TUBERCULOSIS: A CASE FOR INCREASED SCREENING

Stephen A. Weirich, M.D.
NASA Lewis Research Center

Background

Tuberculosis (TB) has plagued people and animals since antiquity. In the early 20th century and before, this disease was epidemic, responsible for killing hundreds of thousands if not millions of people. In earlier days, tuberculosis had been called phthisis, galloping consumption, and white plague. But with the advent of modern medicine which brought antibiotics and infection control practices, and with improved sanitation techniques, nutrition, and hygiene practices, tuberculosis was quickly following the way of small pox in becoming extinct in developed countries like the United States -- that is, until the 1980's.

In 1953 (the first year of national reporting of diseases in the Unied States), there were 84,304 cases of reported TB in this country. Every year following, the number of cases fell about 5 percent annually, until 1984 when fewer than 22,000 new cases of TB were diagnosed. But in 1985 there was no further decline in the number of tuberculosis cases, and in 1986 there was even a 2.6 percent increase in TB cases. From 1985 to 1991 the number of TB cases jumped 16 percent nationally. In 1991 there were 26,283 new cases of TB reported to the Center for Disease Control (CDC) in Atlanta, and over 1,800 people died of tuberculosis. Not only has there been a significant rise in the number of TB cases over the past seven years, but there have been significant epidemiologic changes in the age, sex, ethnicity, and body site distribution of this disease.

Why the recent resurgence of this old foe in this country? Much of the cause has been blamed on the frightening spread of HIV infection and, while this is a major contributor, it is not the only reason. There have been increasing numbers of immigrants and refugees to the United States from TB-endemic countries in Asia, Africa, and the Pacific Islands. Homelessness, drug abuse, prison overcrowding, and cuts in health care funding have added to the problem. And most recently there has been the emergence of drug-resistance strains of tuberculosis which has caused significant concern. Today it is

estimated that 7 percent of the U.S. population (or 15 million people) are infected with tuberculosis, with over 2 billion people infected worldwide.

Epidemiological Shifts

Tuberculosis is increasingly becoming a disease among minorities in this country. Between 1985 and 1990, the number of tuberculosis cases grew 55 percent among Hispanics, 27 percent among non-Hispanic blacks, and 19.6 percent among Asians and Pacific Islanders. At the same time, the incidence of TB has dropped 7 percent among non-Hispanic whites and Native Americans/Alaskans. Members of racial minority groups are now twice as likely to be infected with tuberculosis as are whites. In 1953, non-whites accounted for 24 percent of all TB cases, whereas in 1990, 70 percent of TB cases occurred in non-whites. Foreign-born persons now comprise 24 percent of TB cases, with 60 percent of these people having been in the United States less than five years. Eighty-six percent of childhood tuberculosis (age less than 15) occurs in minority children.

Urban areas have always had higher rates of tuberculosis, and this continues to hold true today -- 37.6 percent of TB occurs in large cities in this country, while only 18 percent of the U.S. population lives in cities. Between 1985 and 1990, Miami, San Francisco, Newark, Tampa, and New York City have consistently ranked among the 10 cities with populations greater than 250,000 with the highest TB rates. The astonishing corollary to this statistic is that TB is also on the rise in smaller cities and rural areas where, overall, most of the cases still occur.

While TB is still predominantly a concern of older age groups, the greatest increase in the numbers of TB cases since 1985 has occurred in the 25 to 44 year old age group. The national median age at diagnosis of tuberculosis dropped from 49 years old in 1985 to 47 years old by 1987. People over 65 years old represent approximately 30 percent of all cases, and since 1985 the incidence of TB has not increased in this age group.

In AIDS patients, 10 percent have concomitant tuberculosis, with TB increasingly heralding the diagnosis of AIDS in HIV-infected people. In one 1988 study from a New York City hospital, 55 percent of their TB patients were HIV-infected. As the incidence of HIV infection continues to shift from a predominantly homosexual, white, middle-class

population to a more impoverished, heterosexual, inner-city minority population with a higher prevalence of TB infection, the contribution of HIV-related TB mortality could be substantial in some areas. The degree to which the estimated 15 million people with latent TB infection in this country overlaps with the estimated 1.5 to 2 million HIV-infected persons is unknown, but will prove to be an increasingly important factor in the future rate of TB.

