History of Tuberculosis & National Jewish Health

Denver TB Course 4/2/2025

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National Jewish Health

Top: https://www.nationaljewish.org/about/history
Bottom: “La Miseria” by Cristobal Rojas (1886)

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Disclosures

- No disclosures

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Colorado: The Centennial State (1876)

- Denver founded on gold and silver, *sustained by consumptives*
- Koch (1882) estimated 1 of 7 people in Europe/U.S. died from TB

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Denver and “Chasing the Cure”

- Colorado as “***the world’s sanatorium***,” with climate thought to be conducive to curing TB
- Boosters draw patients West to “***chase the cure***” aiming to draw those who could make financial contributions to the State
- 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)
- By 1897 calls for “sanatoria” or “reservations” for the poor who were dying in the streets

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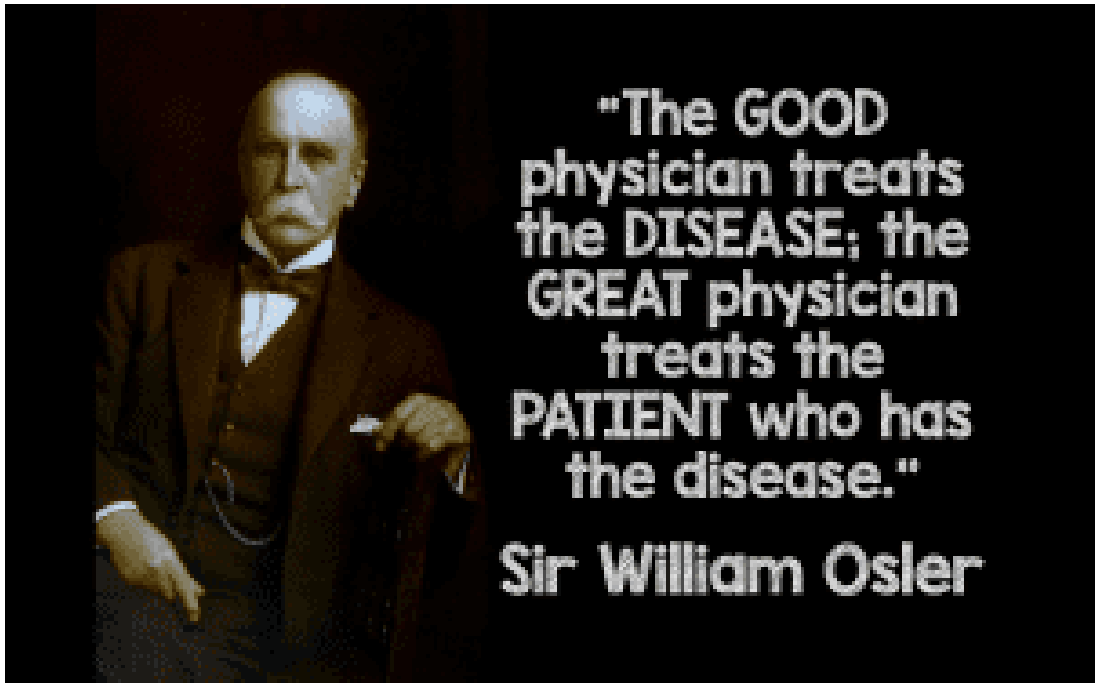
"Tuberculosis is a social disease with a medical aspect"

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)



Lived 1849-1919

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

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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 Historial Society

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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 Historial Society

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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

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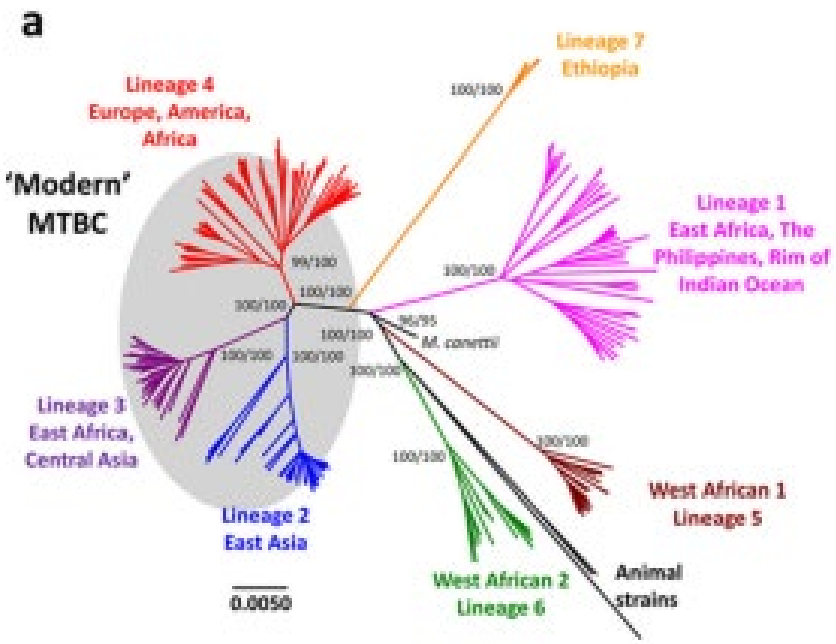
The Beginnings of Tuberculosis

