Evolving Concepts of the Epidemiology, Diagnosis, and Therapy of *Mycobacterium tuberculosis* Infection

JO ELLEN SCHWEINLE, M.D.

Department of Internal Medicine, Section of Infectious Disease, Yale University School of Medicine, New Haven, Connecticut

Received July 18, 1990

Tuberculosis in the United States is evolving in nearly all respects—epidemiology, diagnosis, treatment, and prophylaxis. Today a relatively larger segment of the population has predisposing factors to infection with tuberculosis. There is a greater percentage of people who are elderly, who have immigrated from countries endemic for tuberculosis, or who are immunosuppressed due to medications necessary for other conditions, because of malignancies, or because of infection with HIV. Skin test classifications have been revised to give different meanings to different-sized areas of induration at the injection site for defined populations. More sensitive, more specific, and faster diagnostic laboratory tests for tuberculosis are being developed. Short-course chemotherapy of from six to nine months is now accepted as standard treatment, regardless of exactly which of the proven regimens of antibiotics or accepted lengths of therapy is used. Patient compliance is improved with the shorter courses both for treatment and for prophylaxis. Better compliance with therapy results in better treatment outcomes of infections with *Mycobacterium tuberculosis*.

EPIDEMIOLOGY

Since the beginning of the twentieth century, tuberculosis has declined from being the most common cause of death to a relatively uncommon disease [1–3]. Between 1953 and 1984, the number of cases of tuberculosis reported annually in the United States decreased by 74 percent from 84,304, to 22,255 cases per year, and the annual risk of tuberculosis decreased from 53.0 to 9.4 per 100,000 population [4]. Although the incidence has declined in developed countries, the World Health Organization estimates more than ten million cases and two to three million deaths due to tuberculosis annually [5]. Others estimate that there are at least one billion persons infected with *M. tuberculosis* in the world [6], although, for most, infection is detectable only by tuberculin skin test positivity.

United States

From 1968 through 1978, the average annual decrease in tuberculosis cases in the United States was about 5.9 percent. From 1979 through 1981, the average annual decline was only 1.4 percent. This break in the previous downward trend was due primarily to the influx of Southeast Asian refugees and immigrants from Mexico and the Caribbean [2,7]. An average decline of 6.7 percent from 1982 through 1984 (Fig. 1) indicated resumption of the downward trend [8–10], and, as recently as 1984, it looked as though the national objective of eight cases per 100,000 population per year by 1990 would be met; however, a decline of only 0.2 percent (22,255 to 22,201 cases)

*Abbreviation:* HIV: human immunodeficiency virus

Address reprint requests to: Jo Ellen Schweinle, M.D., P.O. Box 3333, Dept. of Internal Medicine, Yale University School of Medicine, New Haven, CT 06510

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in 1985 [4,11] heralded another slowing of this trend (Fig. 1). In 1986, 22,768 reported tuberculosis cases represented an increase of 2.6 percent. If the downward trend observed between 1981 and 1984 had continued through 1986, 4,832 fewer cases would have been expected. Instead, 567 more cases were actually reported [12]. Previous increases were due to changes in reporting criteria (1963 and 1975) or to a sudden influx of refugees (1980). 1986 represented the first substantial increase in indigenous tuberculosis since 1953, when uniform national reporting was fully implemented.

The number of U.S. tuberculosis cases increased for adults of all racial and ethnic groups except American Indians and Alaskan natives. Cases in children less than five years of age actually decreased substantially. Childhood cases strongly suggest transmission has occurred; thus a decrease in cases of children in the face of an overall increase in total cases signifies that these excess cases may be due to reactivation of latent tuberculous infection rather than increased transmission. Although recent increases in tuberculosis have been reported from many localities, New York experienced the most marked increase. The largest percentage increase was among Hispanics, but the most dramatic increase in number of cases was among non-Hispanic blacks, in whom reported cases almost doubled from 1980 to 1987, primarily in the 30- to 39-year-old age group. In fact, in 1987, there were more cases of tuberculosis among non-Hispanic blacks in the United States than among all non-Hispanic whites [4].