Recently there have been horrifying reports of the development of drug-resistant strains of TB, resistance to the usual antibiotics that have traditionally kept TB infection in check. In New York City, as many as 20 percent of the TB patients are infected with *Mycobacterium tuberculosis* that is resistant to both isoniazid and rifampin, and 33 percent of the cases were resistant to one of these antituberculous antibiotics. But this problem is not unique to New York City. Nationwide, during the first three months of 1992, 14.4 percent of all TB cases demonstrated resistance to at least one antituberculous drug, and 3.3 percent of cases were resistant to both isoniazid and rifampin. In contrast, between 1982 and 1986 only 0.5 percent of TB, nationwide, were resistant to both of these drugs.

Pathophysiology of Tuberculosis

The development of tuberculosis is a two-stage process. The first stage is the acquisition of the infection; the second stage is the development of disease after infection. The causative agent is the bacillus called *Mycobacterium tuberculosis* complex, which is comprised of three specific species: *M. tuberculosis, M. bovis,* and *M. africanum.* Infection occurs predominantly by the inhalation of respiratory droplets that are contaminated with *Mycobacterium tuberculosis* complex produced from people with active pulmonary tuberculosis who are coughing. Twenty-five percent of the people exposed to TB develop infection. The probability of acquiring infection is primarily dependent on the risk of exposure to air contaminants with the bacteria and the number of organisms inhaled (inoculum size). Six groups of people who are at higher risk of being infection with tuberculosis have been identified:

1. Persons infected with HIV or who are at high risk of HIV infection.
2. Close contacts of persons known to have or suspected of having infectious tuberculosis (including their health care providers).
3. Foreign-born persons from countries with a high TB prevalence.

4. Medically under-served, low-income populations.
5. Alcoholics and intravenous drug users.
6. Residents of long-term care facilities, correctional institutions, mental institutions, nursing homes, and other long-term residential facilities.

Once the bacteria is inhaled, it harbors in the lungs. The initial infection provokes an immune response mediated by T lymphocytes that activate macrophages. This same cell-mediated response is responsible for the reaction to a TB skin test. This immune response controls the infection by rendering the organism inactive and dormant. Furthermore, this response provides the host with good, although incomplete, protection against exogenous reinfection which is present for as long as the TB skin test is reactive.

Between 85 and 90 percent of those infected with tuberculosis will never develop the disease, and will, therefore, never be contagious. But approximately 10 percent of infected people will develop clinically apparent disease sometime during their lives. Overall, 3.3 percent of those infected will develop active disease within one year after infection. Twelve special clinical situations have been identified as rendering an individual at higher risk for the eventual development of disease if infection with tuberculosis has already occurred:

1. HIV infected.
2. Silicosis.
3. Abnormal chest X-ray showing fibrotic lesions that are likely to represent old, healed TB.
4. Gastrectomy.
5. Jejunoileal bypass.
6. Weight of 10 percent or more <u>below</u> ideal body weight.
7. Chronic malabsorption syndromes.
8. End-stage renal disease.
9. Diabetes mellitus.
10. Conditions requiring prolonged, high-dose corticosteroid therapy or other immunosuppressive therapy.
11. Hematologic disorders, especially leukemia and Hodgkin's disease.
12. Other malignancies, especially carcinomas of the oropharynx and upper GI tract.

Of people with active tuberculous disease, 90 percent have harbored the infection for greater than one year, indicating that the remaining 10 percent have a progression to disease within one year after initial infection.

Ninety percent of active tuberculous disease is pulmonary, with 10 percent of active TB involving extrapulmonary sites, especially the pleura, lymph nodes, bone, kidney, pericardium, meninges, peritoneum, or intestines. The incidence of extrapulmonary TB, which is more difficult to diagnose because of its insidious symptomatology, is increasing sharply among AIDS patients and intravenous drug users. For HIV-infected people there is a 100-fold greater risk of developing disease once infected with TB, with an average rate of 7 to 10 percent of patients infected with both HIV and tuberculosis going on to develop active tuberculous disease each year.

Screening for Tuberculosis

Prior to 1984, epidemiologists and infectious disease specialists expected tuberculosis in this country to be all but obliterated by 1990. Now with the resurgence of TB, public health officials hope to have TB controlled by the year 2010. To achieve this goal the population needs to be screened, especially people who are either in a high risk group for TB infection or those who are at high risk of developing the disease if infected. Those who are discovered to harbor latent tuberculosis infection need to be treated or at least monitored for the development of disease.

