Tuberculosis: Pathogenesis, Protection, and Control
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Chapter 2

History of Tuberculosis

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EARLY HISTORY OF TUBERCULOSIS

In the paleolithic period, people lived as wanderers, did not settle in villages or permanent locations, and did not congregate in large groups. While tuberculosis may have occurred sporadically, it and other infectious diseases probably did not occur in epidemic form. Beginning in about 8000 B.C., humans developed primitive agricultural techniques that allowed settlement in permanent sites, and with this development came the domestication of cattle, swine, and sheep. In all probability, tuberculosis occurred more frequently in this setting, but it nevertheless remained rare (Clark, 1962). McGrath estimates that a social network of 180 to 440 persons is required to achieve the stable host-pathogen relationship necessary for tuberculous infection to become endemic in a community (McGrath, 1988).

Tuberculosis probably occurred as an endemic disease among animals long before it affected humans (Steele and Ranney, 1958). *Mycobacterium bovis* was the most likely infecting organism, and the first human infections may have been with *M. bovis*. Since *M. tuberculosis* infects all primate species, it is also possible that this species existed in subhuman primates before it became established in humans.

As centuries and millennia passed, human beings began to live in larger and larger communities, and with this shift came environmental changes that were associated with a change in the delicate balance between humans and the tubercle bacillus. Two alternative theories have been proposed to explain the epidemic spread and subsequent decline of tuberculosis that followed. The first and widely accepted explanation involves the development of genetically determined herd immunity (Stead, 1992). As a rule, parasites are short-lived compared to their hosts, and this fact gives parasites a great advantage, since mutations can occur in them more frequently than in their hosts in response to environmental pressure. When the host generation time is much longer than that of the parasite, as is true of humans and the tubercle bacillus, the host cannot adapt as quickly as the parasite. Thus, initially the parasite has a distinct advantage and begins to eliminate the susceptible members of the species before these individuals can pass on their genes to progeny. However, since not all

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hosts of a species are eliminated, the progeny of the survivors form a subset of the population that is characterized by increased resistance to that particular parasite (Hamilton et al., 1990). Thus, over time, the highly advantageous position enjoyed by the parasite diminishes, and after successive generations, the once serious life-threatening infection becomes less devastating. Probably for this reason, no infectious disease has ever killed all of its host population. Many other factors, such as nutrition and overcrowding, contribute to the incidence of disease in a population, but genetic factors are of unquestioned importance in the selective mortality from infection.

Tuberculosis probably occurred as a sporadic and unimportant disease of humans in their early history. Epidemic spread began slowly with increasing population density. This spread and the selective pressure it has exerted have occurred at different times around the globe. The epidemic slowly spread worldwide as a result of infected Europeans traveling to and colonizing distant sites (Diamond, 1992). In the 1700s and early 1800s, tuberculosis prevalence peaked in Western Europe and the United States and was undoubtedly the largest cause of death (reviewed by Bloom and Murray, 1992, and Graunt, 1662), and 100 to 200 years later, it had spread in full force to Eastern Europe, Asia, Africa, and South America. Within a particular population in a defined geographic area, the tuberculosis epidemic reached its peak within 50 to 75 years after its beginning and then slowly declined, possibly as the more resistant host survivors reproduced.

Tuberculosis Epidemics in Europe and North America

It is important to recognize that tuberculosis remained an unimportant disease for humans regardless of its virulence until in feudal Europe the necessary environmental changes occurred to set off an epidemic that came to be called "The Great White Plague" (Dubos and Dubos, 1952; Castiglioni, 1933; Webb, 1936; Cummins, 1949). In the early 1600s, the incidence of tuberculosis in England began to increase sharply. The epidemic grew over the next two centuries and spread through Western Europe. During this phase of the epidemic, almost all Western Europeans became infected with *M. tuberculosis*, and about one in four deaths were due to tuberculosis. In the ever-enlarging cities, the increased population density provided the necessary environmental conditions for person-to-person spread of this airborne pathogen. Such conditions had never been met previously.