**Connecticut**

In Connecticut, there were 6.3 percent fewer cases of tuberculosis in 1987 compared to 1986, but this was the same rate reported in 1985, continuing a stable trend that began here in 1983. The overall incidence was 5.0 cases per 100,000
population, compared to the high of 18.0 in Hawaii and to the low of 0.6 in Wyoming. Connecticut ranked thirty-third in the nation in case rate. In the four target outreach cities—Bridgeport, Hartford, New Haven, and Stamford—cases decreased from 88 cases in 1986 to 84 cases in 1987. In New Haven, however, the case rate increased from 31 to 36 cases, to exceed the average case rate for United States cities with populations over 250,000 by 46 percent. The number of cases in the five Connecticut cities with populations greater than 100,000 decreased by 4 percent. Although they contain only 19 percent of the state's population, they were responsible for 55 percent of statewide cases. Most of these cases were in the 25- to 34-year-old age group and may be AIDS-related. Other contributing factors may be preferential immigration to urban areas, overcrowding, especially among the homeless, and inadequate staffing to carry out intensive tuberculosis prevention programs in urban areas [13].

RISK FACTORS

Racial

For over 30 years, the decrease in cases was smaller among non-whites than whites, resulting in a continuous rise in the ratio of annual risk of tuberculosis among non-whites to whites (Fig. 2). Based on 1987 statistics, the risk compared to non-Hispanic whites is 11.2 times for Asians and Pacific Islanders, 6.4 times for non-Hispanic blacks, 4.7 times for American Indians and Alaskan natives, and 4.3 times for Hispanics [4]. Two recent papers [14,15] looked at racial differences in susceptibility to infection with \textit{M. tuberculosis}. In Arkansas, Stead et al. found the prevalence of
tuberculosis in black residents of nursing homes was twice as high as in whites [14]. They performed skin tests on all residents upon entry into racially integrated nursing homes and found that 25,398 were initially skin test-negative. Of these, 13.8 percent of the black subjects converted their skin tests, while only 7.2 percent of the whites had evidence of new infection. Blacks were infected more often regardless of the race of the source patient. A single white resident with a positive sputum smear typically infected 17.4 percent of the blacks and 11.7 percent of the whites ($p < 0.001$). A comparable black resident typically infected 12.4 percent of the blacks and 7.7 percent of the whites ($p < 0.001$). Interestingly, upon converting their skin tests, there was no racial difference in the percentage of residents who, in the absence of preventive therapy, were later found to have clinical tuberculosis—11.5 percent of black converters versus 10.6 percent of white converters. Data from three outbreaks in two different prisons also showed that blacks were about twice as likely to become infected. The authors concluded from this study that blacks are more readily infected with *M. tuberculosis*, but that this susceptibility varies independently of factors governing progression to clinical disease.

The second study [15] looked *in vitro* for a cellular basis of the long-held belief that blacks are more susceptible to tuberculosis than whites. Using monocyte-derived macrophages from blacks and whites, the investigators found that black donor phagocytes killed more bacilli during phagocytosis than white donor phagocytes, but bacilli grew consistently and significantly faster in successfully infected macrophages from black donors than from white. The results of the above two studies support the impression that blacks are more likely to become infected with *M. tuberculosis*, perhaps partially explaining their slower decrease in incidence over the years and their marked increase relative to other racial groups with the recent rise in number of cases.

