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# Preface

Today, as it has been for centuries, tuberculosis remains the leading cause of death in the world from infectious disease. Approximately a third of the world's population has been infected with *Mycobacterium tuberculosis* and is at risk for developing disease. Globally, tuberculosis accounts for almost 3 million deaths annually and one-fifth of all deaths of adults in developing countries. Tuberculosis is a reemergent problem in many industrialized countries. In the modern world of global interdependency, rapid transportation, expanding trade, and changing social and cultural patterns, tuberculosis in any country is a threat to people in every country. In the context of infectious diseases, there is no place in the world from which we are remote and no one from whom we are disconnected.

Current knowledge of evolutionary biology and genetics makes clear that what is at stake in the battle against infectious diseases is the survival not only of human and animal hosts but of the pathogens themselves, a confrontation that cannot be taken lightly. Human interventions serve as selections for genetic mutations, adaptations, and migrations that enable pathogens to survive. While societies traditionally deal with epidemics and outbreaks of infectious diseases in an episodic or discontinuous fashion, the evolutionary process of the pathogens is a continuous one. That elementary truth demands vigilance rather than complacency in applying the tools we have and a continuing scientific effort both to anticipate new threats from infectious pathogens and to develop new tools with which to protect the public health. In the case of tuberculosis, the demise of the disease in the industrialized world has been taken for granted and its persistence in developing countries largely ignored. Support for research dwindled, and the expertise of a generation of scientists and clinicians knowledgeable about tuberculosis was lost.

The current global reemergence of tuberculosis can be attributed to several factors. The compromise of immune mechanisms in human immunodeficiency virus (HIV)-infected individuals that leads either to reactivation of old tuberculous infections or to increased susceptibility to new infection is a major contributor to the increasing incidence of tuberculosis. Other factors are social dislocations, poverty, overcrowding, and a failure to invest in public health infrastructures. Particularly ominous is the emergence of multidrug-resistant tubercle bacilli. In the preantibiotic era, the case fatality rate of untreated tuberculosis was about 50%. With appropriate treatment, cure rates greater than 85% can now be achieved in both HIV-positive and immunocompetent individuals with conventional tuberculosis, even in developing countries. However, the case fatality rates of multidrug-resistant tuberculosis in the United States are about 40% for immunocompetent individuals and over 80% for HIV-infected individuals. Thus, tuberculosis has emerged as a major and devastating global threat to health, and many of the tools currently available for rapid diagnosis, prevention, and treatment are woefully lacking.

The aim of this book is to provide in one volume an overview of the current state of knowledge about tuberculosis and a critical appraisal of the exciting new molecular, immunological, and epidemiological ap-

proaches to understanding and controlling tuberculosis. The emphasis is on research. The authors hope to make existing knowledge and new avenues of research accessible to a new generation of researchers and clinicians. We hope to encourage scientists, clinicians, and students in many disciplines to undertake research on tuberculosis and want to facilitate the rapid generation of new knowledge, insights, and interventions.

Distinguished scientists knowledgeable in major areas of tuberculosis research and control have contributed critical reviews of current understanding and their thoughts on new approaches to each area. For most chapters in this book, I asked world experts to write collaboratively in order to provide balance, multiple perspectives on key issues, and critical delineation of the areas of consensus and contention. The authors were asked to be provocative rather than comprehensive. Our hope is that most chapters will be read with interest by anyone concerned with tuberculosis. Our intention is for the book to serve both as a challenge to scientists knowledgeable about aspects of tuberculosis and as a useful introduction to those with expertise in other disciplines who may wish to apply their knowledge and skills to the problem of tuberculosis. We hope, too, that the book will make accessible to scientists and students in developing countries, where the needs are greatest, the excitement of the new approaches to pathogenesis, resistance, and control.

This book is intended to honor rather than replace some of the classic sources of knowledge about tuberculosis. The classic studies of A. R. Rich (*The Pathogenesis of Tuberculosis*, 2nd ed., 1,028 p., Charles C Thomas, Publisher, 1951) and G. Canetti (*The Tubercle Bacillus in the Pulmonary Lesion of Man*, 226 p., Springer, 1955) on the pathogenesis of the human disease, of L. Barksdale and K.-S. Kim on the characteristics of the genus *Mycobacterium* (*Bacteriological Reviews*, **41**:217–372, 1977), of M. B. Lurie (*Resistance to Tuberculosis: Experimental Studies in Native and Acquired Defensive Mechanisms*, Harvard University Press, Cambridge, Mass., 1964) on experimental tuberculosis, and of K. Styblo (*Epidemiology of Tuberculosis*, Royal Netherlands Tuberculosis Association Selected Papers, vol. 24, The Hague, 1991) on epidemiology remain important reading for any student of the disease. The comprehensive texts edited by C. Ratledge and J. Stanford (*The Biology of the Mycobacteria*, 2 vol., Academic Press, 1981) and G. B. Kubica and L. G. Wayne (*The Mycobacteria: a Sourcebook*, 2 vol., Marcel Dekker, 1984) remain a repository of much valuable information. Yet the revolution in molecular biology, genetics, and immunology and the advances in understanding epidemiology and control of the disease in both developing and industrialized countries now offer far greater opportunities than were previously available for understanding and developing improved interventions in the disease. We hope this book will make a useful contribution to filling that gap in time and knowledge.

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*Chapter 1*

# Global Burden of Tuberculosis

***Dixie E. Snider, Jr., Mario Raviglione, and Arata Kochi***

## INTRODUCTION

The purpose of this chapter is to review the current epidemiology of tuberculosis (TB) in the world. From a global perspective, the magnitude of the TB problem is enormous. Furthermore, unless aggressive intervention is undertaken soon, the worldwide situation concerning TB will deteriorate rapidly; during this decade, nearly 90 million new cases will occur and 30 million people will die from TB. The disease is now the world's foremost cause of death from a single infectious agent.

Although in this chapter we concentrate on the number of new cases of and deaths from this disease, we recognize that these data do not fully describe the effect of the disease on the population. For example, we have not discussed the economic impact of the disease: direct and indirect costs of treatment of cases and suspected cases, costs of contact investigations, costs of TB screening and preventive therapy programs (where these are used), costs of hospital and institutional infection control programs, and costs to patients in lost income. An increasing number of cases due to organisms multiply resistant to anti-TB drugs could escalate these costs dramatically.

Other factors we do not discuss in this chapter are the frequency of early and late complications and the impact of these complications on morbidity, mortality, and costs. There are few data on the frequency with which complications occur.

We also do not discuss the social impact of TB on the population: for example, loss of employment, decreased likelihood of marriage (especially for women), and creation of orphans and one-parent households. Again, few or no current data in the literature address these issues.

Ideally, we would like to present the exact numbers of new cases of TB and deaths from TB that occur each year. Unfortunately, disease surveillance in many countries is too incomplete to provide this information (Styblo and Rouillon, 1981). Because of this limitation, the burden of TB must be estimated indirectly by using several epidemiological parameters, including the average annual risk of TB infection, the reported incidence of smear-positive pulmonary TB, the estimated coverage of the population by health care services, the estimated proportion of all cases of TB that are smear-positive, and the estimated case-fatality rates for smear-positive and other forms of TB.

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## Tuberculosis Infection

The ability of the tuberculin skin test to detect the presence of *Mycobacterium tuberculosis* infection can be used to measure the prevalence of infection. A method for converting the prevalence of infection into the annual risk of infection has been developed (Styblo et al., 1969; Sutherland, 1976). The annual risk of infection is the probability that any individual will be infected with *M. tuberculosis* in 1 year. If several tuberculin surveys of the same population have been done at different times (using similar techniques and testing a representative sample of non-BCG-vaccinated subjects of the same age), the trend in the annual risk of infection can be estimated. In the absence of good surveillance systems to detect and report incident cases, calculating the annual risk of infection is a valuable technique for estimating the magnitude of the TB problem. Although there are limitations to this approach, Styblo has shown that a 1% annual risk of infection corresponds, on average, to an incidence of 50 smear-positive cases per 100,000 population (Murray et al., 1990).

Cauthen and Ten Dam (1988) have used the results of tuberculin skin test surveys done in developing countries since the 1950s to estimate the annual risks of infection in different regions of the developing world (Table 1). The annual risk of tuberculous infection is probably highest in sub-Saharan Africa, followed closely by risk in Southeast Asia.

Kochi (1991) has estimated that about one-third of the world's population, or about 1.7 billion people, is infected with *M. tuberculosis*. The great majority of the world's population, and thus the majority of infected persons, reside in developing countries. In industrialized countries, 80% of infected individuals are aged 50 years or more, while in developing countries, 75% of infected persons are less than 50 years old (Kochi, 1991).

**Table 1.** Estimated annual risk of TB and trends in developing countries, 1985 to 1990[a]

| Area(s) | Estimated annual (%): | |
|---|---|---|
| | Risk of infection | Decrease in risk |
| Sub-Saharan Africa | 1.5–2.5 | 1–2 |
| North Africa and western Asia | 0.5–1.5 | 5–6 |
| Southeast Asia | 1.0–2.0 | 1–3 |
| South America | 0.5–1.5 | 2–5 |
| Central America and Caribbean | 0.5–1.5 | 1–3 |

[a] Based on data in Cauthen and Ten Dam (1988).

## Annual Incidence of Disease and Death

Table 2 shows the distribution of the present burden of cases and deaths. Over 8 million cases of TB occurred in 1992. Of these cases, 3.3 million were in the World Health Organization's (WHO's) Southeast Asian region, 1.9 million were in the western Pacific region, 1.2 million were in sub-Saharan Africa, and 1.6 million, including 199,000 cases in industrialized countries, were in the remainder of the world. TB has a devastating effect in the developing world, where 95% of cases occur. Eighty percent of these cases occur in persons who are in their productive years (ages 15 to 59). According to a 1989 WHO report, 1.3 million cases and 450,000 deaths from TB in developing countries occur in children under the age of 15 years (World Health Organization, 1989).

In the prechemotherapy era, mortality from TB was about 50 to 60% (Murray et al., 1990). Today, death rates in developing countries are not as high because a significant proportion of cases are detected and treated.

Nevertheless, an estimated 2.7 million persons died from TB in 1992: 1.1 million in the Southeast Asian region, 672,000 in the western Pacific region, 468,000 in the African region, and 426,000 in the remainder of the world (Table 2). TB causes over 25% of

**Table 2.** Estimated global TB incidence and mortality in 1992

| Area | Incidence | | Mortality | |
|---|---|---|---|---|
| | No. of cases | Rate[a] | No. of deaths | Rate[a] |
| Southeast Asia | 3,263,000 | 240 | 1,142,000 | 84 |
| Western Pacific[b] | 1,921,000 | 136 | 672,000 | 48 |
| Africa | 1,182,000 | 214 | 468,000 | 85 |
| Eastern Mediterranean | 683,000 | 166 | 266,000 | 65 |
| Americas[c] | 584,000 | 128 | 117,000 | 26 |
| Eastern Europe | 197,000 | 47 | 29,000 | 7 |
| Industrialized countries[d] | 199,000 | 22 | 14,000 | 2 |
| All regions | 8,029,000 | 146 | 2,708,000 | 49 |

[a] Per 100,000 population.
[b] All countries of the region except Australia, Japan, and New Zealand.
[c] All countries of the region except Canada and the United States.
[d] Western Europe plus Australia, Canada, Japan, New Zealand, and the United States.

avoidable adult deaths in the developing world (Murray et al., 1990).

### Impact of the HIV-AIDS Epidemic

The pandemic of human immunodeficiency virus (HIV) infection and the evidence of an association between tuberculosis and HIV infection has caused marked increases in the incidence of TB in some countries. Because of its ability to destroy the immune system, HIV has emerged as the most significant risk factor for progression of dormant TB infection to clinical disease (Selwyn et al., 1989).

The Global Programme on AIDS of the WHO estimated that in 1992 at least 13 million adults and 1 million children had been infected with HIV worldwide (World Health Organization, 1993). Nearly 85% of HIV infections have occurred in developing countries, and the vast majority have occurred in the age group 15 to 49 years.

