Am. Rev. Respir. Dis. **144:**750–755.
248. **Petersdorf, R. G., and P. B. Beeson.** 1961. Fever of unexplained origin: report of 100 cases. Medicine **40:**1.
249. **Pierce, J. R., S. L. Sims, and G. H. Holman.** 1992. Transmission of tuberculosis to hospital workers by a patient with AIDS. Chest **101:**581–582.

250. **Pierre, C., D. Lecossier, Y. Boussougant, D. Bocart, V. Joly, P. Yeni, and A. J. Hance.** 1991. Use of a reamplification protocol improves sensitivity of detection of *Mycobacterium tuberculosis* in clinical samples by amplification of DNA. J. Clin. Microbiol. **29:**712–717.
251. **Pitchenik, A.** 1990. Tuberculosis control and the AIDS epidemic in developing countries. Ann. Intern. Med. **113:**89–91. (Editorial.)
252. **Pitchenik, A., J. Burr, and C. Cole.** 1986. Tuberculin testing for persons with positive serologic studies for HTLV-III. N. Engl. J. Med. **314:**447. (Letter.)
253. **Pitchenik, A., J. Burr, M. Laufer, G. Miller, R. Cacciatore, W. Bigler, J. Witte, and T. Cleary.** 1990. Outbreaks of drug-resistant tuberculosis at AIDS centre. Lancet **336:**440–441. (Letter.)
254. **Pitchenik, A., J. Burr, M. Suarez, D. Fertel, G. Gonzalez, and C. Moas.** 1987. Human T-cell lymphotropic virus-III (HTLV-III) seropositivity and related disease among 71 consecutive patients in whom tuberculosis was diagnosed. Am. Rev. Respir. Dis. **135:**875–879.
255. **Pitchenik, A., and H. Rubinson.** 1985. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. Am. Rev. Respir. Dis. **131:**393–396.
256. **Pitchenik, A. E., C. Cole, B. W. Russell, M. A. Fischl, T. J. Spira, and D. E. Snider.** 1984. Tuberculosis, atypical mycobacteriosis and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. Ann. Intern. Med. **101:**641–645.
257. **Pitchenik, A. E., B. W. Russell, T. Cleary, I. Pejovic, C. Cole, and D. E. Snider.** 1982. The prevalence of tuberculosis and drug resistance among Haitians. N. Engl. J. Med. **307:**162–165.
258. **Pitlik, S., V. Fainstein, and G. Bodey.** 1984. Tuberculosis mimicking cancer—a reminder. Am. J. Med. **76:**822–825.
259. **Plikaytis, B. B., B. D. Plikaytis, M. A. Yakrus, W. R. Butler, C. L. Woodley, V. A. Silcox, and T. M. Shinnick.** 1992. Differentiation of slowly growing *Mycobacterium* species, including *Mycobacterium tuberculosis*, by gene amplification and restriction fragment length polymorphism analysis. J. Clin. Microbiol. **30:**1815–1822.
260. **Plunkett, R. E., G. W. Weber, W. Siegal, and R. Donk.** 1940. Development of tuberculosis in a controlled environment. Am. J. Public Health. **30:**229–236.
261. **Pomerantz, M., L. Madsen, M. Goble, and M. D. Iseman.** 1991. Surgical management of resistant *Mycobacterium tuberculosis* and other mycobacterial pulmonary infections. Ann. Thorac. Surg. **52:**1108–1112.
262. **Prego, V., A. Glatt, V. Roy, W. Thelmo, H. Dincsoy, and J. Raufman.** 1990. Comparative yield of blood culture for fungi and mycobacteria, liver biopsy, and bone marrow biopsy in the diagnosis of fever of undetermined origin in human immunodeficiency virus-infected patients. Arch. Intern. Med. **150:** 333–336.
263. **Puffer, R. R., H. C. Stewart, and R. S. Gass.** 1945. Tuberculosis in household contacts associates: the influence of age and relationship. Am. Rev. Tuberc. **52:**89–103.