**AIDS**

The rapid increase in New York cases occurred almost exclusively in the 20- to 54-year-old age group, suggesting that endogenous latent tuberculous infection was being reactivated because of some factor particularly prevalent in these young adults [4]. Comparison of citywide registries on AIDS and tuberculosis cases revealed that 5 percent of the first 5,000 adult and adolescent patients with AIDS also had tuberculosis. Fifty-seven percent of tuberculosis/AIDS patients were intravenous drug abusers, whereas only 34 percent of AIDS patients without tuberculosis had this risk factor [16]. Fifty-three percent of a group of male patients between ages 25 and 44 years with tuberculosis were positive for human immunodeficiency virus (HIV) antibody. In Dade County, Florida, 31 percent of consecutively tested patients with tuberculosis were HIV-positive [12], and in San Francisco, California, 28 percent of a study group with tuberculosis were positive by serologic tests for HIV infection [17]. Other studies [18,19] have reported from 20 percent to 60 percent of AIDS patients with tuberculosis. In some geographic areas, tuberculosis may be diagnosed before the patient is known or even suspected to have AIDS. In a prospective study of 520 intravenous drug users, Selwyn et al. [20] clearly demonstrated that although there was little difference in prevalence and incidence of infection with *M. tuberculosis* among HIV-seropositive and HIV-seronegative individuals, only HIV-seropositive subjects with positive tuberculin skin tests had increased risk of developing active tuberculosis within two years. Thus HIV infection seems to be a significant risk factor for developing tuberculosis, especially among some subgroups, just as compromised immunity due to other
disorders is associated with increased risk of developing clinically apparent tuberculosis [21].

Among the infections afflicting AIDS patients, tuberculosis is a unique opportunistic pathogen because untreated *M. tuberculosis* can be transmitted to otherwise healthy individuals, and good, safe, effective therapy exists for tuberculosis. Although early reports suggested AIDS patients with active disease might present with clinically atypical disease [22-26], a more recent study [17] indicated they will have clinically typical tuberculosis that responds well to standard therapy with no greater associated drug toxicity. The treatment for active tuberculosis in HIV-infected persons should include at least three drugs for the first two months. In addition, total duration of treatment should be a minimum of nine months and for at least six months after documented culture conversion [27]. Close monitoring should follow completion of therapy.

The Centers for Disease Control now recommends that a tuberculin skin test be performed on all HIV-infected individuals [27]. Although a skin test may be negative because of anergy, a positive skin test is meaningful. Because they are at increased risk for developing clinical tuberculosis, HIV-infected persons who have or have had in the past a positive tuberculin skin test should receive preventive therapy with isoniazid after active tuberculosis is ruled out regardless of age. Alternatively, HIV testing of all individuals with tuberculosis should be considered [16].

**Age**

The elderly are likely to present with atypical symptoms of tuberculosis. As immune systems decline with aging, senior citizens with healed tuberculous lesions are likely to experience recrudescence of disease. When diabetes, malignancy, corticosteroid therapy, or other debilitating problems are present, relapse rates are even higher. Older citizens may lose former immunity and develop "primary" tuberculosis a second time. Clinical and roentgenographic presentations of initial infections tend to be atypical [28,29]. Thus there exists a potential for prolonged exposure while a lengthy diagnostic work-up is pursued or inappropriate medication is administered. Some investigators [29] feel that nursing home transmission of tuberculosis is much more common than is presently appreciated.

**Other**

Similar to HIV-infected individuals, persons taking immunosuppressive medication are more likely to develop active tuberculosis [4]. Others are at increased risk for tuberculosis because of diseases such as end-stage renal disease requiring maintenance on chronic hemodialysis [30], diabetes, hemophilia, and malnourishment [4]. Persons who are heavy smokers, or who have silicosis, carcinoma of the head or neck, or who have undergone jejunoileal bypass or gastrectomy (or who have achlorhydria for other reasons) have increased risk. Also at risk are persons unlikely to seek medical care or unlikely to comply with treatment regimens (especially alcoholics and drug abusers) [2], North American Indians, inhabitants of ethnic ghettos, prisoners, residents of institutions for the mentally and physically handicapped [31], and immigrants from places with a high prevalence of tuberculosis [4].