It is estimated that about 1,700 million people are infected with *M. tuberculosis* (Kochi, 1991). The impact of HIV infection on the TB situation is greatest in those populations where the prevalence of TB infection in young adults (who are at greatest risk of HIV infection) is high. By using estimates of the prevalence of TB infection in various regions, it has been estimated that since the beginning of the HIV pandemic until mid-1993, more than 5 million persons worldwide have had dual HIV and TB infection. A great majority (3.8 million) of these patients lived in sub-Saharan Africa (Fig. 1). HIV seroprevalence rates of more than 40% are common among patients with TB in many African countries. The annual risk of progression to active TB among individuals infected with both HIV and TB is 5 to 10% (Narain et al., 1992).

The result of this increased risk is evident from the reported numbers of TB cases in several countries. After years of declining incidence of the disease, the number of reported cases of TB increased dramatically during the 1980s in many countries in sub-Saharan Africa. Within a 7-year period from 1985 to 1991, the annual number of cases in Zambia nearly tripled, that in Malawi more than doubled, and those in Tanzania and Burundi increased by about 70 and 40%, respectively. The numbers of deaths from TB have also increased in these countries (Narain et al., 1992).

The situation in some countries in Southeast Asia and the western Pacific is now similar to that in Africa several years ago. Since almost two-thirds of the world's TB-infected population is in Asia, entry of HIV into Asian communities may result in large increases in HIV-associated TB in the coming years. In Bombay, HIV seroprevalence

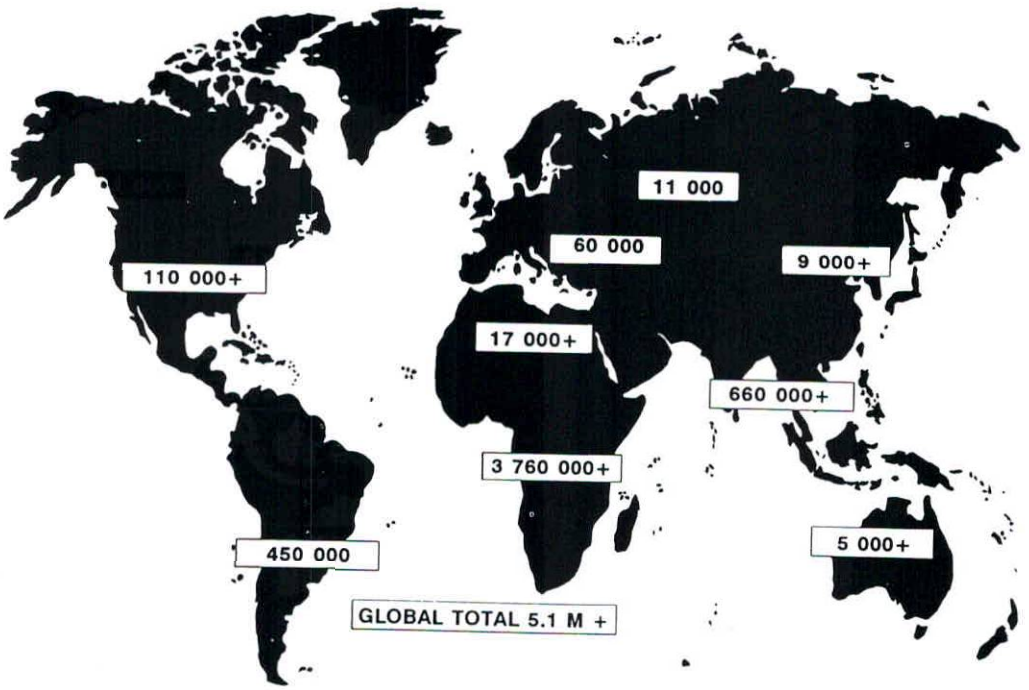


**Figure 1.** Estimated global distribution of adults who have been infected with HIV and TB, as of mid-1993. Source of data is WHO Tuberculosis Programme.

among TB patients increased from 2% in 1988 to 10 to 15% in 1991 and 1992. In northern Thailand, HIV seroprevalence in TB patients increased from 5% in late 1989 to 15% in 1992, and there is evidence that the incidence of TB is increasing (World Health Organization, unpublished data).

In many developing countries, TB has emerged as the most common opportunistic disease associated with HIV infection. Twenty to forty-four percent of AIDS patients in Africa, 18% of patients in Haiti, and up to 25% of patients in some Latin American countries, namely Brazil, Mexico, and Argentina, had clinical TB during the course of HIV infection (Narain et al., 1992).

It is still unclear how the increasing numbers of HIV-positive patients with TB will affect the transmission of TB in the community. It is possible that the increase in the number of TB cases will increase TB transmission to both HIV-positive and HIV-negative populations. Nevertheless, preliminary data from the second round of the National Tuberculin Survey in Tanzania, where the TB control program has achieved an 80% cure rate of patients with newly diagnosed smear-positive cases during the last 5 years and a 65% case detection rate, suggest that the prevalence of infection in school children did not change appreciably from 1983–1985 to 1989–1991, despite the increase in the number of detected new smear-positive cases (Narain et al., 1992). Thus, a good control program may be able to reduce to some extent the increased chance of transmission.

HIV-infected patients with TB also have a higher incidence of noninfectious extrapulmonary forms of disease and higher mortality rates and thus may have a lesser impact on transmission than non-HIV-infected TB patients.


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## TUBERCULOSIS IN INDUSTRIALIZED COUNTRIES

### United States

From 1953, when national surveillance began, through 1984, the United States experienced a significant decline in TB cases: from 84,304 cases in 1953 to only 22,225 cases in 1984. The average annual decline in cases was about 5.3% per year. From 1985 to 1992, however, the number of reported cases has increased by about 20%. Using the trend for 1980 to 1984 to calculate the number of expected cases, the Centers for Disease Control and Prevention (CDC) estimates that from 1985 through 1992, about 51,000 excess cases have accumulated (Fig. 2). Case rates in urban areas have increased more rapidly than those in rural areas.

Of the 26,673 TB cases reported in 1992, 71% occurred in racial and ethnic minorities. From 1985 to 1992, TB case numbers declined about 10% among non-Hispanic whites and 23% among Native Americans. However, case numbers increased 27% among blacks, 46% among Asians and Pacific Islanders, and 75% among Hispanics.

From 1985 through 1992, all age groups, except that of patients 65 years of age and older, experienced an increase in number of cases. The largest numerical and percentage increases (+3,686; +55%) were among persons 25 to 44 years of age. However, there was a 36% increase in case numbers among 0- to 4-year-old patients and a 34% increase among children 5 to 14 years old.

Of all patients with TB reported to the CDC in 1992, 27% were born in another country. The numbers and percentages of foreign-born patients increased from 4,925 and 22% in 1986 to 7,270 and 27% in 1992.

In addition to the effect of immigration on the change in the TB morbidity trend, there is evidence that the HIV epidemic is at least in part contributing to this change. The

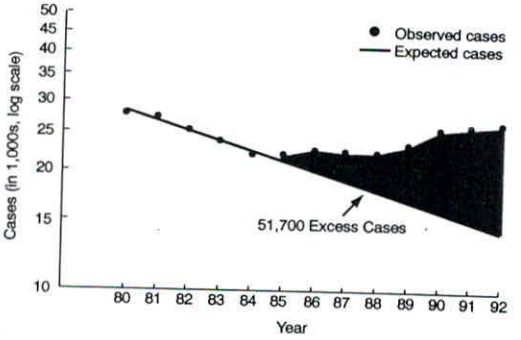


**Figure 2.** Numbers of expected and observed cases of TB in the United States from 1980 through 1992. Table is from the CDC (Centers for Disease Control and Prevention, 1993).

largest increases in reported TB case numbers have occurred in geographic areas and age groups heavily impacted by the HIV epidemic. TB prevalence among AIDS patients is high. Matching of TB and AIDS registries through 1990 revealed that 4.9% of reported AIDS cases were also in the TB registry (CDC, unpublished data). CDC HIV seroprevalence surveys in TB clinics have shown a high prevalence of HIV infection among TB patients. Pooled seroprevalence data from 13 cities that tested at least 50 serum samples per year for 1989, 1990, and 1991 showed seroprevalence rates of 13.1% in 1989, 17.8% in 1990, and 21.4% in 1991. Trend analysis from 1989 through 1991 also showed significant upward trends in HIV seroprevalence among black, Hispanic, and white males with TB or suspected TB. Among females, the upward trend was significant only for blacks (Onorato et al., 1993).

The United States has also experienced an increasing number of outbreaks of TB. Outbreaks have occurred in a variety of settings, including hospitals, correctional facilities, shelters for the homeless, residential care facilities for patients with AIDS, nursing homes, and even crack houses.

The most serious problem has been the outbreaks of multidrug-resistant TB (MDR-

TB), i.e., outbreaks due to organisms resistant to isoniazid and rifampin (and often other drugs as well). From 1990 through 1992, the CDC investigated outbreaks of MDR-TB in eight hospitals and a state correctional system. As of November 1992, 297 cases of MDR-TB had been identified in these outbreaks. Most but not all of the cases occurred in persons infected with HIV. Mortality was high (about 70%), and the median interval from TB diagnosis to death was short (4 to 16 weeks). The outbreak investigations demonstrated transmission of infection to health care workers. At least 17 health care and correctional workers have developed active TB with multidrug-resistant organisms (CDC, unpublished data).

Factors contributing to nosocomial outbreaks include the convergence of highly susceptible, immunocompromised patients and TB patients; the delayed recognition of TB (because of unconsidered diagnoses, nonclassical radiographic findings, and laboratory delays); the delayed recognition of drug resistance; and the delayed initiation of effective anti-TB treatment. Other factors contributing to nosocomial transmission include delayed initiation of isolation, inadequate ventilation for acid-fast bacillus (AFB) isolation, lapses in maintaining AFB isolation, inadequate duration of AFB isolation, and inadequate precautions during cough-inducing procedures.

## Tuberculosis in Other Industrialized Countries

Seven of 15 Western European countries (Denmark, Ireland, Italy, Netherlands, Norway, Spain, and Switzerland) have also recently experienced increases in reported cases (Raviglione et al., 1993). The major factor responsible for most of these increases appears to be immigration from higher-prevalence countries. However, in Italy, 11.4% of AIDS patients reported during the biennium 1988 through 1989 had TB (Raviglione et al., 1993).

In Australia, death rates have remained stable at about 0.4/100,000, and notification rates of all cases have slightly increased from 5.6/100,000 in 1986 to 5.9/100,000 in 1990 (Cheah, 1992a). The HIV epidemic has had little impact on the TB situation in Australia. Two-thirds of the new patients reported in 1991 were foreign born (Cheah, 1992b).

In Canada, a similar stagnation of notifications and rates has been observed over the past 6 years. In 1991, 2,044 cases were reported (rate, 7.6/100,000). Foreign-born patients constituted 48% of all patients in 1989, and native Canadians constituted 20% of patients. TB mortality rates were stable at around 0.5/100,000 during recent years (WHO, unpublished data [from the Canadian Centre for Health Information, Ottawa]).

In Japan, the downward trend of TB notifications continues. The average decline between 1980 and 1991 has been 3.5% per year. However, this decline is smaller than that seen in previous years. Furthermore, the incidence of sputum-smear-positive cases has steadily increased since 1980. In general, mortality rates have regularly decreased at about 4.6% per year since 1980 (WHO, unpublished data [from the Japan Anti-Tuberculosis Association, Tokyo]).

In New Zealand, case notifications have recently increased from a nadir in 1988 of 295 cases reported. In 1991, 335 cases were reported (rate, 9.9/100,000). Mortality rates have decreased from 0.9 to 0.5/100,000 during the period 1980 to 1990 (WHO, unpublished data [from the New Zealand Department of Health, Wellington]).