European migrants brought the tubercle bacillus with them to North America (Diamond, 1992). For example, in Boston, Massachusetts, the mortality rate from tuberculosis was as high as 650/100,000 in 1800, and it decreased to about 400/100,000 by 1860 (Grigg, 1958). In like manner, the tuberculosis death rate in New York was 750 in 1805 and decreased to 400 by 1870. In Baltimore, it was as high as 400 in 1830 and decreased to 210 by 1900. In the cities along the northeastern seaboard, each succeeding generation experienced a decreased death rate. By 1904 the tuberculosis death rate in the United States was 188; it fell to 4/100,000 by 1969. As Western Europeans moved about the globe, the epidemic of tuberculosis followed them. It moved slowly to Eastern Europe. As late as the 1880s, tuberculosis was not commonly seen in Russia, and it was relatively uncommon in India at the same time. Cummins reports that tuberculosis was almost unknown within the interior of sub-Saharan Africa as late as 1908 (Cummins, 1920). It was essentially unknown in the interior of New Guinea as late as 1920, when that area was first explored by Europeans (Brown et al., 1981).

Tuberculosis among Indigenous Peoples of the Western Hemisphere

Although tuberculosis was present in the Western Hemisphere in paleolithic times, Native Americans of North America and South America had little trouble with tuberculosis prior to the European migration. In the immediately pre-Columbian era, about 60 million persons lived in South and North Americas, with the great majority living in South America. There were few, if any, large population centers. Buikstra and Cook reported a review of 14 prehistoric human skeletons from eight population centers in Illinois dating between 100 B.C. and 1300 A.D. (Buikstra and Cook, 1981). Some of these skeletons showed deformities compatible with tuberculosis, but the lesions were not diagnostic of tuberculosis. Perzigian and Widmer (1979) described osseous changes typical of tuberculosis in the vertebral skeletal remains of 6 of 290 persons from an Ohio community dated to 1275 A.D.

Acid-fast bacilli were observed in the lungs of a mummy from southern Peru dated from about 700 A.D., and subsequent additional cases of tuberculosis have been observed in South American mummies (Allison et al., 1973). Deformities suggesting Pott's disease among skeletons dating back to 160 B.C. have been found in Peru. In his review of prehistoric skeletal deformities in Latin America, Ponce describes large numbers of prehistoric figures and drawings depicting Pott's disease (Ponce Sangines, 1969). Endemic tuberculosis in the pre-Columbian South American setting would be compatible with the fairly complex society, densely sited housing, and established agriculture that existed among the inhabitants of Peru as long as 6,000 years ago.

Despite this archaeologic evidence, tuberculosis was a rare disease among native North American Indians even early into the 19th century. Priests who explored the Great Lakes region during this time reported rare cases of glandular infection and chronic pulmonary conditions that were probably tuberculous in nature. It was only after the North American Indians were forced to settle on reservations or to live in barracks and prison camps that outbreaks of tuberculosis were observed. In these settings, contact with white settlers became frequent, and the crowding promoted airborne transmission of the bacillus. In 1887 at the Mount Vernon Barracks, several hundred Apache prisoners were kept in close confinement, and the death rate the first year was 54/1,000, rising to 143/1,000 in the fourth year. Nearly half of these deaths were due to tuberculosis (Bushnell, 1930). By 1886, the tuberculosis death rate for North American Indians reached 9,000/100,000 (Ferguson, 1955). These death rates are the highest ever recorded worldwide and exceed by 10 times the peak death rate observed in Europe in the 17th century.

Tuberculosis in Africa

Tuberculosis of the spine is depicted in several figurines dating from the predynastic era (prior to 3000 B.C.) of Nilotic North Africa (Morse et al., 1964). Some of these figurines appear to have originated from nomadic desert-living tribes. Additional similar figures and paintings clearly depicting angular spinal deformities characteristic of tuberculous spondylitis occur throughout Egyptian dynastic times. Mummies from several Egyptian sites show skeletal changes typical of tuberculosis (Morse et al., 1964), and psoas abscesses and fibrotic pulmonary disease have been observed, further supporting the impression that the skeletal changes were tuberculous in origin. Among 10 early dynastic Nubian skeletons, spinal disease typical of tuberculosis was found in 4. These four skeletons came from two graves, suggesting the familial occurrence of tuberculosis.

