tence, and transmission of drug-resistant organisms. Surveillance systems that are more sensitive and timely can provide information in making critical public health decisions.

Many of the above methods to reduce antimicrobial resistance focus on curative medicine, that is, preserving the ability to treat the ill or infected individual. Curative medicine is, in a sense, a failure of preventive medicine. As antimicrobial resistance increases, health efforts need to be focused on preventing transmission and infection rather than on treating the illness once it has occurred. A very effective mechanism for dealing with the emergence of antimicrobial resistance would be the development of vaccines to prevent diseases that are difficult to treat. There is also a variety of opportunities to disrupt transmission. In hospitals, infection control practices can be enhanced; in the community, hygiene and sanitation can be improved; and on the farm, a number of agricultural and animal husbandry practices can reduce the transmission of organisms between animals and eventually decrease their transmission to humans. The increasing frequency of resistance indicates the need for a stronger partnership between clinical medicine and public health. Unless currently effective antimicrobial agents can be successfully preserved and the transmission of drug-resistant organisms curtailed, the post-antimicrobial era may be rapidly approaching in which infectious disease wards housing untreatable conditions will again be seen.

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Tuberculosis: Commentary on a Reemergent Killer

Barry R. Bloom and Christopher J. L. Murray

Tuberculosis remains the leading cause of death in the world from a single infectious disease, although there is little knowledge of the mechanisms of its pathogenesis and protection from it. After a century of decline in the United States, tuberculosis is increasing, and strains resistant to multiple antibiotics have emerged. This excess of cases is attributable to changes in the social structure in cities, the human immunodeficiency virus epidemic, and a failure in certain major cities to improve public treatment programs. The economic costs of not adequately addressing the problem of tuberculosis in this country are estimated from an epidemiological model.

In an interview on acquired immunodeficiency syndrome (AIDS) earlier this year with the Director of the National Institute for Allergy and Infectious Diseases (NIAID), a distinguished television newscaster asked, "How is it that we have conquered most infectious diseases but are unable to find a cure for AIDS?" The question reveals misperceptions that are costly to the public in both human and economic terms, and it is not a misapprehension solely of the general public. In 1969, the U.S. Surgeon General testified to Congress that it was time to "close the book on infectious diseases" (*1*). In fact, infectious diseases have not been eradicated but remain the largest cause of death in the world today, greater than cardiovascular disease or cancer (*2*). The World Health Organization (WHO) estimates that in 1991 there were still 4.3 million deaths in children from acute respiratory infections, 3.5 million from diarrheal diseases, 0.88 million from measles, and about 1 million from malaria (*3*). To that, one must add an estimated 1.5 million cumulative deaths worldwide from AIDS.

The stark reality, largely overlooked, is that among infectious diseases, tuberculosis (TB) is the leading cause of death (*4*). Each

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year, there are an estimated 8 million new cases of TB and 2.9 million deaths from the disease (5). Approximately one-third of the world's population harbors *Mycobacterium tuberculosis* and is at risk for developing the disease. In global terms, TB accounts for 6.7% of all deaths in the developing world, 18.5% of all deaths in adults aged 15 to 59, and 26% of avoidable adult deaths (4). The steadily declining incidence of TB in the United States since 1882 has been reversed since 1985 (6), with 26,283 cases reported in 1991. To the trend of increasing incidence one must add the ominous emergence of drug-resistant strains that threaten our capability of controlling the disease. One-third of all cases tested in a New York City survey in 1991 were resistant to one or more drugs (7). The case fatality rate for TB resistant to two or more major antibiotics (multidrug resistance) is 40 to 60%, equivalent to untreated TB (8). Last year, cases of TB were reported to the Centers for Disease Control (CDC) by all 50 states, and drug-resistant TB was noted in at least 36 states, the District of Columbia, and Puerto Rico (9). Our aim here is to adumbrate the context and a few scientific challenges of TB and to highlight some economic implications of the failure to adequately address the problem.

A Brief History of Time—Forgotten

Tuberculosis was almost certainly the leading cause of death in Europe and the United States in recorded history, although because of the multifarious forms of the disease, it was often confounded with other maladies (*10, 11*). Probably described first in Indian texts, pulmonary TB was known from the time of Hippocrates (*12*) as phthisis, which is derived from the Greek for "wasting away." The swollen glands of the neck were described as scrofula, and because newly crowned kings of England and France were believed to have special healing powers, the most desired treatment of this "King's Evil" was being touched by kings. TB of the skin was known as lupus vulgaris and that of bone as Pott's disease, characterized by vertebral fusion and deformity of the spine, which enabled historians to establish the existence of TB from mummies dating from 2000 to 4000 B.C. From contemporary descriptions, bills of mortality, and records of the dispensing of the royal touch, estimates suggest that consumption (TB) was responsible for 20% of deaths in London in 1651, reached rates of 700 cases per 100,000 people in 1801, and declined thereafter. Consecutive autopsies by G. L. Bayle and R. T. H. Laennec in the early 19th century indicated that TB may have probably accounted for a third of all deaths in Paris at that time. Upon introduction into new locales, TB assumed an epidemic form; for example, the Pacific Islands had a prevalence of TB in children reaching 81% (*13*).

Franciscus Sylvius in 1679 described the characteristic lung nodules as "tubercula" (small knots), observing their evolution to cavities (lung ulcers), but virtually all of the great pathologists, including Rudolf Virchow, believed the disease to be constitutional, a form of tumor or abnormal gland, rather than infectious. H. Fracastoro included phthisis in a work on contagion in 1546, but the first credible speculation on the infectious nature of TB was made by Benjamin Marten, who proposed in 1722 that the cause of TB was "animaliculae or their seed . . . inimicable to our Nature" that can be transmitted by "a Breath [a consumptive] emits from his Lungs . . . that may be caught by a sound Person" (*12*). It was Robert Morton in 1689 who used the term "consumption" specifically to denote TB, and it took until 1819 for Rene Laennec, inventor of the stethoscope, to first recognize the unity of manifestations of TB. Although the 17th century anatomists A. M. Valsalma and G. B. Morgagni enjoined their students not to perform autopsies on tuberculous cadavers, the first public health edict to prevent transmission of TB was the Decree of Lucca, promulgated in Italy in 1699, that required physicians to notify the General Sanitary Council of the names of patients with phthisis and to destroy their belongings after death (*12*).

The formal demonstration that TB was contagious was made in 1865 by Jean-Antoine Villemin, who successfully transferred pus and fluid from human and bovine lesions to rabbits that then developed TB (*14*). This monumental finding was ignored by his contemporaries and unappreciated by R. Koch, who in 1882 astonished the world by isolating and culturing *M. tuberculosis* from crushed tubercles (*15*). The lessons from the discovery of the anthrax and tubercle bacilli were now generalized into Koch's Postulates: "To prove that tuberculosis . . . is caused by the invasion of bacilli and conditioned by the growth and multiplication of bacilli it was necessary: [i] to isolate the bacilli from the body; [ii] grow them in pure culture; and [iii] by administering the isolated bacilli to animals, reproduce the same morbid condition. . . ." Although a primary inoculation of guinea pigs with tubercle bacilli in the skin produced a nonhealing ulcer, Koch noted that reinoculation of the animals after several weeks produced only a firm, red nodule that eventually healed (the Koch phenomenon), which first suggested the existence of immunity to infection. Unfortunately, in 1890 he also announced that culture filtrates cured the disease, a claim that was promptly discredited. At a time when intellectual property rights were hardly a burning issue, Koch refused to divulge the nature and preparation of the curative material—an action imputed by some to assure a monopoly for the German government and an institute for himself—and this great scientist brought discredit upon himself (*16*). Nevertheless, those filtrates, later partially purified, became the principal means to establish infection, the tuberculin skin test.