In Israel, TB notifications, after being stable in the 1980s, recently increased to 505 in 1991 (rate, 10.2/100,000). However, if rates for Ethiopian immigrants are excluded from the data, the rate among native Jews in 1991 was 4.6/100,000 and that

among native non-Jews was 3.7/100,000. Ethiopians, who generally constitute less than 25% of all cases, constituted 50% of all cases in 1985 and 55% of all cases in 1991, following two waves of migration (Operation Moses and Operation Shlomo) (WHO, unpublished data [from the Israel Ministry of Health, Jerusalem]).

In Turkey, TB notifications during the past few years have decreased, and in 1990, 24,468 cases were reported (rate, 43.8/100,000) (WHO, unpublished data [from the Turkish Ministry of Health, Ankara]).

## DRUG RESISTANCE

Acquired resistance is defined as resistance to at least one anti-TB drug that arises during or after the course of treatment, usually as a result of nonadherence to the recommended regimen or of faulty prescribing. A high level of this type of resistance is a mark of a poorly functioning TB control program.

Primary resistance is defined as the presence of drug resistance to at least one anti-TB drug in a TB patient who has never received prior treatment. It is caused by infection with drug-resistant specimens from another patient excreting a drug-resistant organism; many of these patients acquired resistance as a result of inadequate treatment. Thus, primary resistance is an indicator of efficacy of TB control efforts in the past (Weyer and Kleeberg, 1992).

An accurate picture of the drug resistance problem in the world is not available, because only a limited number of countries (both industrialized and developing) have a reliable drug resistance surveillance system. However, limited available information indicates that, generally speaking, many industrialized countries that faced severe MDR-TB in the late 1950s and early 1960s successfully reduced the problem in a rather short time by improving application of the same regimen used previously and by successfully introducing rifampin-containing short-course chemotherapy. Thus, the incidence of acquired resistance was substantially reduced, and the incidence of primary resistance remains relatively low. In many developing countries, particularly in Asia, the incidence of acquired resistance remains high and the incidence of primary resistance is higher than that in industrialized countries, because national TB control programs in the developing countries have not been able to achieve a high cure rate over a very long period, even after the introduction of short-course chemotherapy.

This already serious situation may quickly worsen as the HIV epidemic spreads. The HIV epidemic may produce increased levels of both acquired and primary resistance not only by overtaxing the national TB control programs as a result of increased caseload but also by affecting compromised immunity (Kochi et al., 1993).

## FUTURE TRENDS

Without recognition of the TB crisis confronting the world and prompt, effective action, the TB epidemic can be expected to worsen for several reasons.

First, demographic forces are at work. Children born in past decades in regions with high population growth rates are now reaching the ages at which morbidity and mortality for TB are high. Even if the age-specific rates of new cases do not increase, the changing sizes of the population age groups will now begin to cause a large increase in the number of TB deaths and new cases.

Second, famine, war, and natural disasters that create large populations of displaced, malnourished people in crowded living conditions may cause increases in TB case rates.

Third, age-specific TB incidence rates can be expected to rise in those areas of the

world where immunity of the population is seriously challenged by HIV infection. By mid-1993, the global cumulative number of persons coinfected with HIV and tubercle bacilli since the beginning of the HIV pandemic was estimated to be over 5 million (Fig. 1). In addition, HIV seroprevalence among TB patients is expected to increase further in areas like sub-Saharan Africa and to increase at least threefold in areas like Southeast Asia during the next decade. As a result, while about 315,000 persons are estimated to have developed HIV-associated TB in 1990, more than 700,000 people are expected to develop HIV-related TB in 1995. In the year 2000, the figure may reach 1.4 million. In 1990, 4.2% of all TB cases were associated with HIV; in the year 2000, an estimated 13.8% of all TB cases may be associated with HIV (Dolin et al., in press).

In addition, there is the threat of the increasing incidence of drug-resistant strains. This phenomenon is largely a consequence of poorly managed and inappropriately focused TB programs and is accelerated and amplified by the HIV coinfection epidemic. Drug-resistant strains are as contagious as the normal TB bacillus. The cure rates of at least 95% that can be achieved for regular TB fall to 70% or less when isoniazid and rifampin resistance occurs.

If the effectiveness and availability of TB control do not improve substantially over those existing now, more than 30 million TB deaths and 90 million new cases are expected to occur in the last decade of this century. Conservative estimates indicate that the incidence of TB can be expected to increase to 8.8 million cases annually by 1995, 10.2 million cases annually by the year 2000, and 11.9 million cases annually by 2005 (Dolin et al., in press). Demographic factors will account for three-quarters of the predicted increase in new cases. Assuming that the availability and effectiveness of treatment programs remain at the 1990 level, 3 million TB deaths can be expected to occur annually by 1995, and 3.5 million deaths will be occurring annually by the year 2000. Action must be taken now to avert this global health disaster.

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*Chapter 3*

# Overview of Clinical Tuberculosis

***Philip C. Hopewell***

The clinical expression of infection with *Mycobacterium tuberculosis* is quite varied and depends on a number of identified factors. Table 1 lists both host- and microbe-related characteristics as well as the consequences of their interactions that influence the manifestations of tuberculous infection. Among generally healthy persons, infection with *M. tuberculosis* is highly likely to be asymptomatic. Data from a variety of sources suggest that the lifetime risk of developing clinically evident tuberculosis after being infected is approximately 10%, with a 90% likelihood of the infection remaining latent (Comstock, 1982). Only a positive tuberculin skin test indicates the presence of the organism in persons with latent infections. In specific subpopulations, for example, in persons with immunodeficiency states or in infants, the proportions who develop evident tuberculosis are much higher (Allen et al., 1992; Comstock, 1982; Selwyn et al., 1992).

Immunization with bacillus of Calmette and Guérin (BCG) in persons with intact cell-mediated immunity minimizes the risk of early disseminated tuberculosis, especially in children. In addition to host factors, there probably are factors related to the organism itself, such as its virulence or predilection for specific tissues, that influence the outcome and features of the infection; however, these features of the organism have not been characterized.

The most obvious and important factor influencing the clinical features of tuberculosis is the site of involvement. Prior to the beginning of the epidemic of infection with the HIV, approximately 85% of reported tuberculosis cases were limited to the lungs, with the remaining 15% involving only nonpulmonary sites or both pulmonary and nonpulmonary sites (Farer et al., 1979) (Fig. 1). This proportional distribution is substantially different among persons with HIV infection. Although there are no national data that describe the sites of involvement in HIV-infected persons with tuberculosis, in one large retrospective study of tuberculosis in patients with advanced HIV infection, it was reported that 38% had only pulmonary involvement, 30% had extrapulmonary sites, and 32% had both pulmonary and nonpulmonary involvement (Small et al., 1991). The multiplicity of sites in HIV-infected persons is typical of what is seen in an individual having an immune system that is limited in its ability to contain infection with *M. tuberculosis*. Included in this category are infants, the elderly, and persons with pri-

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**Table 1.** Factors influencing the clinical features of tuberculosis

| Host factors | Microbial factors | Host-microbe interaction |
|---|---|---|
| Age | Virulence of organism (?) | Sites of involvement |
| Immune status | Predilection (tropism) for specific tissues (?) | Severity of disease |
| Specific immunodeficiency states | | |
| Malnutrition | | |
| Genetic factors (?) | | |
| Coexisting diseases | | |
| Immunization with bacillus of Calmette and Guérin (BCG) | | |

mary or secondary immunodeficiency states resulting from coexisting diseases or malnutrition.

## SYSTEMIC AND REMOTE EFFECTS OF TUBERCULOSIS

Tuberculosis occurring at any site may produce symptoms and findings that are not specifically related to the organ or tissue involved but, rather, are systemic in nature or are remote from the site of disease. Systemic manifestations of the disease, including fever, malaise, and weight loss, are likely mediated by cytokines, especially tumor necrosis factor alpha (TNF-α). Experimental data suggest that TNF-α is an important mediator of the systemic effects of the disease (Takashima et al., 1990; Valone et al., 1988). Of the systemic effects, fever is the most easily quantified. The frequency with which fever has been observed in patients with tuberculosis varies from approximately 37 to 80% (Arango et al., 1978; Kiblawi et al., 1981). In a study by Kiblawi and coworkers (Kiblawi et al., 1981) in which the fever response was specifically examined, 21% of patients had no fever at any point in the course of hospitalization for tuberculosis. Of the febrile patients, 34% were afebrile within 1 week and 64% were afebrile within 2 weeks. The median duration of fever after beginning treatment was 10 days, with a range of 1 to

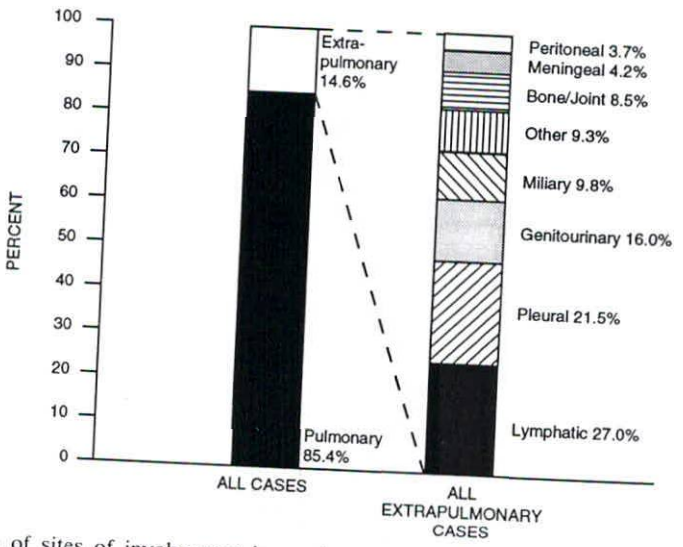



**Figure 1.** Distribution of sites of involvement in newly reported cases of tuberculosis in 1978 prior to the epidemic of infection with HIV.

109 days. Weight loss, weakness, and malaise appear to be less common but are more difficult to quantify.

In addition to these generalized effects of tuberculosis, there are remote manifestations that are not a result of the anatomic site of involvement. These include hematologic abnormalities, hyponatremia, and psychological disorders. The most common hematologic manifestations of tuberculosis are increases in the peripheral blood leukocyte count and anemia, each of which occurs in approximately 10% of patients with apparently localized tuberculosis (Cameron, 1974; Carr et al., 1964). The increase in leukocyte counts is usually slight, but leukemoid reactions may occur. Leukopenia has also been reported. An increase in the peripheral blood monocyte and eosinophil counts also may occur with tuberculosis. Anemia is common when the infection is disseminated. In some instances, anemia or pancytopenia may result from direct involvement of the bone marrow and thus be a local rather than a remote effect.

Other than weight loss, the most frequent metabolic effect of tuberculosis is hyponatremia, which in one series was found to occur in 11% of patients (Chung and Hubbard, 1969). Hyponatremia is caused by production of an antidiuretic hormone-like substance found within affected lung tissue (Vorken et al., 1970). The poor prognosis that in the prechemotherapy era was associated with hyponatremia was probably related simply to the amount of lung involved and perhaps to adrenal involvement. In addition, because the syndrome of inappropriate secretion of antidiuretic hormone is also associated with central nervous system disorders, hyponatremia may be a feature of central nervous system tuberculosis.

The psychological effects of tuberculosis are very poorly defined but were commonly recognized prior to the advent of effective therapy. These effects include depression and, on occasion, hypomania. The best descriptions of the psychological alterations in patients with tuberculosis are found in literary works, such as Thomas Mann's *The Magic Mountain*, rather than in medical writings.

In many patients, tuberculosis is associated with other serious disorders, including HIV infection, alcoholism, chronic renal failure, diabetes mellitus, neoplastic diseases, and drug abuse, to name but a few. The signs and symptoms of these diseases and their complications can easily obscure or modify those of tuberculosis and can result in considerable delays in diagnosis or in misdiagnoses for extended periods, especially in patients with HIV infection (Kramer et al., 1990). For this reason it is important that clinicians have an understanding of the diseases with which tuberculosis may coexist and have a high index of suspicion for a combination of the two disorders.

