ATS Discoveries Series, 2015

The American Thoracic Society (ATS) has a long history, originating as the American Sanatorium Association in 1905, which was established to promote the treatment and prevention of tuberculosis. Since then, the scope of our mission has widened, and the Society has become the premier scientific professional society in respiratory medicine, with more than 15,000 members worldwide who are dedicated to advancing our clinical and scientific understanding of pulmonary diseases, critical illnesses, and sleep-related breathing disorders. Our members provide care for millions of people who suffer daily from asthma, chronic obstructive pulmonary disease, cystic fibrosis, sleep apnea, and lung diseases related to prematurity, to name a few.

In celebration of our 110th anniversary, the ATS journals and 2015 ATS International Conference has highlighted many of the advances in patient care and research in adult and pediatric pulmonary, critical care, and sleep medicine. The ***ATS Discoveries Series*** *is a collection of articles and talks that feature major scientific and clinical breakthroughs that have changed the lives of the patients we treat, as told by leading scientists and clinicians. With input from our membership, the topics range from the ongoing global threat of tuberculosis to the discovery of surfactant, from insights into asthma pathogenesis to the potential of lung regeneration.*

The following article titled "Treatment of Tuberculosis: A Historical Perspective" by John F. Murray, M.D., Dean E. Schraufnagel, M.D., and Philip C. Hopewell, M.D., is the second in the series published in the Annals of the American Thoracic Society. I hope you enjoy learning about the seminal discoveries in the conquest of tuberculosis. Please be sure to read all of the articles in the Discoveries Series published in 2015, not only in AnnalsATS, but also in the American Journal of Respiratory and Critical Care Medicine and American Journal of Respiratory Cell and Molecular Biology during the coming months.

Thomas Ferkol, M.D.
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Treatment of Tuberculosis
A Historical Perspective

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Abstract

Of all achievements in medicine, the successful treatment of tuberculosis has had one of the greatest impacts on society. Tuberculosis was a leading cause of disease and a mortal enemy of humanity for millennia. The first step in finding a cure was the discovery of the cause of tuberculosis by Robert Koch in 1882. The sanatorium movement that began shortly afterward in Europe, and soon spread to the United States, brought attention to the plight of afflicted persons, and catalyzed public health action. The antituberculosis benefit of streptomycin was announced in 1945, although application was limited by the rapid development of resistance. *para*-Aminosalicylic acid, also discovered in 1945, when combined with streptomycin was found to greatly reduce the occurrence of drug resistance. In 1952, isoniazid opened the modern era of treatment; it was inexpensive, well tolerated, and safe. In the early 1960s, ethambutol was shown to be effective and better tolerated than *para*-aminosalicylic acid, which it replaced. In the 1970s, rifampin found its place as a keystone in the therapy of tuberculosis. The use of rifampin enabled the course of treatment to be reduced to nine months. Incorporation of pyrazinamide into the first-line regimen led to a further reduction of treatment duration to six months. Treatment of multiple drug–resistant tuberculosis remains a difficult problem requiring lengthy treatment with toxic drugs. However, shortened regimens show promise, and two new drugs, bedaquiline and delamanid, have demonstrated effectiveness in preliminary studies and are being used for extensively drug-resistant tuberculosis.

Keywords: history; chemotherapy; drug development

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The American Thoracic Society is celebrating its 110th anniversary by highlighting the most important discoveries in its field since its formation in 1905. Of all the achievements in medicine, successful medical treatment of tuberculosis clearly had one of the greatest impacts on society.

The world before a cure for tuberculosis was discovered was a dim one. As the Industrial Revolution, beginning in the mid-1700s, crowded people together, increased pollution, and decreased exposure of urban residents to sunlight, the prevalence of tuberculosis rose. Tuberculosis was considered by far the leading cause of death in Britain and Western Europe in the eighteenth and nineteenth centuries. The disease was estimated to affect 15–30% of adults living in the city of London at the time (1). The important first step in reducing the world prevalence of tuberculosis was the conclusive evidence of its contagious nature by the French physician Jean Antoine Villemin, published in a series of papers in the 1860s (2).

Discovery of *Mycobacterium tuberculosis*

The monumental event in developing a treatment for tuberculosis was the discovery of the cause of tuberculosis by the German physician Robert Koch, which he announced on March 24, 1882. Working alone, it took Koch less than a year to complete one of the most important medical–scientific achievements in human history (3). The culprit bacillus was named *Mycobacterium tuberculosis* (4). Seventeen days later, remarkably fast compared with current publishing norms, details of Koch's discovery appeared in a major scientific journal (4). Every year, many claims of curing tuberculosis were made, but Koch's presentation, a prelude to the formulation of Koch's postulates, was so convincing that even many of the skeptics of the day were swayed. The news traveled quickly to major cities of the world creating enthusiastic acceptance and triumphant recognition. Koch was awarded the Nobel Prize in Physiology or Medicine in 1905 for this achievement (Figure 1).