Despite the fact that tuberculosis was spreading rapidly in Europe, Nilotic North Africa, and the Americas, it remained es-

sentially unknown in sub-Saharan Africa as late as the beginning of the 20th century. A number of medical observers reported the complete absence of tuberculosis in the interior of sub-Saharan Africa. Army medical officers from Great Britain noted that tuberculosis was unknown in those parts of Africa where European immigration had not occurred (Cummins, 1920). Livingstone (1857) found no tuberculosis in parts of South Africa, and Lichenstein found none as late as the first half of the 20th century (Lichenstein, 1928).

Tuberculosis in Asia and the Pacific Islands

The Hawaiian Islands had little or no tuberculosis as late as the 1850s. Wilkinson remarked upon the rarity of tuberculosis in India in the first half of the 19th century and its progressive increase in the middle years of the 19th century as industrialization increased population density (Wilkinson, 1914). Toward the end of the 19th century, India and China experienced peaks in the incidence of tuberculosis, but as late as 1951, tuberculosis was still unknown among the island populations of New Guinea (Brown et al., 1981). Finally, when the disease did reach these latter populations, it produced the typhoidal illness so characteristic of highly susceptible individuals having their first experience with tuberculosis.

TUBERCULOSIS AND THE DAWNING OF BIOMEDICAL SCIENCE

From the time of Hippocrates, tuberculosis was known as "phthisis," a term derived from the Greek for "wasting away." The swollen glands of the neck were known 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. Tuberculosis of the skin was termed lupus vulgaris, and that of the spine was termed Pott's disease. The vertebral fusion and deformity of the spine that characterize Pott's disease have enabled historians to establish the existence of tuberculosis in mummies dating from 2000 to 4000 B.C.

As Europe emerged from the Dark Ages, there was a renaissance not only of the arts but also of medical science. Observant scientists described their world and explored its nature and mechanisms. This European intellectual renaissance began in an era of extraordinarily high tuberculosis prevalence fueled by the industrial revolution and the grinding poverty it engendered in its huddled masses. Hence, it is not surprising that many fundamental concepts of biology emerged in the context of inquiry about the nature of tuberculosis. Weaving together stories of individuals whose lives were dramatically affected by tuberculosis with accounts of pioneering exploration of the pathogenesis of this disease, we will attempt to create a tapestry depicting the genesis of four areas of knowledge about tuberculosis and the human and social contexts in which the knowledge was acquired.

Infectious Etiology of Tuberculosis

Tuberculosis (consumption) was common in European cities during the first half of the 19th century, and one-fifth to one-quarter of all deaths were due to this disease (Waksman, 1964). No one knew what caused tuberculosis. Some doubted that it was a single disease, so varied were its manifestations. That it might be contagious was a notion that occurred to only a few. Thus, Frederick Chopin was not expecting hostility from the inhabitants of Majorca, where he had gone in 1839 to seek relief from his symptoms. However, his doctors alerted the residents of the island that the famous composer and musician was consumptive, public clamor ensued, and his landlord turned him out (Dubos and Dubos, 1952; Waksman, 1964).

Frederick Chopin had been a sickly youth. He first developed clinical tuberculosis at age 16. Dubos and Dubos (1952) quote Georges Sand, who accompanied Chopin to Majorca. She recounted that the landlord who expelled them sought damages for replastering the house they had occupied because it was contaminated. Their departure arrangements were complicated by the refusal of carriage drivers to transport them and their goods. They crossed the island with wheelbarrows. They sailed to Barcelona with a shipload of pigs, and the inn keeper in Barcelona charged them for Chopin's bed, which the local authorities required be burned. Chopin died of tuberculosis a decade later in 1849. He was 39 years old.