## TUBERCULIN SKIN TESTING

As noted above, a positive tuberculin skin test is usually the only evidence of latent tuberculous infection (Sbarbaro, 1986). Among persons with symptoms or clinical findings of tuberculosis, the tuberculin skin test may provide useful diagnostic information. However, in an individual patient a positive test (usually defined as an induration of $\geq$10 mm in immunocompetent persons and $\geq$5 mm in persons with HIV infection) does not establish a diagnosis and a negative test does not exclude tuberculosis. Up to 25% of apparently immunocompetent persons will have negative tuberculin skin tests at the time of diagnosis of tuberculosis (Nash and Douglas, 1980). Among patients with tuberculosis and HIV infection, the frequency of positive tuberculin reactions varies considerably depending on the degree of immune compromise (Reider et al., 1989).

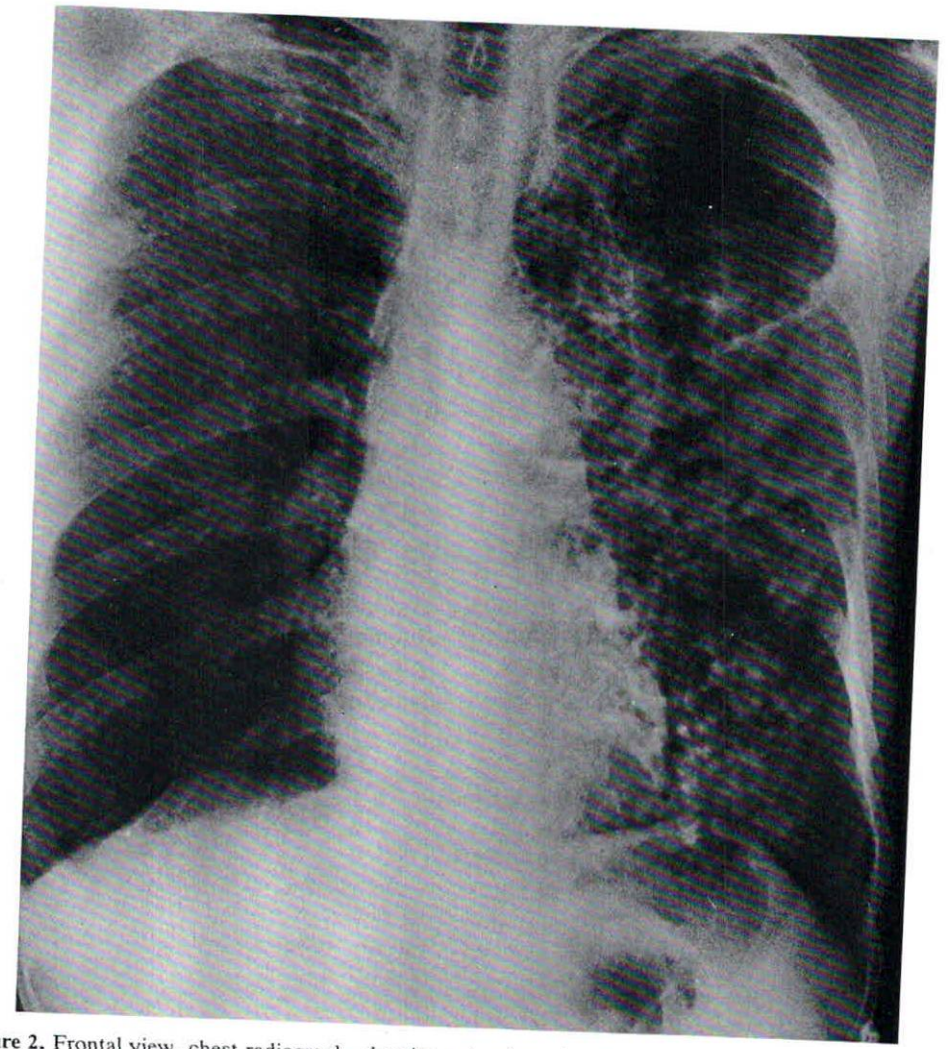


**Figure 2.** Frontal view, chest radiograph, showing extensive tuberculosis causing respiratory failure.

## PULMONARY TUBERCULOSIS

### Symptoms and Physical Findings

Cough is the most common symptom of pulmonary tuberculosis. Early in the course of the illness, the cough may be nonproductive, but subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. Spontaneous pneumothorax may also occur, often causing chest pain and perhaps dyspnea. Dyspnea (difficulty in breathing) as a result of parenchymal lung involvement is unusual unless there is extensive disease. Tuberculosis may, however, cause severe respiratory failure (Huseby and Hudson, 1976; Murray et al., 1978) (Fig. 2). Hemoptysis (coughing blood) may also be a presenting symptom but does not necessarily indicate an active tuberculous process. Hemoptysis may result from residual tuberculous bronchiectasis, rupture of a dilated vessel in the

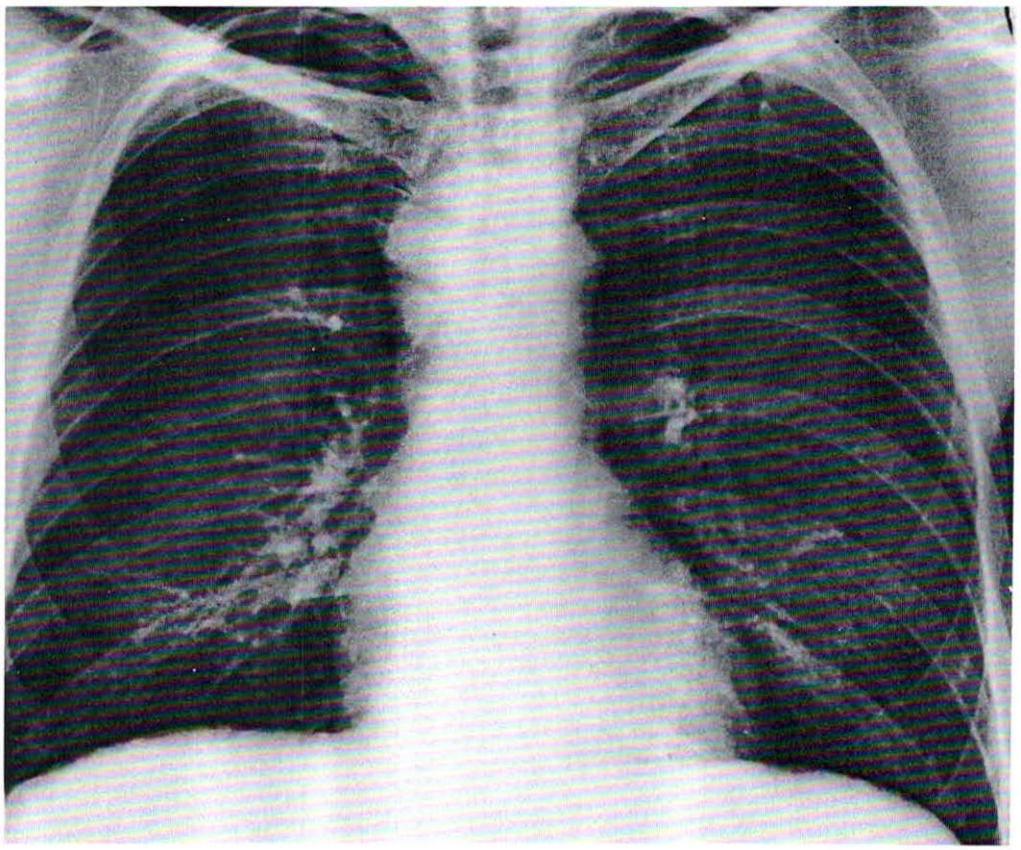


**Figure 3.** Frontal view, chest radiograph, showing right paratracheal adenopathy as a manifestation of recently acquired tuberculous infection.

wall of an old cavity (Rasmussen's aneurysm), bacterial or fungal infection (especially aspergillus in the form of a fungus ball or mycetoma) in a residual cavity, or erosion of calcified lesions into the lumen of an airway (broncholithiasis).

Physical findings in pulmonary tuberculosis are generally not particularly helpful in defining the disease. Rales may be heard in the area of involvement, and bronchial breath sounds may also be heard if there is lung consolidation. Amphoric breath sounds may be indicative of a cavity.

### Radiographic Features of Pulmonary Tuberculosis

In developed countries, radiographic examination of the chest is usually the first diagnostic study undertaken after history and physical examination. Pulmonary tuberculosis nearly always causes abnormalities on the chest film, although an endobronchial lesion may not be associated with a radiographic finding. In primary tuberculosis occurring as a result of recent infection, the process is generally seen as a middle or lower lung zone infiltrate, often associated with ipsilateral hilar adenopathy (Fig. 3). Atelectasis (partial lung collapse) may result from compression of airways by enlarged lymph nodes. If the primary process persists beyond the time when specific cell-mediated immunity develops, cavitation may occur (so-called "progressive primary" tuberculosis).

Tuberculosis that develops as a result of

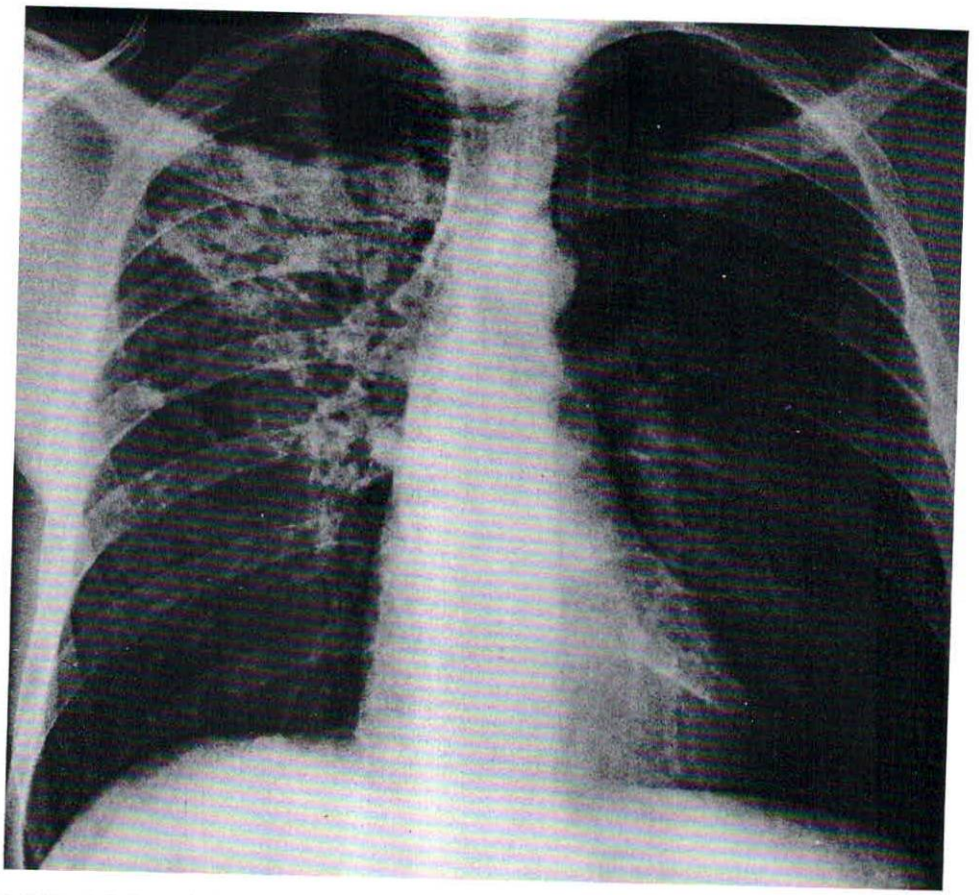


**Figure 4.** Frontal view, chest radiograph, showing the typical findings of endogenous reactivation tuberculosis in an immunocompetent patient. Note the upper lobe location and cavitation.

endogenous reactivation of latent infection usually causes abnormalities in the upper lobes of one or both lungs. Cavitation (destruction of lung tissue) is common in this form of tuberculosis. The most frequent sites of involvement are the apical and posterior segments of the right upper lobe and the apical-posterior segment of the left upper lobe (Fig. 4). Healing of the tuberculous lesions usually results in development of a scar with loss of lung parenchymal volume and, often, calcification. In the immunocompetent adult with tuberculosis, intrathoracic adenopathy is uncommon but may occur, especially with primary infection. As tuberculosis progresses, infected material may be spread via the airways into the lower portions of the lung or to the other lung. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may result in dissemination of the organism and a "miliary" (evenly distributed small nodules) pattern on the chest film (Fig. 5).