Figure 1. Robert Koch demonstrated the bacterial cause of tuberculosis in 1884.

Sanatorium Movement

Despite the atrocious living and working conditions that prevailed during the early decades of the Industrial Revolution, estimates of mortality rates from tuberculosis peaked around 1800 and then began a slow, relatively steady decline for well over 100 years. Koch's discovery of *M. tuberculosis* in 1882 had little immediate influence on the long-established reduction in tuberculosis death rates that was underway. As more was learned about tuberculosis, the sanatorium movement began to have a major influence on the care that patients with all forms of tuberculosis received.

Hermann Brehmer, the acknowledged originator of the sanatorium movement, opened the first-ever high-altitude sanatorium to treat pulmonary consumptives, at Görbersdorf, in the Silesian mountains, today in Poland (5). Brehmer's initial reasoning that the physiological benefits of an active physical life at high altitude would restore health to these patients was faulty (6), but he quickly reversed course and switched to salubrious rest, chiefly in outdoor lounges and, when needed, using open-air shelters to provide optimal airy conditions; mild, calibrated exercise; and a healthful diet.

The first American sanatorium for pulmonary tuberculosis was established in 1875 by a Bavarian, Joseph Gleitsmann, in Ashville, North Carolina. Eleven years later, the Adirondack Cottage Sanatorium at Saranac Lake was founded by Edward Livingston Trudeau and quickly became the best-known institution of its sort in the United States. It was later renamed the Trudeau Sanatorium after the death of Dr. Trudeau (7) (Figure 2). Trudeau himself had tuberculosis and suffered several exacerbations and remissions of the disease

after he finished medical school. He was greatly influenced by the fresh air and bed rest concepts of Brehmer, to which he attributed his remissions. Trudeau soon became a major force in the public battle against tuberculosis and was a founder of the National Association for the Study and Prevention of Tuberculosis (now the American Lung Association) and the American Sanatorium Association (now the American Thoracic Society). Both organizations advocated for increasing the number of sanatoriums throughout the country as the major public policy to combat tuberculosis.

Sanatoriums proliferated wherever they could be funded and staffed. According to Daniel (8), expansion of sanatoriums in America was brisk. In 1904, 115 facilities with about 8,000 beds were operating. By 1923, the number had grown to 656 with more than 66,000 beds. In 1953, toward the end of their lifetimes, 839 institutions with over 136,000 beds were fully functioning (Figure 3).

Interventions

During much of the sanatorium era, several novel therapeutic interventions were introduced and widely used as treatment for pulmonary tuberculosis (9). These included artificial pneumothorax, artificial pneumoperitoneum, thoracoplasty, plombage, phrenic nerve crush, and lung resection (10). Although hundreds of thousands of pneumothoraces and pneumoperitoneums were performed, neither procedure was ever rigorously tested to determine efficacy (Figure 4).

One of the simplest of all procedures—bed rest in the horizontal position—did have a physiological rationale. The gravity-dependent distribution of pulmonary blood flow in the upright position created high oxygen tensions in the apices of the lungs, which favored growth of *M. tuberculosis*; thus, lying flat in bed reduced multiplication of tubercle bacilli (11).

Lung resection was also used in selected cases, but by the time case selection, surgical technique, and postoperative care were sufficiently advanced to minimize surgical morbidity and mortality, chemotherapy was available. However, resection is still useful in selected patients with tuberculosis caused by drug-resistant organisms.

Figure 2. Edward Livingston Trudeau. The U.S. Postal Service commemorated the founder of the U.S. sanatorium movement by issuing this stamp. They called Trudeau a "phthisiologist," even though Trudeau himself referred to the disease as "tuberculosis." Image is copyrighted by the United States Postal Service.

