



History of Tuberculosis & National Jewish Health



Denver TB Course 4/3/2024

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National Jewish Health

Top: <https://www.nationaljewish.org/about/history>



Disclosures

- No disclosures

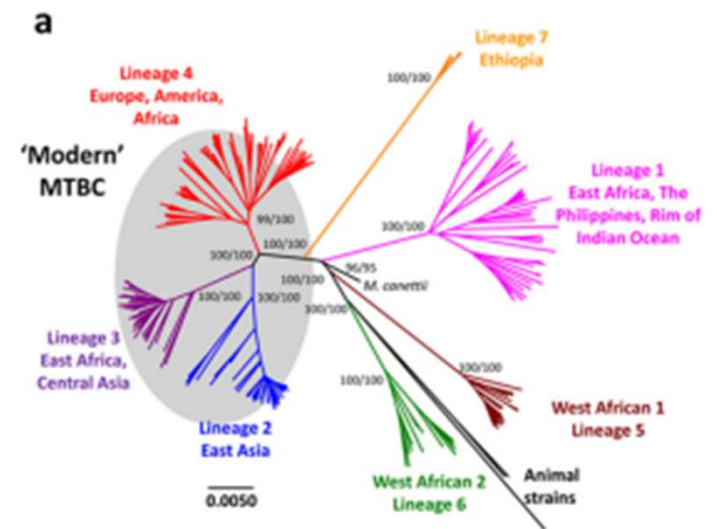
Different Ways to Study TB in History

- How old is tuberculosis?
 - Genetics of populations and bacteria
- Tuberculosis amongst early civilizations
 - Medical writings (retrospective diagnosis), paleopathology, bioarchaeology
- Tuberculosis and advances in the Western history of medicine
 - Great men, breakthroughs in knowledge and technology
- Tuberculosis and modernity, the modern tuberculosis epidemic (18th century-20th century) – the industrial revolution, living/working conditions
- Famous lay-people, literature, sociocultural practices, and tuberculosis
- The sanatorium era and the decline of tuberculosis
- Tuberculosis and the foundation of modern respiratory medicine, the BCG vaccine
- The antibiotic era
- The “forgotten plague” re-emerges

The Beginnings of Tuberculosis

- Tuberculosis in Homo erectus, ? Controversial
- Origin in the horn of Africa?
 - Comas et al. 2015 Current Biology 25: 3260-3266
- The major lineages of MTB mimic co-expanded with modern humans out of Africa
 - Comas et al. 2013 Nat Genet 45(10): 1176-1182

M. tuberculosis DNA found in the bones of a Great Plains Bison in Wyoming ~20,000 years ago, The Natural Trap Cave



The Beginnings of Tuberculosis (2)

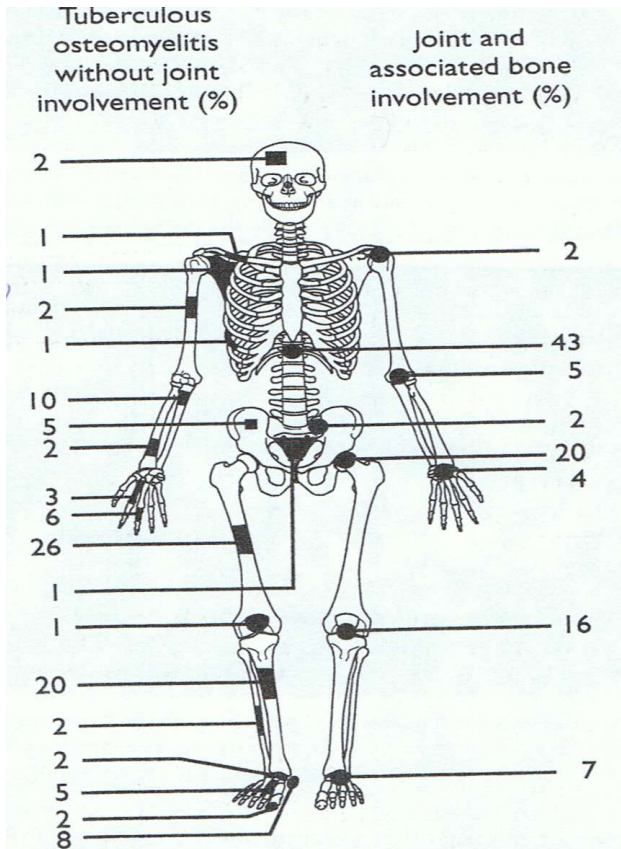
- *M. tuberculosis* is older than *M. bovis* (Brosch et al. 2002. Proc Natl Acad Sci USA 99(6): 3684-9)
- Oldest evidence in humans: Atlit Yam in Israel, 9,000 years ago
- Several findings during the Neolithic Period in Europe
- Seals carried tuberculosis from Africa to South America?
- Not so old? 5,000 years ago? (University of Tübingen)
- Chinese, Egyptian, and Indian written diseases that may have been tuberculosis
- Egyptian mummies (3000-2400 B.C.E.), Americans (100 A.D.)