- 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

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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

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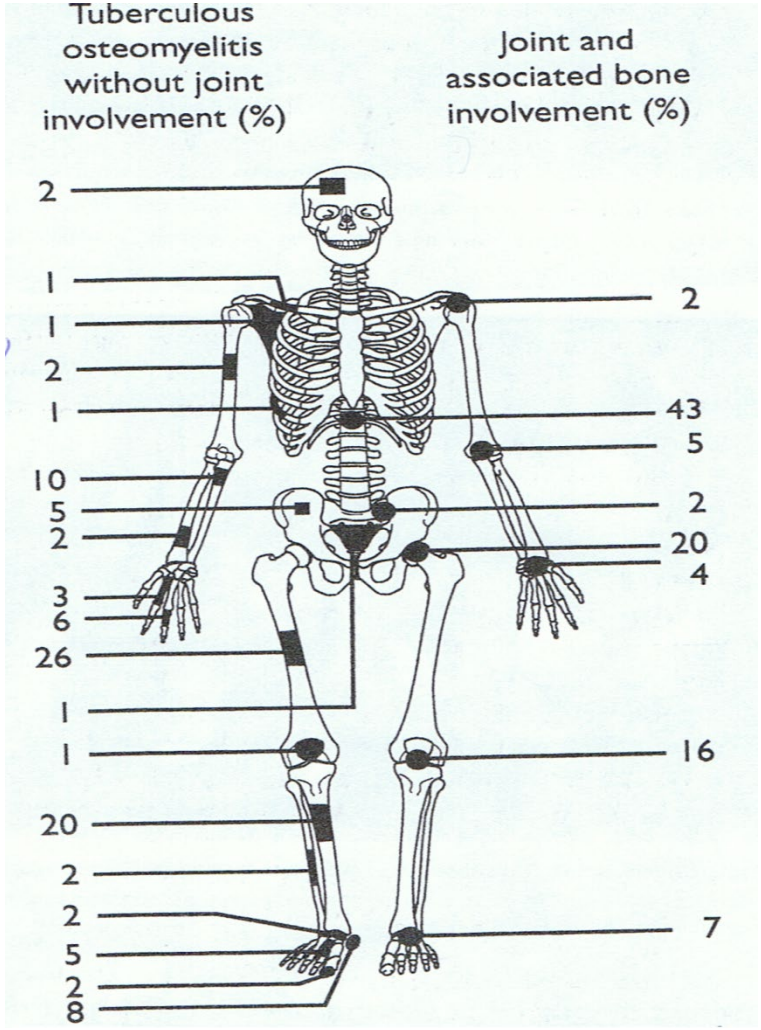
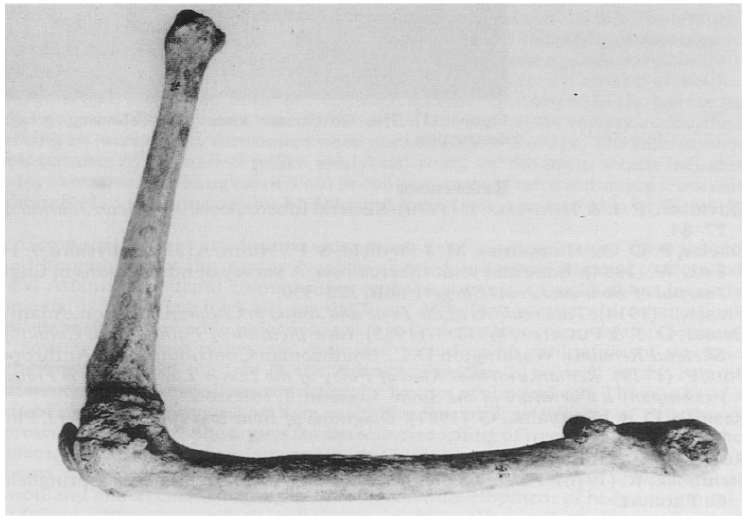
Skeletal Sites for TB