Four historical intervention strategies are noteworthy. The lack of effective treatments prompted Hermann Brehmer in Europe in 1854 to establish the first sanatorium in the belief that exercise and altitude would serve to cure TB. Based on his own recovery from TB in New York's Adirondack mountains, Dr. Edward Livingston Trudeau in 1882 established the first sanatorium in the United States and initiated a public health movement featuring community participation, emphasis on the outdoor life, and ordinances to improve sanitation and slum housing (*17*). Another was the application of pasteurization to cows' milk, reducing the possibility of *M. bovis* being a cause of human TB. In 1908, Albert Calmette and Camille Guerin, seeking to overcome the problem of bacillary clumping associated with mycobacteria, grew bovine tubercle bacilli in dispersed culture that contained ox bile. A morphological variant was observed on the 39th passage that was avirulent in many animal species and provided protection against challenge with virulent *M. tuberculosis*. In the 231st passage, this variant was first used to immunize a child whose mother died in childbirth of TB (*18*). This vaccine, BCG (bacille Calmette-Guerin), is currently the most widely used vaccine in the world (*19*). Finally, the introduction of antibiotics, streptomycin in 1947 (*20*), isoniazid, first synthesized 1912 but allowed to sit on the shelf for 40 years, and then *p*-aminosalicylic acid led to an effective chemotherapy that dramatically reduced mortality from TB. Thus ended the sanatorium era.

"The Captain of All These Men of Death" (*21*)

As in many communicable diseases, it is important in TB to distinguish between infection and disease. There are two basic clinical patterns that follow infection with *M. tuberculosis* (*22*). In the majority of individuals, inhaled tubercle bacilli ingested by phagocytic alveolar macrophages are either directly killed or grow intracellularly to a limited extent in localized lesions called tubercles. Infrequently, in children and in immunocompromised individuals, there is early hematogenous dissemination

with the formation of small miliary (millet-like) lesions or life-threatening meningitis. More commonly, within 2 to 6 weeks after infection, cell-mediated immunity develops, and infiltration into the lesion of immune lymphocytes and activated macrophages results in the killing of most bacilli and the walling-off of this primary infection, often without symptoms being noted by the infected individual. Skin-test reactivity to a purified protein derivative (PPD) of tuberculin and, in some cases, x-ray evidence of a healed, calcified lesion provide the only evidence of the infection. Nevertheless, to an unknown extent, dormant but viable M. *tuberculosis* bacilli persist. The second pattern is the progression or breakdown of infection to active disease. Individuals infected with M. *tuberculosis* have a 10% lifetime risk of developing the disease (*23*). In either case, the bacilli spread from the site of initial infection in the lung through the lymphatics or blood to other parts of the body, the apex of the lung and the regional lymph node being favored sites. Extrapulmonary TB of the pleura, lymphatics, bone, genito-urinary system, meninges, peritoneum, or skin occurs in about 15% of TB patients. Although many bacilli are killed, a large proportion of infiltrating phagocytes and lung parenchymal cells die as well, producing characteristic solid caseous (cheese-like) necrosis in which bacilli may survive but not flourish. If a protective immune response dominates, the lesion may be arrested, albeit with some residual damage to the lung or other tissue. If the necrotic reaction expands, breaking into a bronchus, a cavity is produced in the lung, allowing large numbers of bacilli to spread with coughing to the outside. In the worst case, the solid necrosis, perhaps a result of released hydrolases from inflammatory cells, may liquefy, which creates a rich medium for the proliferation of bacilli, perhaps reaching 10^9 per milliliter (*24*). The pathologic and inflammatory processes produce the characteristic weakness, fever, chest pain, cough, and, when a blood vessel is eroded, bloody sputum.

The case fatality rate of untreated TB wherever studied hovers between 40 and 60% (*23, 25*). The introduction of antibiotics rendered TB a disease that could be cured. There have been many prescribed treatment regimens; the one currently most favored is combinations of isoniazid, rifampicin, and pyrazinamide given over a period of 6 months. This treatment is referred to as short-course chemotherapy (SCC) and, in patients who complete it, produces cure rates of >90% (*26*). For individuals recently infected with conventional M. *tuberculosis* and converting to PPD positivity, chemoprophylaxis with isoniazid has been about 90% effective in preventing the disease (*27*).

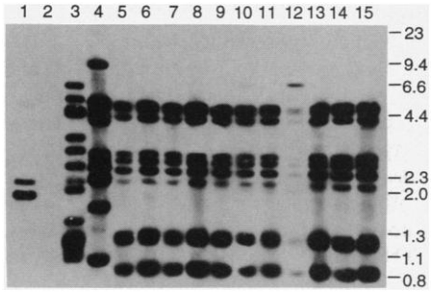

Fig. 1. Restriction fragment length polymorphism analysis of clinical *M. tuberculosis* isolates from residents of an HIV congregate living site in San Francisco. Patients 1 and 2 were receiving chemotherapy when they entered the facility, and their isolates have different banding patterns from 11 patients whose isolates have the same banding pattern. [Reprinted from (*39*), *New England Journal of Medicine*]

The course of TB in individuals infected with the human immunodeficiency virus (HIV) is dramatically different (*28*). Tuberculosis is a sentinel disease for AIDS because, in contrast to most opportunistic infections, it is frequently the first indication of HIV infection. In the United States, the risk of developing TB (reactivation) for individuals who have positive tuberculin skin tests (PPD^+) and then seroconvert to HIV positivity is about 8% a year, in contrast to the 10% lifetime risk for PPD^+ healthy individuals (*29, 30*). Although patients with minimal immunodeficiency may show a normal pattern of the disease, extrapulmonary disease—for example, miliary TB, lymphadenitis, and meningitis—that coexists with pulmonary infection is a more common form of TB in patients with advanced immunodeficiency. Diagnosis is often difficult because PPD reactivity may be compromised in AIDS patients, and x-rays may show only diffuse patterns of infiltration, too often resulting in delayed diagnosis (*31*). Significantly, cure rates with the appropriate regimen appear to be as high for HIV-positive patients as cure rates with standard SCC are for seronegative individuals (*32*).

A Wealth of Ignorance

In few infectious diseases is knowledge of both the pathogen and the host responses to it so essential to understanding of the pathogenesis as in TB. Mycobacteria are daunting organisms to study (*33*). In contrast to the most commonly used organism for molecular biological studies, *Escherichia coli*, which produces a visible colony (10^7 bacilli) in about 8 hours, M. *tuberculosis* requires 3 to 4 weeks to yield a comparable colony. It has a formidable waxy coat comprised of multiple complex lipids and carbohydrates that renders it impermeable to many common drugs. The bacilli tend to form clumps, which makes working with them and quantitation of them difficult (*34*). Because of its pathogenicity and transmission by aerosols, current biosafety regulations require that work with M. *tuberculosis* be carried out under high-level biological containment that is expensive and not widely available. Hence, research on the pathogen is slow and demanding. Although the study of microbial genetics developed over 40 years ago, little beyond the size of its genome and its DNA content was known about M. *tuberculosis* until the last 5 years (*35*). In that short time, methods that enable gene transfer in mycobacteria and selection for recombinants that contain introduced genes and that permit expression of foreign genes have been developed. Perhaps the basic strategy that made molecular study feasible within a lifetime was development of shuttle vectors that allow mycobacterial genes to be manipulated efficiently in *E. coli* and then shuttled into mycobacteria for expression (*36*). These molecular tools, though limited, have made it possible to introduce and express genes for foreign antigens in BCG vaccine strains to create multivalent recombinant BCG vaccines capable of immunization experimentally against multiple protective antigens of several different infectious pathogens simultaneously (*37*).