264. **Puffer, R. R., L. D. Ziedberg, A. Dillion, R. S. Gass, and R. H. Hutcheson.** 1952. Tuberculosis attack and death rates of household associates: the influence of age, sex, race and relationship. Am. Rev. Tuberc. **65:**111–127.
265. **Pyle, M. M.** 1947. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. Proc. Staff Meet. Mayo Clin. **22:**465–472.
266. **Rabalais, G., G. Adams, and B. Stover.** 1991. PPD skin test conversion in health-care workers after exposure to *Mycobacterium tuberculosis* infection in infants. Lancet **338:**826. (Letter.)
267. **Raleigh, J. W., R. H. Wichelhausen, T. A. Rado, and J. H. Bates.** 1975. Evidence for infection by two distinct strains of *Mycobacterium tuberculosis* in pulmonary tuberculosis: report of 9 cases. Am. Rev. Respir. Dis. **112:** 497–503.
268. **Reichman, L.** 1991. The U-shaped curve of concern. Am. Rev. Respir. Dis. **144:**741–742. (Editorial.)
269. **Reichman, L., and T. Jordan.** 1992. Decision analysis comparing the tuberculin screening strategy with BCG vaccine. Am. Rev. Respir. Dis. **145:**732. (Letter.)
270. **Reichman, L. B., and R. O'Day.** 1978. Tuberculous infection in a large urban population. Am. Rev. Respir. Dis. **117:**705–712.
271. **Reider, H. L., G. M. Cauthen, G. D. Kelly, A. B. Bloch, and D. E. Snider.** 1989. Tuberculosis in the United States. JAMA **262:**385–389.
272. **Reves, R., D. Blakey, D. E. Snider, and L. S. Farer.** 1981. Transmission of multiple drug-resistant tuberculosis: report of a school and community outbreak. Am. J. Epidemiol. **113:**423–435.
273. **Riley, L. W., E. Arathoon, and V. D. Loverde.** 1989. The epidemiologic patterns of drug-resistant *Mycobacterium tuberculosis* infections: a community-based study. Am. Rev. Respir. Dis. **139:**1282–1285.
274. **Riley, R., and E. Nardell.** 1989. Clearing the air. Am. Rev. Respir. Dis. **139:**1286–1294.
275. **Roberts, G. D., N. L. Goodman, L. Heifets, H. W. Larsh, T. H. Lindner, J. K. McClatchy, M. R. McGinnis, S. H. Siddiqi, and P. Wright.** 1983. Evaluation of the BACTEC radiometric method for recovery of mycobacteria and drug susceptibility testing of *Mycobacterium tuberculosis* from acid-fast smear-positive specimens. J. Clin. Microbiol. **18:**689–696.
276. **Rodier, G., P. Gravier, J. Sevre, G. Binson, and C. S. Omar.** 1993. Multidrug-resistant tuberculosis in the Horn of Africa. J. Infect. Dis. **168:**523–524.
277. **Rosenberg, T., J. Manfreda, and E. S. Hershfield.** 1993. Two-step tuberculin testing in staff and residents of a nursing home. Am. Rev. Respir. Dis. **148:**1537–1540.
278. **Sacks, J., E. Brenner, D. Breeden, H. Anders, and R. Parker.** 1985. Epidemiology of a tuberculosis outbreak in a South Carolina junior high school. Am. J. Public Health **75:**361–365.
279. **Saiki, R. K., D. H. Gelfand, S. Stoffel, S. J. Scarf, R. Hoguchi, G. T. Horn, K. B. Mullis, and H. A. Erlich.** 1988. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science **239:**487–491.
280. **Saltzman, B., M. Motyl, G. Friedland, J. Mckitrick, and R. Klein.** 1986. Mycobacterium tuberculosis bacteremia in the acquired immunodeficiency syndrome. JAMA **256:**390–391.
281. **Sbarbaro, J.** 1989. To treat or not to treat, that was the question. Am. Rev. Respir. Dis. **139:**865–866. (Editorial.)
282. **Scalicini, M., G. Carre, M. Jean-Daptisue, E. Hershfeld, S. Parker, J. Wolfe, K. Nelz, and R. Long.** 1990. Antituberculous drug resistance in Central Haiti. Am. Rev. Respir. Dis. **142:**508–511.