Mantoux Skin Test

The preferred screening test for tuberculosis infection is the Mantoux skin test. This test involves the *intradermal* injection of 5 tuberculin units (TU) of purified protein derivative (PPD), which is a filtrate of sterile, killed concentrates from cultures of *tubercle bacilli*. Reaction to the injected PPD is a cellular hypersensitivity reaction characterized by induration of the skin at the injection site (not just erythema) which occurs within 48 to 72 hours (when the test should be read) and is typically sustained for at least 5 days.

The sensitivity and specificity of the Mantoux skin test are both very high, rendering the test diagnostic for the presence of tuberculosis infection. The causes of both false positive and false negative results are outlined in Tables 1 and 2, respectively.

Table 1. Causes of False Positive Tuberculin Reactions

1.	Previous vaccination with BCG.
2.	Cross-reactivity to other non-tuberculous mycobacterial infections.

Table 2. Causes of False Negative Tuberculin Reactions

1.	Active infections a. Viral (e.g., mumps, measles, chicken pox) b. Bacterial (e.g., typhus, overwhelming tuberculosis) c. Fungal.
2.	Live virus vaccines (e.g., MMR, oral polio).
3.	Metabolic/nutritional derangement (e.g., chronic renal failure, severe protein deficiency.
4.	Lymph system diseases (e.g., Hodgkin's lymphoma, sarcoidosis).
5.	Immunosuppression (e.g., corticosteroids, chemotherapy, HIV disease).
6.	Age (newborn or the elderly).
7.	Stress (e.g., burns, post-op, mental illness).
8.	Mechanical (injection too deep, inexperienced reader).
9.	Improper storage of PPD (exposure to light or heat).

Classically, a positive Mantoux skin test was interpreted as 10 mm or more of skin induration. This cutoff was determined on the basis of tests performed in over 275,000 naval recruits between 1958 and 1965. The larger the area of induration, the greater the likelihood that the reaction represents infection with tuberculosis. However, the epidemiology of tuberculosis has changed, and the CDC in 1990 issued new guidelines for the interpretation of the tuberculin reaction, outlined in Table 3.

Table 3. Cutoff Points for Significant PPD Test

1. Reaction > = 5 mm
   a. Persons with HIV infection.
   b. Household or close contact of a patient with infectious tuberculosis.
   c. Persons with chest X-rays consistent with old, healed tuberculosis.

2. Reaction > = 10 mm
   a. Foreign-born persons from countries with high tuberculosis prevalence.
   b. Medically under-served, low-income populations, including high-risk minorities.
   c. Intravenous drug users.
   d. Persons with other medical factors known to increase the risk of development of disease.
   e. Other populations that have been identified locally.

3. Reaction > = 15
   a. All other persons.

Because reaction to PPD requires intact cellular immunity, there is a high rate of anergy to PPD among HIV-infected people whose cellular immunity has been destroyed by the HIV virus. Also, in general, 10 percent of all people with tuberculosis infection (with or without HIV infection) are anergic. Therefore, for HIV-infected people or those who are suspected to be anergic, the CDC recommends the simultaneous intradermal injection of an anergy control panel comprised of *Candida*, mumps, tetanus toxoid and/or trichophyton -- ubiquitous substances which also require intact cellular immunity for a

positive reaction. If a patient develops induration at any of the anergy panel test sites, then he or she is not anergic and the reaction at the PPD site is accurate.

Repeated skin testing of individuals not previously infected with tuberculosis will not cause sensitization to tuberculin. However, delayed hypersensitivity to tuberculin may gradually wane over the years. The stimulus of an initial test may "boost" or increase the size of the reaction following a second test if it is given within one year after the first. This "booster phenomenon" is encountered most frequently in people over the age of 55 who were initially infected with tuberculosis many years earlier, and frequently leads to the inappropriate diagnosis of a new infection.

BCG (*bacille Calmette-Guerin*) Vaccination

The BCG vaccine is an attenuated substrain of *M. bovis* which has been widely used in many countries since 1929. The U.S. and the Netherlands are the only two countries that have never used the BCG vaccine on a national scale. In ten randomized, controlled trials performed since the 1930's, the protective effect against TB rendered by BCG vaccination has ranged from 0 to 80 percent in different populations. The interpretation of a PPD skin test following BCG vaccination is difficult since prior BCG vaccination is a common cause for false positive PPD skin test results. But the probability that a skin test reaction results from infection of tuberculosis increases:

1. When the size of the reaction increases with subsequent skin tests.
2. When the patient is a known contact of a person with tuberculosis.
3. When there is a family history of tuberculosis or when a patient's country of origin has a high tuberculosis prevalence.
4. As the length of time between vaccination and PPD skin testing increases.