Individual isolates or strains of M. *tuberculosis* have several repetitive DNA elements with distinct banding patterns in DNA fingerprinting analysis (*38, 39*) (Fig. 1). When multiple isolates from different patients exhibit the same DNA fingerprint pattern, it is highly suggestive that each derives from a common source. This molecular epidemiology can be used to track sources of infection and transmission of individual strains, including drug-resistant organisms. The commonly used diagnostic methods for TB, aside from staining for bacilli in sputum (which is relatively insensitive), require 2 to 8 weeks. With the use of M. *tuberculosis*–specific repetitive or single-copy DNA sequences, the polymerase chain reaction potentially could provide specific and sensitive diagnosis in a few hours (*40*), although it is not yet clear how readily the technology, which is expensive and technically demanding, will be applicable to routine diagnosis. It is disquieting that the current methodology for assessing patterns of antibiotic resistance and susceptibility of strains requires from 3 to 12 weeks for completion.

Our ignorance of the molecular basis of virulence and pathogenesis is great. As W. R. Jacobs, Jr. (*41*), has suggested, molecular evidence analogous to Koch's postulates is required—that is, the establishment of avirulent strains, the identification and cloning

of putative virulence genes of the pathogen, and the demonstration that virulence can be conveyed to an avirulent strain by those genes. Although avirulent strains of *M. bovis* and *M. tuberculosis* exist (*17, 42*), the nature of the mutations is unknown. Not a single gene involved in the pathogenesis of TB has been defined. The molecular bases of invasion of host cells, intracellular survival, growth, spread, or tissue tropism are not known (*43*). None of the targets of existing drugs has been characterized at a molecular level, and the mechanism of resistance to any drug has not been defined; no new mycobacterial target for drug development has been characterized in 20 years. Nonetheless, it is gratifying that although the Human Genome Project did not initially entertain proposals on any human pathogens, *M. tuberculosis* and *M. leprae* have recently been included. With appropriate support, in 3 to 5 years the entire DNA sequence of these pathogens should be known, empowering prediction of every protein, every enzyme, every drug target, and every antigen—a farsighted scientific investment.

After decades of controversy, the rapid course of TB in HIV-seropositive individuals has compellingly established that immunity plays a major role in restricting TB infection in immunocompetent hosts. T cells rather than antibodies are involved, but the precise nature of protective immunity is not known. There are ample data that indicate that the BCG vaccine protects against disseminated TB and meningitis in children (*44*). It is puzzling, however, that BCG's protective efficacy against pulmonary TB in adults has varied from 0 to 77% in different trials (*45*) and that, even in trials with a high percentage of efficacy, skin-test reactivity did not correlate with protection (*46*); thus, surrogate end points for protection are badly needed.

Cell-mediated immunity is required for protection in experimental TB but may also be responsible for much of the tissue damage in the disease (*47*). For example, the most destructive tissue lesions—that is, cavities of the lung—occur only in PPD^+ individuals. Lymphokines produced by T cells are involved in activating macrophages to kill or inhibit the growth of *M. tuberculosis*. Although *M. tuberculosis* can grow extracellularly, it survives predominantly in macrophages. It is resistant to generally cytocidal reactive oxygen intermediates, such as hydrogen peroxide and hydroxyl radical, but is susceptible to reactive nitrogen intermediates (RNI), particularly nitric oxide (NO) (*48*). Activated mouse macrophages and human endothelial cells produce NO, but it is unclear whether human monocytes can do so. The lymphokines required to activate murine macrophages to produce RNI are interferon-γ and tumor necrosis factor–α (TNF-α). TNF-α is critically important for walling off infection and preventing dissemination (*49*) and has been identified in tuberculous pleural fluids (*50*). But TNF and other products of activated macrophages—for example, radicals, proteases, and cytokines—are toxic molecules that can contribute to tissue damage (*51*). Cytotoxic lymphocytes, $CD4^+$, $CD8^+$, γ,δ T cells, and natural killer cells may participate in killing infected macrophages that harbor the bacilli (*52*). Although over a dozen somatic and secreted antigens of *M. tuberculosis* have been cloned (*53*), it is not known which are important for engendering protective immunity. Because killed mycobacteria are far less protective in animal models than live bacteria, current hopes for protective antigens center about secreted molecules (*54*). Fundamental questions remain about the nature of immune responses required for protection, the antigens that engender them, and the extent to which pathogenesis in TB is the price we pay for protection.

Can I Catch TB from Riding the Bus?

The principal risk behavior for acquiring TB infection is breathing. Yet, the idea that microbes exist in sufficient concentration in air to represent a significant source of disease transmission was counterintuitive, and the importance of airborne infection was not established until the first quarter of this century. Careful observations established that coughing, sneezing, and speaking release organism-bearing particles (*55*). For example, a sneeze may contain over a million particles <100 μm in diameter, the mean being about 10 μm. Two types of organism-bearing particles have been found: droplet nuclei and dust-associated particles. After ejection from the nose and mouth, an aerosol droplet rapidly begins to evaporate. The evaporation continues until the vapor pressure of the droplet equals atmospheric pressure. The residue of a droplet that contains any organism is the droplet nucleus, which settles very slowly (12.2 mm per minute) and essentially remains suspended on small air currents until removed by ventilation. The second and less efficient mode of airborne transmission is from rapidly sedimented organisms associated with dust, which can be transiently resuspended by disturbance in air motion and which can serve as a reservoir for the bacilli.

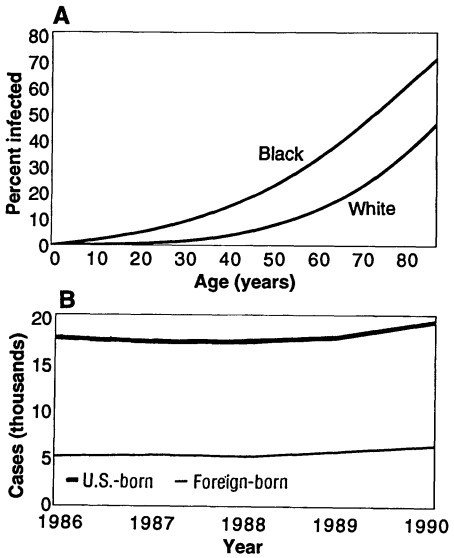

Fig. 2. (**A**) Prevalence of previous infection with *M. tuberculosis* by age for whites and blacks in the United States during 1990. (**B**) Number of cases of TB in U.S.– and foreign-born individuals in the United States from 1986 to 1990. Cases of unknown origin have been proportionately distributed.