**TRANSMISSION**

Tuberculosis is not, however, an easily transmitted disease [2]. Generally, household contacts of cases rather than casual contacts become infected. Of those exposed,
M. tuberculosis is opsonized by the alternative complement pathway for ingestion by monocytes via linking of mycobacteria-bound C3 to complement receptors CR1 and CR3 [32]. This process is important in the pathogenesis of M. tuberculosis, since physiologic functioning of host immunity (both humoral and cell-mediated systems) is subverted by the organism to facilitate entry into cells it will live in, sometimes for decades. The first phagocytic cell to arrive at the site of the infection is the polymorphonuclear leukocyte. Neutrophils are capable of ingesting and killing the tubercle bacillus [33]. The organisms survive intracellularly for years, but the short life of neutrophils makes them unlikely to harbor dormant infections. In fact, mycobacteria hide in macrophages, somehow preventing fusion of phagosomes and lysosomes and avoiding the usually lethal consequences of phagosome-lysosome fusion. Exposure to specific antisera does not destroy infectivity, and, when ingested by macrophages, antiserum-treated bacilli continue to multiply. Replication proceeds despite the fact that antibody-coated mycobacteria permit phagosome-lysosome fusion! It appears that this intracellular parasite has evolved not one, but at least two ways of evading the consequences of lysosomal fusion (reviewed in [34]). The second mechanism probably is related to the ability of one or more mycobacterial products to interact with lysosomal structures essential for lysosomal acidification. Somehow these elements inhibit lysosomal acidification and provide a safe haven for the mycobacteria.

Phagocytosed mycobacteria may lie dormant within granulomas for years and never cause problems for the life of the host. A positive tuberculin skin test reaction may be the only remaining clue to the infection. Alternatively, after years or even decades, the granulomas may break down, and chronic secondary tuberculosis may emerge, usually involving the lungs. Extrapulmonary disease is seen to occur in lymph nodes, pleura, pericardium, peritoneum, intestines, kidneys, adrenals, genitalia, bones, joints, or meninges. One study [35] reported that extrapulmonary tuberculosis accounted for 37 percent of all new cases of tuberculous infection identified during an 11-year period at Waterbury Hospital Health Center, a 552-bed, university-affiliated, community teaching hospital in Connecticut.
TABLE 1
Interpretation of Intracutaneous Mantoux Test

1. A reaction of 5 millimeters or more of induration is classified as positive in the following groups:
   a. Persons who have had close recent contact with tuberculosis
   b. Persons who have chest radiographs consistent with tuberculosis
   c. Immunosuppressed persons

2. A reaction of 10 millimeters or more of induration is classified as positive in persons who do not meet
   the above criteria but who have other risk factors for tuberculosis. These include:
   a. Foreign-born persons from high-prevalence countries in Asia, Africa, and Latin America
   b. Users of intravenous drugs
   c. Homeless individuals
   d. Residents of nursing homes
   e. Residents of correctional institutions
   f. Persons with factors which increase the risk of tuberculosis, such as silicosis, diabetes mellitus, immuno-
      suppressive therapy, some hematologic and reticuloendothelial disease, and clinical situations associ-
      ated with substantial rapid weight loss or undernutrition

3. A reaction of 15 millimeters or more of induration is classified as positive in all other persons.

Intracutaneous with 5TU tuberculin PPD
Reactions below the indicated size in each category are considered negative.

DIAGNOSIS

Tuberculosis is a systemic disease with protean manifestations. Direction of diagnostic studies will be dictated by data obtained from the history, physical examination, roentgenograms, and skin testing.