A scant 20 years prior to Chopin's ejection from Majorca, Theophile Laennec published his classic text on diseases of the chest (Laennec, 1962). While Laennec is best known to students of medicine for his description of alcoholic cirrhosis of the liver, his principal interest throughout his life was tuberculosis. Major credits Laennec with first recognizing that tuberculosis, in all of its forms and anatomic sites, is a single disease (Major, 1945). This view was not espoused by most of the pathologists of Laennec's era. Laennec died of tuberculosis in 1826. Waksman points out that this was the same year in which Chopin developed his tuberculosis (Waksman, 1964).

In 1679, Franciscus Sylvius described the characteristic lung nodules as "tubercula" or "small knots" and observed their evolution to cavities, 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 understanding that tuberculosis might be due to infectious microorganisms was made in 1722 by Benjamin Marten of London, who proposed that the cause of tuberculosis 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" (Doetsch, 1978; Castiglioni, 1933). More than a century after Laennec's birth, Villemin performed experiments on rabbits, injecting infectious sputum and caseous material into healthy animals to produce disease. These studies, published in 1868 and cited by Major (1945), provided the first convincing evidence of the infectious nature of tuberculosis. Gradually, the infectious nature of tuberculosis became more widely recognized. As early as 1699, Italy and later Spain enacted restrictive quarantine laws, while in Northern Europe, tuberculosis was not widely viewed as a public health problem.

On March 24, 1882, a third of a century after Chopin's death, Robert Koch made a presentation to the Berlin Physiological Society that changed thinking about tuberculosis and infectious diseases forever and that can be thought of as establishing the science of microbiology. He described the tubercle bacillus, *M. tuberculosis*, an organism still known to many as Koch's bacillus, and convincingly demonstrated it to be the cause of tuberculosis (Koch, 1932; Sakula, 1982; Grange and Bishop, 1982). To carry out his pioneering studies, Koch developed staining techniques and was the first to employ culture on solid media. This landmark technical advance allowed the subculturing of individual colonies, clearly a fundamental technical advance in microbiology. His criteria for proof that the organism he discovered caused tuberculosis have been widely adopted and have become known as Koch's postulates. He specified that, "it was necessary to isolate the bacilli from the body; to grow them in pure culture . . .; and, by administering the isolated bacilli to animals, to reproduce the same morbid condition . . ." (Koch, 1932). Regrettably, in 1890 he also announced that culture filtrates cured the disease, a claim

that was immediately controversial and promptly discredited. Sadly, Koch refused to divulge the nature and preparation of the curative material, an action for which he was accused of trying to give his government a monopoly and himself an institute (Bloom and Murray, 1992). Nevertheless, those filtrates, later partially purified, became the principal means of establishing the presence of infection in an individual, i.e., the tuberculin skin test.

Koch's initial presentation, made to the physiologists because Virchow refused to allow him to address the pathologists in Berlin, was received with great excitement, and his observations were rapidly confirmed by others. Among those who heard him was Paul Ehrlich, who hastened to develop improved staining techniques; Ziehl and Neelson quickly made further refinements, upon which diagnostic sputum smears are still based today. Subsequently, Ehrlich stained acid-fast bacilli in his own sputum to establish his personal diagnosis of tuberculosis. Edward Livingston Trudeau, whose own youthful, nearly fatal bout with tuberculosis led him to devote his life to the study and treatment of this disease, learned of Koch's work. He established his laboratory at Saranac Lake, New York, and repeated and extended Koch's observations. Fundamental work on tuberculosis continued at that laboratory for decades, and when Trudeau's cottage sanatorium finally closed, its endowment was used to establish the Trudeau Institute, where research on the immunology of tuberculosis continues to this day.