In experimental studies in rabbits, droplet nuclei were found to be the major source of *M. tuberculosis* infection (*55*). The number of tubercles in the lungs was approximately equivalent to the number of live bacilli inhaled on droplet nuclei of a settling velocity of 9.14 mm per minute. Only 6% of the bacilli that were inhaled on larger particles reached the alveoli and produced tubercles; the majority settled in the upper respiratory mucosa where they were expelled by ciliary action. Oral infection is far less (10^{-4}) efficient in transmission of TB than inhalation of droplet nuclei, partially because mycobacterial viability is reduced by stomach acidity (*56*). Droplet nuclei were shown to be important in transmission of TB by the passage of air from the ventilating system of a hospital ward with patients with advanced TB through a large exposure chamber in which 71 out of 156 guinea pigs acquired infection (*57*). However, when half the air taken from the ward was vented to a duct where it was exposed to strong ultraviolet (UV) irradiation before passing through the chamber with the guinea pigs, none of the animals became infected, thus establishing the effectiveness of UV in killing tubercle bacilli on droplet nuclei. UV, if properly employed, remains an inexpensive means to decontaminate droplet nuclei (*58*). The number of bacilli present in the source case is a critical variable. The number of bacilli in solid nodular lesions varies between 10^2 and 10^4, whereas in cavitary lesions, the number of organisms is on the order of 10^7 to 10^9 (*24*). Animal studies indicate that as few as one to ten bacilli in droplet nuclei are sufficient to cause infection.

Clearly, there is no simple answer to the question posed above (*59*). TB infection is a stochastic process, and there appears to be

no threshold of organisms required to produce infection. The main determinants of individual risk are the concentration of organism-bearing particles exhaled by the source, their aerodynamic characteristics, the rate of ventilation, and the duration of exposure. Although large outbreaks of infection have been traceable to exposure to a single infected source case (60), epidemiological findings support the likelihood that the majority of patients infected with TB have acquired infection from nonintimate contacts (61).

The Changing Epidemiology of TB

The widespread use of skin tests with tuberculin PPD to detect past or present infection with M. *tuberculosis* has been developed into a valuable tool for epidemiological monitoring of the disease. A body of surveys provides direct measurements on the prevalence of past infection in children and adolescents throughout the world (62). In the 1960s, statistical methods were developed that used survey data on the prevalence of infection by age to estimate the annual risk of being infected with the bacillus each year (63). The most recent regional estimates for the annual risk of infection in the developing world (Table 1) show that the highest risks are in sub-Saharan Africa, where up to 2% of the population may be infected each year (4). Social and economic consequences of the enormous burden of TB morbidity and mortality are only magnified by the concentration of TB in young adults in the developing world. As BCG vaccination also produces skin-test reactivity to PPD, the value of the PPD test will diminish as the number of children vaccinated with BCG increases.

The annual risk of infection also provides a framework for understanding the epidemiological trends over this century. With the use of data on the prevalence of infection in army recruits each year, trends in the annual risk of infection in the Netherlands since the turn of the century have been reconstructed (63, 64). Before effective chemotherapy, the annual risk of infection in the Netherlands and other industrialized countries is believed to have decreased at a rate of 5 to 6% per year because of social and economic changes and the possible quarantine effect of the sanatorium movement. Since 1950 and the widespread use of chemotherapy, the annual risk of infection has been declining at a rate of nearly 10% per year.

The prevalence of positive PPD skin tests of U.S. Navy recruits has been used to estimate the annual risk of infection in the United States for whites as 0.1% in 1970 and 0.04% in 1990 (65). On the basis of these data as well as more recent data on Navy recruits (66) and taking into account methodological differences (67), we have estimated the prevalence by age of ever being infected (Fig. 2) (68). This methodology allows us to estimate that the total population currently living that has ever been infected with M. *tuberculosis* in the United States is 19 million (69).

Reflecting the declining annual risk of infection in the United States, the number of reported cases in the United States decreased every year but one from 1953, the beginning of national reporting, until the mid-1980s. Since 1985, TB cases have increased 18% nationwide. To delve deeper into the causes of this resurgence, we have disaggregated TB cases into four types: (i) reactivation of distant infections and new cases, estimated from annual risk of infection data, (ii) cases in foreign-born individuals, (iii) cases that are a result of HIV and TB co-infection, and (iv) cases in specific risk groups that result from increased active transmission. We estimated the number of cases expected to occur each year since 1978 from the prevalence of infection by age and breakdown rates (Fig. 3) (70). Cases beyond this number are defined as excess cases that can be attributed to immigration, HIV, or increased active transmission.

Several researchers have attributed a significant portion of the past and recent incidences of TB outbreaks to immigrants who enter the country with a greater prevalence of infection than the general U.S. population (6, 71). The CDC has followed cases in foreign- versus U.S.-born individuals for selected areas in the United States since 1979 and for the country after 1985. From 1986 to 1990 (the last year completed in its study), the proportion of total cases in foreign-born individuals in the United States has increased from 22.8 to 24.8%, although the largest share of the increased cases is among U.S.-born individuals (Fig. 2B). Of the excess cases in 1990 (calculated below), only 31% can be attributed to foreign-born individuals, which is only

Table 1. Estimated annual risk of TB infection, new cases, and deaths from TB for the developing world, 1985–1990 (4).

Area	Annual risk of TB infection	New cases per year	Deaths per year
Sub-Saharan Africa	1.5 to 2.5%	1,313,000	586,000
North Africa and western Asia	0.5 to 1.5%	323,000	91,000
Asia	1.0 to 2.0%	5,102,000	1,825,000
South America	0.5 to 1.5%	356,000	111,000
Central America and the Caribbean	0.5 to 1.5%	185,000	80,000
Total developing world		7,280,000	2,692,000

Table 2. Percentage of patients completing 12 continuous months of chemotherapy from 1976 to 1985 and the percentage of patients completing 6 continuous months of chemotherapy from 1986 to 1990 for the United States and selected cities within it. Figures shown are the average of annual percentage for those years with data. The number of areas reporting chemotherapy continuity data each year varies substantially. Within those areas that do report, the number of cases diagnosed each year that are included in the treatment completion database is substantially less than 100%. For the United States as a whole, the percentage of diagnosed cases included in this database has increased from 28% in 1975 to 64% in 1989. As these numbers are averages of a variable number of observations for each city, they should be taken only as indicative of the situation. Blank spaces indicate that no data were reported during that entire period. It is interesting to note that data for Los Angeles are not available for almost all years.

Years	Patients completing chemotherapy by location (%)										
	United States	Chicago	New York	District of Columbia	New Orleans	Detroit	Miami	Atlanta	San Francisco	Dallas	El Paso
1976–1980	82.6%	36.2%	59.7%	50.7%	29.2%		74.7%		83.3%	91.3%	93.5%
1981–1985	81.9%	39.8%	59.6%	60.4%	71.4%	71.1%	82.0%	84.7%	88.2%	95.2%	96.0%
1986–1990	83.7%	57.8%	53.6%	59.9%	81.3%	68.3%	82.5%	84.2%	96.5%	93.3%	99.2%

slightly more than expected in light of their share of total cases.

We estimate the number of excess cases from 1985 to 1991 that resulted from coinfection to be 18,000 (*72*). Although the number of individuals with TB who are also HIV-positive may be higher, the component that is due to active transmission among the same groups that have high HIV seropositivity is difficult to measure. A more refined understanding of the interaction between TB and HIV, including the prior prevalence of TB infection, is needed.

The presence of active transmission beyond that predicted by the small and declining annual risk of infection would cast the resurgence of TB in a different light. Increased active transmission is a sensitive indicator of the failure of a control program to promptly detect and institute effective treatment for infectious cases of TB. Several studies and routine data hint at the importance of active transmission in certain risk groups. Clear evidence of active transmission has been provided for residents of homeless shelters (*73*) and prisons (*74*) and for health-care workers (*75*). A prospective study showed that the annual risk of PPD conversion in initially negative intravenous (IV) drug abusers was 6.7% (*29*), considerably higher than for the general population in the poorest developing countries. Even more worrisome is the possibility that active transmission has been spilling out of high-risk groups into the general population. The number of cases of TB in U.S.–born children under the age of 5 has increased 34% from 1987 to 1990. Because all of these infections must have occurred in the last 5 years, this implies an increase of more than 10% per year in the risk of infection—except for those few cases that are a result of HIV infection in infants and children. In an attempt to quantify the possible role of heightened active transmission, we attributed the excess cases that cannot be explained by HIV infection or by the expected cases from past infection and the declining risks of infection to active transmission (Fig. 3) (*76*). From 1985 to 1991, this excess totals 13,700 cases.

