
TUBERCULOSIS

AND NONTUBERCULOUS

MYCOBACTERIAL INFECTIONS

EDITED BY DAVID SCHLOSSBERG



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MYCOBACTERIAL INFECTIONS

SEVENTH EDITION

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TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

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SEVENTH EDITION



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Dedication

This volume is dedicated to Dr. Menachem M. Meller, with respect, admiration, and affection.

“A faithful friend is the medicine of life.”

—Ben Sira, 6:16

“The Captain of all these men of death that came against him to take him away, was the consumption; for it was that that brought him down to the grave.”

John Bunyan
The Life and Death of Mr. Badman

The weariness, the fever, and the fret
Here, where men sit and hear each other groan;
Where palsy shakes a few, sad, last gray hairs,
Where youth grows pale, and spectre-thin, and dies;
Where but to think is to be full of sorrow
And leaden-eyed despairs,
Where beauty cannot keep her lustrous eyes,
Or new love pine at them beyond tomorrow.

John Keats
Ode to a Nightingale

There is a dread disease which so prepares its victim, as it were, for death...a dread disease, in which the struggle between soul and body is so gradual, quiet, and solemn, and the results so sure, that day by day, and grain by grain, the mortal part wastes and withers away, so that the spirit grows light...a disease in which death and life are so strangely blended that death takes the glow and hue of life, and life the gaunt and grisly form of death—a disease which medicine never cured, wealth warded off, or poverty could boast exemption from—which sometimes moves in giant strides, or sometimes at a tardy sluggish pace, but, slow or quick, is ever sure and certain.

Charles Dickens
Nicholas Nickleby

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Preface

We are pleased to present the Seventh Edition of *Tuberculosis and Nontuberculous Mycobacterial Infections*.

Tuberculosis remains epidemic in much of the world, causing several million deaths each year. Although most of these deaths occur in developing nations, the developed world continues to struggle with tuberculosis, with evolving challenges from drug resistance, immigration, immunosuppression, and the expanding awareness of nontuberculous mycobacterial infection.

The previous structure of this book has been maintained. Section I presents basic concepts of epidemiology, pathophysiology, diagnosis, medical and surgical therapy, resistant tuberculosis, vaccines, tuberculosis in enclosed populations, and the role of the health department. Section II describes both classic and more recently described clinical manifestations of tuberculous infection. Virtually every organ system is included, as are the endocrinologic and hematologic complications of tuberculosis. Separate chapters address issues unique to pregnancy, infants and children, HIV infection, and the immune reconstitution syndrome. Section III comprises nontuberculous mycobacterial infection, with an overview of clinical syndromes produced by these organisms as well as individual chapters on *Mycobacterium avium-intracellulare*, *M. fortuitum* and other rapidly growing mycobacteria, *M. kansasii*, *M. marinum*, and additional less common pathogenic mycobacteria.

Four new chapters have been added. “The Role of Therapeutic Drug Monitoring in Mycobacterial Infections” explores the vital importance of monitoring serum levels of the antituberculosis drugs; “Crisis-Affected Populations and Tuberculosis” describes the interrelationship of groups affected by social upheaval; in “Diabetes and Tuberculosis” we see the growing influence of each of these afflictions on the other; and “Biologic Agents and Tuberculosis” details the effect of these increasingly used agents on the incidence of tuberculosis. In

addition to the new chapters, every chapter has been thoroughly updated. New clinical data impact our understanding of interferon gamma release assays, the HIV-tuberculosis interaction, immune reconstitution inflammatory syndrome, and extremely drug-resistant tuberculosis. The protean presentations of pulmonary and extrapulmonary tuberculosis continue to challenge the clinician, as does the growing list of nontuberculous mycobacterial pathogens. Epidemiologic issues include airline-associated infection, the explosion of tuberculosis in areas of the developing world, and the critical roles of the World Health Organization and departments of public health in tuberculosis control.

We hope that this text continues to provide a complete and user-friendly resource for everyone—clinician, scientist, epidemiologist—involved in the diagnosis and treatment of tuberculosis and related infections.

I am grateful for the guidance, wisdom, and professionalism of the staff at ASM Press, particularly Christine Charlip, Megan Angelini, and Greg Payne.

David Schlossberg, MD, FACP

General Considerations



Thomas M. Daniel¹

Tuberculosis in History: Did It Change the Way We Live?

1

INTRODUCTION

Tuberculosis is one of the oldest of humankind's plagues (1). The genus of the causative organism, *Mycobacterium*, may be millions of years old. *Mycobacterium tuberculosis* probably emerged as a pathogen of our early ancestors 20,000 to 15,000 years ago in east Africa. As humans peopled the globe, they took their diseases with them, including tuberculosis. DNA of *M. tuberculosis* and typical tuberculous lesions containing acid-fast bacilli have been identified in both Egyptian and Peruvian mummies. Further documentation of the ancient spread of tuberculosis is contained in ancient texts and is documented at archeological sites.