Palaeopathology (& osteoarchaeology)

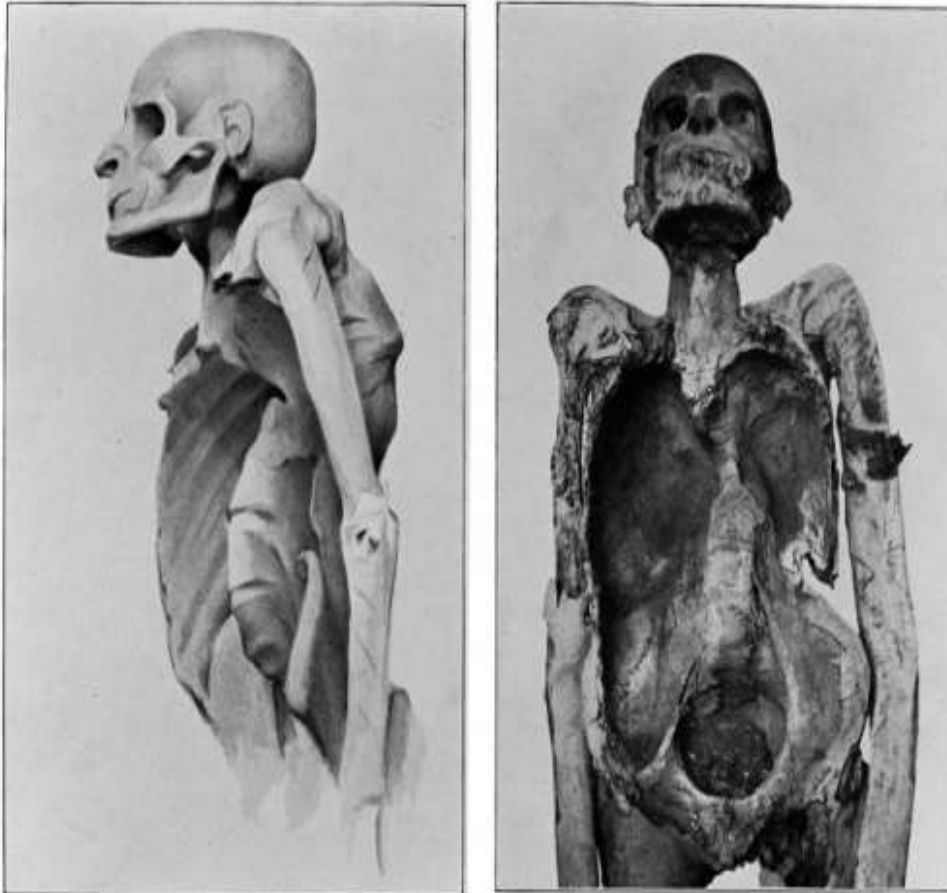


- Mid-late 19th century more serious investigations by physicians and anthropologists
- Between world wars: radiology, histology (tissues under the microscope)
- After WWII interest in whole populations (epidemiology, demography)
- As of 1980s-90s: biomolecular methods

Skeletal Sites for TB



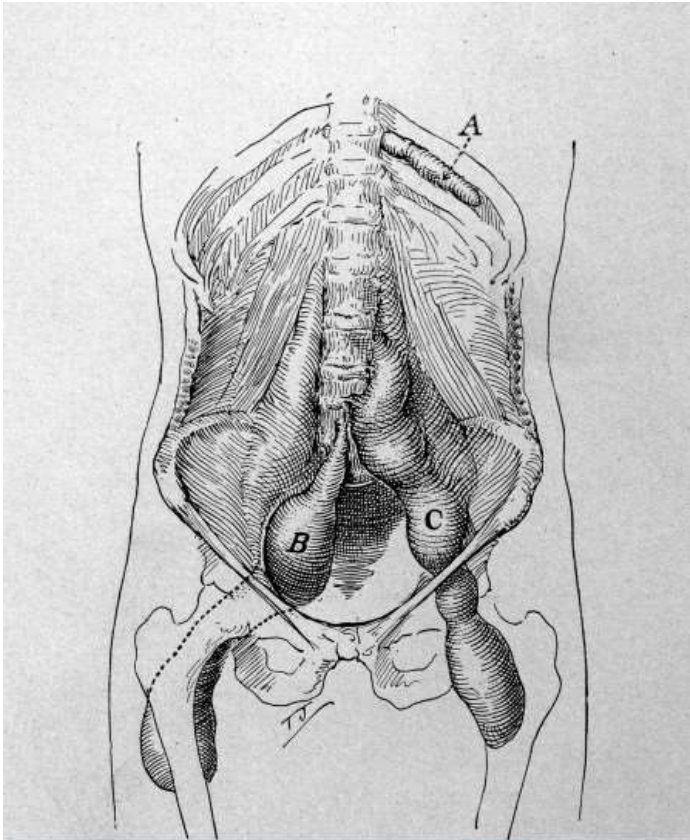
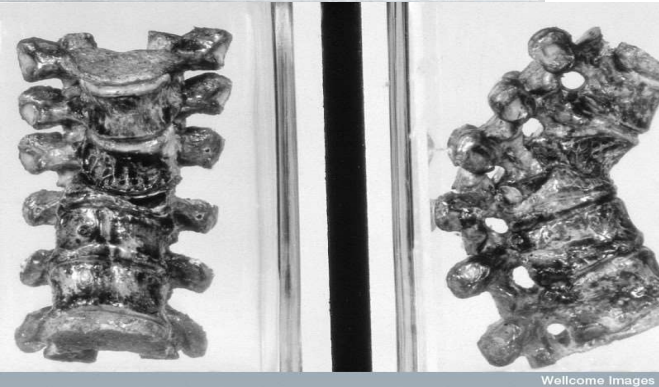
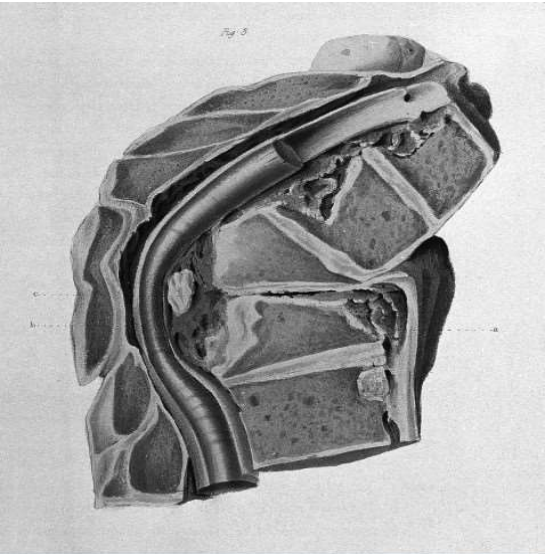
Pott's Disease (Tuberculous Spondylitis)