The End of the Sanatorium Era

With the advent of effective chemotherapy in the mid-1950s, sanatoriums began to become superfluous. By the mid-1960s most were closed. Hospital care was no longer required to provide effective treatment; moreover, patients receiving effective drug treatment quickly became noninfectious. A study in Madras, in which patients with

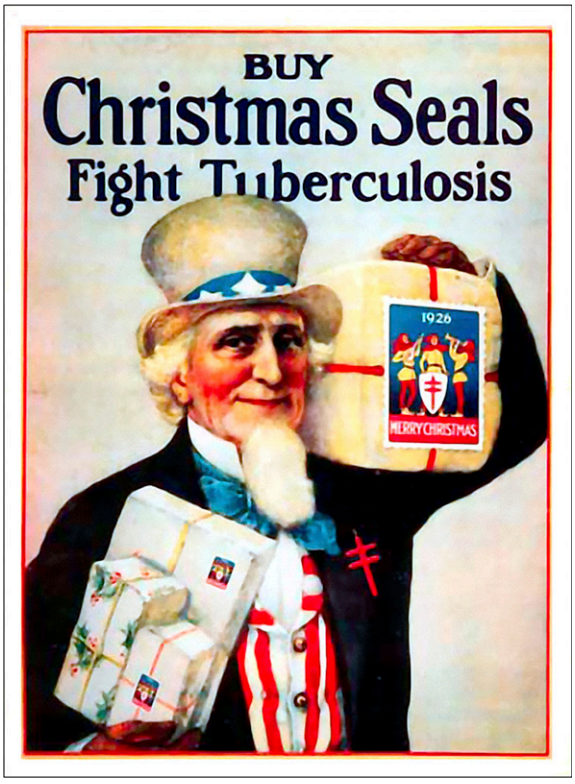


Figure 3. Beginning in 1907, Christmas Seals were first sold through U.S. post offices, and later directly through the mail. Purchasers affixed the seals to Christmas greeting cards and gift wrappers. Proceeds supported sanatoriums for the treatment of tuberculosis. This image shows one of several posters commissioned by the American Lung Association to promote sales of Seals. George V. Curtis is the artist. Image courtesy of the American Lung Association.

Figure 4. Tools of the "pneumo-clinic" including x-ray film frames and a view box (*A*) used by Albert Schweitzer in his hospital in Lambaréné, Gabon, photographed by Dean Schraufnagel (rights reserved). Rest was believed to aid the healing of tuberculosis. From the 1930s through the 1950s, physicians attended "pneumo-clinics" where patients came regularly to have artificial pneumothoraces induced, and to have periodic "refills" of air (J. A. P. Paré, personal communication). Physicians would supply a precise air pressure (as measured with a manometer, *B*) and check to determine the degree of lung deflation by fluoroscopy and radiography (*C*).

tuberculosis were randomly assigned to either sanatorium or home treatment, showed no difference in either clinical outcomes or infection in the household contacts (12). Sanatoriums had become obsolete.

Chemotherapy

Nobel Laureate Paul Ehrlich, convinced that a "magic bullet" could kill microorganisms without killing their human host, systematically tested one chemical substance after another, until finally, in 1909–1910, Compound 606, arsphenamine (Salvarsan), proved successful against the spirochetes of syphilis: the first stunning victory of systemic chemotherapy. Antibiotics, starting with penicillin discovered by Alexander Fleming in 1929, were not used medically until 1940. The sulfur compound, sulfonamidochrysoïdine, first synthesized in 1908, was rediscovered in 1932 by Gerhard Domagk and trademarked by Bayer Laboratories as Prontosil Solubile. Later, sulfonamidochrysoïdine was found to be a prodrug. Prontosil was replaced by the active metabolite, sulfonamide, and produced by Bayer as Prontalbin. Domagk later won the Nobel Prize in Physiology or Medicine for introducing the "first modern miracle drug" (13). But neither penicillin nor sulfa drugs were effective against tuberculosis.

Early leaders in the battle against tuberculosis, the scientific team of H. Corwin Hinshaw and Hugh Feldman developed a guinea pig model to rigorously test the efficacy of newly developed chemotherapeutic agents (Figure 5). An early candidate was Promin (sodium glucosulfate), but the results failed to convince the audience of "experts" at the National Tuberculosis Association in 1942, and the drug had only a brief experimental trial (14). Promin later proved to be the first successful drug against leprosy (15).

But Hinshaw and Feldman did not give up. They had heard about a promising new antibiotic called streptomycin, which was discovered by Schatz, Bugie, and Waksman in Rutgers, New Jersey, and reported in January 1944 (16) (Figure 6). Three months later, Waksman sent 10 g of streptomycin to Hinshaw and Feldman, enough to test four guinea pigs infected with virulent *M. tuberculosis* (17). The results were sufficiently impressive that Waksman provided additional extremely scarce streptomycin to complete the studies. Their 1945 report on the results of control and streptomycin-treated guinea pigs was definitive: marked and striking improvement in the 25 animals treated with streptomycin after 49 days compared with the outcome of the 24 control animals (18).