283. **Schieffelbein, C. W., and D. E. Snider.** 1988. Tuberculosis control among homeless populations. Arch. Intern. Med. **148:**1843–1846.
284. **Schluger, N., and W. Rom.** 1994. Current approaches to the diagnosis of active pulmonary tuberculosis. Am. J. Respir. Crit. Care Med. **149:**264–267.
285. **Selwyn, P., D. Hartel, V. Lewis, E. E. Schoenbaum, S. Vermund, R. Klein, A. T. Walker, and G. H. Friedland.** 1989. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N. Engl. J. Med. **320:**545–550.
286. **Selwyn, P. A., B. M. Sckell, P. Alcabes, G. H. Friedland, R. S. Klein, and E. E. Schoenbaum.** 1992. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA **268:**504–509.
287. **Sepkowitz, K. A.** 1994. Tuberculosis and the health care worker: a historical perspective. Ann. Intern. Med. **120:**71–79.
288. **Sepkowitz, K. A., P. Fella, P. Rivera, N. Villa, and J. De Hovitz.** Prevalence of PPD positivity among new employees at a hospital in New York City. Infect. Control Hosp. Epidemiol., in press.
289. **Sepkowitz, K. A., E. E. Telzak, M. Carrow, and D. Armstrong.** 1993. Fever among outpatients with advanced HIV infection. Arch. Intern. Med. **153:** 1909–1912.
290. **Sepkowitz, K. A., E. E. Telzak, S. Recalde, D. Armstrong, and the New York City Area Tuberculosis Working Group.** 1994. Tuberculosis susceptibility trends in New York City, 1987–1991. Clin. Infect. Dis. **18:**755–759.
291. **Shafer, R. W., K. D. Chirgwin, A. E. Glatt, M. A. Dahdouh, S. H. Landesman, and B. Suster.** 1991. HIV prevalence, immunosuppression, and drug resistance in patients with tuberculosis in an area endemic for AIDS. AIDS **5:**399–405.
292. **Shafer, R. W., D. S. Kim, J. P. Weiss, and J. M. Quale.** 1991. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine (Baltimore) **70:**384–397.
293. **Shafer, R. W., P. M. Small, C. Larkin, P. Kelly, M. F. Sierra, S. P. Singh, G. K. Skoolnick, and K. D. Chirgwin.** 1993. Temporal trends in multidrug-resistant (MDR) TB among HIV− and HIV+ patients at a New York City hospital, abstr. 605, p. 229. *In* Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
294. **Sharp, V., B. Lockhart, K. E. Squires, A. Chopra, and K. A. Sepkowitz.** 1993. Dramatic decrease of MDR-TB after implementing CDC/New York State TB control measures at a New York City outbreak hospital, abstr. PO-B07-1161, p. 329. *In* Program and abstracts of the 9th International Conference on AIDS 1993.
295. **Sharp, V., B. Lockhart, K. E. Squires, and K. A. Sepkowitz.** 1993. Pulmonary tuberculosis with a normal admission chest X-ray: incidence and clinical characteristics, abstr. PO-B07-1243, p. 342. *In* Program and abstracts of the 9th International Conference on AIDS 1993.
296. **Shaw, J., and N. Wynn-Williams.** 1954. Infectivity of pulmonary tuberculosis in relation to sputum status. Am. Rev. Tuberc. **69:**724–732.
297. **Shawar, R. M., F. A. K. El-Zaatari, A. Nataraj, and J. E. Clarridge.** 1993. Detection of *Mycobacterium tuberculosis* in clinical samples by two-step polymerase chain reaction and nonisotopic hybridization methods. J. Clin. Microbiol. **31:**61–65.
298. **Shireman, P.** 1992. Endometrial tuberculosis acquired by a health care worker in a clinical laboratory. Arch. Pathol. Lab. Med. **116:**521–523.