With the infectious nature of tuberculosis firmly established and the tubercle bacillus a pathogen that could be identified in laboratories, public health officials urged actions to interdict its spread: the beginning of the public health movement in the United States. Coughing and spitting in public were the subject of regulations and became socially unacceptable. In hospitals, the burning of Chopin's bed linen was repeated again and again as concern over fomites grew. In the 1930s, William Wells injected both common sense and reason into controlling the transmission of infectious particles when he pointed out that the tubercle bacillus is an airborne, inhaled pathogen. He emphasized the role of infectious droplet nuclei and undertook studies of their aerial spread. This work culminated in the classic study by Riley, a pupil of Wells (Riley et al., 1962). In this study, air from a tuberculosis ward was delivered untreated to an animal exposure chamber and, after UV irradiation, to a control chamber. Each chamber housed 120 guinea pigs. No infections occurred in guinea pigs receiving irradiated air, while 63 animals receiving untreated air became infected. Thus, the aerial spread of tuberculosis was firmly established. By matching microbial drug susceptibility patterns, one patient with tuberculosis laryngitis was identified as particularly infectious. Modern parallels are presented by microepidemics in poorly ventilated areas, of which few are more dramatic than the one described by Catanzaro just 100 years after Koch's demonstration of the tubercle bacillus (Catanzaro, 1982). Among hospital personnel caring for a patient with unrecognized infectious tuberculosis in an intensive care unit, primary infections occurred in 31% of susceptible exposed individuals, with the attack rate reaching 77% in persons attending a bronchoscopy. The patient was estimated to be generating 249 infectious units per h, and the ventilation in the patient area provided only 1.2 air turnovers per h.

Resistance to Tuberculosis

The romantic age of the 19th century glamorized the sallow, wan physical appearance typical of patients with tuberculosis. Thus, when Daniel Chester French began his work on the statue of John Harvard that remains a notable feature of the

Harvard Yard, he seized upon the fact that John Harvard was known to have had tuberculosis to model a face "delicate- . . . and sensitive in expression" (Richman, 1977). But this romantic view of tuberculosis belies the facts. The variable course of tuberculosis makes it evident to all observers that some individuals are much more susceptible to the ravages of this disease than others. Some tuberculous patients are hardy and robust while still diseased; others suffer more.

John Keats was a remarkable poet who died of tuberculosis in 1821 at the age of 26. He met tuberculosis in his family at an early age; his mother died of this disease when he was 14, and his brother later developed tuberculosis. Keats studied medicine and was torn between it and poetry, for which he was acclaimed in his lifetime. In the summer of 1820 he developed hemoptysis, which he recognized as his death warrant, and from that point his course was steadily downhill. His short life ended in Italy in February 1821. During his final weeks, his treatment included phlebotomies, the same ineffective therapy used for Laennec. Although Keats succumbed rather rapidly to what must have been fulminant disease, it is incorrect to think of him as weak or asthenic. As a youth he was robust and athletic. He enjoying wrestling, mountain climbing, and long walking trips over rough terrain.

Robert Louis Stevenson's life and death contrast with those of Keats. Also a writer acclaimed in his time, Stevenson traveled across the world seeking a benevolent climate where he would find relief from his tuberculosis. He wrote *The Master of Ballantrae* and other stories published as the Scribner series while a patient at Trudeau's cottage sanatorium in Saranac Lake. His Saranac Lake home is open today as a museum. Chronically but never acutely ill, debilitated by disease of relatively stability, he continued writing and traveling, finally dying in the South Pacific in 1894 of vascular disease probably unrelated to his tuberculosis.

Perhaps the most illustrative example of familial tendency toward tuberculosis is the Brontë family. This literary British family shared a passion for learning and writing and a strong predisposition for acquiring tuberculosis. The Reverend Brontë and his wife Maria had six children in less than 7 years: Maria (1813), Elizabeth (1815), Charlotte (1816), Patrick Branwell (1817), Emily (1818), and Anne (1820) (Chadwick, 1914). All six children died of tuberculosis before they reached their 40th birthdays.

Less than a year after the birth of Anne, Mrs. Brontë died at age 39 in 1821. It is unclear whether she died from cancer, a postpartum complication, or septicemia. Three years later, in July 1824, Reverend Brontë found himself unable to care for his young daughters, and he sent the four eldest to a boarding school for the daughters of clergy at Cowan Bridge. The harsh regimen, poor diet, and walks in the freezing rain did not agree with the young girls' "delicate constitutions." In April of 1825, the eldest daughter, Maria, developed the symptoms of tuberculosis and was sent home, only to die in May at the age of 12. Elizabeth followed, returning home in May to die of the same disease in less than a month at the age of 11.