Meanwhile, a gifted scientist named Jörgen Lehmann in Gothenburg, Sweden was designing a chemical agent, largely by deduction, that would feed and nourish tubercle bacilli but would also kill them: that compound turned out to be *para*-aminosalicyclic acid (PAS) (19, 20) (Figure 7). A little known but noteworthy fact in historical records proves that on October 30, 1944, Lehman and tuberculosis expert Gylfe Vallentin treated a moribund young Swedish woman named Sigrid with oral PAS, and she made a "dramatic recovery" (21). Three weeks later, on November 20, 1944, Hinshaw, Feldman,

Figure 5. William Feldman (*right*) and H. Corwin Hinshaw (*left*) were the first to test streptomycin, a revolutionary treatment for tuberculosis.

and the American tuberculosis specialist Karl Pfuetze treated a patient named Patricia with streptomycin; Patricia had a stormy course, but survived, left the hospital, and led an active life (22). It turns out that although PAS was developed before streptomycin, Swedish acceptance and administration of PAS was considerably slower than that of streptomycin; consequently, it is commonly believed that PAS appeared 2 years after streptomycin.

Figure 6. Selman Waksman received the Nobel Prize for "ingenious, systematic and successful studies of the soil microbes that led to the discovery of streptomycin." The testing and bringing to market of streptomycin involved a larger group of people, including Feldman, Hinshaw, and others.

Streptomycin and PAS were moderately effective, but had significant side effects and each when given alone caused the development of drug resistance (23, 24). Accordingly, a momentous clinical trial by the British Medical Research Council (BMRC) documented the superior value of combined treatment compared with either streptomycin or PAS alone (25) (Figure 8). Moreover, the BMRC trial led to an axiom of treatment: never treat active tuberculosis with a single agent, and it originated the technique of random allocation of experimental subjects.

The next major discovery opened the modern era of antituberculous chemotherapy, the recognition of the profound benefit of isoniazid in both experimental and human tuberculosis (26). In 1951, an astonishing therapeutic coincidence occurred: pharmaceutical experts at Hoffmann-La Roche and Squibb, both from the United States, and Bayer Chemical in Germany, all "discovered" isoniazid at almost the same time and began to use it (21); what might have been an expensive, time-consuming legal battle over patent rights was avoided when it was later learned that two Czech predoctoral students had synthesized the drug in 1912.

The April 1952 issue of the *American Review of Tuberculosis* (which became the *American Journal of Respiratory and Critical Care Medicine*) was largely devoted to studies of isoniazid, its chemistry, pharmacology, and effects on experimental and human tuberculosis (27). Isoniazid represented a colossal breakthrough; it was the most potent drug introduced thus far and was inexpensive, well tolerated, and safe (Figure 9). It was so compelling that it was thought initially that isoniazid alone was quite effective, but patients subsequently relapsed, with about three-fourths of them having organisms resistant to isoniazid, again demonstrating that multiple drug therapy was necessary.

After its discovery, many trials took place to define the optimal combination of isoniazid with streptomycin and/or with PAS (28). The commanding and lasting outcome: "*triple therapy*," which included oral isoniazid together with PAS for 18 to 24 months, plus intramuscular streptomycin for the first 6 months (29). All together, "triple therapy" remained the standard treatment for all forms of tuberculosis for nearly 15 years (21).

Despite these successes, side effects, drug resistance, and the large numbers of affected people drove further drug

Figure 7. Jörgen Lehmann developed *para*-aminosalicyclic acid, which, when combined with streptomycin, resulted in a lasting cure for tuberculosis.

development exploration. In 1961, experiments in mice showed that ethambutol was effective on isoniazid- and streptomycin-resistant organisms (30).The drug was initially used in retreatment regimens and found to be well tolerated. Subsequently, clinical trials comparing ethambutol with PAS showed that the drug, even in a dose as little as 6 mg/kg, was as effective as PAS when combined with isoniazid (31, 32).

The rifamycins were discovered in 1957 in Italy as part of an investigation into the antibiotic properties of *Nocardia mediterranei* (33, 34). Rifampin was first used clinically in 1966 and during the next decade found its place as the keystone in tuberculosis chemotherapy regimens. Rifampin combined with isoniazid and ethambutol enabled therapy to be shortened to 9 months and led to improved cure rates (35).