Five possible factors could explain the reversal of the nearly century-long decline in the annual risk of infection: (i) the HIV epidemic; (ii) an increasing homeless population with high potential for transmission and breakdown through adverse living conditions; (iii) increasing numbers of IV drug users with similar living conditions; (iv) the concentration of all three of these risk factors in the same individuals or population subgroups, such that those at high risk for breakdown are at a high risk for transmission; and (v) at a time when the needs for TB control have increased, many city and state governments have been unable to maintain or improve their TB treatment programs (*77*).

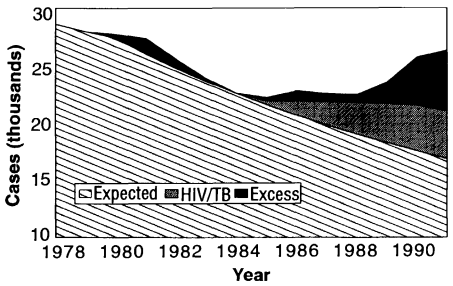

Fig. 3. Estimated cases of TB in the United States from 1978 to 1991, disaggregated into cases expected on the basis of trends in the risk of infection, cases of HIV and TB coinfection, and excess cases.

With depreciating infrastructure, declining real recurrent budgets, and a patient population that is more difficult to treat, programs to treat TB patients in a group of major cities had poor results. Table 2 summarizes the treatment results for the United States and a sample of cities with more than 100 cases of TB a year (*78*). During the time period in which treatment completion data have been collected by CDC, a number of cities have had very poor performance, whereas others have had excellent programs. The apparent failure of a number of urban programs to ensure a continuity of therapy for a higher percentage of their patients is difficult to ascribe to poverty or to general social conditions when other countries such as Mozambique, Tanzania, and Malawi are able to achieve high cure rates (*79*). With the use of CDC definitions, treatment completion in Malawi from 1984 to 1988 was 96% and in Tanzania from 1982 to 1988 was 86%. The experience of these and other developing countries illustrates that high rates of treatment completion have been achieved in the most difficult social, political, and economic circumstances. A common denominator of success has been investment in guaranteeing compliance through hospitalization or direct supervision of ambulatory treatment.

Compliance, Complacence, and Drug Resistance

From the earliest studies, it became apparent that resistance to any single antibiotic developed readily, and combinations of antibiotics were necessary to prevent the emergence of resistance (*80*). The problem in effectively treating sensitive *M. tuberculosis* has been patient compliance with long drug regimens (*81*). After 2 to 4 weeks of treatment, the debilitating symptoms of TB wane, and without active intervention more and more patients drop out of therapy. Many of those who fail to complete an adequate course of chemotherapy will relapse and require retreatment if they are diagnosed. Such circumstances create the conditions for the selection of drug-resistant organisms. For example, in New York from 1982 to 1984, although 9.8% of isolates from untreated patients were resistant to one or more drugs, 52% of isolates from relapsed cases were resistant (*9*). The low compliance and lack of immunological resistance mechanisms in some groups of HIV-seropositive cases have allowed the selection of multidrug organisms refractory to virtually the entire pharmacopoeia of effective drugs. Although the numbers remain too small to be certain, the case fatality rate of multidrug-resistant TB may be between 40 and 60% (*8*). In HIV-positive individuals, the case fatality rate may be higher than 80%, and the time from diagnosis to death may be dramatically accelerated; in one case series, it ranged from 4 to 16 weeks (*82*).

Case numbers tell only part of the story; the resurgence of TB is severely complicated by emerging drug resistance. Because isoniazid and rifampicin are microbicidal and the most effective drugs, resistance to both drugs is a very serious clinical and public health problem. A CDC survey of drug resistance from 1982 to 1986 showed that isolates from 9% of patients who were never previously treated were resistant to one or more drugs and that 22.8% of isolates from previously treated patients were resistant (*83*). In new cases in that

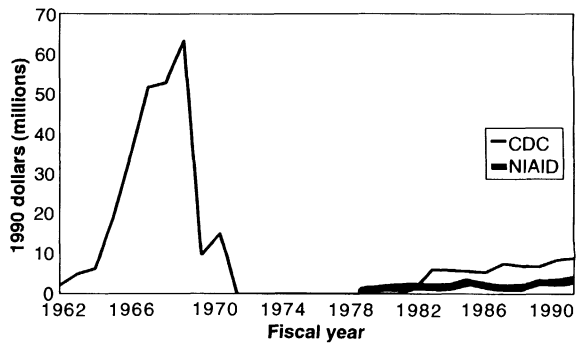

Fig. 4. Federal funding of the CDC for grants to the states for TB control and to NIAID (NIH) for research on TB.

survey, resistance to both isoniazid and rifampicin was 0.5% and in recurrent cases was 3.0%. The most recent data from the CDC, based on a set of reporting areas, indicate that for the first quarter of 1991, 14.4% of isolates were resistant to one or more drugs, whereas 3.1% of new and 6.9% of recurrent cases were resistant to isoniazid and rifampicin (9). These increasing rates of drug resistance challenge previous suggestions that drug-resistant bacilli are less infectious. Drug resistance is a much larger problem in certain cities, most notably New York (7); a study of all isolates in April 1991 showed that in new cases 23% were resistant to one or more drug, and 7% were resistant to isoniazid and rifampicin. In previously treated patients, 44% of isolates were resistant to one or more drug, and 30% were resistant to isoniazid and rifampicin. Experience from the developing world illustrates that programs with good results have comparatively low rates of drug resistance (84).

The Costs of Inaction

According to the simple model outlined above, about half of the increase of the occurrences of TB was unavoidable, a consequence of the natural history of TB and HIV co-infection. Many of the excess cases that resulted from increasing active transmission, however, could have been avoided through effective treatment programs in certain major cities. What has been the cost of our lack of vision in the 1980s when we did not act to strengthen these programs? The direct treatment costs of the excess cases since 1985 that were a result of increased active transmission equal $340 million (85). To this sum, we should add the human suffering quantified as 4,400 discounted years of healthy life lost and the economic indirect costs of lost productivity and social contribution, all totaling $300 million (86).

Predicting the course of the TB resurgence is difficult. Case numbers in this model that result solely from the increased breakdown rate from HIV infection will remain roughly constant at 4000 to 5000 new cases per year in the United States over the next decade. If there were no increased transmission between groups at high risk for HIV and TB because of dramatically improved treatment programs in the major cities, then case numbers in the United States could peak and begin declining again by the middle of this decade. However, we know from outbreak studies that there is a continuing risk of increased active transmission among these groups and into the general population. This threat is only heightened by drug resistance, because of which the treatment of cases and the reduction of transmission potential will be more difficult. In a worst-case scenario, total TB cases might continue to rise at the same rate as in the period of 1985 to 1991 (87). This would mean an excess of 86,000 cases in the United States that were a result of active transmission before the end of the decade. The direct treatment costs of these cases would total $2.2 billion, and the indirect costs would total $1.9 billion. These figures do not include infrastructure costs, which would be considerable—for example, for construction of isolation and negative-pressure facilities and for additional personnel required for directly observed therapy.