Prophylaxis for People with Positive PPD Skin tests

After a patient is determined to be infected with tuberculosis by a true positive PPD skin test, the presence of active disease needs to be ruled out. If there is no evidence of active disease, then chemoprophylaxis with antituberculous medications may be indicated.

Typically, tuberculosis prophylaxis involves taking isoniazid (INH) daily at a dose of 300 mg a day in adults and 10-14 mg/kg (maximum dose of 300 mg) a day in children for 6 months to 1 year. INH prophylaxis is 93 to 98 percent effective in curing TB if a person is 100 percent compliant with his/her treatment. However, because compliance is rarely 100 percent, INH therapy is actually effective between 60 and 80 percent of the time.

The major side effect of INH is the development of drug-induced hepatitis, which is age-related, frequently self-limited, and can occur in up to 10 to 20 percent of people in varying degrees who take the medication. Despite the notoriety of INH-induced hepatitis, the percentage of people who develop it to the point of having to discontinue the drug is actually quite low, as outlined in Table 4.

Table 4. Risk of Isoniazid-Related Hepatitis

Age (years)	Percentage with Hepatitis
0-19	0
20-34	0.3
35-49	1.2
50-64	2.3

Other side effects of INH include drug interactions with phenytoin (Dilantin), where there is an increase in the serum phenytoin levels that can lead to phenytoin toxicity, and disulfiram (Antabuse), where behavioral changes can develop. Also, 1 percent of patients on INH develop a peripheral neuropathy due to pyridoxine (Vitamin B6) deficiency which can be prevented by the administration of pyridoxine at a dosage of 10 to 25 mg a day. Finally, INH can induce a Lupus erythematosus-like syndrome, skin rash, or drug fever.

In general, those who should receive INH prophylaxis among PPD reactors include:

1. Household and close contacts, regardless of age, of infectious TB cases.
2. Newly infected persons, regardless of age, because the risk of developing disease is greatest in the first two years after infection.
3. Persons, regardless of age, with past clinical TB who have not previously been treated with adequate chemotherapy.
4. Persons, regardless of age, with significant reactions to PPD and abnormal chest X-rays (even if asymptomatic).
5. Persons with significant reactions to PPD in the twelve special clinical situations outlined earlier.
6. PPD reactors under the age of 35 years.

Recommendations

Given the worrisome rise in tuberculous disease since 1985, health care providers need to participate in more widespread screening for tuberculosis infection and consider both pulmonary and extrapulmonary disease higher up in their differential diagnoses if it is appropriate given the specific clinical picture. Certainly, if a patient falls into one of the CDC's six high-risk groups for TB infection outlined earlier, then screening for TB is strongly recommended. Similarly, if a patient proves to harbor *M. tuberculosis* complex infection, it may be prudent to encourage that patient to undergo confidential, if not anonymous, HIV antibody testing, given the more fulminant and atypical course of tuberculous disease in HIV-infected individuals.

In an Occupational Health Clinic, certainly all of the health care providers should be screened annually for tuberculous infection, as should facility paramedics and fire fighters. A strong case can be made to include cafeteria workers and security guards in an annual screening program. I also recommend that the PPD status of all employees easily be ascertained by incorporating at least a baseline test, one time, in the employees' annual health physical. The PPD test should then be repeated when an employee reaches the age of 55 or soon thereafter. The cost of PPD (Aplisol) is about $29.25 per 5 cc vial which contains 50 tests, or 58.5 cents per test. The added costs of nursing/physician time and the supplies required to perform the test are truly negligible if the process is incorporated into an already scheduled physical exam. In addition, employees may have

better compliance returning to an office-based health clinic in two or three days to have their PPD test read than would be the case if they had to go to an off-site private physician's office or health center.

When treating sick employees with a nagging cough that has "just hung on," the health care provider needs to strongly consider, along with bronchitis, community-acquired pneumonia, post-viral cough, chronic sinusitis, and asthma, the possibility of whether this could be tuberculous disease, and think about recommending PPD skin testing.

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