Wellcome Images

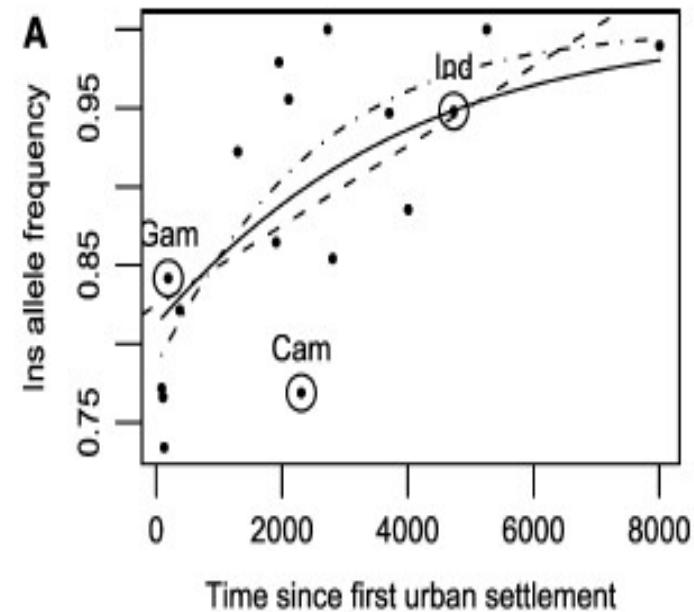
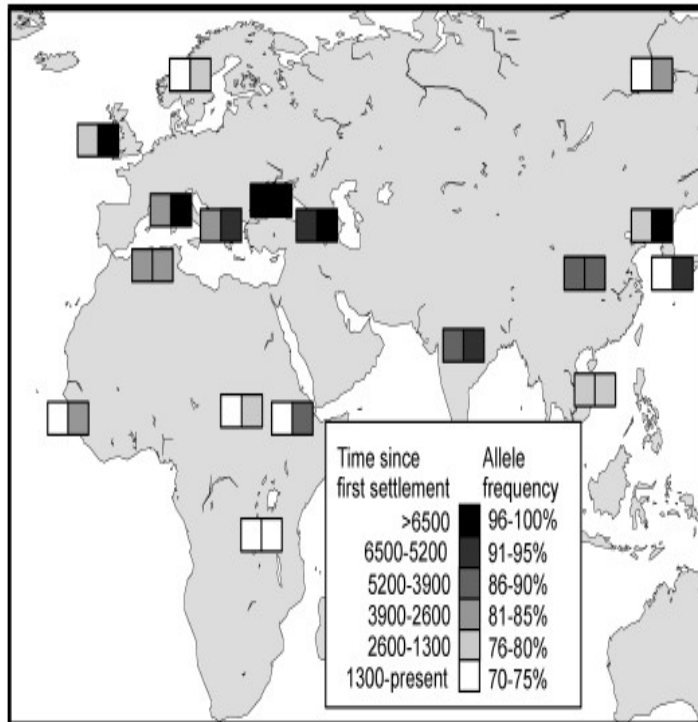
- **M0019338 Credit:** Wellcome Library, London
Pott's disease in a mummy of a priest of Ammon of the 21st Dynasty. Lateral view showing protusion of spine
From: Studies in the palaeopathology of Egypt
By: [Ruffer, Sir Marc Armand \[edited by Roy L. Moodie\]](#)
Published: The University of Chicago PressChicago, Illionis 1921
Plate I, Figure 1
Collection: [General Collections](#)
- **M0019339 Credit:** Wellcome Library, London
Anterior aspect of the mummy of a priest of the 21st dynasty showing huge psoas abscess into which the pus for the tubercular lesion had drained
Drawing By: [Cecil M. Firth](#)
From: Studies in paleopathology of Egypt
By: [Ruffer, Sir Marc Armand \[edited by Roy L. Moodie\]](#)
Published: The University of Chicago PressChicago, Illionis 1921
Plate I, Figure 2
Collection: [General Collections](#)

Pott's Disease



Barnes et al. (2010)

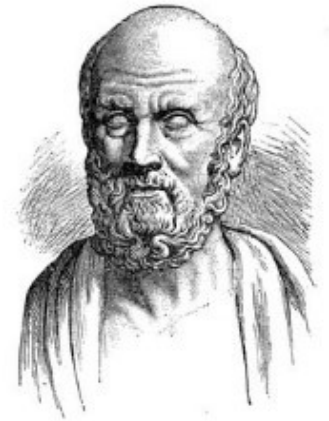
- ***Ancient urbanization predicts genetic resistance to tuberculosis***
- Natural Resistance-Associated Macrophage Protein 1 (NRAMP1), SLC11A1 gene, allele 1729+55del4



Barnes et al.
(2010)
Evolution
65(3): 842-848

Phthisis in Greek and Roman Medicine

- Greek concept of *phthisis* “withering” or “being consumed”
- Several different types of *phthisis* in the Hippocratic Corpus, ca. 4th century B.C.E. , usually a respiratory condition
- Roman imperial medicine: *phthisis* as a well-defined nosological entity based on respiratory/systemic symptoms



Aretaeus of Cappadocia (ca. 100 C.E.) Greek physician practicing in Rome

De causis et signis acutorum morborum Book I, Ch VIII “On Phthisis,” Francis Adams ed.

“If an ulcer form in the lungs from an abscess, or from a chronic cough, or from the rejection of blood, and if the patient spit up pus, the disease is called *Pye* and *Phthisis*...