Where There is No Vision, the People Perish

Current recognition of the global importance of TB and renewed interest in addressing the problem derive, curiously, not primarily from public health institutions but from the World Bank. In a farsighted and comprehensive review of health problems of developing countries, it concluded that the impact of TB on development had been largely overlooked (88). The World Bank has recently made substantial loans to China and Bangladesh for TB control. But the hero of the piece is the International Union Against Tuberculosis and Lung Diseases (IUATLD) (89) that, on an annual budget of $4 million, has established control programs that detect approximately two-thirds of all cases, treat 65,000 cases, and provide cure rates of 80 to 85% in seven developing countries, including Tanzania, Malawi, Mozambique, and Nicaragua. From their detailed control program data, it was possible to estimate the burden of the disease and establish the cost-effectiveness of providing SCC (79). The WHO over the previous 15 years tragically allowed its Tuberculosis Unit to decline to the point that a single professional remained in 1989. Fortunately, WHO has recently initiated a new program in TB to both provide technical expertise requested by developing countries and develop an international research program that, if given appropriate resources, could make a significant impact (90). It is to be hoped that the considerable expertise of the Tropical Disease Research Programme and other WHO scientific programs will be engaged to strengthen the TB research effort.

In the United States, a generation of expertise has been lost. NIH support for research dwindled in the 1970s and, though now rising, is inadequate to address the scientific challenges of TB (91). Although drug resistance has been emerging unnoticed overseas, the importance to the United States of NIH engagement in research on international health problems has never been adequately appreciated or funded. The CDC receives federal funds to disburse through cooperative agreements with states and locales to control TB (Fig. 4). Additional special funding for HIV and TB demonstration projects in the United States, of particular importance for confronting TB drug resistance in AIDS patients, currently amounts to $10.8 million. It is hoped that these funds will double in the 1993 U.S. federal budget (92), although the proposed $35 million in grants to states is less than the request from New York City alone. With the loss of $340 million in the past 5 years attributable to excess cases of TB and the projected loss of more than $2.2 billion by the end of the decade, it is unlikely that the present resources will be adequate. It is essential to determine the true costs required to stem the increase of TB in this country.

In the world of infectious diseases, there is nothing from which we are remote and no one from whom we are disconnected. We will continue to be challenged by emergent threats to health, new agents and vectors, and new evolutionarily selected and man-made variants. The United States spends 12% of its gross national product on health care, although one wonders how much is spent to prevent disease rather than to treat it. We know how to cure and prevent conventional TB; we must quickly develop the capacity to prevent the spread of drug-resistant TB. If we do not learn from the current epidemic of TB and if we do not develop new scientific tools to diagnose, prevent, and treat the disease, the tragedy unfolding in New York City could be repeated in any city in America that has homeless people, AIDS, prisons, hospitals, and nursing homes. The fundamental principle of infectious disease control that we have yet to apprehend was best articulated in 1513, not by a physician but by the political scientist Machiavelli (93):

> It happens then as it does to physicians in the treatment of Consumption, which in the commencement is easy to cure and difficult to understand; but when it has neither been discovered in due time nor treated upon a proper principle, it becomes easy to understand and difficult to cure. The same thing happens in state affairs; by foreseeing them at a distance, which is only done by men of talents, the evils which might arise from them are soon cured; but when, from want of foresight, they are suffered to increase to such a height that they are perceptible to everyone, there is no longer any remedy.

Note added in proof: The first molecular target for any antituberculosis drug, isoniazid, has recently been defined (94).