Pyrazinamide was discovered in the late 1940s, based on the observation that nicotinamide had activity against *M. tuberculosis* in animal models. Synthesis of analogs of nicotinamide led to the identification of pyrazinamide (36). At first, it was considered too toxic for first-line therapy, but lower doses (37) later led to another breakthrough, further shortening the course. The Singapore Tuberculosis Service and British Medical Research Council trial showed that pyrazinamide could reduce the time of therapy to 6 months when combined with isoniazid and rifampin (38).

Other drugs developed during this time, including cycloserine (39), ethionamide (40), kanamycin (41), and capreomycin (42) have played an important role in treating drug-resistant tuberculosis.

Complacency and Neglect

The discovery of streptomycin brought about a great flurry of drug discovery research that lasted from the 1940s through the 1960s. As the decline in tuberculosis case rates became steeper, the awareness of the public waned. The war on tuberculosis was considered winnable with the tools at hand (43). Public health departments relegated tuberculosis care to general clinics and the fervor for new drug discovery fell.

Decreased attention to tuberculosis control and poor public health infrastructure worldwide led to a resurgence of tuberculosis in the late 1980s and early 1990s. Between 1985 and 1992, tuberculosis cases increased by about 20% in the United States. Multiple drug–resistant tuberculosis (tuberculosis caused by organisms with resistance to at least isoniazid and rifampin) began to be recognized. The problems of drug-resistant tuberculosis and difficult-to-treat populations brought back to light the scourge of tuberculosis and led health leaders to reconsider all aspects of disease management. Advocacy and financial support have led to a renewal in finding drugs to eliminate tuberculosis.

New Therapies: Old Drugs Reevaluated

The first plans for new treatments were to explore the usefulness of existing drugs. Their activity and side effects were familiar and the cost of bringing them to market would be a fraction of that required to develop new compounds. Drugs in this category include the rifampicins, quinolones, linezolid, and clofazimine.

Rifamycins

Several studies have shown that rifampin may be more effective at a higher dose (44). Fewer patients reach the maximal therapeutic concentration for rifampin compared with other antituberculous drugs. Furthermore, rifampin serum concentrations tend to be lower in patients with more severe illness (45, 46). Thus, changing dosing recommendations might result in more potent regimens.

Rifapentine is more potent and longer acting than rifampin. The minimal inhibitory concentration (MIC) for rifapentine is 0.06 μg/ml compared with that of rifampin, which is 0.25 μg/ml (47). For the treatment of latent tuberculosis, rifapentine and isoniazid given as 12 once-weekly doses performed as well as the standard therapy of isoniazid alone for 9 months. Rifapentine is safe and has a higher completion and lower drug discontinuation rate than rifampin (48). Other large trials of rifapentine have shown similar good results (49). The U.S. Centers for Disease Control and Prevention (Atlanta, GA) now recommends this rifapentine–isoniazid regimen as an acceptable alternative to 9 months of isoniazid. It is not recommended for children under 2 years of age, persons with HIV taking antiretroviral drugs, and pregnant women because these conditions have not been studied (50).

Once-weekly rifapentine and isoniazid was also found to be effective in the

A TABLE 1. RESULTS OF BRITISH MEDICAL RESEARCH COUNCIL STREPTOMYCIN TRIAL

Regimen	No. of Patients	Deaths	X-ray Improvement (%)	Culture Negative 3 mo	Culture Negative 6 mo
SM	54	4	69	10*	8
Control	50	14	33	1	2

Definition of abbreviation: SM = streptomycin.
Data from Reference 13.
* Forty-one patients with resistant strains; two with sensitive strains (assessments are on the basis of modern criteria of drug resistance).

B

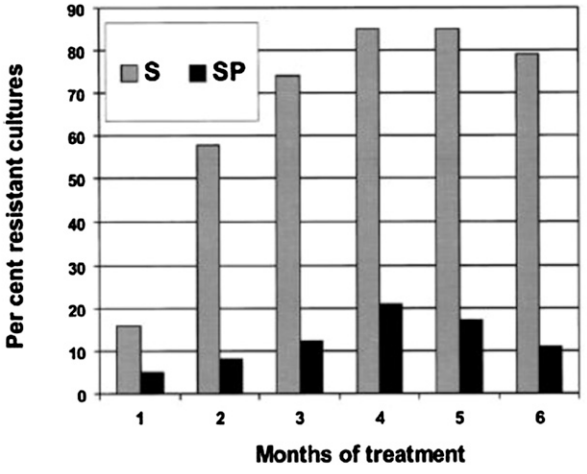


Figure 1. p-aminosalicylic acid (PAS) given with streptomycin (SM) reduces the emergence of SM resistance. The percentage of strains that is SM resistant in the SM series (indicated by S) and the SM plus PAS series (indicated by SP) during 6 months of treatment. Data from Reference 16.