Skin Testing

Information used to determine whether or not an individual is infected with mycobacteria include results of a tuberculin skin test. The Centers for Disease Control has recently changed the classification of tuberculin skin test reactors which will be contained in the revision of “Diagnostic Standards and Classification of Tuberculosis” to be published as joint American Thoracic Society/Centers for Disease Control statements in the American Review of Respiratory Diseases [36]. The new classification says that reactions to the intracutaneous Mantoux test (with 5TU tuberculin PPD) should be interpreted as follows (Table 1): A reaction of 5 millimeters or more of induration is classified as positive in persons who have recently been in contact with tuberculosis, have chest radiographs consistent with tuberculosis, or who are immunosuppressed. A reaction of 10 millimeters or more of induration is classified as positive in persons who do not meet the above criteria but who have other risk factors for tuberculosis, such as foreign-born persons from high-prevalence countries, intravenous drug users, homeless individuals, residents of nursing homes or of correctional institutions, and persons with factors that increase the risk of tuberculosis, such as silicosis, diabetes mellitus, immunosuppressive therapy, some hematologic and reticuloendothelial disease, and clinical situations associated with substantial rapid weight loss or undernutrition. A reaction of 15 millimeters or more of induration is classified as positive in all other persons. Reactions below the indicated size in each category are considered negative. Although these recommendations appear to be more complicated that those of the past, there are scientific and ethical reasons for making them. The scientific reasons consider factors that influence the sensitivity and specificity of the test and the estimated prevalence of tuberculosis infection in the population tested.
Ethical considerations include the consequences of misclassifying someone as infected or not infected [36]. Of particular concern is the potential spread of tuberculosis by someone who develops active pulmonary tuberculosis all the while believing himself or herself free of infection based on skin test interpretation.

**Stains**

To reach a definitive diagnosis, one must demonstrate *M. tuberculosis* by staining techniques and microscopy and/or culture. Acid-fast staining, such as Kinyoun carbol fuchsin, is quick and inexpensive, but not specific. Other mycobacteria, nocardia, and some legionella are also acid-fast. Some laboratories rapidly screen sputum smears using acid-fast fluorescent dyes that attach to mycobacteria; ultraviolet light activates the dye to produce fluorescence. The sensitivity and specificity of carbol fuchsin and fluorochrome stains are comparable, but examination of fluorochrome-stained organisms is much more efficient. While carbol fuchsin stains must be examined using the 100× oil immersion objective, fluorochrome-stained samples are examined with a 25× objective [37]. There must be about 1 × 10⁴ organisms/ml sputum to detect their presence on smear. With presently available technology, it is important to obtain diagnostic studies early in the disease, preferably before beginning treatment. In the presence of isoniazid therapy alone, the number of organisms drops one log per day the first two to three days. The rate of decline is even greater if rifampin is included in the treatment. Organisms not killed are less hardy and less likely to be recovered by culture on artificial media.

**Cultures**

Ideally, the organism is recovered by culture, allowing distinction of *M. tuberculosis* from other mycobacteria and testing of the isolate for drug susceptibility. Culture is considerably more sensitive than smear techniques but much more expensive and time-consuming. Some laboratories use a BACTEC TB System [38] that may reduce the time required to grow mycobacteria from an average of three weeks to a matter of days. The BACTEC system uses a liquid medium containing a growth-promoting substance, polyoxyethylene stearate, and also containing polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin to suppress growth of contaminating microorganisms. The system detects mycobacterial growth by measuring ¹⁴CO₂ released into the atmosphere above the medium as a result of metabolism of a ¹⁴C-labeled substrate in the media. Although cultures may not be considered negative for growth until they have been observed for at least three weeks, some will show evidence of mycobacterial metabolism in about a week or ten days. Drug susceptibility testing can also be done, as well as tests to differentiate the tuberculosis complex from other mycobacteria. All these techniques are complementary. A positive acid-fast smear considered with other data may allow one to initiate reasonable therapy while waiting for the results of cultures and sensitivity testing.

**Others**

Other laboratory detection techniques have been used experimentally. Measurement of cerebrospinal fluid adenosine deaminase activity to detect meningeal tuberculosis [39] or detection of tuberculostearic acid in sputum by gas chromatography-mass spectrometry [40] are examples. More recently, DNA amplification by polymerase chain reaction, using probes specific for *M. tuberculosis*, has been investigated as a
diagnostic technique [41]. The probes used are particularly interesting because the probe DNA sequence is repeated several times in the bacterial chromosome. These studies may provide a basis for an assay to detect easily very small numbers of \textit{M. tuberculosis} directly in clinical specimen.