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48. J. Chan *et al.*, *J. Exp. Med.* **175**, 1111 (1992); M. Denis, *Cell Immunol.* **132**, 150 (1992). NO production could provide insight into the classical literary characterization of TB as a beatific and often passionate illness that in Dickens's word "refines" death [S. Sontag, *Illness as Metaphor* (Penguin, New York, 1983), p. 90]. If NO were produced in TB infection, it is tempting to speculate that the historical optimism of TB (spes phthisica) and romanticization of this disease may have a physiological basis. NO has been found to act as a retrograde potentiator of the *N*-methyl-D-aspartate neurotransmitter excitatory pathway and to potentiate dopaminergic neurotransmission, which enhances affective and pleasure centers in the brain [J. Garthwaite, *Trends Neurosci.* **14**, 60 (1991); M. J. Kuhar, M. C. Ritz, J. W. Boja, *ibid.*, p. 299; E. R. Kandel, J. H. Schwartz, T. M. Jessell, *Principles of Neural Science* (Elsevier, New York, ed. 3, 1991), pp. 863–867]. It may be of interest to note that iproniazid, an antituberculosis drug related to isoniazid, is a monamine oxidase inhibitor and was the first antidepressive drug described (*ibid.*, p. 877).
49. The importance of TNF in granuloma formation was shown by V. Kindler, A.-P. Sappino, G. E. Grau, P.-F. Piguet, and P. Vassalli [*Cell* **56**, 731 (1989)], and P. Amiri *et al.* [*Nature* **356**, 604 (1992)].
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58. _____ and E. A. Nardell, *Am. Rev. Respir. Dis.* **139**, 1286 (1989).
59. Relevant, however, is evidence that a measles outbreak was spread by droplet nuclei among children at the Cato-Meridian school in rural New York who took the same school bus to school [J. E. Perkins, A. M. Bahlke, H. F. Silverman, *Am. J. Public Health* **37**, 529 (1947)].
60. Within the recent past, a single, HIV-seronegative schoolteacher in St. Louis, who believed he had smokers' cough, infected 175 out of 353 school children (56%), 33 of whom developed TB (D. Snider, personal communication), and 28% of his colleagues converted to PPD positivity. In a hospital infection, 44% of HIV-positive inpatients developed TB from exposure to a single source case, as shown by DiPerri *et al.* (*30*).
61. S. Grzybowski, G. D. Barnett, K. Styblo, *Bull. Int. Union Tuberc.* **50**, 90 (1975).
62. G. M. Cauthen, A. Pio, H. G. ten Dam, *Annual Risk of Tuberculous Infection* (WHO/TB 88.154, WHO, Geneva, 1988).
63. K. Styblo, J. Meijer, I. Sutherland, *Bull. Int. Union Tuberc.* **42**, 5 (1969); I. Sutherland *et al.*, *ibid.* **44**, 75 (1971). For a review of the history of the risk of infection, see I. Sutherland [*ibid.* **66**, 189 (1991)].
64. I. Sutherland, *Adv. Tuberc. Res.* **19**, 1 (1976).
65. G. M. Cauthen, personal communication. Estimates were based on their analysis of the unadjusted Navy recruit skin test data. A slightly faster rate of decline and thus lower prevalence would be estimated if the methods of Rust and Thomas (*67*), which are discussed in the paper, had been used.
66. E. R. Cross and K. C. Hyams, *Am. J. Public Health* **80**, 435 (1990).
67. P. Rust and J. Thomas, *Am. J. Epidemiol.* **101**, 311 (1975).
68. Survey data on the prevalence of PPD positivity by age often shows a decline in prevalence at older ages. This cannot reflect lower rates of cumulative infection because the annual risk of infection appears to have been declining over most of this century. This decline of skin test positivity with age has been ascribed to age-related anergy, loss of delayed-type hypersensitivity, or the selective mortality of PPD^+ individuals [W. W. Stead and T. To, *Ann. Intern. Med.* **107**, 837 (1987); E. Dorken, S. Grzybowski, E. A. Allen, *Chest* **92**, 237 (1987); L. S. Palitz and M. H. Aronsohn, *Am. Rev. Respir. Dis.* **75**, 461 (1957)]. A range of estimates of the rate of decline in the annual risk of infection is possible on the basis of different cutoffs for PPD induration size and other criteria. For whites, we chose to estimate prevalence using an 8% annual decline from 1950 to the present because this proves a more realistic fit to the observed rate of decline in cases and the prevalence of infection in U.S. Navy recruits in the 1980s. For the years before 1950, we assumed a 5% decline on the basis of the experience of the Netherlands before chemotherapy (*63, 64*). For nonwhites, we assume a 4.5% decline in the annual risk of infection. We calculated prevalence at each age using the equations developed by Sutherland (*64*).
69. This is a considerable underestimate because it does not include immigrants from countries with a higher prevalence of infection than the U.S.-born population. Also, these estimates assume all nonwhites have the same prevalence of infection as African-Americans.
70. Estimates of the long-term reactivation rate and short-term breakdown rate from this regression that fit with previous studies were selected to give the best fit to reported case numbers from 1960 to 1984. For estimates of the long-term breakdown rate, see O. Horwitz, E. Wilbek, and P. A. Erickson [*Bull. WHO* **41**, 95 (1969)] and G. W. Comstock, V. T. Livesay, and S. F. Woolpert [*Am. J. Epidemiol.* **99**, 131 (1974)].
71. H. L. Reider, *Bull. Int. Union Tuberc.* **65**, 85 (1990); _____, G. M. Cauthen, L. B. Reichman, S. Ruggiero, *Health Serv. Rep.* **89**, 177 (1974); K. E. Powell, M. P. Meador, L. S. Farer, *Am. J. Public Health* **71**, 1223 (1974); American Thoracic Society, *Am. Rev. Respir. Dis.* **116**, 561 (1977).
72. Various models provide reconstructions of HIV seroprevalence for the United States [*Morb. Mortal. Wkly. Rep.* **39**, 1 (1990)]. The age distribution of seroprevalence has been based on the age distribution of AIDS cases retrospectively projected by 5 to 10 years. The number of co-infections has been based on the assumption that the probability of being HIV-positive in the population is independent of the probability of being infected with *M. tuberculosis* for two groups: white and nonwhite. Refined estimates incorporating risk factors beyond ethnicity are required. The task is made more complex because the same groups in which TB prevalence and HIV seroprevalence are concentrated are also at highest risk for increased active transmission. Breakdown rates for TB and HIV co-infection are assumed to be 8% per year on the basis of the results of Selwyn *et al.* (*29*). On the basis of these estimates, there should have been a considerable number of cases early in the 1980s that were a result of HIV and TB co-infection, but there is little evidence of excess cases during this time period. For this model, we have assumed that the risks of TB and HIV breakdown are some function of CD4 counts, so that there would be a delay from the onset of the HIV epidemic until TB cases began appearing. A delay of 4 years provides the best fit with the observed data.
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75. C. E. Haley *et al.*, *Infect. Control Hosp. Epidemiol.* **10**, 204 (1989); *Morb. Mortal. Wkly. Rep.* **37**, 718 (1990); P. D. Greenberg, K. G. Lax, C. B. Schechter, *Am. Rev. Respir. Dis.* **143**, 490 (1991); E. Barrett-Connor, *J. Am. Med. Assoc.* **241**, 33 (1979).
76. The predicted cases include some occurrences of TB in foreign-born individuals, because they are counted in the population totals for whites and nonwhites. Cases that result from a higher prevalence in foreign-born individuals than in U.S.-born individuals of the same ethnic group are not included in the modeled expected case numbers. These cases would be included in the category of excess cases.
77. K. Brudney and J. Dobkin, *Am. Rev. Respir. Dis.* **144**, 745 (1991). At Harlem Hospital in New York City, the case completion rate for 224 consecutive TB patients was 11% [A. Vennema, *Public Health Rep.* **97**, 127 (1982)].
78. Data on the outcome of treating the cohort of patients diagnosed each year are not available in the United States in a form that is readily comparable to the rest of the world. Although IUATLD standard cohort definitions include patients who die or transfer out of programs, these patients are excluded both from the numerator and denominator of program result data in the United States. Interpretation of program data from the United States is also complicated by changes in the reporting system over the last two decades. From 1975 to 1986, city and state programs were asked to inform CDC of patients completing 12 months of chemotherapy continuously and patients completing their regimen in 24 months. In 1986, this was changed to patients completing 6 months of chemotherapy continuously and those completing their regimen in 12 months. Data are provided to CDC on a voluntary basis; the result is that treatment completion data are available for any given year for 28 to 64% of patients diagnosed, depending on the year. Poor results may imply a poor program or a poor information system; experience shows that these are often correlated.
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80. If the mutation rate for resistance to a single antibiotic is of the order of 10^{-6}, then the theoretical probability of developing resistance simultaneously to three drugs, assuming they act independently and have similar pharmacoenetics, would be 10^{-18}. For the problem of drug resistance in TB control, see T. Shimao [*Tubercle* **68** (suppl.), 5 (1987)].
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82. *Morb. Mortal. Wkly. Rep.* **40**, 585 (1991).
83. D. E. Snider *et al.*, *Am. Rev. Respir. Dis.* **144**, 732 (1991).
84. S. Spinaci, personal communication.
85. The major costs of treatment of TB are hospitalization; on the basis of limited data, we estimate the average treatment costs per patient are $25,000. If drug-resistance rates continue to rise, the costs of treating excess TB patients could dramatically increase. Drug costs for resistant cases are about ten times higher than for sensitive cases, and the overall costs of treatment are five to ten times higher. In an outbreak of multidrug-resistant TB in 1990 in Fort Worth, Texas, the cost of treating ten patients was $950,433 [*Morb. Mortal. Wkly. Rep.* **39**, 369 (1990)]. The cost of treating multidrug-resistant patients at the National Jewish Hospital, Denver, is estimated to be $100,000 to 200,000 per patient (M. Iseman, personal communication).
86. We calculated indirect costs assuming that half of the individuals in the excess cases would be infected with HIV and lose five discounted productive years of life and that the other half would lose 16 discounted productive years. Average cost of a discounted productive year of life is assumed to be $20,000 with a discount rate of 3%.
87. A linear regression of case number and year from 1985 to 1991 would predict an increase of 569 cases each year until the end of the decade.
88. D. T. Jamison and W. H. Mosley, Eds., *Disease Control Priorities in Developing Countries* (Oxford Univ. Press for the World Bank, New York, in press).
89. In one of few precedents for the notion of a "thousand points of light," in 1904 38 voluntary societies against TB in the United States banded together to form the Society for the Study and Prevention of Tuberculosis with Dr. Edward Livingstone Trudeau as its first president. This evolved domestically into the National Tuberculosis Association and is now the American Lung Association, in which TB has been relegated in recent years to a minor cause. Numerous national TB associations form the IUATLD, which has carried on heroic work with minuscule resources assisting some of the least developed countries to establish effective TB control programs [A. Rouillon, *Bull. Int. Union Tuberc.* **66**, 159 (1991)].
90. WHO, *Tuberculosis Control and Research Strategy for the 1990s* (WHO/TB 91.157, WHO, Geneva, 1991). The 1992 WHO Tuberculosis Program budget for disease control activities is $4.3 million; for operational research, $1.1 million; for immunology and chemotherapy research, $0.9 million; and for

