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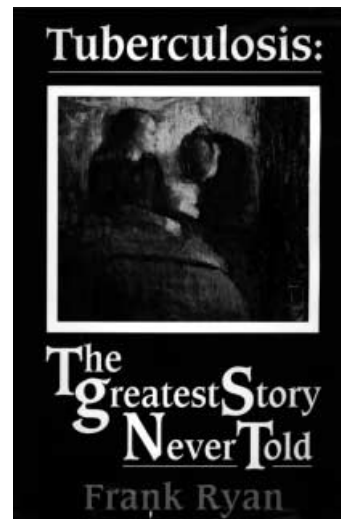
Frank Ryan: Tuberculosis: the greatest story never told

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This narrative engages the reader throughout. From the pallid dying redhead depicted on its cover by Norway's greatest artist, Edvard Munch, to the admonition of the last pages— that the synergy between AIDS and multi-drug-resistant tuberculosis has primed “a global time bomb”— the great story has not been told before. The breathless prose, combined with an impressive level of scholarship, reinforces the commitment of microbiologists, chemists, pharmacologists and physicians to a truth far more original and fascinating than that in any novel. The message throughout the book is clear: the mycobacterium of tuberculosis is no recent stranger subject to our demand that it be exiled. Rather the tuberculosis bug is an ancient entanglement whose fossil record reveals a long-term intimacy with our species and our domestic animals that will not disappear because we banish it. The disease that baffles our defenses, makes us hemorrhage, incessantly cough up foul sputum, burn with fever and disfigures our faces takes its own sweet time as it spreads from lung or bowel to bladder, kidney, or bone, and from grandfather to child and mother to sister.

From the evidence of Stone Age skeletons, tuberculosis was well-established in mainland Europe 4,000 years ago, and when the Europeans occupied the Americas the mycobacterium had preceded it. It consumed the bravest and the best: John Keats at the age of 25, Frederic Chopin in Mallorca, George Orwell (Eric Arthur Blair) as he finished writing *1984*, David Herbert Lawrence at age 44, Simonetta Vespucci (who inspired Botticelli's *Venus*) was “called back” at age 23, the actress Vivien Leigh, heroine of *Gone with the Wind* died of it in July of 1967. Marie Louise, the beloved first wife of the irrepressible Rene Dubos, (who figures prominently in this “white plague” story, in part as the discoverer of gramicidin, an antibiotic from soil microbes) succumbed as well. And some of the worst: Neither Adolf Hitler nor



his father were immune to this devastation; Hitler's father Alois hemorrhaged suddenly on the street, January 1903, and died a few moments later from acute tuberculosis. In the United States in 1990 (the latest data available in this book) some 26,000 active cases were known. Worldwide the disease is a major killer of adults between 25 and 45 years old. Of over 1,700 million people who incubate the bacterium, many if not most are unaware they are infected.

Everyone was touched by tuberculosis prior to the late 1970s. No wonder so many of the medical men in this book sought to ameliorate the suffering of their family and acquaintances. But as all biologists will appreciate, there is no single cure, no magic bullet. No “cause of the disease” (the mycobacterial “germ”) will be permanently eradicated by its unconditional surrender to any “miracle drug.”

In *Tuberculosis: the greatest story never told* (published under the title *The forgotten plague* by Bullfinch in the USA), Frank Ryan tells the whole tale with intelligence and passionate intensity. As usual, it is a story of many characters, many good guys and, yes, even heroes.

Most of all it is a true tale of evolution in action. Ryan is a physician, accomplished novelist, science writer and historian, who today, in the UK (Sheffield), is completing a book on evolution. His first step on this great odyssey was when, as a medical student, he read "Streptomycin is obtained from *Streptomyces griseus* which was cultured by Waksman in 1944 from a heavily manured field and also from a chicken's throat." Spurred on to know who Waksman really was, his curiosity was further aroused by his exposure to a severely ill 19-year-old patient. After Ryan watched her almost die as a victim of "the white plague", only to respond to the cure, he began this journey of his own discovery.