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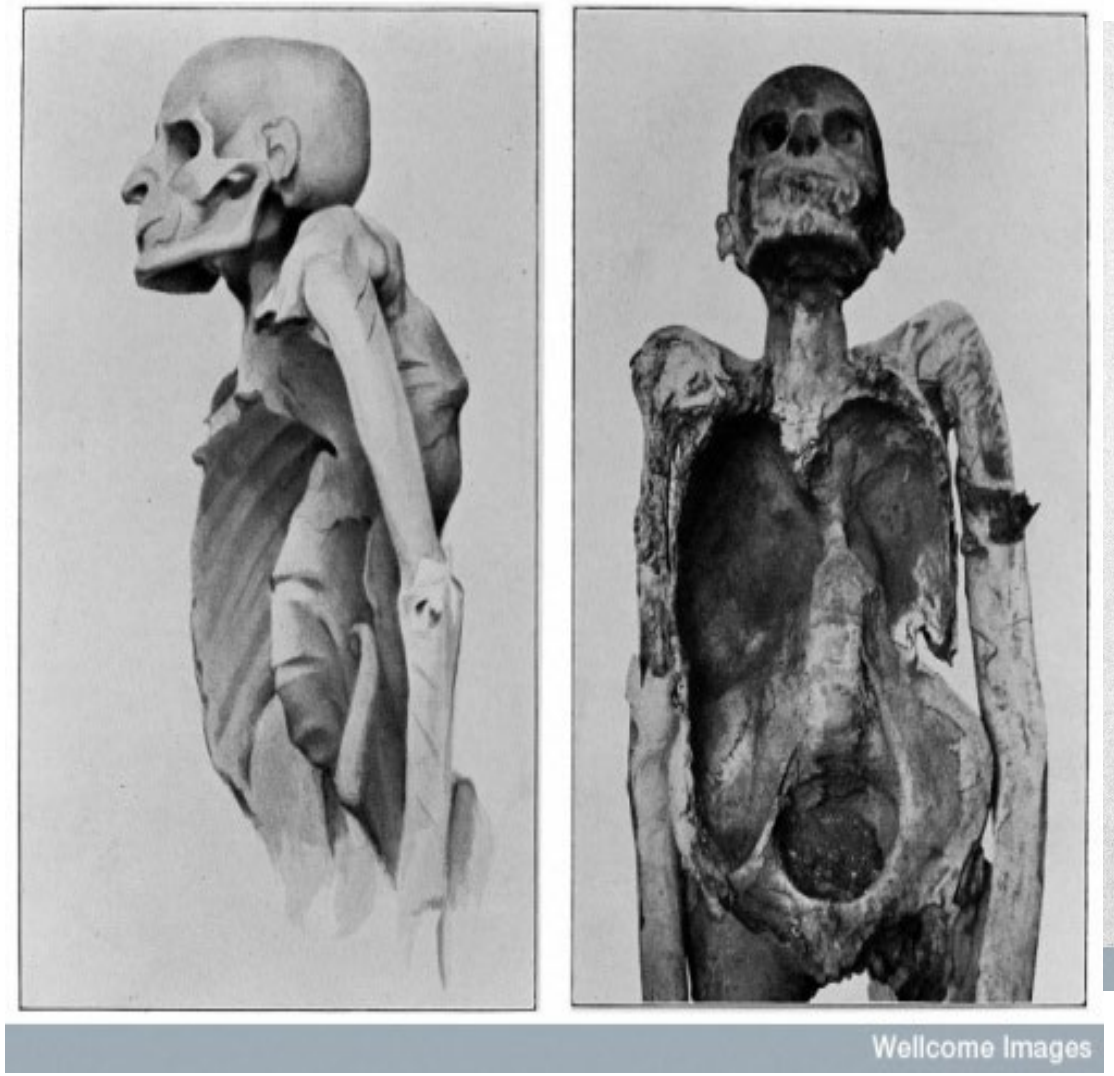
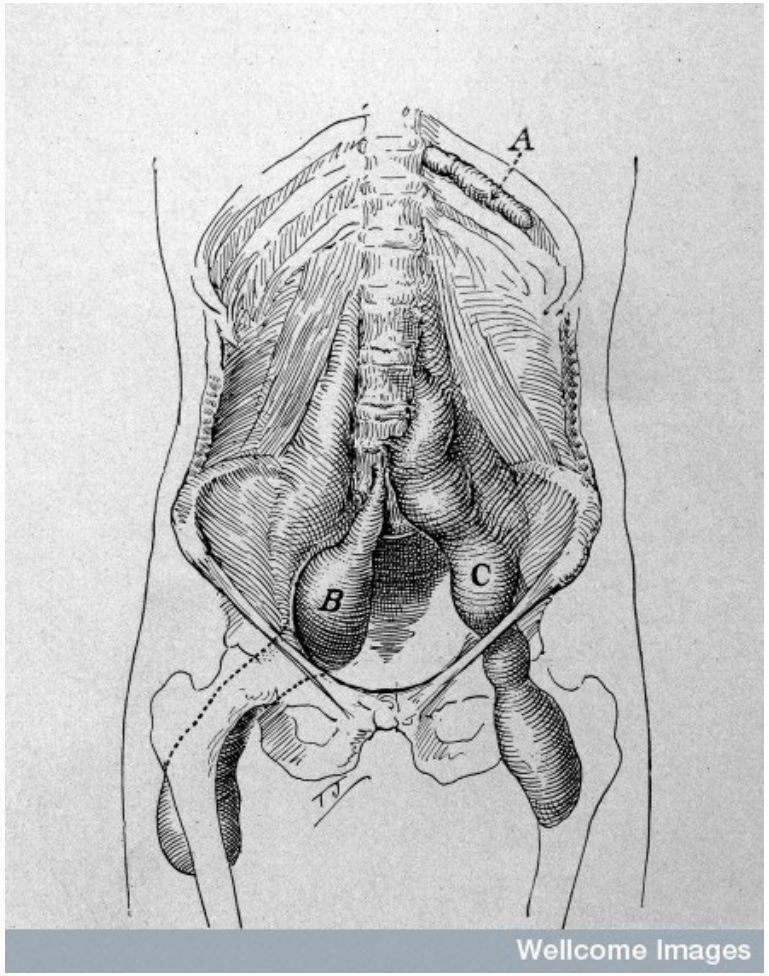
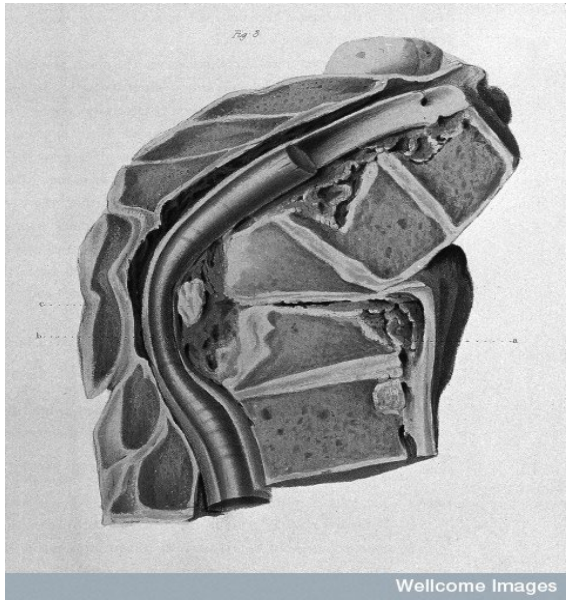
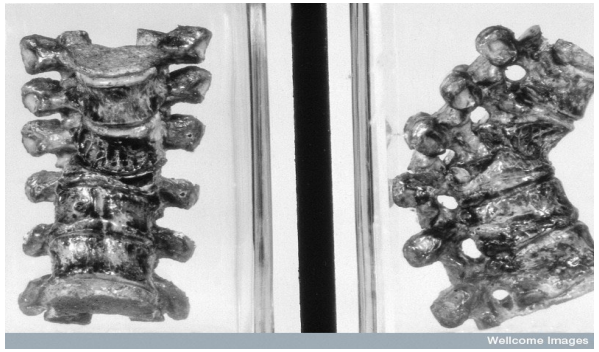
Pott's Disease (Tuberculous Spondylitis)