The Brontë family then enjoyed a 23-year hiatus from tuberculosis, during which each of the children wrote pieces that became cornerstones of British literature. In 1848, however, the opium-addicted poet Branwell Brontë died from tuberculosis at the age of 31 (Fraser, 1988). According to Fraser, he might have contracted tuberculosis in the village, "where it was endemic, which would explain the speed with which it killed Emily and Anne" (Fraser, 1988). Other possible sources "were either Emily or Charlotte herself, who was carrying a form of chronic fibrotic tuberculosis which periodically flared up, or Mr. Brontë, who is believed to have suffered from chronic

tubercular bronchitis" (Fraser, 1988). At her brother's funeral, Emily Brontë, author of *Wuthering Heights*, caught a cold that was said to have weakened her in her bereaved state, and in December 1848 she succumbed to "galloping consumption" at the age of 30. After losing her only brother and older sister in less than 3 months, Anne Brontë sadly soon followed, dying in May of 1849 at the age of 29, leaving behind her novel *Agnes Grey*. Only Charlotte Brontë remained. Six years later, on July 29, 1854, she married for the first time at the age of 38. Her marriage lasted less than a year. While walking on the moors with her husband, she caught a cold that developed into full tuberculosis, and she died on March 31, 1855, at the age of 39. The Reverend Brontë outlived his entire family, dying in 1861 at the age of 85.

Max Lurie emigrated from Lithuania to the United States in 1908 at the age of 15. He entered medical school at Cornell University and graduated in 1921, but he did not practice medicine, for he developed tuberculosis, making his own diagnosis. Although medical students were at increased exposure risk of tuberculosis in that time, Lurie felt that he was disposed to this disease by his family history. His mother had tuberculosis; her father and grandmother had died of it.

Beginning his studies while a patient at the National Jewish Hospital in Denver and continuing at the Phipps Institute of the University of Pennsylvania, Lurie dedicated his life to studies of the experimental pathology of tuberculosis. He recognized the central role of monocytes and their tissue forms (macrophages) in host resistance. He understood clearly the differences between host responses to initial and subsequent infections with mycobacteria. He became intrigued with the factors that made some individuals and some kindreds susceptible and others resistant to the ravages of this infection.

Lurie chose bovine tuberculosis in rabbits for his studies, feeling it to be the animal model that best approximated the pathogenesis of human tuberculosis. He undertook studies with inbred families of rabbits, developing strains that "exhibit varying characteristic inherited resistance to tuberculosis, generation after inbred generation" (Lurie, 1964). This work set the stage for the widespread use of inbred laboratory animals to elucidate genetic aspects of many diseases. Studies in twins have shown that Lurie's concepts are applicable to humans (Comstock, 1978), an observation not surprising to clinicians and other observers of people, who have long recognized the occurrence of tuberculosis in families.

Immunology of Tuberculosis

Samuel Johnson suffered from scrofula, the King's Evil. In 1712 he was touched by Queen Anne, whose ancestors, beginning with King Clovis of France in the fifth century, claimed the divine power to heal this affliction. Knowing that tuberculosis adenitis usually represents primary infection, that its course is often benign, and that primary infection confers immunity against reinfection, it is easy to understand how royal claims of a cure might have gained widespread acceptance.

In 1891, Robert Koch, already famous for his discovery of the tubercle bacillus, described experiments with guinea pigs that extended his earlier observations and clearly demonstrated acquired immunity following primary infection, and the term "Koch phenomenon" has been applied to the results he described (Bothamley and Grange, 1991). Koch noted that healthy guinea pigs inoculated cutaneously with tubercle bacilli healed the primary inoculation lesion, only to die later of disseminated infection. However, a second inoculation of virulent organisms produced a very different result. The wound became indurated in 1 or 2 days and then ulcerated; dissemi-

nation did not result. When tubercle bacilli killed by boiling were used for the initial inoculation, the same result followed. Koch noted that a sterile culture filtrate of bacilli, which he named tuberculin, evoked the cutaneous induration as well as whole organisms did, and he attributed the hypersensitivity thus demonstrated to something in this filtrate. Indeed, he proposed treating tuberculous patients with tuberculin, a measure that failed to have therapeutic benefit.