Attempts to develop a reliable serologic test for infection with \textit{M. tuberculosis} began shortly after Koch identified the tubercle bacillus. Of late, investigators have focused on developing an enzyme-linked immunosorbent assay for testing serum. As yet, no serologic test with sufficiently high sensitivity and specificity has been produced, although the need for such a technique remains high [42].

**TREATMENT**

\textit{History}

It is now clear that shorter courses of chemotherapy are as successful as more traditional longer courses of antibiotics. Effective chemotherapy began in the mid-1940s, with the discovery of streptomycin. In the early 1950s, a second bactericidal drug, isoniazid, was discovered. Later, p-aminosalicylic acid and ethambutol were available. In the late 1960s, rifampin, a third bactericidal drug, was introduced. Over the next decade, use of isoniazid and rifampin in combination made it possible to shorten therapy from the conventional 18 to 24 months. Complementary bactericidal activities of these two drugs made it possible actually to sterilize tuberculous lesions [43]. Since Dutt et al. [44] reported in August 1984, their success with a nine-month course of chemotherapy administered by local practitioners and public health nurses, experience has proven that treatment for longer periods of time is not necessary for pulmonary or extrapulmonary [45] tuberculosis.

**Effective Treatment Schedules**

Two recent publications [46,47] show that as few as six months of therapy is successful in curing tuberculosis, even when for a significant part of that time medications are administered only twice weekly. In both studies, the subjects took at least two bactericidal drugs, isoniazid and rifampin. Two effective, relatively nontoxic, acceptable treatment schedules emerged from these studies (Table 2). In the work by Combs et al. [46], patients were selected on the basis of having sputum culture isolates of \textit{M. tuberculosis} that were susceptible to the study drugs. About half the subjects were assigned to the six-month regimen and the other half to the nine-month regimen. All patients self-administered isoniazid and rifampin daily for 24 weeks (Table 2 USPHS Tuberculosis Short-Course Chemotherapy). In addition, patients in the six-month regimen took pyrazinamide daily during the first eight weeks. Patients in the six-month regimen had bacteriologic sputum conversion more rapidly than patients on the nine-month regimen, had similar rates of adverse drug reactions, and similar relapse rates 96 weeks after completion of therapy. Of importance is the fact that patients on the six-month regimen had lower noncompliance rates, and a significantly greater proportion successfully completed therapy. Beginning in 1984, a third treatment regimen was added. Some of the patients were treated for six months with Rifater (Merrell Dow Research Institute, Cincinnati, OH), a combination tablet of isoniazid, rifampin, and pyrazinamide. These patients also had successful outcomes. They experienced bacteriologic conversion to negative at a more rapid rate, but they also had a slightly higher rate of adverse effects. The authors concluded that the six-month
### TABLE 2
Acceptable Treatment Regimens for Tuberculosis

**The Denver Metro Center Regimen** [46]

| Regimen | Description |
|---------|-------------|
| First two weeks | Isoniazid, 300 mg*<sup>a</sup>  
Rifampin, 600 mg  
Pyrazinamide, 1.5 g if ≤50 kg body weight; 2.0 g if 51 to 74 kg; 2.5 g if ≥75 kg  
Streptomycin, 750 mg if ≤50 kg body weight; 1.0 g if >50 kg |
| Week 3 through week 8 (given twice weekly) | Isoniazid, 15 mg/kg body weight  
Rifampin, 600 mg  
Pyrazinamide, 3.0 g if ≤50 kg body weight; 3.5 g if 51 to 74 kg; 4 g if ≥75 kg  
Streptomycin, 1.0 g if ≤50 kg body weight; 1.25 g if 51 to 74 kg; 1.5 g if ≥75 kg |
| Week 9 through week 26 (given twice weekly) | Isoniazid, 14 mg/kg body weight  
Rifampin, 600 mg |