“It is accompanied with febrile heat of a continual character, but... concealed during the day by the sweating and coldness of the body... is manifested by the uneasiness, loss of strength, and colliquative wasting.

The varieties of the sputa are numerous: livid, black, streaked, yellowish-white, or whitish-green...

For if one of the common people see a man pale, weak, affected with cough, and emaciated, he truly augurs that it is phthoe (consumption).”

The Middle Ages

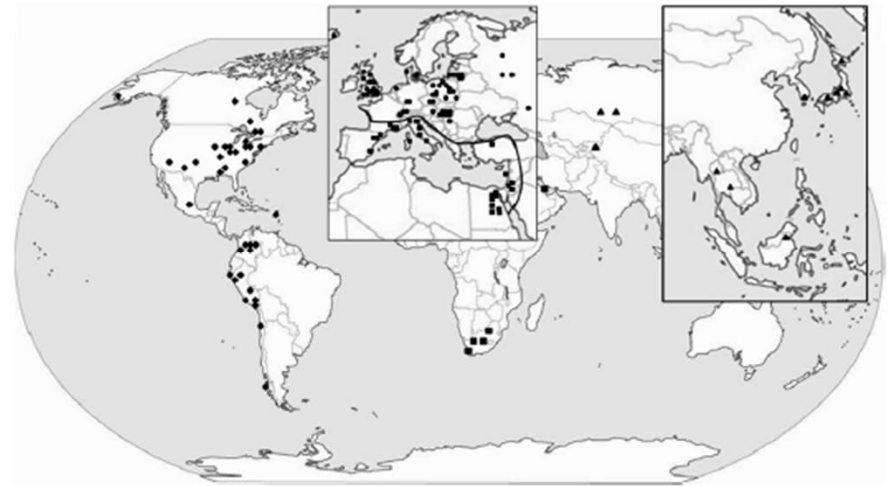
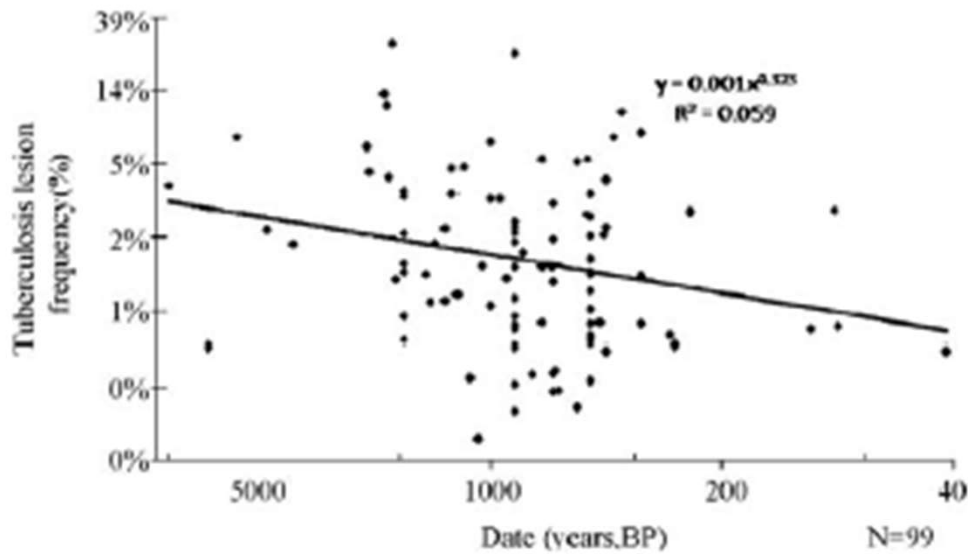


Fig. 1. Map showing the location of paleopathological cases of tuberculosis included in the meta-analysis (N= 531). Cases were grouped into regions: Northern Europe (circles), New World (diamonds), Asia (triangles) and Mediterranean (squares). The black squares are enlargements of the European and Asian regions.

Holloway et al. 2011. HOMO
62: 402-458

The King's Touch/Scrofula



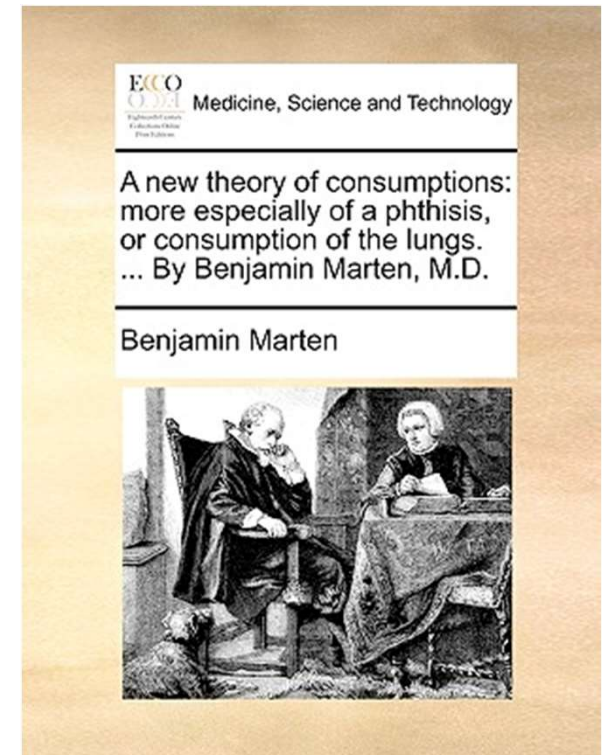
Girolamo Fracastoro (c. 1476-1478)

- An Italian physician, poet and scholar
- In 1546 he proposed that epidemic disease were caused by tiny particles that could be transmitted by direct or indirect contact
- He formally described “contagion”-at-a-distance via infectious particles or “*seminaria*”



Benjamin Marten (c. 1690-1752)