In patients with HIV infection, the nature of the radiographic findings depends to a certain extent on the degree of immunocompromise produced by the infection. Tuberculosis that occurs relatively early in the course of HIV infection tends to have the typical radiographic findings described above (Chaisson et al., 1987; Pitchenik and

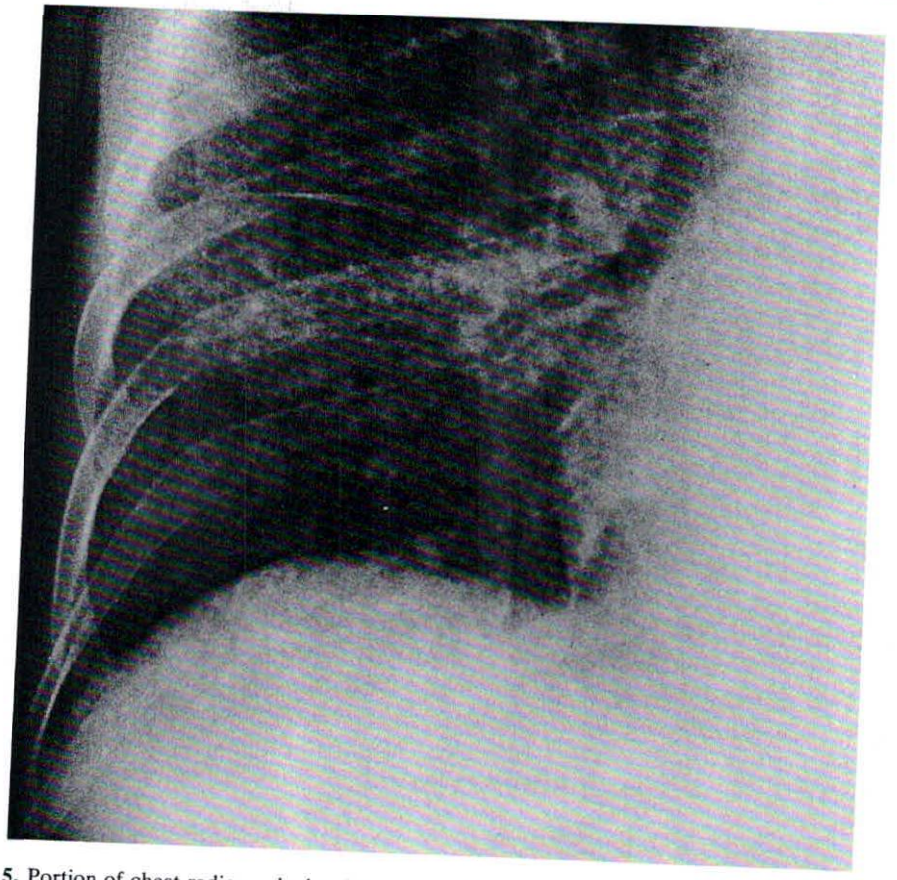


**Figure 5.** Portion of chest radiograph showing nodular lesions in a patient with disseminated tuberculosis.

Rubinson, 1985). With more advanced HIV disease, the radiographic findings become more "atypical": cavitation is uncommon, and lower lung zone or diffuse infiltrates and intrathoracic adenopathy are frequent (Fig. 6).

### Bacteriologic Evaluation

At present, a definitive diagnosis of tuberculosis can be established only by isolation of tubercle bacilli in culture, although tests that identify specific *M. tuberculosis* DNA should soon be available for clinical use. When the lung is involved, sputum is the initial diagnostic specimen of choice. Sputum specimens should be collected at the time of the initial evaluation. Single early-morning specimens have a higher yield and a lower rate of contamination than pooled specimens. The sensitivity of sputum examination increases with the number of specimens, but there is no increase in cumulative recovery of organisms with more than five specimens, and the increased yield between three and five specimens is slight (Kubica et al., 1975).

There are several ways of obtaining specimens from patients who are not producing sputum. The first and most useful is inducing sputum production by the inhalation of a mist of hypertonic (3 to 5%) saline generated by an ultrasonic nebulizer. This is a benign and well-tolerated procedure, al-

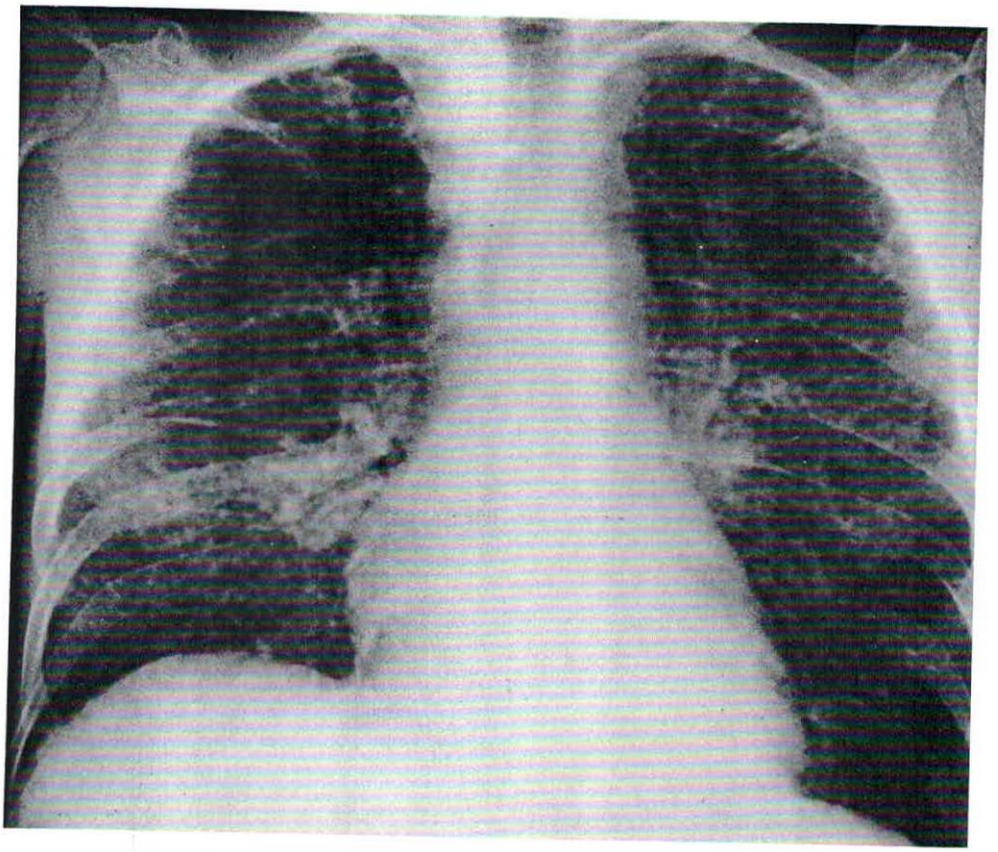


**Figure 6.** Frontal view, chest radiograph, showing diffuse infiltration caused by *M. tuberculosis* in a patient with HIV infection.

though bronchospasm may occasionally be precipitated in asthmatics. Samples of gastric contents obtained via a nasogastric tube have lower yields than induced sputum, and the procedure is more complicated and uncomfortable for the patient. However, in children and some adults, gastric contents may be the only specimen that can be obtained.

Usually, fiberoptic bronchoscopy is the next diagnostic step if the sputum is negative or cannot be obtained by induction. In general, the bronchoscopic procedure should include bronchoalveolar lavage and transbronchial lung biopsy. The yield of bronchoscopy has been high both for miliary tuberculosis and for localized disease (Burk et al., 1978; Danek and Bower, 1979; So et al., 1982). For larger nodular lesions, needle aspiration biopsy may also provide specimens from which *M. tuberculosis* can be isolated. This technique is more suited to the evaluation of lesions when there is a suspicion of malignancy.

In some situations, a therapeutic trial of antituberculosis chemotherapy may be indicated before more invasive studies are undertaken (Gordin et al., 1989). Improvement in the chest film concomitant with antituberculosis treatment would be sufficient reason for making a diagnosis of tuberculosis and continuing with a full course of therapy. If a response is going to occur, it should be seen within 3

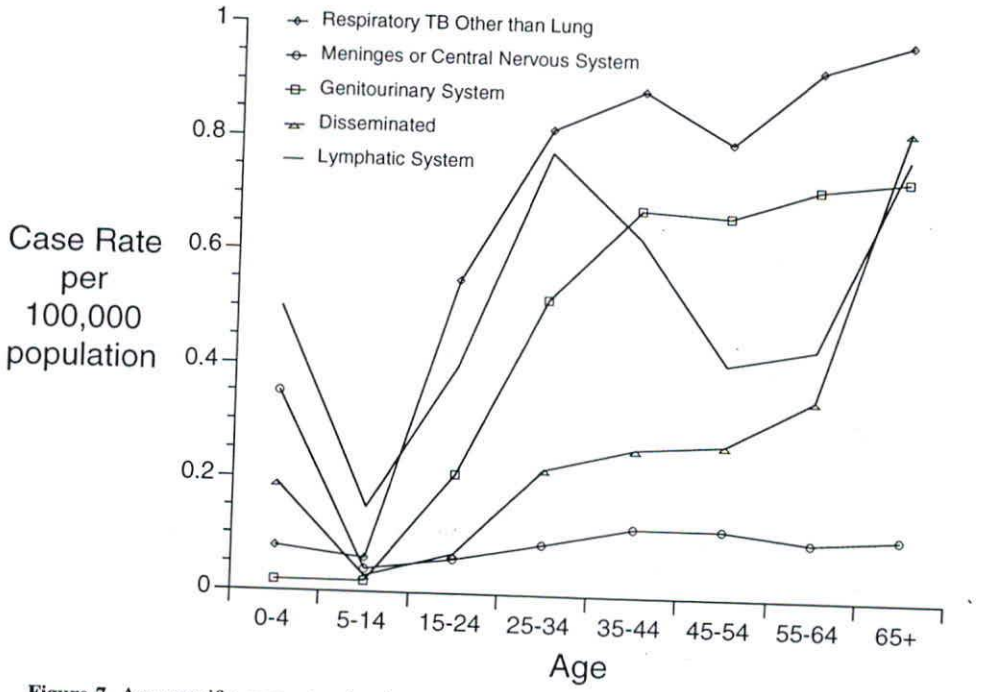



**Figure 7.** Age-specific case rates for the most frequent forms of extrapulmonary tuberculosis.

months of starting treatment. In the United States, the criteria for defining a case of tuberculosis allow for culture negativity if the patient in question has a positive tuberculin skin test and responds to multidrug chemotherapy.

## EXTRAPULMONARY TUBERCULOSIS

As noted above, prior to the epidemic of HIV infection, approximately 15% of newly reported cases of tuberculosis involved only extrapulmonary sites (Farer et al., 1979). For reasons that are not understood, as rates of pulmonary tuberculosis decreased, rates of extrapulmonary disease remained constant, resulting in an increasing proportion of cases being extrapulmonary. With the onset of the HIV epidemic, however, both absolute and relative rates of extrapulmonary involvement have increased.

Extrapulmonary tuberculosis presents more of a diagnostic and therapeutic problem than pulmonary tuberculosis. In part, this problem relates to its being less common and therefore less familiar to most clinicians (Alvarez and McCabe, 1984; Weir and Thornton, 1985). In addition, extrapulmonary tuberculosis involves relatively inaccessible sites, and because of the nature of the sites involved, fewer bacilli can cause much greater damage. The combination of small numbers of bacilli and inaccessible sites makes bacteriologic confirmation of a diagnosis more difficult, and invasive procedures are frequently required to establish a diagnosis.