Figure 8. Results of the British Medical Research Council studies of streptomycin and of streptomycin plus *para*-aminosalicylic acid (PAS). (*A*) As shown in the table, streptomycin alone decreased deaths and brought about radiographic improvement, but many patients remained culture positive. (*B*) The dramatic effect of combining PAS with streptomycin in reducing the percentage of isolates that were streptomycin resistant. Reprinted by permission from Reference 75.

continuation phase of tuberculosis treatment, except for persons infected with HIV. In this study, resistance developed to the rifampicins, but not to isoniazid (51), which implies that rifapentine was left unprotected. For the continuation phase, it seems that rifapentine needs a partner that is effective against dormant bacilli (52). Although rifapentine was not superior to rifampin in a study that compared the two (53), the outcomes were good in both arms.

Fluoroquinolones

Fluoroquinolones are a crucial component of regimens for multidrug-resistant tuberculosis, but have not yet assumed a regular role in treating drug-susceptible disease. Although moxifloxacin is more effective than ethambutol in achieving sputum conversion at 8 weeks (54), clinical trials have not shown that the use of fluoroquinolones enables current regimens to be shortened to 4 months. A 4-month trial of both moxifloxacin and gatifloxacin plus rifampin, isoniazid, and pyrazinamide given three times weekly versus the 6-month standard of rifampin, isoniazid, pyrazinamide, and ethambutol had to be stopped early because of high relapse in the quinolone group (55). Levofloxacin and moxifloxacin appear to be equal in their effectiveness against tuberculosis (56). Moxifloxacin did not improve outcomes when added to rifampin, isoniazid, pyrazinamide, and ethambutol. When substituted for pyrazinamide or rifampin, the results were worse. When it was used instead of isoniazid, there was an earlier sputum conversion (57).

Linezolid

The use of linezolid, an oxazolidinone antimicrobial, is generally limited to treatment of extensively drug-resistant tuberculosis (tuberculosis caused by multiple drug–resistant organisms with additional resistance to at least a fluoroquinolone and one of the injectable drugs). Its major limitation has been a high frequency of side effects—up to 59%—with 68% of these being major (58). The side effects are greater with higher doses and longer duration of treatment. New oxazolidinones under development include sutezolid (PNU-100480), posizolid (AZD-5847), torezolid, and radezolid.