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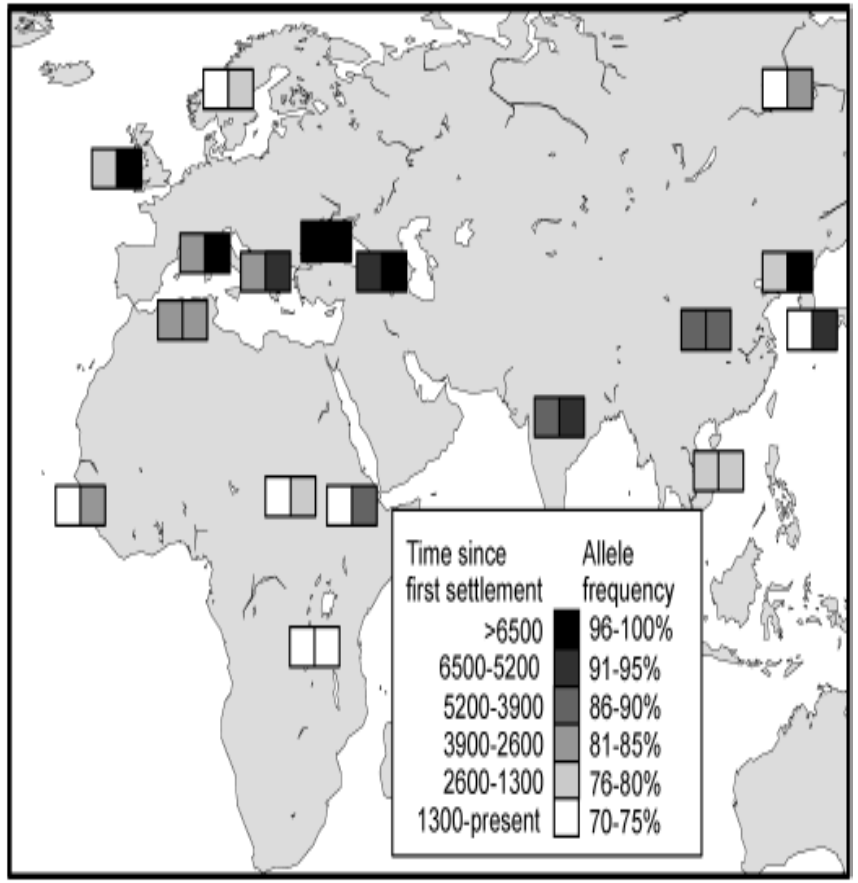
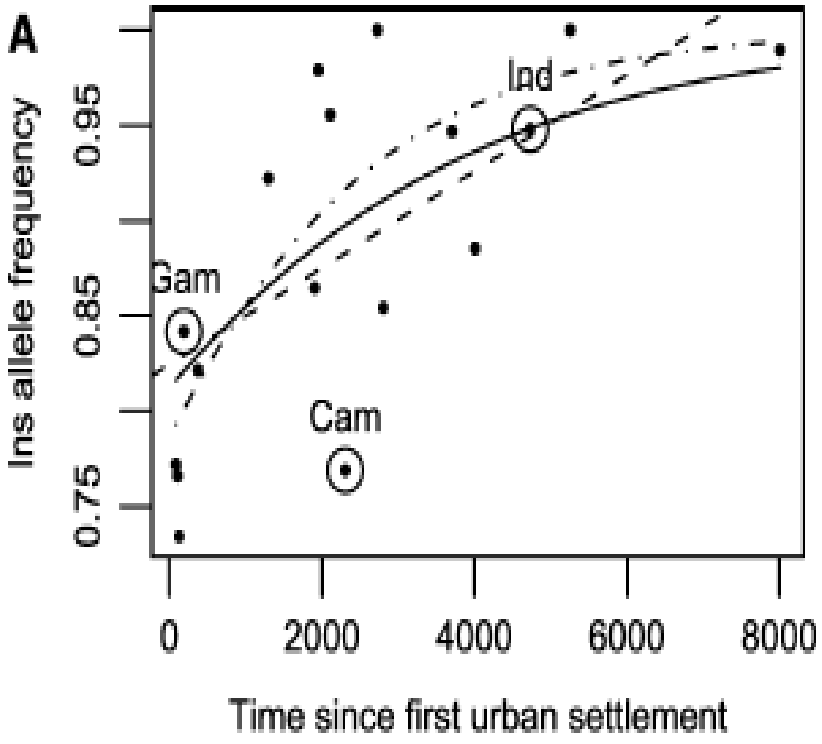
Barnes et al. (2010)