The relative frequencies of tuberculosis at various sites in persons without immunocompromise are shown in Fig. 1, and distribution by age is shown in Fig. 7 (Farer et al., 1979). As can be seen, in general, the incidence for each extrapulmonary site increases with increasing age, except for lymphatic and meningeal tuberculosis, which

**Table 2.** Recovery of *M. tuberculosis* from various sites in patients with tuberculosis and HIV infection[a]

| Specimen | No. positive/no. tested (%) | |
|---|---|---|
| | Smear | Culture |
| Sputum | 43/69 (62) | 64/69 (93) |
| Bronchoalveolar lavage | 9/44 (20) | 39/44 (89) |
| Transbronchial biopsy | 1/10 (10) | 7/10 (7) |
| Lymph node | 21/44 (48) | 39/44 (91) |
| Blood | | 15/46 (33) |
| Bone marrow | 4/22 (18) | 13/22 (62) |
| Cerebrospinal fluid | | 4/21 (19) |
| Urine | | 12/17 (71) |
| Other[b] | 5/31 (16) | 24/31 (76) |

[a] Data are from Small et al. (1991).
[b] Pleural fluid or tissue, pericardial fluid or tissue, liver peritoneal fluid, abscess drainage, or bone.

are relatively more common in young children.

### Extrapulmonary Tuberculosis in HIV-Infected Patients

Presumably, the basis for the frequency of extrapulmonary tuberculosis among patients with HIV infection is the failure of the immune response to contain *M. tuberculosis*, thereby enabling hematogenous dissemination and subsequent involvement of single or multiple nonpulmonary sites. As evidence of this sequence, tuberculosis bacillemia has been documented in HIV-infected patients on a number of occasions (Handwerger et al., 1987; Kramer et al., 1990; Shafer et al., 1989). Because of the frequency of extrapulmonary tuberculosis among HIV-infected patients, diagnostic specimens from any suspected site of disease should be examined for mycobacteria. Moreover, cultures of blood and bone marrow may reveal *M. tuberculosis* in patients who do not have an obvious localized site of disease but who are being evaluated because of fever. Table 2 lists the sites from which *M. tuberculosis* was recovered in a group of patients with advanced HIV infection (Small et al., 1991).

### Disseminated Tuberculosis

The epidemic of HIV infection has considerably altered the frequency and descriptive epidemiology of disseminated tuberculosis. Disseminated or miliary tuberculosis occurs because of the inadequacy of host defenses in containing tuberculous infection. This failure of containment may occur in either latent or recently acquired tuberculous infection. Because of HIV or other causes of immunosuppression, the organism proliferates and disseminates throughout the body. Multiorgan involvement is probably much more common than is recognized, because generally, once *M. tuberculosis* is identified in any specimen, other sites are not evaluated. The term "miliary" is derived from the visual similarity of the lesions to millet seeds. Grossly, these lesions are 1- to 2-mm-diameter yellowish nodules that, histologically, are granulomas. Persons with HIV infection may not be able to form granulomas; thus, the individual lesions may not be present. Instead, a diffuse uniform pattern of lymphocytic infiltration and edema is seen.

Although disseminated tuberculosis nearly always involves the lungs, it is considered among the extrapulmonary forms of the disease because of the multiplicity of organs affected. In the past, miliary tuberculosis occurred mainly in young children; currently, however, except among HIV-infected persons, it is more common among older persons (Farer et al., 1979). The shift

in age-specific incidence presumably has been caused by the paucity of new infections relative to the number of endogenous reactivations that take place in the United States. The sex incidence is nearly equal except in the HIV-infected population, wherein men predominate.

Because of the multisystem involvement in disseminated tuberculosis, the clinical manifestations are protean. The presenting symptoms and signs are generally nonspecific and are dominated by the systemic effects, particularly fever, weight loss, anorexia, and weakness (Grieco and Chmel, 1974; Munt, 1971; Prout and Benatar, 1980; Sahn and Neff, 1974; Slavin et al., 1980). Other symptoms depend on the relative severity of disease in the organs involved. Cough and shortness of breath are common; headache and mental status changes are less frequent and are usually associated with meningeal involvement (Munt, 1971). Physical findings are likewise variable. Fever, wasting, hepatomegaly, pulmonary findings, lymphadenopathy, and splenomegaly occur in descending order of frequency. The only physical finding that is specific for disseminated tuberculosis is the choroidal tubercle, a granuloma located in the choroid of the retina (Massaro et al., 1964).

Initial screening laboratory studies are not particularly helpful for the diagnosis of miliary tuberculosis. Both leukopenia and leukocytosis may be seen, but the majority of patients have normal leukocyte counts. Anemia is common and may be normocytic, normochronic, or microcytic and hypochromic. Coagulation disorders are unusual, but disseminated intravascular coagulation has been reported in association with miliary tuberculosis in severely ill patients (Huseby and Hudson, 1976; Murray et al., 1978). Hyponatremia also occurs, as discussed above. The most frequent abnormality of liver function is an increased alkaline phosphatase concentration. Bilirubin and alanine aminotransferase levels may also be increased.

The chest film is abnormal in most but not all patients with disseminated tuberculosis. In the series reported by Grieco and Chmel (1974), only 14 (50%) of 28 patients had a miliary pattern on chest film, whereas 90% of 69 patients reported by Munt (1971) had a miliary pattern. Overall, it appears that at the time of diagnosis, approximately 85% of patients have the characteristic radiographic findings of miliary tuberculosis. Other radiographic abnormalities may be present as well. These include upper lobe infiltrates with or without cavitation, pleural effusion, and pericardial effusion. In patients with HIV infection, the radiographic pattern is one of diffuse infiltration rather than discrete nodules.

The tuberculin skin test is positive less frequently in patients with disseminated tuberculosis than in those with other forms of the disease. The rate of positivity at the time of diagnosis in apparently immunocompetent persons ranges from approximately 50 to 75% (Grieco and Chmel, 1974; Munt, 1971; Sahn and Neff, 1974; Slavin et al., 1980). As the disease is treated, tuberculin reactivity tends to return unless there is systemic immunocompromise.

Autopsy series have shown the liver, lungs, bone marrow, kidneys, adrenals, and spleen to be the organs most frequently involved in miliary tuberculosis, but any organ can be the site of disease (Slavin et al., 1980). Because of the multiplicity of sites involved, there are many potential sources of material used to provide a diagnosis. Acid-fast smears of sputum are positive in 20 to 25% of patients, and *M. tuberculosis* is isolated from sputum in 30 to 65% of patients (Grieco and Chmel, 1974; Munt, 1971; Sahn and Neff, 1974; Slavin et al., 1980). Gastric washings or induced sputum may be positive when the patient is not expectorating spontaneously. In a patient with an abnormal chest film and negative sputum examinations, bronchos-

copy should be the next step. Combinations of bronchoalveolar lavage and transbroncheal biopsy would be expected to have a high yield. Other potential sites for biopsy include liver and bone marrow, each of which has a high likelihood of showing granulomas (70 to 80%) but only a 25 to 40% chance of providing bacteriologic confirmation (Sahn and Neff, 1974). Urine is easy to obtain and may be positive in up to 25% of patients (Sahn and Neff, 1974). Selection of other potential sources of diagnostic material should be guided by specific findings.

## Lymph Node Tuberculosis

Prior to the HIV epidemic, lymph node tuberculosis made up approximately 20% of the cases of extrapulmonary tuberculosis in the United States (Farer et al., 1979). Although the basic descriptive epidemiology of tuberculosis applies to lymphatic tuberculosis, there are two main differences: lymphatic tuberculosis is relatively more common among children, and it occurs more frequently in women. It also appears to be more common among Asians and Pacific Islanders than among blacks and whites. Among HIV-infected persons, the demographic features of tuberculous lymphadenitis parallel those of HIV infection.

Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa. Frequently, the process is bilateral, and other noncontiguous groups of nodes can be involved (Kent, 1967). At least initially, the nodes are discrete and the overlying skin is normal. With continuing disease, the nodes may become matted and the overlying skin inflamed. Rupture of the node can result in formation of a sinus tract, which may be difficult to heal. Intrathoracic adenopathy may compress bronchi, causing atelectasis and leading to lung infection and perhaps bronchiectasis.

In non-HIV-infected persons with tuberculous lymphadenitis, systemic symptoms are not common unless there is concomitant tuberculosis elsewhere. The frequency of pulmonary involvement in reported series of patients with tuberculous lymphadenitis is quite variable, ranging from approximately 5 to 70%. In HIV-infected persons, lymphadenitis is commonly associated with multiple-organ involvement, although localized lymphadenitis, as described above, may occur as well.

The diagnosis of tuberculous lymphadenopathy is established by lymph node biopsy or aspiration with histologic examination, including stains for acid-fast organisms, and culture of the material. Smears show acid-fast organisms in approximately 25 to 50% of biopsy specimens, and *M. tuberculosis* is isolated in roughly 70% of instances in which the diagnosis is tuberculosis (Huhti et al., 1975). Caseating granulomas are seen in nearly all biopsy samples from immunocompetent patients. In immunodeficiency states, granulomas may be poorly formed or absent (Marchevsky et al., 1985).

## Pleural Tuberculosis

The epidemiology of pleural tuberculosis parallels that of the overall pattern for tuberculosis, with the disease being more common among males and increasing in incidence with increasing age between ages 5 and 45 (Farer et al., 1979). As noted above, this epidemiologic pattern is modified by the occurrence of HIV infection, although pleural involvement seems relatively less frequent among HIV-infected persons.

There are two mechanisms by which the pleural space becomes involved in tuberculosis, and the difference in pathogenesis results in different clinical presentations, approaches to diagnosis, treatment, and sequelae. Early in the course of a tuberculous infection, a few organisms may gain

access to the pleural space, and in the presence of cell-mediated immunity, they can cause a hypersensitivity response (Berger and Mejia, 1973; Ellner, 1978). Commonly, this form of tuberculous pleuritis goes unnoticed, and the process resolves spontaneously. In some patients, however, tuberculous involvement of the pleura is manifested as an acute illness with fever and pleuritic pain. If the effusion is large enough, dyspnea may occur, although the effusions generally are small and rarely are bilateral. In approximately 30% of patients, there is no radiographic evidence of involvement of the lung parenchyma; however, parenchymal disease is nearly always present, as evidenced by findings by lung dissections (Stead et al., 1955).

The diagnosis of pleural tuberculosis is generally established by analysis of pleural fluid and/or pleural biopsy. A thoracentesis (aspiration of fluid from the chest) should be performed, and sufficient fluid for cell count, cytologic examination, biochemical analysis, and microbiologic evaluation should be obtained, leaving enough to allow a needle biopsy to be performed if the fluid is exudative and no diagnosis is evident. The fluid is nearly always straw colored, although it may be slightly bloody. Cell counts are usually in the range of 100 to 5,000/μl (Jay, 1985). Early in the course of the process, polymorphonuclear leukocytes may predominate, but mononuclear cells soon become the majority. The fluid is exudative, with a protein concentration greater than 50% of the serum protein concentration, and the glucose level may be normal to low.