The warp thread of acquired immunity was deftly woven into the fabric of the history of tuberculosis by Albert Calmette and Camille Guérin (Sakula, 1983). Calmette, a French physician with extensive experience in infectious and tropical diseases, was appointed to the directorship of the newly founded Pasteur Institute of Lille in 1895. He was joined there by Guérin, his assistant and a veterinarian, in 1897. They knew of Koch's experiments, of early work done by von Pirquet and others on tuberculin hypersensitivity, and of the apparent success of Pasteur in vaccinating against rabies. With great hope, they began in 1908 to attenuate a strain of *M. bovis* by serial passage. By 1919 they had completed 230 passages, and their vaccine strain was found to be avirulent in guinea pigs, rabbits, cattle, and horses. It was first given to a human in 1921. Without detailing the long history of conflicting results from clinical trials, the efficacy of bacille Calmette-Guérin (BCG) remains unknown today. However, it is currently in widespread use throughout the world.

Today, the immunology of tuberculosis is well known. While many important questions are yet to be answered, it is clear that T lymphocytes responding to protein antigens of mycobacteria and lymphokines, prominently including interleukins 1 and 2, gamma interferon, and tumor necrosis factor alpha, are major mediators of protective immune responses in tuberculosis. Among the contributions of many, the seminal observations of Merrill Chase deserve special note (Chase, 1985, 1988). Chase was engaged in the study of contact dermatitis in the laboratory of Karl Landsteiner. Landsteiner was convinced that cell-fixed antibodies were responsible for this and other forms of delayed hypersensitivity. In 1941 and 1942, partly by accident, Chase found that dermal-contact hypersensitivity could be transferred by cell suspensions. Two years later, the observation was extended to tuberculin reactivity induced with mycobacteria. The science of cellular immunology was born, rising from these experiments with guinea pigs infected with tubercle bacilli.

Treatment of Tuberculosis

Alice Marble was born on September 28, 1913, in a settlement named Dutch Flat in Plumas County, California, the daughter of a lumberman and a nurse (Davidson and Jones, 1971). By her early teenage years, her athletic prowess was manifest, and she enjoyed the privilege of participating in pregame warm-ups of the San Francisco Seals, a minor league baseball team. Her oldest brother, Dan, concerned about his 15-year-old tomboy sister, returned home one evening with a gift for Alice—a tennis racquet. He hoped that she would apply herself to a more ladylike sport than baseball.

Eight months later, Alice Marble won her first tournament, and in 1931 she traveled to the East Coast to participate in the national tennis championships. In less than a year, she was ranked seventh in the national senior rankings. A new coach, Eleanor "Teach" Tennant, helped her become accustomed to the grass courts of the east, and in 1933 she traveled to Great Britain to represent the United States in the Wightman Cup. Her skills improved, and her game, marked by a masculine and powerful style exhibited in volleys and serves, seemed near perfection. Then tragedy struck. In 1934, Alice Marble collapsed

during competition on the tennis court in Stade Roland Garros in Paris. She awoke in a hospital to a diagnosis of tuberculosis and the disheartening medical opinion that her tennis career was over (Marble and Leatherman, 1991).

Alice Marble left Paris by wheelchair and sailed on the S.S. *Aquitania* to New York, where she was greeted by a physician's assessment that she "would never play tennis again." She returned to her home in California and then entered Pottenger's Sanitorium in Monrovia, California. Dr. Pottenger examined her weekly with the conclusion that she was "doing nicely" (Marble and Leatherman, 1991). After 6 weeks, Pottenger declared that she need to stay for at least another 6 weeks and forbade any physical activity. Just before her 21st birthday, she received a letter from actress Carol Lombard, urging her to fight the medical odds to recover from her disease.

After 8 months of hospitalization and with the covert aid of her tennis coach, Alice Marble fled the sanatorium and refused to return. She initiated a gradual exercise program and within less than a year had returned to the tennis circuit. She won the U.S. women's singles tennis championship in each of the three ensuing years. She died in 1990 at the age of 77 without having suffered subsequent relapses of tuberculosis.