299. **Siddiqi, S. H., C. C. Hwangbo, V. Silcox, R. C. Good, D. E. Snider, Jr., and G. Middlebrook.** 1984. Rapid radiometric methods to detect and differentiate *Mycobacterium tuberculosis*/*M. bovis* from other mycobacterial species. Am. Rev. Respir. Dis. **130:**634–640.
300. **Singapore Tuberculosis Service/British Medical Research Council.** 1981. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis: the results up to 30 months. Tubercle **62:**95–102.
301. **Singapore Tuberculosis Service/British Medical Research Council.** 1985. Clinical trial of three 6-months regimens of chemotherapy given intermit-

tently in the continuation phase in the treatment of pulmonary tuberculosis. Am. Rev. Respir. Dis. **132:**374–378.
302. **Singapore Tuberculosis Service/British Medical Research Council.** 1988. Five-year follow-up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Am. Rev. Respir. Dis. **137:**1147–1150.
303. **Singapore Tuberculosis Service/British Medical Research Council.** 1991. Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Am. Rev. Respir. Dis. **143:**707–712.
304. **Slutkin, G., G. Schecter, and P. Hopewell.** 1988. The results of 9-month isoniazid-rifampin therapy for pulmonary tuberculosis under program conditions in San Francisco. Am. Rev. Respir. Dis. **138:**1622–1624.
305. **Slutsker, L., K. G. Castro, J. W. Ward, and S. W. Dooley.** 1993. Epidemiology of extrapulmonary tuberculosis among persons with AIDS in the United States. Clin. Infect. Dis. **16:**513–518.
306. **Small, P., G. Schecter, P. Goodman, M. Sande, R. Chaisson, and P. Hopewell.** 1991. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N. Engl. J. Med. **324:**289–294.
307. **Small, P., R. Shafer, P. Hopewell, S. Singh, M. Murphy, E. Desmond, M. Sierra, and G. Schoolnik.** 1993. Exogenous reinfection with multidrug-resistant mycobacterium tuberculosis in patients with advanced HIV infection. N. Engl. J. Med. **328:**1137–1144.
308. **Smith, M. H. D.** 1989. Tuberculosis in children and adolescents. Clin. Chest Med. **10:**381–395.
309. **Snider, D., and M. Hutton.** 1989. Tuberculosis in correctional institutions. JAMA **261:**436–437.
310. **Snider, D., and W. Roper.** 1992. The new tuberculosis. N. Engl. J. Med. **326:**735–736. (Editorial.)
311. **Snider, D. E., G. M. Cauthen, L. S. Farer, G. Kelly, J. Kilburn, R. Good, and S. Dooley.** 1991. Drug resistant tuberculosis. Am. Rev. Respir. Dis. **144:**732.
312. **Snider, D. E., J. Graczyk, E. Bek, and J. Rogowski.** 1984. Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin, and pyrazinamide with and without streptomycin. Am. Rev. Respir. Dis. **130:**1091–1094.
313. **Snider, D. E., M. W. Long, F. S. Cross, and L. S. Farer.** 1984. Six-months isoniazid-rifampin therapy for pulmonary tuberculosis: report of a United States Public Health Cooperative trial. Am. Rev. Respir. Dis. **129:**573–579.
314. **Soeiro, R.** 1993. A tale of two mutants. N. Engl. J. Med. **328:**1192–1193. (Editorial.)
315. **Sommers, H. M., and J. K. McClatchy.** 1983. Cumitech 16, Laboratory diagnosis of the mycobacterioses. Coordinating ed., J. A. Morello. American Society for Microbiology, Washington, D.C.
316. **Stack, R., L. Bickley, and I. Coppel.** 1990. Miliary tuberculosis presenting as skin lesions in a patient with acquired immunodeficiency syndrome. J. Am. Acad. Dermatol. **23:**1031–1035.
317. **Stead, W. W.** 1967. Pathogenesis of the sporadic case of tuberculosis. N. Engl. J. Med. **277:**1008–1012.
318. **Stead, W. W.** 1967. Pathogenesis of a first episode of chronic pulmonary tuberculosis in man: recrudescence of residuals or of the primary infection or exogenous reinfection? Am. Rev. Respir. Dis. **95:**729–745.