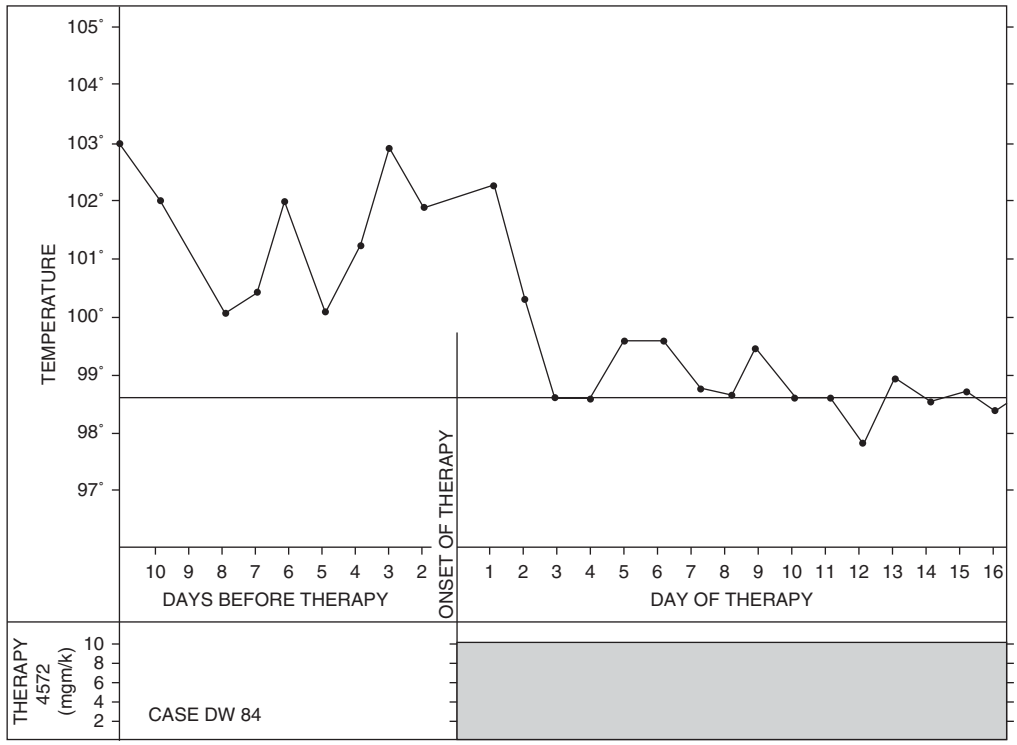
Clofazimine

Clofazimine was developed in 1950s as an antileprosy agent, but was discarded as ineffective against tuberculosis, possibly because isoniazid and other agents brought on the market at about the same time were superior. Its main toxicity is skin pigmentation, which occurs in 75–100% of patients, and gastrointestinal upset, which occurs in 40 to 50% of persons (59). Clofazimine is the best third drug in combination with bedaquiline and pyrazinamide in a mouse model (60), but it has yet to find a clinical niche except in the treatment of drug-resistant tuberculosis. The long duration of action of clofazimine and its activity against dormant tubercle bacilli (61) raise the possibility of it being a partner with rifapentine in the continuation phase of latent tuberculosis.

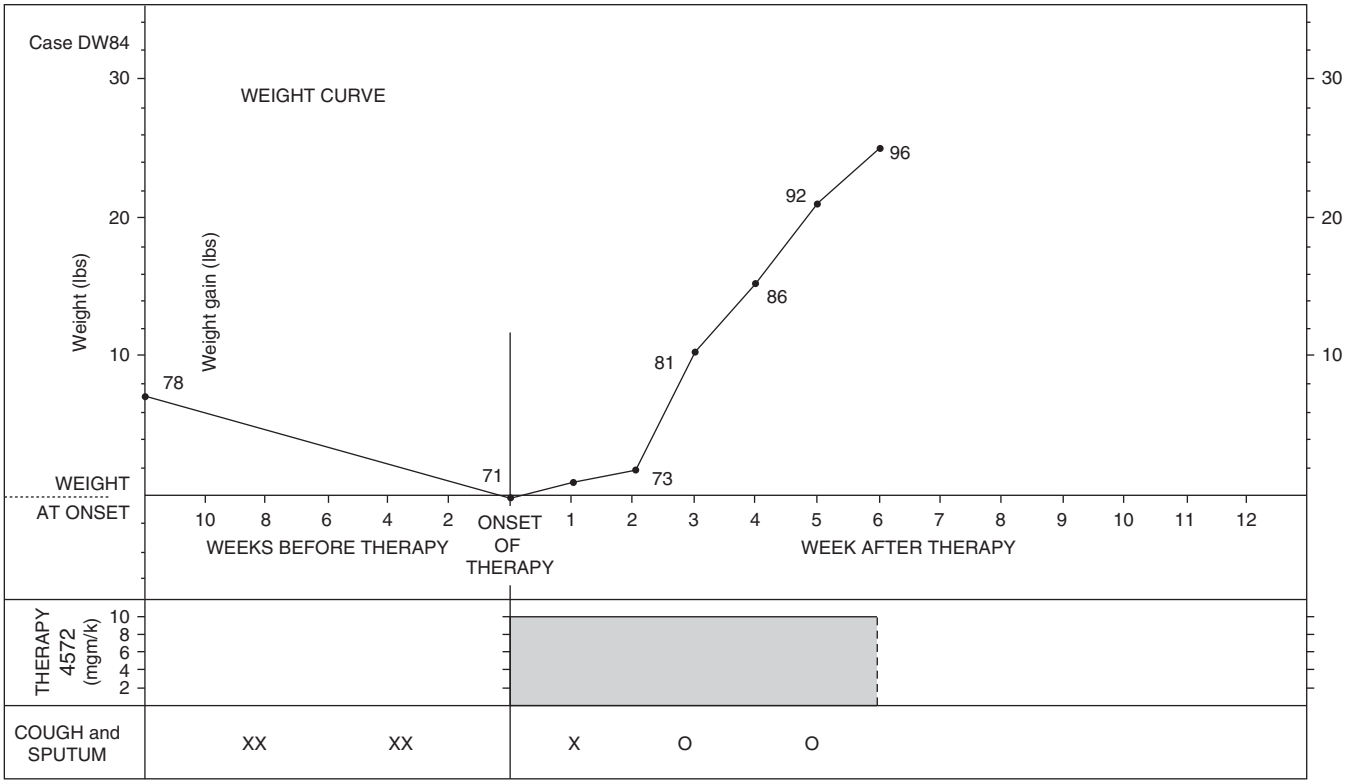
New Drugs

Bedaquiline

Bedaquiline is a diarylquinoline that blocks ATPase synthesis. There has been no cross-resistance with other drugs so far. Bedaquiline has high tissue binding, which partly accounts for its half-life of more than 24 hours. The early bacterial activity is similar to isoniazid and rifampin after 5 days (62). For extensively drug-resistant tuberculosis, bedaquiline added to the best available baseline regimen (kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine) showed improved clearance,



Temperature curve indicating persistently elevated temperature returning to normal on the third day after institution of therapy.