- A precocious British physician, foresaw the vector of consumption:
- *“... Certain species of animalculae or wonderfully minute living creatures that, by their peculiar shape or disagreeable parts, are inimical to our natures...”* (~ 1730)



Contribution of Autopsy



- Formal study of diseases through autopsy
 - **Sylvius** (1679) – described “tubercules”
 - **Morton** (1689)– furthered the descriptive pathology of pulmonary and extrapulmonary TB
 - **Manget** (1702)– miliary tuberculosis

Richard Morton (1637-1698)

- Established the pulmonary form associated with **tubercles** as a pathology (1689)

Phthisiologia: or, a treatise of consumptions. Wherein the difference, nature, causes, signs, and cure of all sorts of consumptions are explained. Containing three books: I. Of the original consumptions from the whole habit of the body. II. Of an original consumption of the lungs. III. Of symptomatical consumptions, or such as are the effects of some other distempers. Illustrated by particular cases, and observations added to every book. With a compleat table of the most remarkable things. Translated from the original / [Richard Morton].

Morton, Richard, 1637-1698 | Date: 1694

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René Théophile-Hyacinthe Laennec (1781-1826)

“The French Connection”: Bayle and Laennec

Working under Corvisart in Paris in the Napoleonic Era:

Bayle and Laennec, through clinical observations and meticulous post-mortem analysis, substantially characterized both pulmonary and extrapulmonary TB



Jean Antoine Villemin (1827-1892)

- Villemin (1865) did classic animal transmission studies but was unable to stain or grow AFB



Heinrich Hermann Robert Koch (1843-1910)

Robert Koch (March 24, 1882), after 217 days of research in his home lab, presented at the Berlin Physiological Society:

- A technique to stain the tubercle bacillus
- A means to cultivate the bacillus
- Animal models to confirm infectiousness (postulates)
- Evidence that the bacilli were present in sputum of consumptives



Tools and Techniques of Microbiology

van Leeuwenhoek and the microscope (1674's)

Pasteur, Lister and culture (1850's)

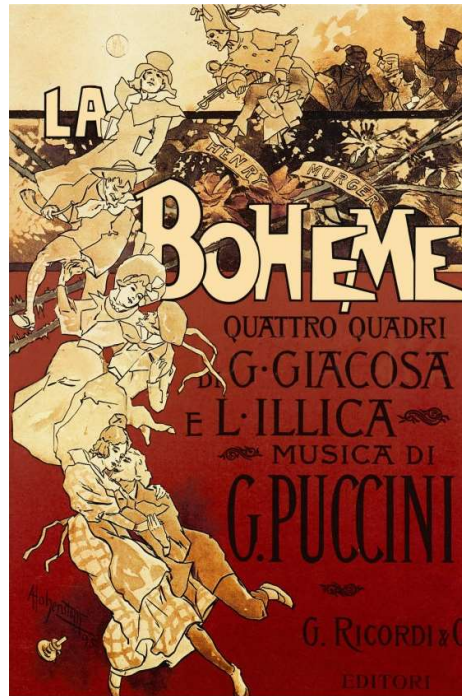
Erhlich and staining (1860's)



Leeuwenhoek
Microscope
(circa late 1600s)

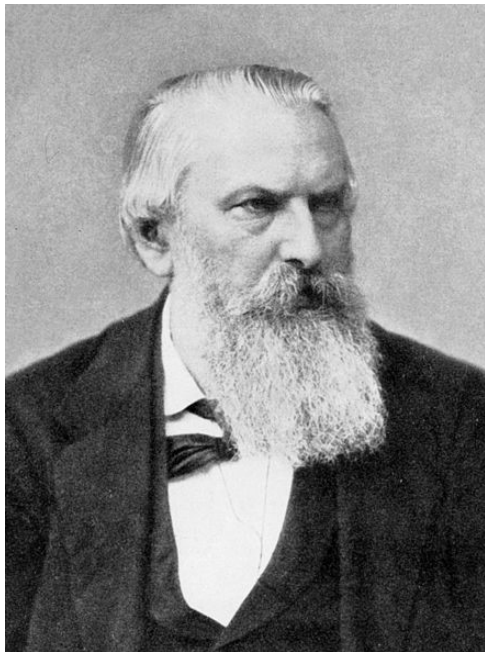
TB & Society: The Romantic Era

- TB as “fashionable”
- Association with artists
 - Robert Louis Stevenson
 - The Bronte family
 - Frederic Chopin



<https://www.pbs.org/wgbh/americanexperience/features/plague-gallery/> Credit: Getty Images

The Sanatorium Movement



- **Hermann Brehmer (1826-1889)** is acknowledged as the originator of the sanatorium movement
- Opened first-ever high-altitude sanatorium (1854) to treat pulmonary consumptives at Gorbetsdorf in the Silesian mountains (Poland)
 - Salubrious rest primarily in outdoor settings
 - Optimal airy conditions
 - Calibrated exercise
 - Healthful diet

The Sanatorium Movement in the United States

- First American sanatorium was established in 1875 by H.P. Gatchell in Asheville, North Carolina.
- 11 years later, the Adirondack Cottage Sanatorium at Saranac Lake was founded by **Edward Livingston Trudeau**
- Later renamed the Trudeau Sanatorium after his death.