As Europe emerged from the Middle Ages and the Industrial Revolution swept into Europe and North America, the lives of inhabitants of those regions changed dramatically. As computer chips, automobiles, and cell phones dominate our age, machines and urban living dominated in the 18th and 19th centuries. The writings of classical Greek and Roman physicians make it clear that they recognized tuberculosis. Regarding the Middle Ages, little is known of most diseases, including tuberculosis, although royal touching for scrofula began with Clovis in 496 and archeological sites have revealed bony evidence of the disease. During the 17th and 18th centuries, tuberculosis exploded with soaring prevalence. In 1680 John Bunyan described it as “the

Captain among these men of death” (2). During the next 200 years this sobriquet would hold, as tuberculosis became a leading cause of death in Europe and North America. Then tuberculosis waned, as have all disease epidemics, for reasons that remain unclear.

A unified concept of tuberculosis first emerged with the work of Laënnec in the early 19th century, and from that time forward one can recognize the impact that this disease has had on the way we live. This impact can be illustrated by the life stories of many individuals, some often told, others less commonly recounted. A few have been selected for this account.

IMPACT ON THE PRACTICE OF MEDICINE

For scores of years the treatment of tuberculosis pervaded the practice of nearly every physician. Early therapeutic regimens were intended to remove malevolent humors and included bleeding, leeches, cupping, and vesicants. Sir James Clark, physician to Queen Victoria and to the dying John Keats, estimated that pulmonary tuberculosis caused about one-fifth of all deaths in Europe and North America in his era, the early 19th century. Clark was a moderate, and his therapy was largely palliative. He urged restraint in bloodletting and advocated travel to salubrious climates. “The change of scene and the constant succession of new objects exert

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a direct and most beneficial influence,” he wrote (3). Later in that century Sir William Osler recommended optimum nutrition and palliation of symptoms (4). He also argued for removing patients to favorable environments, citing the Adirondack experience of Edward Livingston Trudeau, who retreated to the wilderness, recovered his health, and opened his famous Adirondack Cottage Sanitarium at Saranac Lake, NY. Trudeau ultimately succumbed to tuberculosis.

In the first half of the 20th century, tuberculosis sanatoria assumed a major position in medical care. In fact, by the mid-1950s, when the advent of chemotherapy would lead to the rapid closing of these nearly ubiquitous institutions, there were 839 sanatoria in the United States, comprising more than 130,000 beds for tuberculosis patients (5). The world’s first voluntary health agency, the National Association for the Study and Prevention of Tuberculosis, now the American Lung Association, was founded as an advocacy agency for sanatorium patients in 1904.

The modern science of epidemiology owes much of its gestation to the work of Wade Hampton Frost. Frost developed tuberculosis in 1918 and recovered in Asheville, NC, a much-favored location at that time. In elegant studies of tuberculosis in Williamson County, TN, Frost first developed the concept of the index case, now known to every epidemiologist and public health investigator (6). Mass radiographic surveys were a prominent part of American and Canadian public health efforts for two decades, from the mid-1940s until they were abandoned in the face of rapidly declining disease incidence.

Modern clinical practice relies upon data collected in randomized, controlled clinical trials to establish its standards of care. The studies of tuberculosis treatment protocols conducted by the British Medical Research Council are often cited as pioneering in this arena (7, 8). In fact, the first randomized, placebo-controlled, double-blind clinical trial in the history of medicine was conducted in 1926 and 1927 at the William H. Maybury Sanatorium in Detroit, MI, by J. Burns Amberson, B. T. McMahon, and Max Pinner to evaluate the efficacy of sanocrysin, a gold salt, in treatment of tuberculosis (9). Twenty-four patients with tuberculosis were randomly assigned by the flip of a coin to receive injections of either sanocrysin or a saline placebo. Only the one nurse giving the injections knew which patients were in which group. When the results were analyzed, sanocrysin was found to have no therapeutic benefit but significant toxicity.

The life stories of many pioneering tuberculosis physicians enrich our understanding of the era of great

tuberculosis prevalence. Some of them had enormous influence on the practice of medicine in their times and later. Early in the van of these exceptional men of medicine was René Théophile Hyacinthe Laënnec (10, 11). Laënnec was born on 17 February 1781 in Quimper on the Brittany coast of France. Because his mother was too ill with tuberculosis to care for him, he was placed with an uncle. When the latter died of tuberculosis, Laënnec was sent to the home of a physician uncle in Nantes. There he began his studies of medicine in 1795, moving to Paris in 1801 to study at the *École de Médecine* at the Hôpital Charité under the tutelage of pioneering anatomist Jean Nicolas Corvisart. In 1804, while near the end of his medical studies but still a student, he presented a paper in which he challenged existing concepts and argued that disease manifested by tubercles in whatever part of the body they were found was one disease that should be called tuberculosis.