319. **Stead, W. W.** 1978. Undetected tuberculosis in prison: source of infection for community at large. JAMA **240:**2544–2547.
320. **Stead, W. W.** 1981. Tuberculosis among elderly persons: an outbreak in a nursing home. Ann. Intern. Med. **94:**606–610.
321. **Stead, W. W.** 1987. Annual tuberculosis screening of hospital employees—an idea whose time has not passed. Am. Rev. Respir. Dis. **136:**803–804.
322. **Stead, W. W., T. To, R. W. Harrison, and J. H. Abraham.** 1987. Benefit-risk considerations in preventive treatment for tuberculosis in elderly persons. Ann. Intern. Med. **107:**843–845.
323. **Steele, M., R. Burk, and R. DesPrez.** 1991. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest **99:**465–471.
324. **Steiner, P., M. Rao, M. S. Victoria, J. Hunt, and M. Steiner.** 1983. A continuing study of primary drug-resistant tuberculosis among children observed at Kings County Hospital Medical Center between the years 1961 and 1980. Am. Rev. Respir. Dis. **128:**425–428.
325. **Stoeckle, M. Y., L. Guan, N. Reigler, I. Weitzman, B. Kreiswirth, J. Kornblum, F. Laraque, and L. Riley.** 1993. Catalase-peroxidase gene sequences in isoniazid-sensitive and -resistant strains of *Mycobacterium tuberculosis* in New York City. J. Infect. Dis. **168:**1063–1065.
326. **Sumartojo, E.** 1993. When tuberculosis treatment fails: a social behavioral account of patient adherence. Am. Rev. Respir. Dis. **147:**1311–1320.
327. **Sunderam, G., B. Mangura, J. Lombardo, and L. Reichman.** 1987. Failure of optimal four-drug short-course tuberculosis chemotherapy in a compliant patient with human immunodeficiency virus. Am. Rev. Respir. Dis. **136:**1475–1478.
328. **Sunderam, G., R. McDonald, R. J. Maniatis, T. Oleske, R. Kapila, and L. B. Reichman.** 1986. Tuberculosis as a manifestation of the acquired immunodeficiency syndrome (AIDS). JAMA **256:**362–366.
329. **Takewaki, S. I., K. Okuzumi, H. Ishiko, K. I. Nakahara, A. Ohkubo, and R. Nagai.** 1993. Genus-specific polymerase chain reaction for the mycobacterial *dnaJ* gene and species-specific oligonucleotide probes. J. Clin. Microbiol. **31:**446–450.
330. **Telenti, A., F. Marchesi, M. Balz, F. Bally, E. C. Bottger, and T. Bodmer.** 1993. Rapid identification of mycobacteria to the species level by polymerase chain reaction and restriction enzyme analysis. J. Clin. Microbiol. **31:**175–178.
331. **Tenover, F. C., J. T. Crawford, R. E. Huebner, L. J. Geiter, C. R. Horsburgh, Jr., and R. C. Good.** 1993. The resurgence of tuberculosis: is your laboratory ready? J. Clin. Microbiol. **31:**767–770.
332. **Thierry, D., A. Brisson-Noel, V. Vincent-Levy-Frebault, S. Nguyen, J. L. Guesdeon, and B. Gicquel.** 1990. Characterization of a *Mycobacterium tuberculosis* insertion sequence, IS*6110*, and its application in diagnosis. J. Clin. Microbiol. **28:**2668–2673.
333. **Toossi, Z., J. G. Sierra-Madero, R. A. Blinkhorn, M. A. Mettler, and E. A. Rich.** 1993. Enhanced susceptibility of blood monocytes from patients with pulmonary tuberculosis to productive infection with human immunodeficiency virus type 1. J. Exp. Med. **177:**1511–1516.
334. **Torres, R., S. Mani, J. Altholz, and P. Brickner.** 1990. Human immunodeficiency virus infection among homeless men in a New York City shelter—association with *Mycobacterium tuberculosis* infection. Arch. Intern. Med. **150:**2030–2036.
335. **Twinam, C. W., and A. Pope.** 1942. Pulmonary tuberculosis resulting from extra-familial contacts. Am. J. Public Health **32:**1215–1218.