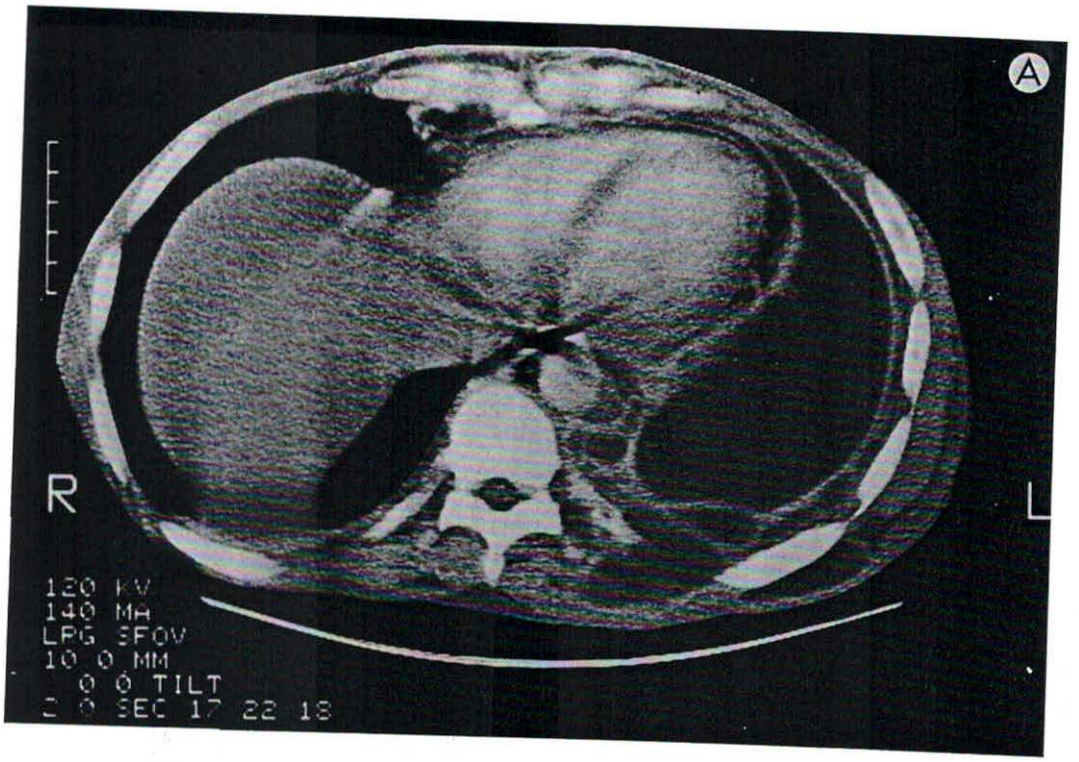
Because few organisms are present in the pleural space, smears of pleural fluid are rarely positive, and *M. tuberculosis* is isolated by culture in only 20 to 40% of patients with proved tuberculous pleuritis (Levine et al., 1970; Scharer and McClement, 1968). A single blind needle biopsy of the pleura will confirm the diagnosis in approximately 65 to 75% of patients in whom tuberculous pleuritis is ultimately diagnosed (Levine et al., 1970; Scharer and McClement, 1968). In a patient who has a pleural effusion that remains undiagnosed after a full evaluation, including pleural biopsy, and who has a positive tuberculin skin test reaction, antituberculosis treatment should be initiated.

The second variety of tuberculous involvement of the pleura is a true empyema (pus in the pleura). This condition is much less common than tuberculous pleurisy with effusion and results from a large number of organisms spilling into the pleural space, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula (Johnson et al., 1973). A tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films, and air may be seen in the pleural space. In this situation, the fluid is generally thick and cloudy and may contain cholesterol, causing the fluid to look like chyle (pseudochylous effusion). The fluid is exudative and usually has a relatively high leukocyte count, with nearly all of the leukocytes being lymphocytes. Acid-fast smears and mycobacterial cultures are usually positive, making pleural biopsy unnecessary. This type of pleural involvement has a tendency to burrow through soft tissues and may drain spontaneously through the chest wall. An example of this type of tuberculosis is shown in Fig. 8.

### Genitourinary Tuberculosis

As with pleural tuberculosis, the epidemiologic pattern of genitourinary tuberculosis parallels that of tuberculosis in general except that the incidence is nearly equal in men and women. The pathogenesis appears to be one of seeding of the kidney at the time of the initial infection and bacillemia.

In patients with genitourinary tuberculosis, local symptoms predominate, and systemic symptoms are less common (Christensen, 1974; Simon et al., 1977). Dysuria,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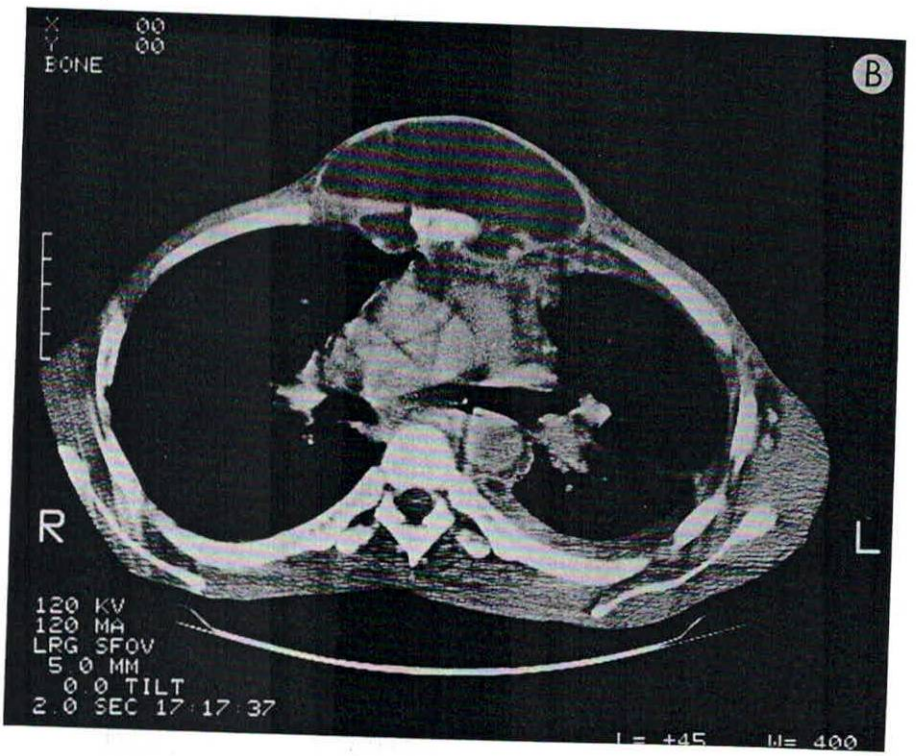
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hematuria, and frequent urination are common, and flank pain may also be noted. However, the symptoms may be very subtle, and often there is advanced destruction of the kidneys by the time a diagnosis is established (Lattimer, 1965). Genital involvement without renal tuberculosis is more common in women than in men and may cause pelvic pain, menstrual irregularities, and infertility as presenting complaints (Simon et al., 1977). In men, a painless or only slightly painful scrotal mass is probably the most common presenting symptom of genital involvement, but symptoms of prostatitis, orchitis, or epididymitis may also occur (Christensen, 1974). A substantial number of patients with any form of genitourinary tuberculosis are asymptomatic and are detected because of an evaluation for an abnormal routine urinalysis. In more than 90% of patients with renal or genital tuberculosis, urinalyses are abnormal, with the main finding being pyuria and/or hematuria. The finding of pyuria (pus in urine) in an acid urine with no organisms isolated from a routine urine culture should prompt an evaluation for tuberculosis. The suspicion of genitourinary tuberculosis should be heightened by the presence of abnormalities on the chest film. In most series, approximately 40 to 75% of patients have chest radiographic abnormalities, although in many patients, these abnormalities may be the result of previous, not current, tuberculosis (Christensen, 1974; Simon et al., 1977).

When genitourinary tuberculosis is suspected, at least three first-voided early-morning urine specimens should be collected for acid-fast stains and cultures. *M. tuberculosis* is isolated from the urine in 80 to 95% of cases of genitourinary tuberculosis (Christensen, 1974; Simon et al., 1977). Diagnosis of isolated genital lesions usually requires biopsy, because the differential diagnosis often includes neoplasia as well as other infectious processes.

Significant effects of tuberculosis on renal function are unusual, but renal failure may occur, especially in patients with pre-existing renal disease. Nephrolithiasis and recurrent bacterial infections in seriously damaged kidneys also occur. Hypertension that responds to nephrectomy has also been described but is rare.

### Skeletal Tuberculosis

The incidence of tuberculosis involving the joints and bones increases with increasing age and is equally frequent among men and women, overall making up approximately 9% of cases of extrapulmonary tuberculosis (Farer et al., 1979). Compared to blacks and whites, other racial groups are less likely to have skeletal involvement. Skeletal tuberculosis does not appear to be frequent among persons with HIV infection.

It is presumed that most osteoarticular tuberculosis results from endogenous reactivation of foci of infection seeded during the initial bacillemia, although spread from paravertebral lymph nodes has been postulated to account for the common localization of spinal tuberculosis to the lower thoracic and upper lumbar vertebrae (Burke, 1950). It is also postulated that the predilection for tuberculosis to localize in the metaphyses of long bones is due to the relatively rich blood supply and the scarcity of phagocytic cells in this portion of the bone (Berney et al., 1972). After beginning in the subchondral region on the bone, the infection spreads to involve the cartilage, synovium, and joint space. This produces the typical findings of metaphyseal erosion and cysts and the loss of cartilage, with

**Figure 8.** Computed tomographic scan of the chest showing a tuberculous empyema with adjacent chest wall involvement (A) and a large chest wall abscess overlying the sternum with mediastinal involvement (B).

narrowing of the joint space. Typically, in the spine these changes involve two adjacent vertebrae and the intervertebral disk. Paravertebral or other para-articular abscesses may develop, with occasional formation of sinus tracts. Although weight-bearing joints are the most common sites for skeletal tuberculosis, any bone or joint may be involved (Berney et al., 1972). In most series, tuberculosis of the spine (Pott's disease) makes up 50 to 70% of the cases reported. In adults, the lower thoracic and upper lumbar vertebrae are most commonly involved, whereas in children, the upper thoracic spine is the most frequent site of vertebral tuberculosis. The hip or knee is involved in 15 to 20% of cases, and shoulders, elbows, ankles, wrists, and other bones or joints are also involved in 15 to 20% of cases. Usually only one bone or joint is involved, but occasionally the process is multifocal (Cremin et al., 1970; McTammany et al., 1963). Evidence of either previous or current pulmonary tuberculosis is found in approximately one-half of the reported patients, and other extrapulmonary sites may also be involved.

The usual presenting symptom of skeletal tuberculosis is pain (Berney et al., 1972). Swelling of the involved joint may be noted, as may limitation of motion and occasionally sinus tracts. Systemic symptoms of infection are not common. Because of the subtle nature of the symptoms, diagnostic evaluations often are not undertaken until the process is advanced. Delay in diagnosis can be especially catastrophic in vertebral tuberculosis, in which compression of the spinal cord may cause severe and irreversible neurologic sequelae, including paraplegia.

The first diagnostic test undertaken is usually a radiograph of the involved area. The typical findings just described represent the more severe end of the spectrum. Early in the process, the only abnormality noted may be soft tissue swelling. Subsequently, subchondral osteoporosis, cystic changes, and sclerosis may be noted before the joint space is actually narrowed. The early changes of spinal tuberculosis may be particularly difficult to detect by standard films of the spine. Computed tomographic scans and magnetic resonance imaging of the spine are considerably more sensitive than routine films and should be obtained when there is a high index of suspicion of an infectious process.

Confirmation of the diagnosis is obtained by aspiration of joint fluid or periarticular abscesses or by biopsy of bone or synovium with histologic and microbiologic evaluation of the material obtained. Acid-fast stains of joint fluid are positive in 20 to 25% of those examined, and *M. tuberculosis* is isolated in approximately 60 to 80% (Berney et al., 1972). Biopsies of synovium or bone have a higher yield and allow histologic examination as well. Evidence of granulomatous inflammation even in the absence of bacteriologic proof of the diagnosis is sufficient evidence of tuberculosis to begin therapy unless another etiology is found.

### Central Nervous System Tuberculosis

Meningitis is the most frequent form of central nervous system tuberculosis; solitary or multiple tuberculomas occur less commonly. The epidemiologic pattern of central nervous system tuberculosis is quite different from either pulmonary or other forms of extrapulmonary tuberculosis in that the peak incidence is in children in the zero- to 4-year age group, but an appreciable number of cases occur in adults (Barrett-Connor, 1967; Farer et al., 1979). Central nervous system disease accounts for only approximately 5% of all cases of extrapulmonary tuberculosis, and the cases are equally divided between males and females.