Christmas Seals

- In 1904, Einar Holbøll in Denmark came up with the idea of Christmas seals
- Beginning in 1907, Christmas seals were first sold in the US
- Proceeds supported sanatoriums for the treatment of TB



Edward Livingston Trudeau (1848-1915)

- Trudeau, a physician, suffered from TB which he developed during medical school
- He was influenced by Brehmer
- Founder of the National Association for the study and Prevention of Tuberculosis (American Lung Association) and the American Sanatorium Association (American Thoracic Society)



The Evolution of Modern Treatment & Prevention of TB:

- **Rest:** sanatoria of Bremer (Alps) and Trudeau (Adirondacks), 1865/1884
- **Pneumothorax:** Carson (Scotland, 1820s) Potoin (France 1880's) and Forlanini (Italy 1880-90s) and “collapse” therapy
- **Phrenicclasis:** Stuertz (Germany, 1911)
- **Thoracoplasty;** Brauer (Germany, 1920s)
- Paraffin or Lucite Ball **Plombage** (1930s - 1940s)
- **Pneumoperitoneum** (1940s)

Artificial Pneumothorax

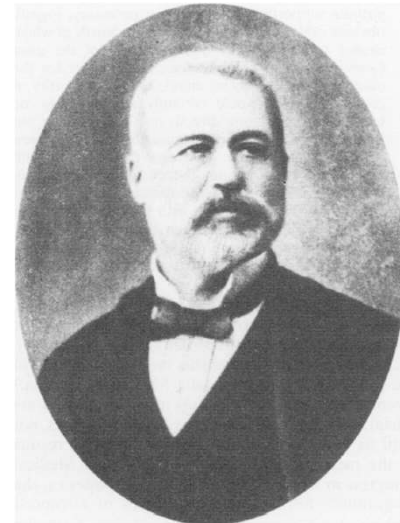
In 1696, Giorgio Baglivi reported improvement in a TB patient who suffered a pneumothorax following a sword wound.



J. Carson of Liverpool, suggested this method for treating pulmonary TB in 1820

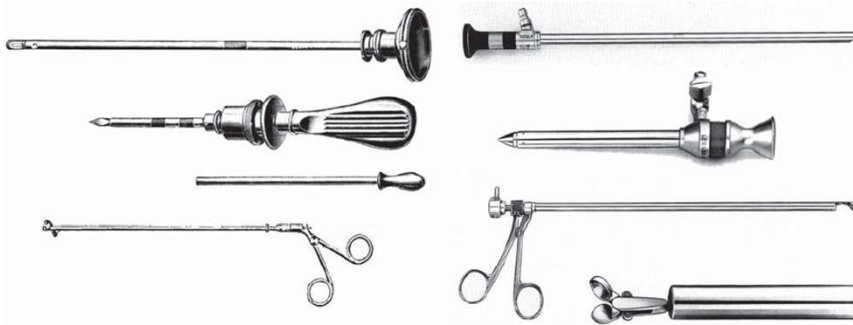


C. Forlanini began to apply artificial pneumothorax in clinical practice in 1888



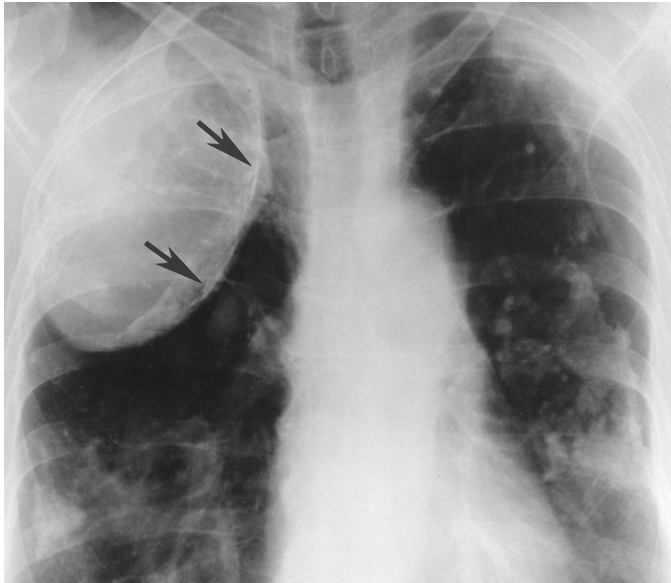
Internal Pneumolysis

- The Swedish internist Hans Christian Jacobaeus (1879-1937)
- Initiated thoracoscopy to lyse pleural adhesions