**USPHS Tuberculosis Short-Course Chemotherapy**<sup>b</sup> [47]

| Regimen | Description |
|---------|-------------|
| Nine-month regimen (36 weeks) | Isoniazid, 300 mg  
Rifampin, 600 mg |
| Six-month regimen | First eight weeks  
Isoniazid, 300 mg  
Rifampin, 600 mg  
Pyrazinamide, 30 mg/kg body weight  
Week 9 through week 16  
Isoniazid, 300 mg  
Rifampin, 600 mg |

<sup>a</sup>Medications given as one daily dose  
<sup>b</sup>Isoniazid, rifampin, and pyrazinamide given by mouth; streptomycin given intramuscularly  
<sup>c</sup>If *M. tuberculosis* isolates are resistant to isoniazid, change the regimen to rifampin, pyrazinamide, and streptomycin twice weekly, and if resistant to streptomycin, give the above regimen without streptomycin.  
<sup>d</sup>Add daily ethambutol, 15 mg/kg body weight, if patients have a history of previous isoniazid therapy or have emigrated within the past 30 years from a country where a high proportion of tuberculosis patients have drug-resistant disease. Adjust medications when results of sensitivity testing are available.

The regimen was similar in effectiveness, toxicity, and acceptability to the nine-month course for treatment for pulmonary tuberculosis.

Cohn and colleagues [47] studied a 62-dose, six-month regimen (Table 2, Denver Metro Center Regimen) of treatment for pulmonary and extrapulmonary tuberculosis. Patients with known or suspected tuberculosis took isoniazid, rifampin, pyrazinamide, and streptomycin daily for two weeks. Then these drugs were given in higher doses twice weekly for six weeks, followed by isoniazid and rifampin twice weekly for 18 weeks, for a total of 62 doses. All therapy was directly observed by a nurse or an outreach worker. There were no treatment failures among evaluable patients, and only two patients had relapses of pulmonary tuberculosis. Although the group of patients with extrapulmonary tuberculosis contained too few patients to state with certainty that the regimen is effective in treating extrapulmonary tuberculosis, the results are consistent with other reports of the efficacy of six- and nine-month treatment regimens for extrapulmonary tuberculosis [45,48]. No mention is made in this article [45] of the role of surgery in tuberculous osteomyelitis. There is controversy about the benefits of surgery in Pott's disease, but earlier studies [45] showed enhanced healing when early
drainage and complete debridement of necrotic tissue were performed in the presence of bone destruction and abscess formation.

**Monitoring Response and Toxicity**

Rapid sterilizing activity of the four drugs used in the initial phase of the Denver study rendered patients non-infectious more quickly, a characteristic that may be especially important for noncompliant patients. The regimen was no more toxic than others. To follow response and toxicity, these authors recommended the following microbiologic and laboratory monitoring (Table 3): (1) Three sputum specimens for acid-fast bacilli before treatment, one specimen per month during treatment until conversion to culture-negativity, and one specimen after completion of therapy; (2) a complete blood count, liver function tests, and uric acid assessment before treatment and once monthly during treatment; and (3) a chest roentgenogram before treatment, at one month, and after the completion of therapy. Others believe the non-microbiologic laboratory studies need to be performed only if the patient becomes symptomatic for drug toxicity, especially young, otherwise healthy adults without impaired liver function.