- ***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

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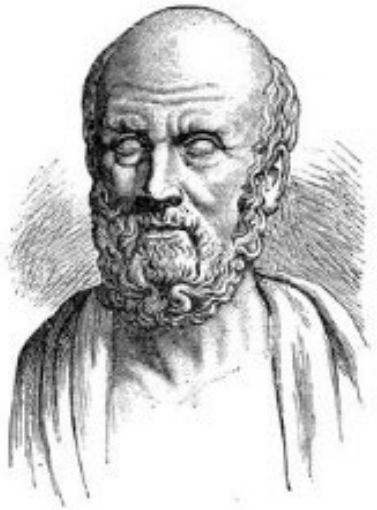
Greek phthisis

- Hippocratic Corpus ~60 treatises, ca. 5th-4th c. BCE
- "phthisis" φθ, "wasting," several definitions
- Usually respiratory



Ancient Greek Religious Sanctuaries (explorethemed.com); explorethemed.com/GreekRel.asp

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Phthisis in Greek and Roman Medicine

- 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.

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"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 King’s Touch/Scrofula

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Contagiousness of TB Difficult to Accept

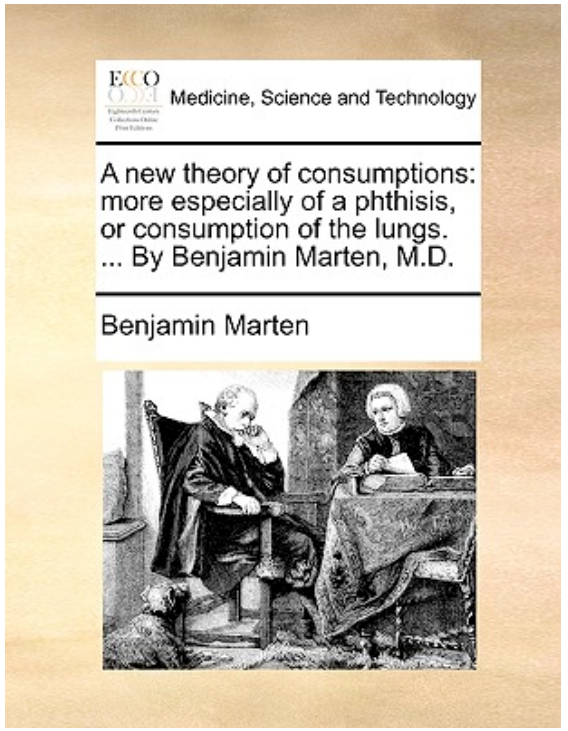
- Low infectiousness - prolonged contact required
- Low pathogenicity - few infected developed TB
- High virulence - up to half of cases died
- Variable, prolonged latency - disease long after exposure
- Variable manifestations - phthisis, pleuritis, scrofula, meningitis, renal disease, infertility
- Historically assumed to be inheritable (e.g., multiple members of the same household die from TB)