336. **van Embden, J. D. A., M. D. Cave, J. T. Crawford, J. W. Dale, K. D. Eisenach, B. Gicquel, P. Hermans, C. Martin, R. McAdam, T. M. Shinnick, and P. M. Small.** 1993. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: recommendations for a standardized methodology. J. Clin. Microbiol. **31:**406–409.
337. **Vennema, A.** 1992. Contact investigation and isoniazid chemoprophylaxis in New York City, 1979–1987. N. Y. State J. Med. **92:**185–188.
338. **Wallis, R. S., M. Vjecha, M. Amir-Tahmasseb, A. Okwera, F. Byekwaso, J. Nyole, J. Kabengera, R. D. Mugerwa, and J. J. Ellner.** 1992. Influence of tuberculosis on HIV: enhanced cytokine expression and elevated beta-2-microglobulin in HIV-1 associated tuberculosis. J. Infect. Dis. **167:**43–48.
339. **Weis, S., P. Slocum, F. Blais, B. King, M. Nunn, B. Matney, E. Gomez, and B. Foresman.** 1994. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N. Engl. J. Med. **330:**1179–1184.
340. **Welsh, C.** 1991. Drug-resistant tuberculosis after gastrectomy. Chest **99:** 245–247.
341. **Werhane, M. J., G. Snukst-Torbeck, and D. Schraufnagel.** 1989. The tuberculosis clinic. Chest **96:**815–818.
342. **Wilson, S. M., R. McNerney, P. M. Nye, P. D. Godfrey-Faussett, N. G. Stoker, and A. Voller.** 1993. Progress toward a simplified polymerase chain reaction and its application to diagnosis of tuberculosis. J. Clin. Microbiol. **31:**776–782.
343. **Witebsky, F. G., J. F. Keiser, P. S. Conville, R. Bryan, C. H. Park, R. Walker, and S. H. Siddiqi.** 1988. Comparison of BACTEC 13A medium and Du Pont Isolator for detection of mycobacteremia. J. Clin. Microbiol. **26:**1501–1505.
344. **Yew, W., S. Kwan, W. Ma, M. Khin, and P. Chau.** 1990. In-vitro activity of ofloxacin against *Mycobacterium tuberculosis* and its clinical efficacy in multiply resistant pulmonary tuberculosis. J. Antimicrob. Chemother. **26:**227–236.
345. **Yew, W. W., C. F. Wong, P. C. Wong, J. Lee, and C. H. Chau.** 1993. Adverse neurological reactions in patients with multidrug-resistant pulmonary tuberculosis after coadministration of cycloserine and ofloxacin. Clin. Infect. Dis. **17:**288–289.
346. **Youmans, G. P., E. H. Williston, W. H. Feldman, and H. C. Hinshaw.** 1946. Increase in resistance of tubercle bacilli to streptomycin: a preliminary report. Proc. Staff Meet. Mayo Clin. **21:**126–127.
347. **Zaza, S., H. Blumberg, C. Beck-Sague, C. Parrish, M. Pineda, C. Woodley, J. Crawford, J. McGowan, and W. Jarvis.** 1992. Nosocomial transmission of *Mycobacterium tuberculosis* among health care workers, abstr. 53B, p. 53. Program and abstracts of the 1992 World Congress on Tuberculosis.
348. **Zeidberg, L. D., R. Gass, A. Dillion, and R. H. Hutcheson.** 1963. The Williamson County tuberculosis study. A twenty-four-year epidemiologic study. Am. Rev. Respir. Dis. **87**(Suppl.)**:**1–88.
349. **Zierski, M., E. Bek, M. W. Long, and D. E. Snider.** 1980. Short-course (6 month) cooperative tuberculosis study in Poland: results 18 months after completion of treatment. Am. Rev. Respir. Dis. **122:**879–889.
350. **Zhang, Y., B. Heym, B. Allen, D. Young, and S. Cole.** 1992. The catalase-peroxidase gene and isoniazid resistance of *Mycobacterium tuberculosis*. Nature (London) **358:**591–593.