**Resistance**

Immigrants who arrive from many geographic areas infected with *M. tuberculosis* may bring with them drug-resistant organisms. In developing nations, resistance of *M. tuberculosis* to the major treatment drugs, especially isoniazid and streptomycin, may occur in 20 percent to 30 percent of new cases. Resistance rates are particularly high among Hispanic and Asian ethnic groups [2]. Drug sensitivity studies [49] on isolates of *M. tuberculosis* from Indochinese immigrants found resistance to one or more drugs in 33 percent of the isolates. Twenty-two percent were resistant to streptomycin, 25 percent to isoniazid, and 3 percent each to rifampin and ethambutol. Fortunately, primary resistance to rifampin and ethambutol is relatively rare, even in areas where resistance to other drugs is common. Inclusion of these two drugs in initial treatment regimens enhances the possibility that the organism will be affected by the regimen.
PROPHYLAXIS

Antimicrobial Agent and Duration

The regimen for prophylaxis against tuberculosis is less well defined. Isoniazid is the only drug proven effective for this purpose. Rifampin may be effective but is untested and expensive and should only be used in extraordinary cases. It is generally accepted that 300 mg of isoniazid taken daily for one year with good compliance reduces disease due to tuberculosis by 90 to 95 percent [50]. Prophylactic treatment for 12 weeks only slightly reduces active disease, whereas a 24-week regimen produces a 65 percent reduction [51]. When all patients are considered together, very compliant and less compliant, one year of therapy with isoniazid improves the protection from overt tuberculosis by 75 percent. This rate is only slightly better than the 65 percent reduction achieved with the 24-week course. The American College of Chest Physicians considered the preventive recommendations at the National ACCP Consensus Conference on tuberculosis [52] in 1985. From this conference came a recommendation for nine months of daily isoniazid for prophylaxis. It was felt that ultimately the recommended schedule will be for only six months. Compliance is likely to be superior in this shorter version of prophylaxis [53,54]. An alternative prophylactic schedule considered by some would be a short course of medications that include rifampin and pyrazinamide if they could be produced and sold at prices substantially lower than their present cost [54].

Even now, if a patient misses more than one month of isoniazid prophylaxis but has completed more than six months of treatment at the time of his lapse, consideration for terminating the program should be given, unless one is convinced the patient will finish the full course. If he or she has completed less than six months at the time of the lapse of more than one month, therapy should be restarted with the goal of completing six subsequent months of therapy. In particularly recalcitrant patients, a goal of a total of six months’ therapy, counting both the months before and months after the lapse, may be considered enough [52].

Candidates for Prophylaxis

Deciding what drugs to use for prophylaxis may be easier than determining who should be treated. The most severe adverse effect associated with isoniazid is hepatitis [55]. Risk for hepatotoxicity increases with age, concomitant use of rifampin, consumption of alcohol on a daily basis, and the presence of liver disease [2]. Persons who rapidly acetylate isoniazid also are at increased risk. For these reasons, isoniazid prophylaxis is recommended for tuberculin reactors (Table 1) less than 35 years old and for reactors of any age who (1) have recently been in contact with an active case, (2) have converted from known negative reaction to positive within the last two years [52], (3) have had tuberculosis in the past with no or inadequate treatment, (4) have a chest radiograph showing stable lesions consistent with tuberculosis (lesions that have not changed after three months’ treatment for active tuberculosis, or (5) have extenuating clinical problems such as silicosis, diabetes mellitus, or compromised immune systems. Isoniazid prophylaxis is safe even in the very elderly when properly monitored [56]. Careful instruction on signs and symptoms of hepatitis should be given, and drug toxicity followed on clinical rather than laboratory bases in uncomplicated patients younger than 35 years of age. Fulminant, fatal hepatitis occurs only when isoniazid is continued despite clinical evidence of hepatitis.
SUMMARY

In summary, the face of tuberculosis in the United States is changing. Increases in the numbers of immigrants, elderly people, and immunosuppressed persons, whether from administration of necessary medications or because of conditions such as lymphatic malignancies or HIV infections, have caused a revision in classification of skin test reactors. New diagnostic laboratory techniques are available or on the horizon. Studies on the efficacy of shorter courses of chemotherapy for clinical tuberculosis have demonstrated that treatment for as short a period as six months produces outcomes comparable to those obtained with longer courses. Successful treatment of clinically apparent tuberculosis and of tuberculous infection is more likely if patient compliance can be assured. Measures should be adopted to enhance compliance with medication regimens regardless of length of treatment.

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