Contagion

- **Girolamo Fracastoro (c. 1476-1578)**, Italian physician, poet and scholar

- In 1546 he proposed that epidemic disease were caused by tiny particles "***seminaria***" that could be transmitted by direct or indirect contact via "***contagion***"

- **Benjamin Marten (c. 1690-1752)**, precocious British physician who 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)*



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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

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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

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Jean Antoine Villemin (1827-1892)

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

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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

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TB & Society: The Romantic Era

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

- *“It was the fashion to suffer from the lungs; everybody was consumptive, poets, especially; it was good form to spit blood after each emotion that was at all sensational, and to die before the age of thirty…”*

  - Alexandre Dumas, memoirs

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

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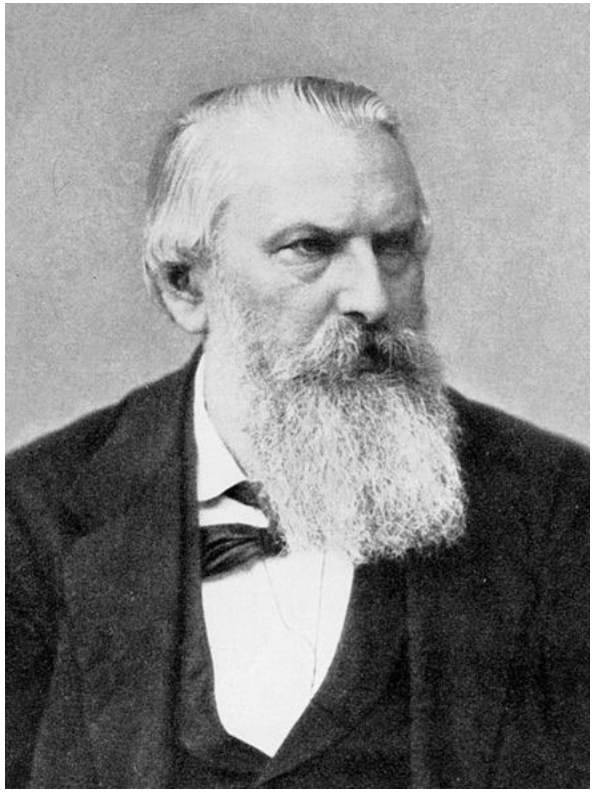
The Sanatorium Movement



- **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 Gorbersdorf in the Silesian mountains (Poland)
  - Salubrious rest primarily in outdoor settings
  - Optimal airy conditions
  - Calibrated exercise
  - Healthful diet

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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.

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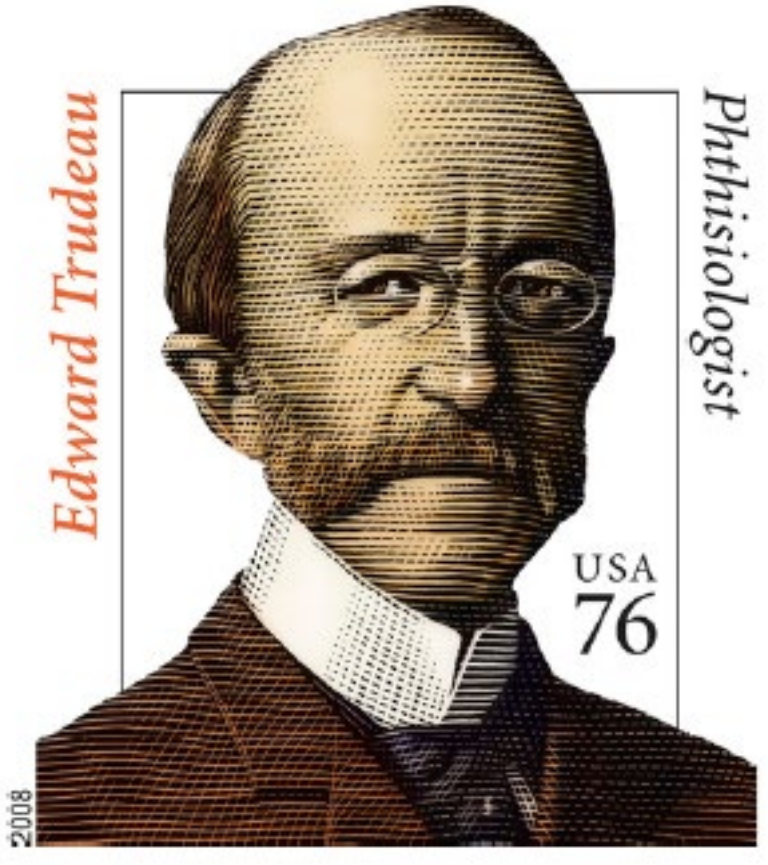
Edward Livingston Trudeau (1848-1915)