Ryan untangles the contribution of the Russian-born Jewish Selman Waksman (Rutgers University, New Brunswick, New Jersey), the soil microbiologist who was to receive the Nobel Prize in 1952 for his work on streptomycin, and he discovers several other heroes distantly separated in place and time. Their work was essential to whatever cures we do enjoy today. They include Albert Schatz, another Russian Jew whose superhuman efforts made crystalline streptomycin from a murky microbial sticky mush. Crucial to the tale, too, were William Feldman and Corwin Hinshaw, who tested streptomycin on consumptive people, and George Merck himself, who gave Waksman and his team his blessing to go ahead with this research when the world was focused on penicillin's miraculous ability to halt the infections of the wounds of war. Nonhuman heroes include the charming Guinea pigs who are entirely susceptible to our tuberculosis mycobacterium and, in dramatic experiments, were entirely cured with streptomycin.

Twin lines of investigation weave a tapestry of this tale. Ryan has identified the protagonists on the European side of the Atlantic and their "competitive inhibition" concept that supplemented the "antibiotic" approach of the west. Most outstanding was the marvelous pathologist who experienced first hand the hideous horrors of the wars, both I and II: Gerhard Johannes Paul Domagk, gentleman of perfect integrity and grit, who changed the paradigm. A researcher at Bayer, he began the antibiotic "miracle drug" revolution through meticulous studies of the dyes that became the drugs of the "sulfa" type. Domagk was a fine writer as well as an original bench scientist. Although it is his best-known work, *The Chemotherapy of Bacterial Infections* (1940), that provided many facts, it is more the fact that he kept a careful diary (now in the Bayer archives) that enlightened the story line for Frank Ryan. A truly patriotic German and a servant of the public dedicated to the promotion, not the destruction, of lives, Domagk was arrested at gunpoint and humiliated by the Nazis who prevented him from visiting Stockholm to receive his Nobel prize the year it was offered (1939).

The importance of PAS (*para*-amino-salicylic acid, an aspirin-like compound) in the double whammy cure, such as it is, was worked out by the charming, brilliant and highly original Danish hero Jorgen Lehmann. The independent-minded Lehmann was originally intrigued by a puzzling observation and this led to the successful therapeutic use of PAS as, alas, a temporary cure of the scourge. Frederick Bernheim, Duke University in North Carolina, had published that adding a milligram of salicylic acid (aspirin) to a growing culture of tuberculosis bacteria stimulated their oxygen uptake by greater than 100%.

One only hopes that Ryan's superb but hard-to-find contribution to the accessible literature of outstanding science will quickly be translated into many languages especially German, French, Italian, Danish and Spanish (and that an English-language paperback be made available). I can think of no more compelling story than this for the budding molecular biologists, microbiologists and genomics scientists of the world to read so that they can develop their own perspectives on some of the crucial truths of world-class research. Ryan makes this clear: Scientific investigation absolutely depends on curious, highly talented, hard working individuals. It is an intrinsically international enterprise, it can not be done without enlightened financial sponsors, and it is sensitive to political boundaries, historical traditions and educational institutions.

All of these components of a successful scientific undertaking were implicitly recognized in October of 1944 when Dr. D.C. Balfour, president of the famous Mayo Foundation of Minnesota (that runs the Mayo Clinic), introduced the dinner speaker Selman Waksman to a gathering of the senior staff with these words: "We have with us today a representative from an agricultural institution, one who has no medical degree and has never even received any training in medicine. He is going to address us tonight on a subject that is at the moment of great importance to medical science and clinical practice. The fact that you, Dr. Waksman, have been invited to deliver an address before a great medical organization such as ours, suggests that you are bringing to us a very important message."

Even today, no prospective graduate student, faculty member, or employee at my land-grant university is permitted to enter the payroll system until he or she is certified to be free of active tuberculosis. I had always thought that to be an excessive, quaint and annoying little piece of bureaucracy. I entirely changed my mind after reading Ryan's book. His carefully constructed argument that the "evils of AIDS and tuberculosis [have] come together in a synergy of terror" (p. 395) now make me grateful to those who have had the foresight and determination to protect our public health.