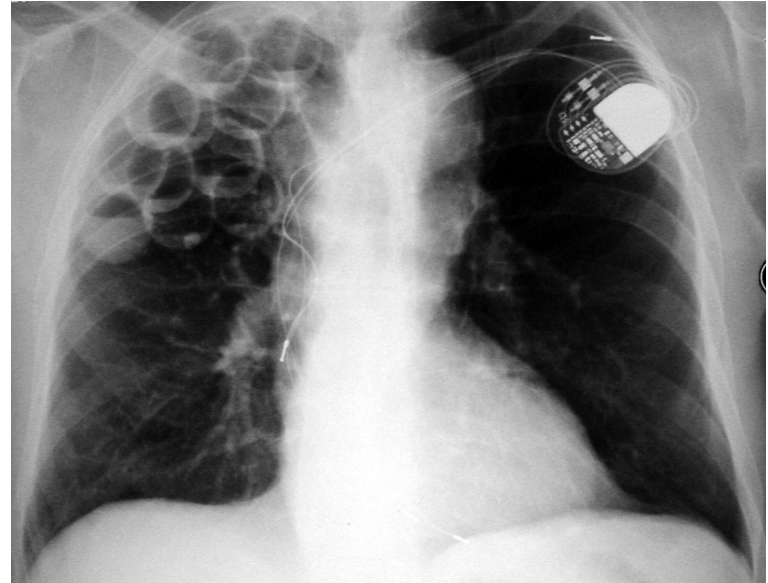
Plombage

Oleothorax



Sputum negative in 30-60%

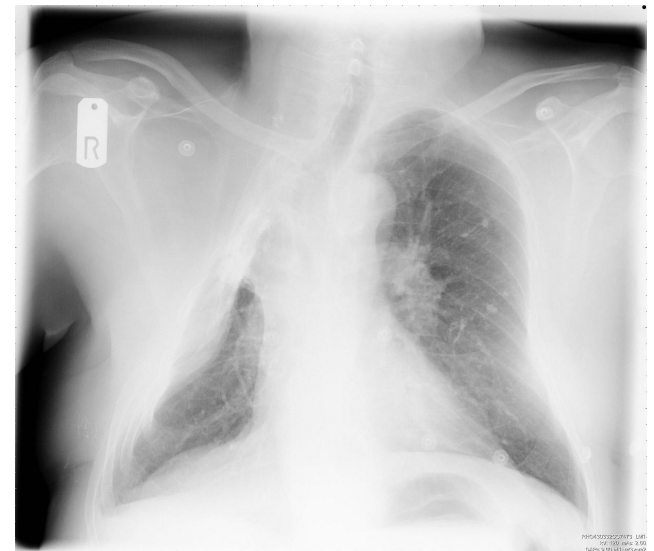
Lucite Balls



Thoracoplasty

- 1885 – de Cereville collapsed TB cavities by resecting portions of the 2nd and 3rd ribs
- 1907 – Friederich resected ribs 2-9 (mortality-30%)
- 1920 - Sauberuch modified the procedure and recommended two stages
- 1925 – Alexander developed the standard operation used today

Closure of cavity in 60-80%;
mortality 10%



Denver and “Chasing the Cure”

- Denver founded on gold and silver, sustained by consumptives
- Colorado’s climate thought to be conducive to curing TB, “the world’s sanatorium”
- Boosters draw patients West to “chase the cure” aiming to draw those who could make financial contributions to the State
- By 1897 calls for “sanatoria” or “reservations” for the poor who were dying in the streets
- By 1925 it is estimated that 60% of Denver’s population had come because of TB, including spouses, children, and parents
- In the late 19th century no institutions existed to serve consumptives, civil society stepped up as opposed to government (Progressive Era)

4 Charitable Institutions in Denver

- The National Jewish Hospital (1899)
- The Jewish Consumptives' Relief Society (1904)
- The Evangelical Lutheran Sanitarium (1905)
- The Swedish National Sanatorium (1905, 1908)

- Ethnic and religious groups pooled resources to provide healthcare: medical institutions as a symbol of community identity and responsibility (Charles Rosenberg, historian)

- Part of a larger sanatorium movement, e.g., Edward Trudeau in 1884

Abrams 1990 "Blazing the Tuberculosis Trail" The Colorado Historical Society



Frances Wisebart Jacobs (1843-1892)

- “Denver’s Mother of Charities”
- Middle-class, married to a prominent merchant
- Tireless campaign for the poor, lobbied city leaders
- Died before National Jewish was built
- Enlisted the help of Rabbi William Friedman of Denver’s reform temple, Congregation Emmanuel
- Hospital stood empty until B’nai B’rith, a national Jewish fraternal organization came to its rescue



Abrams 1990 “Blazing the Tuberculosis Trail” The Colorado Historical Society

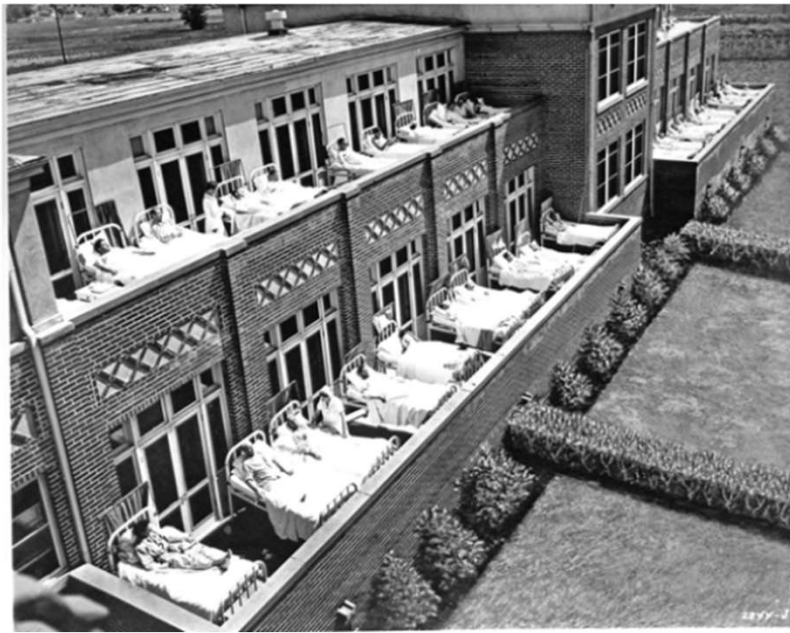
The Early History of National Jewish

- Denver's first tuberculosis sanatorium
- Perhaps the first institution in the nation to make the care of the poor with tuberculosis its primary goal
- Free care for all: "None may enter who can pay – None can pay who enter"
- By 1924 2,200/4,511 patients treated are Russian immigrants

Abrams 1990 "Blazing the Tuberculosis Trail" The Colorado Historical Society



Early National Jewish (continued)



<https://www.nationaljewish.org/about/history/clinical>

<https://www.du.edu/news/history-colorado-exhibit-explores-jewish-leadership-colorados-health-care>

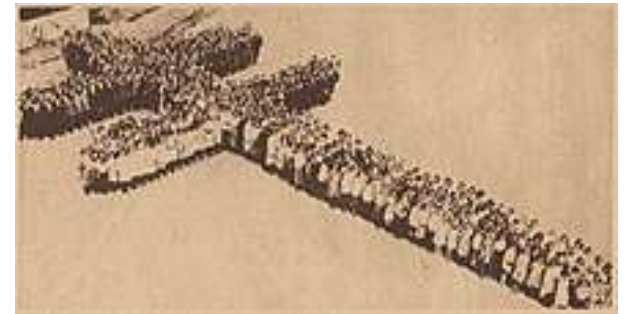
- 3 core aspects of treatment (rest, nutrition, outdoor exposure)
- Other treatments: surgery, lung collapse therapy (pneumothorax)
- Average stay 7 months; rehabilitation, social/education programs to allow functioning in society upon discharge
- Hofheim Preventorium (1920) for impoverished children
- B'nai B'rith Infirmary built to provide more beds, state of the art facility: operating rooms, X-ray, drug departments, opens 1926