In 1816 Laënnec invented the stethoscope, for which he was widely acclaimed. Using his instrument he described most of the physical signs of pulmonary disease, coining such terms as “ronchus” and “egophany,” which are still taught to medical students. Laënnec published his work in 1819 under the title *De l’Auscultation Médiate*; it was translated into English and extensively reworked by John Forbes in 1821 (12). The publication of this work and especially its translation into English mark the beginning of pulmonary medicine as a clinical specialty.

Laënnec suffered from tuberculosis. He was undoubtedly infected as a child. While in Nantes he incurred a prosector’s wart when he inadvertently inoculated his hand while performing an autopsy on an individual who had died of tuberculosis. In Paris he increasingly suffered from respiratory disease. He returned to his native Brittany in 1918 and recovered somewhat. Later he imported bottles of air from Brittany to his Paris apartment. Famous in his time and much sought for his clinical expertise, he was elected to the French Academy of Medicine and, in 1824, made a Chevalier of the Legion of Honor. His tuberculous disease progressed, however, and in April 1826 he returned to his beloved Brittany for the last time. Tuberculosis claimed his life at age 45 on 13 August 1826. It took from the world one of the greatest physicians of the time, a man of then-unequaled clinical skills. One can only speculate on what more he might have contributed to medicine.

IMPACT ON WORLD POLITICS

Tuberculosis is not prominent in the personal histories of many of the world’s historically notable politicians

and leaders. It took the life of France's Louis XIII. So, also, did tuberculosis bring premature death to Charles IX of England. More notably, in modern times, South Africa's Nelson Mandela developed tuberculosis while a prisoner but recovered with drug therapy. In none of these instances can one assert that the course of world history was altered.

The British Empire would seem to owe much to its explorers who went to Africa seeking relief from tuberculosis. James Bruce, a Scotsman, discovered the Ethiopian source of the Blue Nile in 1770. Mungo Park explored West Africa in 1795. Both of these men set off on their adventurous journeys seeking relief from tuberculosis; travel was a common prescription for consumptives at that time.

Cecil Rhodes brought South Africa under British hegemony; he had a lasting impact on the future course of sub-Saharan Africa. When the 17-year-old Rhodes arrived in South Africa in 1870, the region included two Boer republics, two British colonies, two independent states, and a number of indigenous territories that England controlled as protectorates. Three years earlier diamonds had been discovered, and the region was booming with prospectors. Rhodes's oldest brother, Herbert, had preceded him to South Africa by a year and become a planter. In the diamond frenzy, Herbert had staked a claim that was to yield enormous numbers of the precious gems.

Cecil Rhodes was born in Hertfordshire, England, on 5 July 1853 (13). He developed tuberculosis at age 16 and went to South Africa to join his brother because a sea voyage and change in climate were considered likely to benefit his health. Indeed, he did regain vigorous health and within 2 years was managing his brother's diamond mine. Herbert Rhodes sold his claim in 1873. Cecil Rhodes, now a wealthy young man, returned to England to study at Oxford. His tuberculosis recurred about 6 months later, and within the year he was back in South Africa and once more recovering his well-being.

Rhodes's business acumen was extraordinary. By his 35th birthday, he controlled more than 90% of South Africa's diamond production and held a dominant position in its gold mining industry. With some of his business colleagues, he founded the British South Africa Company. By force or negotiation, he obtained concessions from local tribal chiefs. In October 1889, Queen Victoria granted the company a royal charter. Investors eagerly subscribed to its stock offerings. Rhodes envisioned expansion of his and England's realms northwards, but the Boer settlers fought this expansion vigorously. Some native tribes revolted. Much of Rhodes's time and efforts went into consolidating and securing

the company's holdings. He traveled between England and South Africa to negotiate and lead the empire-building effort.

In 1902 the 49-year-old Rhodes became ill. The nature of this illness is not clear, although it was thought that his heart was failing. Indeed, some biographers dispute the generally held belief that Rhodes had tuberculosis, arguing that he suffered from congenital heart disease (14); that assertion seems difficult to reconcile with what is known of the course of his disease during an often very active life. Rhodes died in South Africa, a land he loved, on 26 March 1902.

Taking place in more recent times, the story of Manuel Quezon and his leadership of the people of the Philippines reflects his battle with tuberculosis. Afflicted with the disease since his youth, he defied it and ignored it through an active life of leadership that resulted in his election as the first president of the Philippine Commonwealth in 1935. In fact, in his autobiography, completed during his terminal illness and published posthumously in 1946, Quezon makes but scant reference to his illness (15). In 1927, while in the United States lobbying for the appointment of a Philippine governor, he was found to have tuberculosis. Quezon was hospitalized at the Pottenger Sanatorium in Monrovia, CA, but was unhappy with his treatment there and left after a short stay. After the Japanese invasions of the Philippines in World War II, he left his country to lead a government in exile, initially in Australia and then in the United States. With his tuberculosis again active, he conducted his government's affairs from a cottage at Saranac Lake, where he died following a massive hemoptysis in July 1944 (16).