Central nervous system involvement, especially tuberculomas, seems to occur with greater frequency among HIV-infected per-

sons. Tuberculomas have been reported even in patients who are receiving what should be adequate chemotherapy (Bishberg et al., 1986). The findings produced by tuberculomas may be indistinguishable on computed tomographic scan from those of toxoplasmosis. For this reason, a specific diagnosis should be sought when such lesions are noted.

Meningitis presumably can result from direct meningeal seeding and proliferation during a tuberculous bacillemia either at the time of initial infection or at the time of breakdown of an old pulmonary focus, or it can result from breakdown of an old parameningeal focus with rupture into the subarachnoid space. The consequences of the subarachnoid space contamination include diffuse meningitis, a localized arteritis, encephalitis, or myelitis. With meningitis, the process takes place primarily at the base of the brain (Auerbach, 1951). Symptoms therefore include those related to cranial nerve involvement in addition to headache, decreased level of consciousness, and neck stiffness. The duration of illness prior to diagnosis is quite variable and relates in part to the presence or absence of other sites of involvement. In most series, over 50% of patients with meningitis have abnormalities on chest film that are consistent with an old or current tuberculous process, often miliary tuberculosis. At autopsy, disseminated disease is found in a very high percentage of patients with meningitis (Auerbach, 1951). In patients with tuberculous meningitis, sputum cultures have been positive in 40 to 50%; thus, a substantial number of patients will have pulmonary and systemic symptoms in addition to those referable to the central nervous system. Arteritis may be the predominant manifestation of meningitis and can result in a variety of focal ischemic syndromes in addition to the symptoms already described.

Physical findings and screening laboratory studies are not particularly helpful in establishing a diagnosis. In the presence of meningeal signs on physical examination, lumbar puncture is usually the next step in the diagnostic sequence. If there are focal findings on examination or if there are suggestions of increased intracranial pressure, a computerized tomographic scan of the head, if it can be obtained expeditiously, should be performed before the lumbar puncture. With meningitis, the scan may be normal, but it can also show diffuse edema or obstructive hydrocephalus. Tuberculomas are generally seen as ring-enhancing mass lesions.

In tuberculous meningitis, the lumbar puncture usually shows increased opening pressure and the cerebrospinal fluid usually contains between 100 and 1,000 cells per μl. In approximately 65 to 75% of patients, lymphocytes predominate, whereas polymorphonuclear leukocytes predominate in the remainder of patients, generally early in the course of the illness. The protein concentration is elevated in nearly all patients. Very high (>300 mg/dl) protein concentrations have been associated with a poor prognosis (Weiss and Flippin, 1961). The glucose concentration in cerebrospinal fluid is usually low but not as low as concentrations that occur during pyogenic bacterial meningitis. Acid-fast organisms are seen on smears of cerebrospinal fluid in only 10 to 20% of patients, and the rate of culture positivity varies from 55 to 80% (Barrett-Connor, 1967). A substantial number of patients will have *M. tuberculosis* isolated from other sources, and in the presence of compatible cerebrospinal fluid findings, such isolation is sufficient to diagnose tuberculous meningitis. Given the severity of tuberculous meningitis, a presumptive diagnosis justifies empiric treatment if no other diagnosis can be established promptly.

The other major central nervous system form of tuberculosis, the tuberculoma, presents a more subtle clinical picture than tuberculous meningitis (Damergis et al., 1979). The usual presentation is that of a

slowly growing focal lesion, although a few patients have increased intracranial pressure and no focal findings. The cerebrospinal fluid is usually normal, and the diagnosis is established by computed tomographic or magnetic resonance scanning and subsequent resection, biopsy, or aspiration of any ring-enhancing lesion.

### Abdominal Tuberculosis

Tuberculosis can involve any intra-abdominal organ as well as the peritoneum. The age distribution of abdominal tuberculosis shows a relatively higher incidence in young adults and a second peak in older persons. Males and females have a similar incidence. Intra-abdominal tuberculosis has not been common in HIV-infected persons.

Abdominal tuberculosis presumably results from seeding at the time of initial infection and then either direct or late progression to clinical disease. Peritonitis can also be caused by rupture of tuberculous lymph nodes within the abdomen. Intestinal tuberculosis may also result from ingested tubercle bacilli with direct implantation in the gut. Before chemotherapy, tuberculous enteritis was quite common in patients with advanced pulmonary tuberculosis, presumably being caused by bacilli from the lungs that were swallowed. In a prospective study conducted between 1924 and 1949, intestinal abnormalities compatible with tuberculous enteritis were found by contrast radiography in 1, 4.5, and 24.7% of patients with minimal, moderately advanced, and far advanced pulmonary tuberculosis, respectively (Mitchell and Bristol, 1954).

The clinical manifestations of abdominal tuberculosis depend on the areas of involvement. In the gut itself, tuberculosis may occur in any location from the mouth to the anus, although lesions proximal to the terminal ileum are unusual. The most common sites of involvement are the terminal ileum and the cecum, with other portions of the colon and the rectum involved less frequently (Bhansali, 1977). In the terminal ileum or cecum, the most common manifestations are pain, which may be misdiagnosed as appendicitis, and intestinal obstruction. A palpable mass may be noted and, together with the appearance of the abnormality on barium enema or small-bowel films, may easily be mistaken as a carcinoma. Rectal lesions usually present as anal fissures or fistulae or as perirectal abscesses. Because of the concern with carcinoma, the diagnosis often is made at surgery.

For tuberculous peritonitis, pain, often accompanied by abdominal swelling, is commonly the presenting manifestation (Bhansali, 1977; Borhanmanesh et al., 1972; Burack and Hollister, 1960; Singh et al., 1968). Fever, weight loss, and anorexia are also common. Active pulmonary tuberculosis is uncommon in patients with tuberculous peritonitis. Because the process frequently coexists with other disorders, especially hepatic cirrhosis with ascites, the symptoms of tuberculosis may be obscured. The combination of fever and abdominal tenderness in a person with ascites should always prompt an evaluation for intra-abdominal infection, and a paracentesis should be performed. Ascitic fluid in tuberculous peritonitis is exudative (fluid protein content greater than 50% of serum protein concentration) and contains between 50 and 10,000 leukocytes per μl, the majority of them being lymphocytes, although polymorphonuclear leukocytes occasionally predominate (Borhanmanesh et al., 1972; Singh et al., 1968). Acid-fast organisms are rarely seen on smears of the fluid, and cultures are positive in only approximately 50% of patients. Because of the generally low yield from culture of the fluid, laparoscopic biopsy is often necessary to confirm the diagnosis.

Microscopic evidence of liver involvement is common in patients with all forms

of tuberculosis, but actual hepatic tuberculosis of functional consequence is rare. A variety of histologic abnormalities may be seen, but none is specific for tuberculosis unless *M. tuberculosis* is isolated from hepatic tissue (Frank and Raffensperger, 1965). For this reason, all liver biopsy specimens should be cultured for mycobacteria.

### Pericardial Tuberculosis

The descriptive epidemiology of pericardial tuberculosis is not well defined, but in general the disease tends to occur among older persons, with approximately 50% of the patients being older than 55 years (Farer et al., 1979). Nonwhites and men have a relatively higher frequency of tuberculous pericarditis. Before the use of antituberculosis chemotherapy, tuberculous pericarditis was found in 0.4 to 1.0% of all autopsied patients and in 3 to 8% of autopsied patients in whom there was other evidence of tuberculosis (Schepers, 1962). A clinical diagnosis of tuberculous pericarditis was made in 0.35% of approximately 10,000 patients with any form of tuberculosis admitted to Kings County Hospital Center, Brooklyn, N.Y., between 1 January 1960 and 31 December 1966 (Rooney et al., 1970).

The pericardium may become involved during the initial bacillemia, with early progression to clinically evident disease or recrudescence following a quiescent period. Hematogenous seeding may also occur during the course of endogenous reactivation. Alternatively, there may be direct extension of an adjacent focus of disease into the pericardium. This focus may be in lung parenchyma, pleura, or tracheobronchial lymph nodes. In fact, all of these mechanisms probably occur and may account for some of the variability in the characteristics of the pericardial fluid, severity of the process, and prognosis (Schepers, 1962). It is likely that tuberculin hypersensitivity plays a role in producing the inflammatory response in the pericardium, as presumably occurs in the pleura. On the other hand, rupture of a caseous lymph node into the pericardium may cause contamination with a much greater number of organisms; a greater inflammatory response with thicker, more purulent fluid; and a greater likelihood of either early or late hemodynamic effects.

The most common form or stage of tuberculous pericarditis is characterized by pericardial effusion with little pericardial thickening or epicardial involvement. The fluid itself is usually serosanguineous or occasionally grossly bloody, is exudative, and has a leukocyte count of 500/mm$^3$ to as high as 50,000/mm$^3$, with an average of 5,000 to 7,000/mm$^3$ (Harvey and Whitehill, 1937). The cells are predominantly mononuclear, although polymorphonuclear leukocytes occasionally predominate. Tubercle bacilli have been identified in pericardial fluid in approximately 25 to 30% of cases (smear and culture combined) (Rooney et al., 1970). Biopsy of the pericardium with both histologic and bacteriologic evaluation is much more likely to provide a diagnosis, although a nonspecific histologic pattern and failure to recover the organisms do not exclude a tuberculous etiology.

With persistence of the inflammation, there is thickening of the pericardium and progressive epicardial involvement. Granulomas, various amounts of free or loculated fluid, and fibrosis may be present during this stage, and evidence of cardiac constriction may begin to appear. The necrosis associated with the granulomatous inflammation may involve the myocardium, with consequent functional and electrocardiographic manifestations.

Although it is not well documented, it appears that if the patient survives the subacute phase without treatment, chronic fibrotic pericarditis nearly always follows. Prior to the advent of antituberculous therapy, 88% of one series of patients who had tuberculous pericarditis developed evidence

of chronic constriction (Harvey and Whitehill, 1937). Constriction has also been observed to develop during the course of antituberculous chemotherapy, although this development appears to be uncommon in patients who have had symptoms for less than 3 months. In the series reported by Hageman and coworkers (Hageman et al., 1964), 11 of 13 patients who had symptoms for more than 6 months required pericardiectomy.

The fibrotic reaction noted above progresses to complete fusion of visceral and parietal pericardium and encasement of the heart in a rigid scar. There are various amounts of calcium within the fibrotic mass. Impairment of coronary circulation is common. At this point, the histologic pattern is usually nonspecific; thus, confirmation of a tuberculous etiology is infrequent.

The symptoms, physical findings, and laboratory abnormalities associated with tuberculous pericarditis may be the result of either the infectious process per se or the pericardial inflammation causing pain, effusion, and eventually hemodynamic effects. The systemic symptoms produced by the infection are quite nonspecific. Fever, weight loss, and night sweats are common in reported series (Harvey and Whitehill, 1937; Rooney et al., 1970; Schepers, 1962). Symptoms of cardiopulmonary origin tend to occur later and include cough, dyspnea, orthopnea, ankle swelling, and chest pain. The chest pain may occasionally mimic angina but usually is described as being dull, aching, and often affected by position and by inspiration.

Apart from fever, the most common physical findings are those caused by the pericardial fluid or fibrosis-cardiac tamponade or constriction. Various proportions of patients in reported series have signs of full-blown cardiac constriction when first evaluated. It is assumed that in these patients, the acute phase of the process was unnoticed.

The definitive diagnosis of tuberculous pericarditis requires identification of tubercle bacilli in pericardial fluid or tissue. Although not conclusive, demonstration of caseating granulomata in the pericardium and consistent clinical circumstances is convincing evidence of a tuberculous etiology. Less conclusive but still persuasive evidence is the finding of another form of tuberculosis in a patient with pericarditis of undetermined etiology. Approximately 25 to 50% of patients with tuberculous pericarditis have evidence of other organ involvement, particularly pleuritis, at the time pericarditis is diagnosed (Gooi and Smith, 1978; Harvey and Whitehill, 1937). Still less direct and more circumstantial evidence of a tuberculous etiology is the combination of a positive intermediate-strength tuberculin skin test reaction and pericarditis of unproven etiology.

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