NJH in the 40's and Beyond

- 1948-1968 cardiology service
- 1953 UN/WHO assistance to become a clearinghouse for displaced persons suspected of having TB including Holocaust survivors
- Holistic approach, psychiatric concerns
- One of the first hospitals to use chemotherapy (streptomycin)
- Bed rest gives way to physical activity
- Asthma and allergy program in the mid-1950s
- Other lung conditions, cardiac conditions, 1960s
- Shift to outpatient care 1990s, pediatric & adult day units 1995-1996

American Lung Association

- Formed in 1904, originally the National Association for the Study and Prevention of Tuberculosis
- Christmas Seal campaign begins, 1907
- Medical (Osler, Flick, Trudeau) and Lay (Carnegie, Frick, Rockefeller, Phipps) celebrities



1919, Philadelphia school children

The Holy Grail: Curative Chemotherapy

- **Para-aminosalicylate (PAS):** Lehmann (Denmark 1943-44)
- **Streptomycin (SM):** Waxman & Schatz (U.S. 1943)
- **Isonicotinic Acid Hydrazine (INH):** Domagk (Germany), Fox and Bernstein (U.S. 1952)

Jörgen Lehmann (1898-1989)

- Lehmann, in Gothenburg, Sweden designed para-aminosalicylic acid (PAS)
- On October 30th, 1944, Lehman and TB expert Gylfe Vallentin treated a moribund young Swedish woman (Sigrid) with oral PAS and reported a "dramatic recovery"



Streptomycin discovered, 1947

- In 1943 Rutgers graduate student Albert Schatz, working under Dr. Selman A. Waksman discovered bacteria that would later create the antibiotic streptomycin
- Isolated from *Streptomyces griseus* in soil



<https://www.pbs.org/wgbh/americanexperience/features/plague-gallery/> Credit: Rutgers University



Hugh Feldman and Corwin Hinshaw

- Waksman sent 10 gm of streptomycin to them and they tested it on 4 guinea pigs. It was so effective he sent them additional drug and they demonstrated its effectiveness in a larger guinea pig study
- On November 20, 1944, Hinshaw, Feldman, and Pfuetze gave streptomycin to a patient who was cured.



Hugh Feldman



Corwin Hinshaw

British Medical Research Council Streptomycin Trial

Regimen	No. of Patients	Deaths	X-ray Improvement (%)	Culture Negative	
				3 mo	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).

Mitchison DA. Am J Respir Crit Care Med 2005;171:699-706.

PAS + SM Decreased Development of Resistance

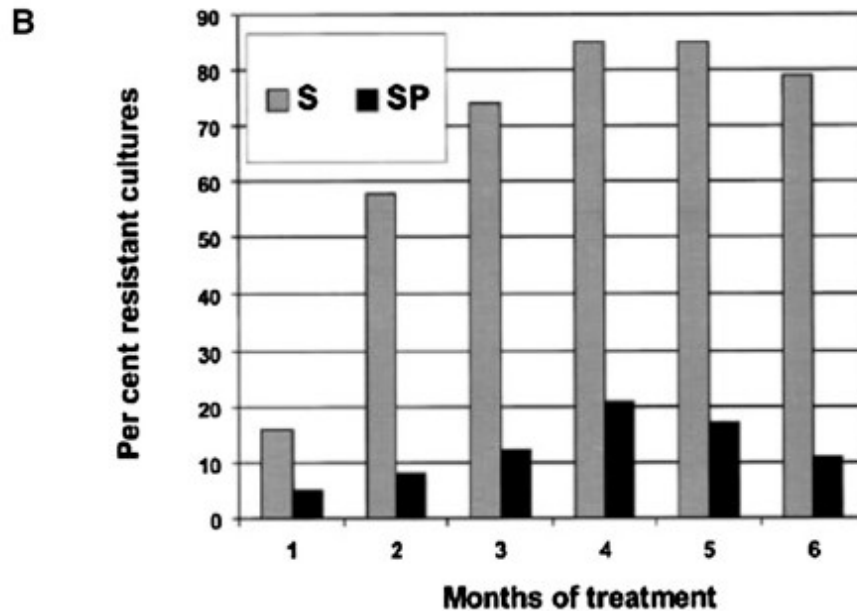


Figure 1. p-aminosalicylic acid (PAS) given with streptomycin (SM) reduces the emergence of SM resistance. The percentage of strains that is SM resistant in the SM series (indicated by S) and the SM plus PAS series (indicated by SP) during 6 months of treatment. Data from Reference 16.

Mitchison DA. Am J Respir Crit Care Med 2005;171:699-706.

Chronology of TB Drug Discovery



- Diarylquinolines
- InhA inhibitors
- LeuRS inhibitor
- Mycobacterial gyrase inhibitors
- Pyrazinamide analogs
- Riminophenazines
- Ruthenium (II) complexes
- Spectinamides
- Translocase-1 inhibitor
- CPZEN-45
- DC-159a
- Q201
- SPR-10199
- SQ609
- SQ641
- BTZ043
- TBA-354
- AZD5847
- Bedaquiline (TMC-207)
- Linezolid
- PA-824
- Rifapentine
- SQ-109
- Sutezolid (PNU-100480)
- Delamanid (OPC-67683)
- Gatifloxacin
- Moxifloxacin

Wong EB, et al. Trends Micro 2013