Josephine Baker, an African-American dancer, chanteuse, and comic who exiled herself to France because of racial segregation in American entertainment venues, was a remarkable woman, sometimes remembered for dancing at the Folies-Bergère wearing only a bunch of bananas (17). During the World War II Nazi occupation of France, she was entertaining in Marseilles. The French underground approached her with a request that she serve as a courier of secret messages, exploiting her freedom to travel and carry music on which information was transcribed in invisible ink. Having a cough, she sought a physician's order to be released from the obligations of a contract and go to Morocco. The physician obtained a chest radiograph that showed bilateral tuberculosis. He told her to go to Morocco and to rest. She left Marseilles but did not rest: she embarked on an espionage career that supported the French resistance effort throughout the German occupation of France. Her selfless effort was recognized by

the French government after the war with the award of Chevalier of the Legion of Honor. Her tuberculosis remained quiescent throughout the rest of her life.

Rhodes was an exceptional empire builder. Had he lived longer, the British hegemony over much of Africa might have been extended further. Quezon and Baker played roles in sustaining the resistance of those living under Japanese and German wartime occupation.

IMPACT ON CIVIL SOCIETY

Not all history is political. The lives of ordinary citizens are often affected by the actions of not-so-ordinary individuals. There are numerous instances in which tuberculosis played a role in these actions and their impact. Francis of Assisi emerged from prison wasted and an apparent victim of tuberculosis (18). During the next decade he led a life of poverty and ministry to the poor that led to his sainthood and the founding of the Franciscan order. He succumbed in 1226. Saint Thérèse of Lisieux died of tuberculosis in 1897 at age 24. John Harvard, whose 1638 bequest of 400 books and half of his estate put his name on one of America's most prestigious universities, died of tuberculosis. Tuberculosis claimed the life of 43-year-old Louis Braille, who made writing available to blind persons, in 1852. Alexander Graham Bell, the telephone's inventor, moved with his parents from Edinburgh, Scotland, to the putatively more salubrious Nova Scotia, Canada, in 1870 following the death of his two older brothers from tuberculosis. Six years later he made the world's first telephone call. Desmond Tutu developed tuberculosis as a teenager and spent 2 years at the Rietfontein Chest Hospital in South Africa, where he underwent collapse therapy with pneumothorax. George Balanchine was ill with tuberculosis in 1935. Eleanor Roosevelt was hospitalized with tuberculosis in France as a young woman. Ignoring the advice to seek further treatment upon her return to the United States, she embarked on a disease-free, remarkable humanitarian life, only to succumb to disseminated tuberculosis at age 75 in 1962.

John Batterson Stetson was born in Orange, NJ, in 1830, the seventh of 12 children of Stephen Stetson, a hatter (19–21). Apprenticed to the family hat business as a youth, he developed tuberculosis at about age 21. A standard prescription of the day was travel to the American West. Thus, Stetson headed west, settling first in St. Joseph, MO, where he worked in and later became owner of a brickyard. The business flourished, but his health did not, so after about 2 years he headed further west to Colorado. There he began making hats.

He knew the art of felting, and he applied his skill to fur from pelts his hunting friends discarded. Soon he had made a broad-brimmed felt hat, which he sold for a five-dollar gold piece. The Stetson hat was born. Today, no Western movie is complete without Stetson-wearing cowboys and cattle rustlers, white hats for heroes and black ones for villains.

Stetson relocated to Philadelphia, PA, where he founded the John B. Stetson Company and built a factory. By 1906 he was producing two million hats a year. He wintered in DeLand, FL, and in 1887 he became a trustee of DeLand College. Two years later he became president of the board of trustees. He donated generously to the college, and in 1889 DeLand College was renamed Stetson University (20).

Athletes who made lasting marks on their sports also suffered from tuberculosis. It took the life of Christopher "Christy" (also called "Matty") Mathewson, perhaps the greatest baseball pitcher in the history of the sport (22). Pitching for the New York Giants in 1905, Mathewson won 31 games out of 39 starts. His earned run average that year was 1.27. He worked 339 innings, striking out 206 batters and walking only 64. In the World Series against Philadelphia that year, he pitched 27 innings, won three shutouts, and had an earned run average of 0.00. Mathewson slumped the following year; he was not well and was plagued by a cough. By 1909 he was back in form, winning 37 games, 12 of them shutouts, and losing only 11. His earned run average for the year was 1.43.

Mathewson was born in Factoryville, PA, in 1880. In high school and on sandlots, he played baseball whenever the opportunity arose. At Bucknell University he starred on both football and baseball teams and also distinguished himself academically. In 1900 he joined the New York Giants to begin his record-setting career in major league baseball. Mathewson was an instant star on the baseball diamond, success following success.