Weight curve indicating apparent gain in second week, rapid therafter.

Figure 9. Graphs showing the dramatic effects of isoniazid alone on temperature and weight in a single patient in the first clinical study of isoniazid in treating pulmonary tuberculosis. Although this is one of a group of "selected patients" whose data are displayed from among 44 patients in the study, the average weight gain for the group treated for at least 8 weeks was more than 20 pounds. Reprinted by permission from Reference 27.

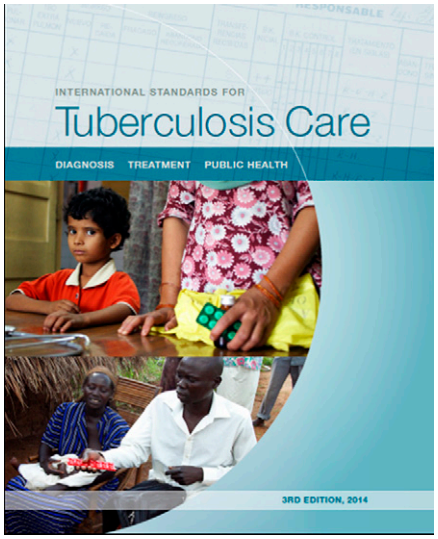


Figure 10. *International Standards for Tuberculosis Care* promote best practices for managing patients with tuberculosis or suspected of having tuberculosis. These measures lead to better, uniform care worldwide and reduce drug resistance. Directly observed therapy has also improved adherence and the success of prescribed regimens. These measures are every bit as consequential as new drug discovery.

with a median culture conversion time of 83 versus 125 days. However, despite better bacterial clearance, the bedaquiline treatment group had more deaths, 10 of 79 (12.7%) versus 2 of 81 (2.5%), than the placebo group in a comparative study (63). The cause of death did not fit a pattern and may be unrelated to the medication.

Delamanid

Delamanid, a nitro-dihydro-imidazoxazole also derived from metronidazole, is effective in replicating and nonreplicating organisms. Its MIC of 0.006–0.024 μg/ml is impressive; its intracellular activity at 0.1 μg/ml overshadows rifampin at 1–3 μg/ml. It also has delayed killing kinetics. Delamanid plus pyrazinamide and rifampin was superior to rifampin, pyrazinamide, isoniazid, and ethambutol in culture conversion in mice (64). In humans, delamanid is well tolerated and has good early bacterial activity (65).

Pretomanid (PA-824)

Pretomanid is a nitroimidazo-oxazine compound also derived from metronidazole. Similar to delamanid, it inhibits the nitro reduction in *M. tuberculosis*. Pretomanid also inhibits ketomycolates that are necessary for cell wall synthesis. Its MIC is 0.125 μg/ml, and it is effective against both replicating and nonreplicating organisms. It also has delayed killing over 24 days (66, 67). Pretomanid, like several other drugs, is much less effective when pyrazinamide is not present (68).

The Future

Today the strategy for new antibiotic development is to study the genetics and metabolism of microbial organisms to find vulnerabilities and then develop agents that target one or more of the potential targets. Using this drug development strategy, pharmaceutical companies have identified many compounds with antimycobacterial potential. The task for them is to consider which to develop because the cost of development is great. Drug development now explores many different avenues of attack, such as drug delivery methods (69), adjunctive immune regulation (70), therapeutic vaccines (71), inhibiting efflux pumps (72), and silencing RNA (73, 74), all of which hold therapeutic promise.

Although there are now many drugs for tuberculosis in development, there are also many obstacles to face before these agents supersede current regimens. The main challenges are discerning which signaling and metabolic pathway attack points are most productive, designing drug combinations, developing reliable markers to reduce the time required to determine whether an agent is effective, and the long and arduous task of designing trials and awaiting results.

Tuberculosis continues to kill—1.5 million people in 2013—but improvements in public health and new therapeutic developments should make the future story of finding and applying cures for tuberculosis as exciting and productive as in the past (Figure 10). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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