- 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)



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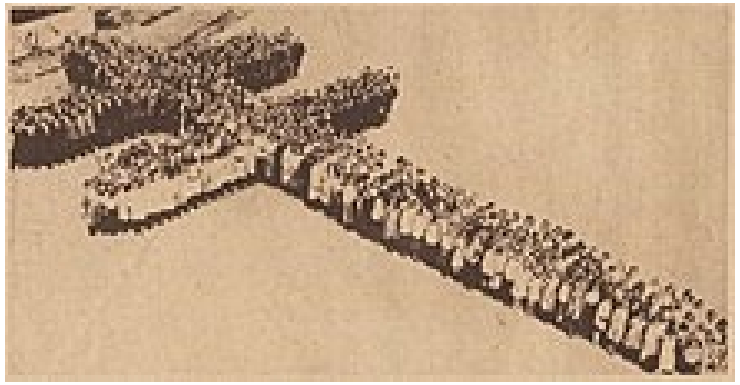
American Lung Association

- 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

American Lung Association.



1919, Philadelphia school children

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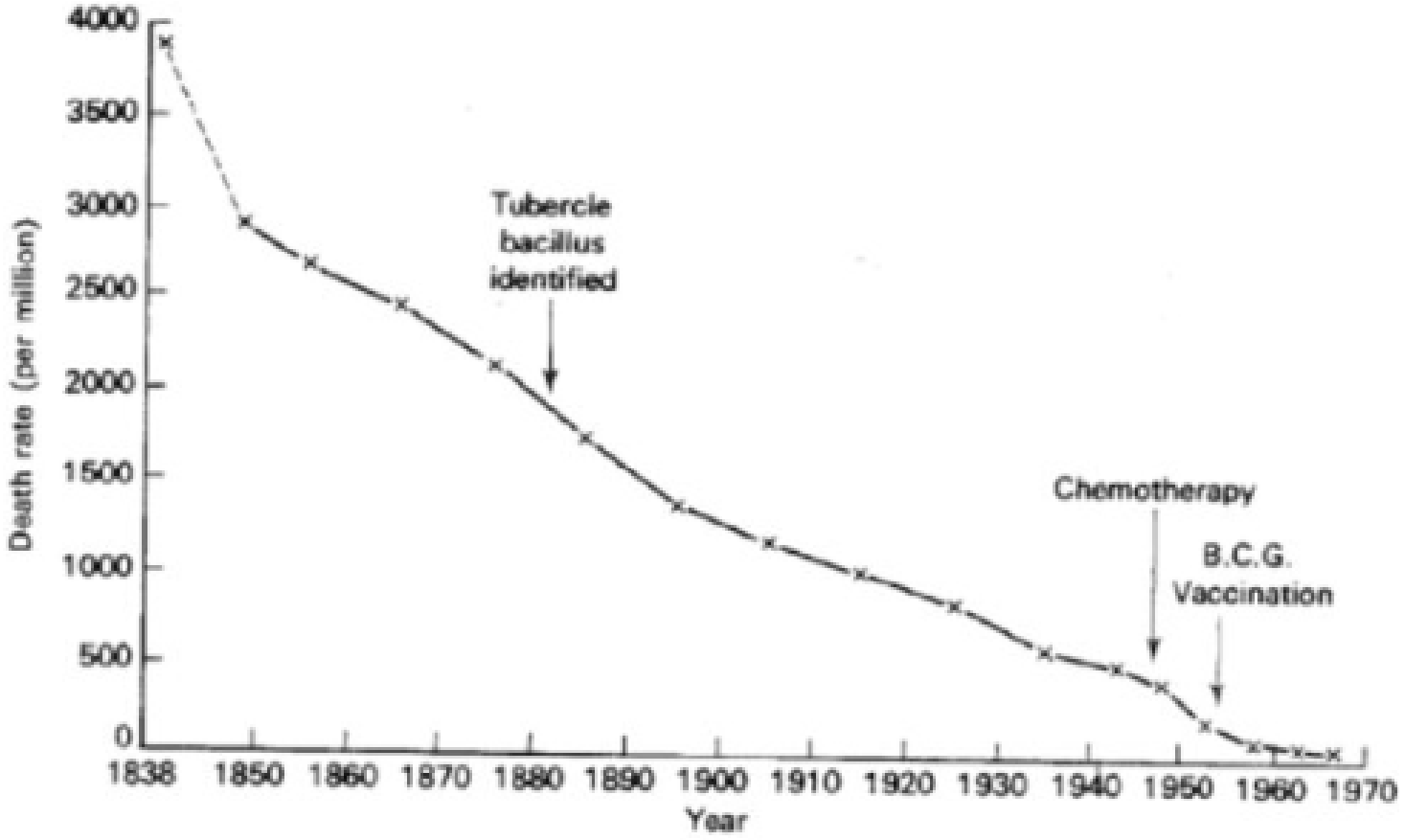
Thomas McKeown