In 1915, however, Mathewson began a slump that seemed irreversible. One bad year followed another; he was often tired, coughing, and unwell. He dropped from the lineup to become a coach. In 1920 his doctors gave him the diagnosis of tuberculosis, and in July he went to Saranac Lake, hoping to recover his health. In 1923 he was well enough to assume the position of president of the Boston Braves, but the following year found him back at Saranac Lake. He passed the remainder of his life there, succumbing to tuberculosis on 7 October 1925. Tuberculosis had claimed one of baseball's greatest legends, a 30-game winner in four seasons and a Hall-of-Famer from the first year that institution opened.

Alice Marble was one of the most outstanding female competitors in the history of tennis. Her life was also touched by tuberculosis (23). Growing up in San Francisco, CA, she was a tomboy who loved sports—baseball initially but then tennis. Given a racquet while in high school, she soon became the top female player on the West Coast. At age 18 she made her debut at Forest Hills in New York City, losing miserably in singles but winning the women's doubles championship with fellow Californian Bonnie Miller. The following year she began working with Eleanor “Teach” Tennant, the coach and lifelong friend who would shape her raw talent into the form and skills that made her the greatest female tennis player of her time.

In May 1934 Marble collapsed during a tournament in France. She was carried from the court to the American Hospital at Neuilly, where she learned she had tuberculosis. She would never play tennis again, was her doctor's prognosis. She returned to her native California and entered Pottenger's Sanatorium in Monrovia. An initial 6 weeks stretched to 8 months. Marble, gaining weight and losing the physical fitness that had graced her athletic form, was despondent. Then one day she received a letter from Carol Lombard, whom “Teach” Tennant also coached and who had learned of Marble's illness from Tennant. Glamorous movie star Lombard had suffered disfiguring wounds to her face in an automobile accident but regained her movie stardom after multiple surgical procedures. “I made my career come true, just as you can—if you'll fight. If I can do it, so can you,” Lombard wrote (23). Soon thereafter, Marble walked out of the sanatorium. In 1936 she won the U.S. women's championship at Forest Hills. Her disease never recurred.

IMPACT ON CREATIVITY IN LITERATURE AND THE ARTS

Creative works of art, music, dance, and literature all express the lives of their creators, and thus tuberculosis in these lives affected their works. Some were greatly afflicted by the disease, others less so or were treated and fared well. And so it is that while the works of some reflect their struggles with tuberculosis, the creativity of others was little affected. George Balanchine developed tuberculosis shortly after his 1933 arrival in New York City, but it had little influence on his life and creativity. Igor Stravinsky suffered recurrent bouts of tuberculosis before being treated and cured with newly developed drugs; he lived to be 88 years old. Sarah Bernhardt was given a diagnosis of tuberculosis as a 15-year-old but recovered to star on the stage and live to be 78. Andrew Wyeth was ill as a child. Tuberculo-

sis, the doctor said. Yet he lived to be 91 without further evidence of the disease.

Stephen Crane died at age 28 of tuberculosis, but he had produced his masterpiece, *The Red Badge of Courage*, 4 years earlier. Amadeo Modigliani died of tuberculous meningitis in 1920 at age 35. Finnish composer Ernst Mielck was said to have been Max Bruch's favorite student. He succumbed to tuberculosis when he was 21 years old. Band leader Chick Webb, “First King of Swing,” died of tuberculosis at age 34. What works might the genius of these talented persons have yielded had their lives not been taken by tuberculosis?

Frédéric Chopin developed tuberculosis while a young émigré in Paris. He struggled with his illness, constantly sick, slowly losing ground to the “Captain of Death” but always productive. While seeking relief in Mallorca, Spain, with Georges Sand, his paramour, he wrote despairingly to his publisher:

I can't send you the manuscript, for it's not finished. I have been sick as a dog these last two weeks; I caught cold in spite of 18 degrees of heat, roses, oranges, palms, figs and three most famous doctors of the island. One sniffed at what I spat up, the second tapped where I spat it from, the third poked about and listened how I spat it. One said I had died, the second that I am dying, the 3rd that I shall die (24).

Yet Chopin did compose while in Mallorca. He struggled on, increasingly disabled, writing music and performing on the piano until he died at age 39 of pulmonary insufficiency resulting from the destruction of his lungs by tuberculosis.

Norwegian painter Edvard Munch was born in 1863 (25). Two weeks after his 13th birthday, tuberculosis entered his life with a frightening episode of hemoptysis. He later wrote:

The illness followed me all through my childhood and youth—the germ of consumption placed its blood-red banner victoriously on the white handkerchief (25).

In fact, he recovered and was then relatively well for the next several years, until tuberculosis recurred when he was 36. One lung was badly damaged, his doctor told him, the other less so. He was repeatedly confined to tuberculosis sanatoria during his middle thirties. Often ill, he lived on to reach the age of 80.

The effect of tuberculosis on Munch's art is complicated by his recurrent depression—probably manic-depressive bipolar disease—which also almost certainly affected his work. There is no doubt that these two illnesses, tuberculosis prominently of the two, had a great impact on his work. In his words:

I must retain my physical weaknesses; they are an integral part of me. I don't *want* to get rid of illness, however unsympathetically I may depict it in my art. . . . My sufferings are a part of my self and my art (25).