While rest resulted in the cure of some patients with tuberculosis, not all of those afflicted were so lucky. In the prechemotherapy era, the ultimate mortality of patients admitted to New York State sanatoria with tuberculosis in 1938 through 1948 was 69% for those with far-advanced disease, 23% for those with moderately advanced disease, and 13% for those with minimal disease (Alling and Bosworth, 1960). Pottenger, who treated Alice Marble, notes in his text published in 1948 that "tuberculosis shows great tendency to heal and, even though quantitatively and qualitatively severe, it may heal spontaneously" (Pottenger, 1948).

The grim prognosis of tuberculosis changed dramatically in November 1944, when a 21-year-old woman with progressive, far-advanced pulmonary tuberculosis who had failed to respond to both rest and thoracoplasty received the first injection of streptomycin, isolated only 11 months previously by Selman Waksman (Pfuetze et al., 1955). She improved during the ensuing 5 months and was discharged from the hospital in 1947. She was evaluated in 1954 and found to be well and the happy mother of three children.

Equally or more dramatic were the results of the first use of isoniazid reported by Robitzek and Selikoff in 1952 (Robitzek and Selikoff, 1952). Of 44 febrile patients, the temperatures of 42 "subsided promptly and sometimes precipitously." Weight gains in the treated patients were "most spectacular," with the average weight gain 19.7 lb (1 lb = 453.6 g). Appetites of treated patients were described as "ravenous," and a 50% increase in food consumption on the treatment ward was noted. Clearing of tubercle bacilli from the sputum was noted in most but not all patients, and radiographic clearing was observed in half. Side effects were minimal. With these dramatic therapeutic results, the era of successful chemotherapy for tuberculosis was launched. The conquest of tuberculosis seemed imminent.

EBB AND FLOW: THE FAILED CONQUEST

That tuberculosis was disappearing from the United States was recognized by Wade Hampton Frost in a landmark paper published posthumously in 1939 (Frost, 1939). He used Massachusetts public health data from several preceding decades to project epidemiologic trends and to explain changing age-specific tuberculin reactor rates. Clearly, tuberculosis had been on the wane

long before effective therapy was introduced. National individual tuberculosis case reporting was introduced in the United States in 1953, and annual data thereafter documented a steady decline in tuberculosis incidence. Beginning in 1985, that trend changed, and on Sunday, July 15, 1990, the headline of the lead story on the front page of the New York Times read, "Tuberculosis germ resurges as peril to public health; Highest threat in cities; Re-emergence borne on tide of AIDS, homelessness, drugs and alcohol abuse." In fact, rising tuberculosis case rates since 1985 mean that more than 40,000 cases have occurred that would not have happened had historical trends continued.

There are many reasons for the resurgence of tuberculosis in the United States. The AIDS epidemic is an important factor, and infection with human immunodeficiency virus is the single greatest risk factor known for progression from primary infection to disease. The lymphocytes first identified by Chase are, of course, destroyed by this virus. The entry into the United States of large numbers of persons from countries with high tuberculosis prevalence rates has substantially changed the epidemiology of tuberculosis in this country. Tuberculosis remains the number one infectious disease cause of death in the world (Kochi, 1991), and immigrants bring with them the epidemiology of their homelands. Finally, in some parts of this country, public health measures have collapsed or been abandoned, and facilities to serve high-risk individuals are inadequate. Thus, 89% of patients with active tuberculosis discharged from Harlem Hospital were found to be noncompliant with their prescribed therapy (Brudney and Dobkin, 1991).

Not only does the United States face the gloomy scenario of increasing tuberculosis incidence, but multidrug-resistant tuberculosis has emerged in several major urban centers (Frieden et al., 1993). Patients infected with such organisms face the same prospects for cure or progressive disease that Alice Marble did, and our country lacks facilities to provide for their chronic care and for protection of others from airborne spread of their virulent bacilli. Clearly, there is a need for major strides forward both in tuberculosis control and in tuberculosis research.

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