improved diagnostics, $0.18 million.
91. The NIAID increase for TB research proposed in the 1993 federal budget is $200,000 (Hearing on Tuberculosis, Government Operations Subcommittee, House of Representatives, 2 April 1992).
92. Fiscal year 1993, Justification of Appropriation Estimates for the Committee on Appropriations.
93. N. Machiavelli, *The Prince*, L. Ricci, Ed. (English edition, Oxford Univ. Press, Oxford, 1933), chap. 3, p. 1513 [transl. in G. B. Webb (*12*), p. 178].
94. Y. Zhang, B. Heym, B. Allen, D. Young, S. Cole, *Nature*, in press.
95. We gratefully acknowledge the help we received from P. Arno, R. Ashley, P. Barnes, D. Brown, D. Burke, K. Brudney, R. Bumgarner, G. Cauthen, J. Cook, A. Dannenberg, S. Dooley, M. Earle, D. Enarson, P. Fine, T. Frieden, L. Garrett, D. Gwynn, M. Hamburg, G. Hardy, C. Hayden, J. Hill, P. Hopewell, M. Iseman, W. Jacobs, Jr., A. Kochi, L. Reichman, A. Rouillon, C. Schieffelbein, G. Schoolnik, J. Schwartz, P. Smith, D. Snider, S. Spinacci, K. Styblo, H. ten Dam, and G. Uhl. Special thanks are due to D. Snider and T. Frieden for their thoughtful comments on the manuscript and to the library staff at Albert Einstein College of Medicine for bibliographic assistance. The support provided by the Edna McConnell Clark Foundation (C.J.L.M.) is gratefully acknowledged.

The Crisis in Antibiotic Resistance

Harold C. Neu

The synthesis of large numbers of antibiotics over the past three decades has caused complacency about the threat of bacterial resistance. Bacteria have become resistant to antimicrobial agents as a result of chromosomal changes or the exchange of genetic material via plasmids and transposons. *Streptococcus pneumoniae, Streptococcus pyogenes*, and staphylococci, organisms that cause respiratory and cutaneous infections, and members of the *Enterobacteriaceae* and *Pseudomonas* families, organisms that cause diarrhea, urinary infection, and sepsis, are now resistant to virtually all of the older antibiotics. The extensive use of antibiotics in the community and hospitals has fueled this crisis. Mechanisms such as antibiotic control programs, better hygiene, and synthesis of agents with improved antimicrobial activity need to be adopted in order to limit bacterial resistance.

The stunning success of the pharmaceutical industry in the United States, Japan, the United Kingdom, France, and Germany in creating new antibiotics over the past three decades has caused society and the scientific community to become complacent about the potential of bacterial resistance. There are countless antibiotics: more than 50 penicillins, 70 cephalosporins, 12 tetracyclines, 8 aminoglycosides, 1 monobactam, 3 carbapenems, 9 macrolides, 2 new streptogramins, and 3 dihydrofolate reductase inhibitors (*1*). Despite all these antibiotics, a person could die in a hospital in New York, San Francisco, Paris, Barcelona, Tokyo, or Singapore as a result of a resistant bacterial infection.

Antibiotics are available that effectively inhibit bacterial cell wall synthesis, protein synthesis, and DNA replication (Fig. 1 and Table 1). Bacteria can resist antibiotics as a result of chromosomal mutation or inductive expression of a latent chromosomal gene or by exchange of genetic material through transformation (the exchange of DNA), transduction (bacteriophage), or conjugation by plasmids (extrachromosomal DNA) (*2*). Conjugation with plasmid transfer of DNA is particularly common among the *Enterobacteriaceae*, *Pseudomonas*, and anaerobic species (*2, 3*). In addition to conjugative plasmids, bacteria may possess transposons, the so-called jumping genes, that have the ability to enter transmissible plasmids or chromosomes (*4*). Resistance can be transferred horizontally by plasmids or by chromosomally located conjugative transposons that spread the resistance to other species. It has been postulated that *Escherichia coli* transferred the ability to produce β-lactamase enzymes that destroy compounds with a β-lactam nucleus (Fig. 2) into *Haemophilus influenzae* by initially infecting *Haemophilus parainfluenzae* (*5*). Intergenus spread of resistance can occur between Gram-positive species such as staphylococci and enterococci and between *Enterobacteriaceae* and *Pseudomonas* or anaerobes such as *Bacteroides* (*6*). Gram-positive species can transfer resistance to Gram-negative species, but the reverse is uncommon.

Antimicrobial agents are rendered inactive by three major mechanisms: (i) inactivation of the antibiotic by destruction or modification, (ii) prevention of access to the target, and (iii) alteration of the antibiotic target site (*3*). Some examples of inactivation are β-lactamase and aminoglycoside-inactivating enzymes (*7, 8*) (Table 2). The alteration of permeability or efflux of an agent occurs for β-lactams, aminoglycosides, and tetracyclines (*9*), and a single amino acid change in an enzyme alters the sensitivity of the targets for β-lactams, macrolides, and folate synthesis antagonists (*3, 10, 11*).

Staphylococci

In 1941, virtually all strains of *Staphylococcus aureus* worldwide were susceptible to penicillin G, but by 1944 *S. aureus* was

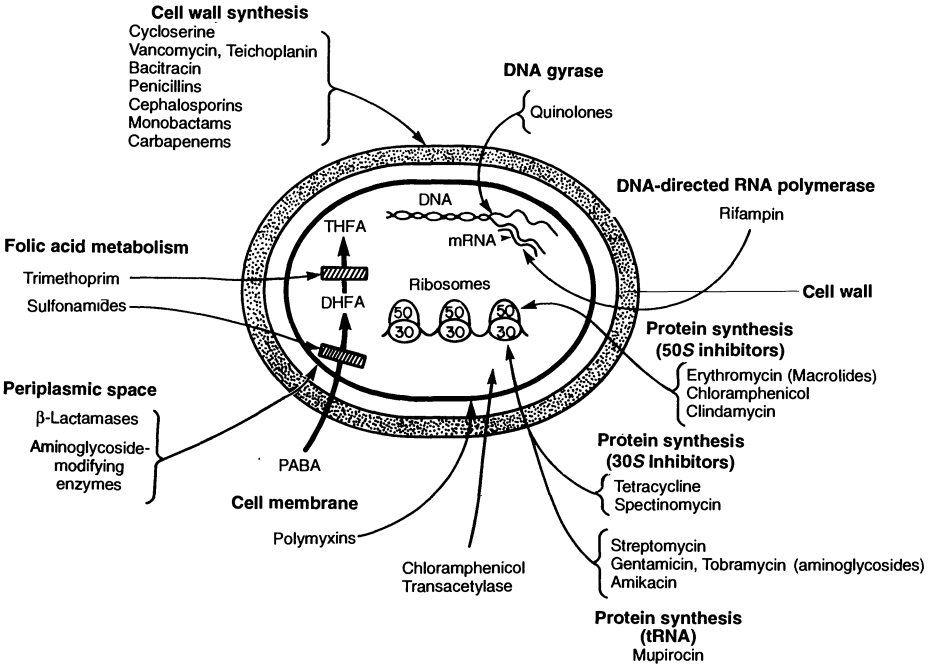

Fig. 1. Sites of action of various antimicrobial agents; mRNA, messenger RNA; tRNA, transfer RNA; PABA, *p*-aminobenzoic acid; DHFA, dihydrofolic acid; THFA, tetrahydrofolic acid.

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