Munch often portrayed death. *The Sick Child*, dating to 1885–1886, when Munch had recovered from his adolescent bout with tuberculosis and not yet been again stricken, evokes sympathy and serenity. The pale-faced, red-headed child smiles at her grieving mother, a look of serenity on the girl's face. *Death in the Sickroom* (1893), *The Deathbed* (1895), and *Dead Mother and Child* (1899) portray quite different images of death. They are somber, with gray and black tones, and evoke grief and despair. Their mood is one of unremitting sorrow. Munch was ill, in and out of tuberculosis sanatoria, during the years these paintings came from his palette.

Literature is replete with descriptions of tuberculosis, often reflecting the authors' lives. John Keats, Anton Chekhov, and W. Somerset Maugham all suffered from the disease, and it is reflected in their writings. Katherine Mansfield, on the other hand, was recurrently ill before dying following a massive hemoptysis, but she did not mention tuberculosis in any of her many short stories.

Striking examples of tuberculosis in literature are provided by the novels of the Brontë sisters. The Reverend Patrick Brontë was plagued with cough throughout the 84 years of his life. He almost certainly had chronic tuberculosis (26, 27). He probably infected his wife and six children, all of whom succumbed to the disease. The three of his five daughters who survived to adulthood wrote both prose and poetry. Their novels are icons of Victorian Age literature.

Emily Brontë died in December 1848. Her death certificate stated that her illness was of 2 months' duration, but the letters of her sister, Charlotte, make it clear that her illness was well established at an earlier date (28). Emily Brontë's novel, *Wuthering Heights*, was published in 1847. She may have been ill as she was writing; certainly she knew tuberculosis well, for she had watched her mother and two sisters, Maria and Elizabeth, succumb while she was a child. *Wuthering Heights* is an extraordinary literary work. A complex tale of the struggle of good to overcome evil, the work is pervaded by tuberculosis. Malevolent Heathcliff mourns the loss of Catherine Earnshaw, who dies of tuberculosis early in the book.

The doctor says she must go: he says she's been in a consumption these many months....One night...a fit of coughing took her—a very slight one...her face changed, and she was dead (29).

Death from tuberculosis is also described in *Jane Eyre*, by Charlotte Brontë, in a passage set in a Cowan Bridge School:

I am very happy, Jane; and when you hear that I am dead, you must be sure and not grieve; there is nothing to grieve about. We must all die one day, and the illness which is removing me is not painful; it is gentle and gradual: my mind is at rest (30).

This part of *Jane Eyre* is considered by most scholars to be autobiographical, the dying Helen representing Charlotte Brontë's sister Maria.

Eugene O'Neill was America's greatest dramatist. His plays won four Pulitzer Prizes and the Nobel Prize. Critics uniformly acclaimed him. He had tuberculosis, and the disease figures prominently in two of his plays. *The Straw* was written while he was a sanatorium patient, and it is loosely based on his experiences there. It has not been considered one of his better works. *Long Day's Journey into Night* is frankly autobiographical and deals with the time when O'Neill was told he must go to a tuberculosis sanatorium. It is a universally acclaimed masterpiece.

O'Neill was born on 16 October 1888, the youngest of two surviving sons of successful actor James O'Neill and Ellen O'Neill. The O'Neills were an Irish immigrant family with strong roots in Catholicism, but their family life was disrupted by James O'Neill's tours with theatrical companies. As in many Irish families in America at that time, alcohol consumption was frequent and copious. Ellen O'Neill was addicted to opiates (31).

Eugene O'Neill's life was marked by a variety of excesses and tragedies. Educated initially in boarding schools, he entered Princeton University in 1906. He married a casual girlfriend, whom he had impregnated—this would be the first of three marriages—but then deserted her, left Princeton, and spent more than a year as a seaman and wanderer in South America. He returned to divorce his wife and soon thereafter was stricken with tuberculosis. In a sanatorium he began writing plays (32).

O'Neill's powerful, autobiographical drama, *Long Day's Journey into Night*, is set in 1912, the year in which O'Neill was found to have tuberculosis, in an oceanfront house presumably in New London, CT, the O'Neill family residence (33). The play was written in 1940. Initially he asked that it not be published until 25 years after his death, but he later relaxed this injunction, and it was produced in 1956, 3 years after his death. The action of the drama takes place in one day, beginning with a sunny noon and progressing through a foggy afternoon to a dark midnight. True to the actual O'Neill family history, the Tyrone family of the

play consists of father James, an actor who cannot quite deal with the multiple problems in his family; mother Mary, fading from reality during the day and night as she takes additional amounts of opiates; their oldest son, James, Jr., a drunkard; and their youngest son, Edmund, who has just been given a diagnosis of tuberculosis and told he must go to a sanatorium. Putting aside much of the powerfully presented multiple dynamics of this dysfunctional family, Edmund's tuberculosis is central to the tense interactions of the Tyrone family throughout the long day and night chronicled in the play (33). His plight is that his penurious father wants to send him to the "state farm" to avoid paying the \$7.00-per-day cost of a private sanatorium, where Edmund feels he would be better treated. "So why waste money? That's why you're sending me to a state farm—," Edmund challenges his father. His mother refuses to accept the diagnosis. "A summer cold makes anyone irritable... It is just a cold! Anyone can tell that!"

In actuality, Eugene O'Neill was initially hospitalized at Laurel Heights, a Connecticut state farm for consumptives, for 2 days before being transferred to highly regarded Gaylord Farm Sanatorium on Christmas Eve of 1912. O'Neill's disease had begun about 2 months earlier. It presented as pleurisy with effusion, a form of tuberculosis with a relatively favorable prognosis. And O'Neill did well, being discharged after 6 months as "arrested" (at that time, no patient was ever considered cured, as relapses were common). O'Neill's tuberculosis did not recur. However, he never forgot it during his often tumultuous life, and it was three decades later that he wrote his dramatic account of the diagnosis. After an enormously productive if often anguished life, O'Neill died in November 1953 of what was then called Parkinsonism but from a modern perspective sounds more like Alzheimer's disease.

CONCLUSIONS

Reflecting on the history of tuberculosis, let us now ask again, did it affect the way we lived? One must conclude that it did, variously at various times, and sometimes only subtly. During the 19th century, the "Captain of Death" was present in the lives of many. Scarcely did a family not count a member or relative who was afflicted. The tuberculous deaths of all six Brontë children and their mother may have been remarkable—perhaps the family carried one of the genetic polymorphisms that decrease native resistance—but it was not out of keeping with the epidemiology of tuberculosis at that time. Chopin struggled with his disease but continued to compose and perform. As the course of history

moved into the 20th and 21st centuries, tuberculosis incidence declined. Fewer dramatic instances of disease occurred. Yet it robbed baseball of the life of one of its greatest athletes in 1925.

The practice of medicine has reflected the prevalence of tuberculosis over the course of time. During the sanatorium era, an entire parallel health system devoted itself to the care of consumptives. Tuberculosis has intruded upon the political arena, but its impact has been minor. That Quezon conducted the Philippine government in exile from his bed in Saranac Lake cannot be said to have changed the course of war in the Pacific. Josephine Baker's espionage efforts were commendable, but the Allies would have won the war without them. Civilian life produced more notable examples. Can one imagine John Wayne without a Stetson hat?

In the world of creative arts, the impact of tuberculosis is most readily seen and was often dramatic. The Brontë novels presented it prominently, but also as something not exceptional—as an ordinary, 19th-century, life-ending event. Edvard Munch's depictions of death certainly reflected his continuing struggle with the disease. No short life taken by tuberculosis is better known than that of John Keats. Three months after the hemoptysis that led him to make his own diagnosis of tuberculosis, he wrote:

Darkling I listen, and, for many a time
I have been half in love with easeful death,
Call'd him soft names in many a mused rhyme,
To take into the air my quiet breath (34).

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Epidemiology and Host Factors

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Tuberculosis is an ancient infection that has plagued humans throughout recorded and archeological history. It is always a surprise to those of us who live in Western countries that even today the infection remains the cause of higher rates of morbidity and mortality than any other infection in the world. This is because of its great prevalence in the densely populated developing countries; however, the incidence of tuberculosis is grossly underreported in these countries. According to estimates of the World Health Organization (WHO), in 2014 there were approximately 9.6 million active cases, of which 3 to 4 million cases were infectious, with positive sputum smears (1). Deaths due to tuberculosis occur in 1.5 million people worldwide each year (1, 2). The estimates are that a death from tuberculosis occurs every minute. Thus, tuberculosis is still a major cause of disease and death, and its elimination will be extremely difficult as long as poverty, overpopulation, and multidrug-resistant (MDR) disease characterize large portions of the earth. Human immunodeficiency virus (HIV) is already deemed the number one preventable cause of death in developing countries (3).

The tubercle bacillus was discovered in 1882 and has been the subject of extensive research ever since. There is still much to be learned about the nature of the organism, its virulence, its genetic characteristics, and the response of the host to the infection.

HISTORY

Tuberculosis appears to be as old as humanity itself. Skeletal remains of prehistoric humans dating back to 8000 BC, found in Germany, show clear evidence of the disease. Egyptian skeletons dating back from 2500 to 1000 BC have revealed evidence of Pott's disease of the spine. Ancient Hindu and Chinese writings have documented the presence of the disease. From these descriptions, however, it is impossible to differentiate tuberculosis from diseases that produce similar pathology. Perhaps the best proof of tuberculosis has come from an Inca mummy of an 8-year-old boy who lived about 700 AD. The radiographic picture of the lumbar spine showed evidence of Pott's disease, and the smears of the lesion revealed acid-fast bacilli (AFB), most likely *Mycobacterium bovis*.

Tubercle bacilli can remain viable for many years in the tissues of healthy persons. When they produce disease, it runs a chronic and protracted course that gives ample time for transmission to susceptible hosts. The infection can produce disease in a human being after decades of dormancy. Thus, the infection becomes endemic when a large proportion of the population is infected. It can produce an epidemic, however, when introduced into a population of which only a small portion is immunologically protected by already having been infected. The history of tuberculosis in Europe

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and North America is better known for the past 150 years; however, there is a paucity of historic information on the epidemiology of tuberculosis in other parts of the world (4).

“EPIDEMIC WAVES” OF TUBERCULOSIS

When a new infection is introduced into a susceptible population, the morbidity and mortality rates take the predictable form of an epidemic wave (5). There is a sharp rise to a peak, followed by a more gradual descent. For many infectious diseases this curve is measured in weeks or months, but for tuberculosis it is measured in decades and centuries. Epidemiological information, though incomplete, reflects the incidence and prevalence of disease over a period of two or three centuries.

The waveform of the tuberculosis epidemic occurs by natural selection of susceptible persons and runs its course in about 300 years. Grigg (5) has described, on hypothetical grounds, three separate curves of mortality (elimination of susceptible persons), morbidity (disease in the more resistant), and unapparent infections (infection without disease in the highly resistant) (Fig. 1). The three curves peak successively at 50- to 100-year intervals. With the decline of the epidemic, the death rate declines first, followed by morbidity and, finally, by unapparent infections.

In England the present epidemic wave began in the 16th century and probably reached its peak in about 1780 as a result of the Industrial Revolution and the growth of cities, which allowed the spread of disease from person to person. The epidemic then rapidly spread from England to other large cities in Western Europe, reaching a peak in the early 1800s. In Eastern Europe the peaks came in about 1870 and 1888, and by 1900 North American and South American epidemic waves had peaked. In the developing countries of Asia and Africa the wave has not peaked yet. Thus, as a global phenomenon, the epidemic is declining in one geographic area while still rising or just reaching its peak in another.

Industrialization and overcrowding of the cities can produce an epidemic of tuberculosis by bringing together large numbers of susceptible people and promoting transmission of *Mycobacterium tuberculosis* to new hosts. In addition, psychological stresses of urban life may lower individual resistance to infection. Grigg (5) has published curves to show the major tuberculosis waves in two contrasting imaginary settings, rural and urban (Fig. 2). These communities are assumed to remain isolated and to have a constant degree of urbanization. From the graph, one can conclude that after elimination of the susceptible persons, the survivors become relatively resistant and the epidemic starts to decline. The rate of decline is exponential, though

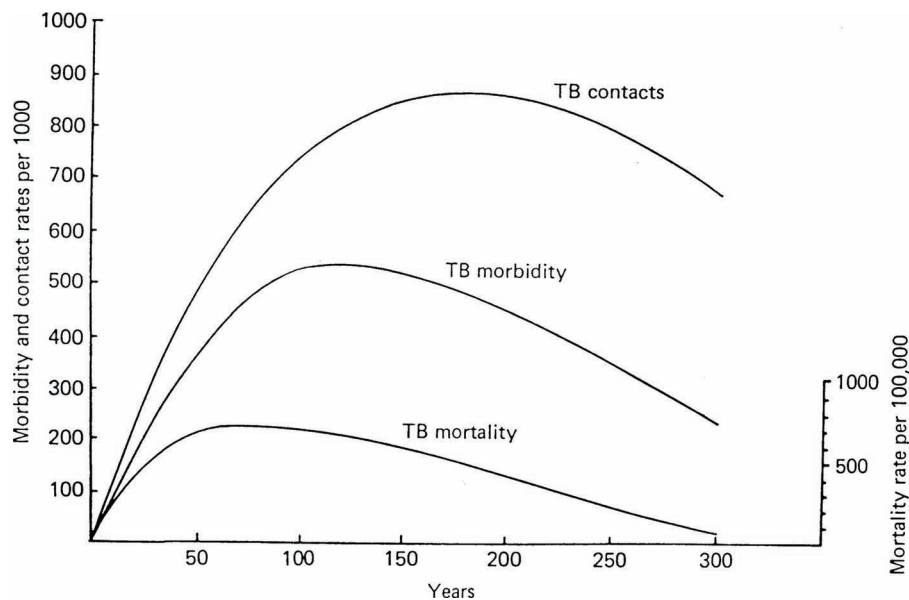


Figure 1 Theoretical concept of the development of tuberculosis (TB) in a community. Tuberculosis is assumed to appear for the first time at zero. The death rate, rate of morbidity, and rate of contacts are shown in reference to a living population. All these curves show a steep ascending limb and a prolonged exponentially decelerated descending limb. Adapted from reference 5 with permission of the American Thoracic Society.