5.1 Respiratory tuberculosis: death rates, England and Wales.

- From "The Modern Rise of Population" 1976, p. 93
- Importance of standards of living, nutrition

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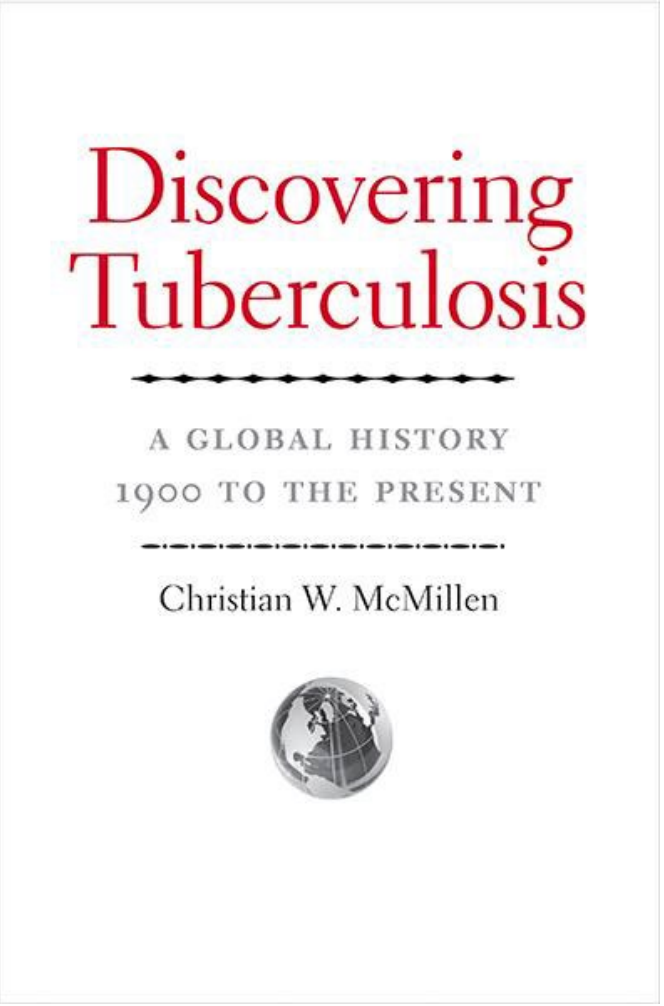
Race and Susceptibility/Resistance

- “Virgin soil” epidemics: increased transmission and mortality in a population previously unexposed to an infectious disease
- Certain “primitive peoples” considered to have increased susceptibility or decreased resistance
- Disproven by survey studies of the 1930s-1940s (CXR with documentation of healed lesions)
- Living conditions the true cause of apparent disparity between races



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
- ***Phreniclasis***: Stuertz (Germany, 1911)
- ***Thoracoplasty***; Brauer (Germany, 1920s)
- Paraffin or Lucite Ball ***Plombage*** (1930s - 1940s)
- ***Pneumoperitoneum*** (1940s)

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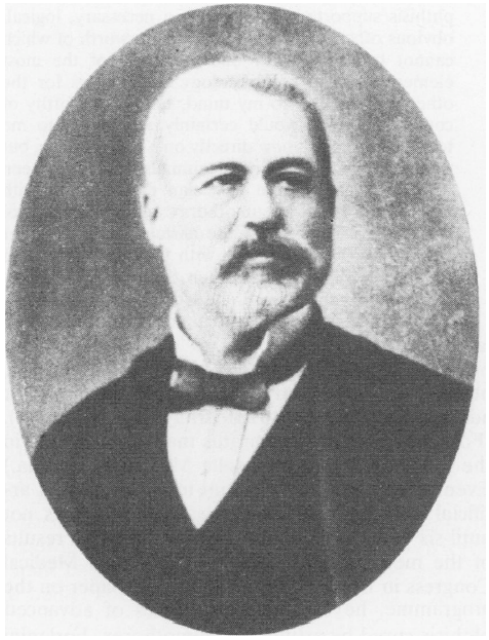
Artificial Pneumothorax

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



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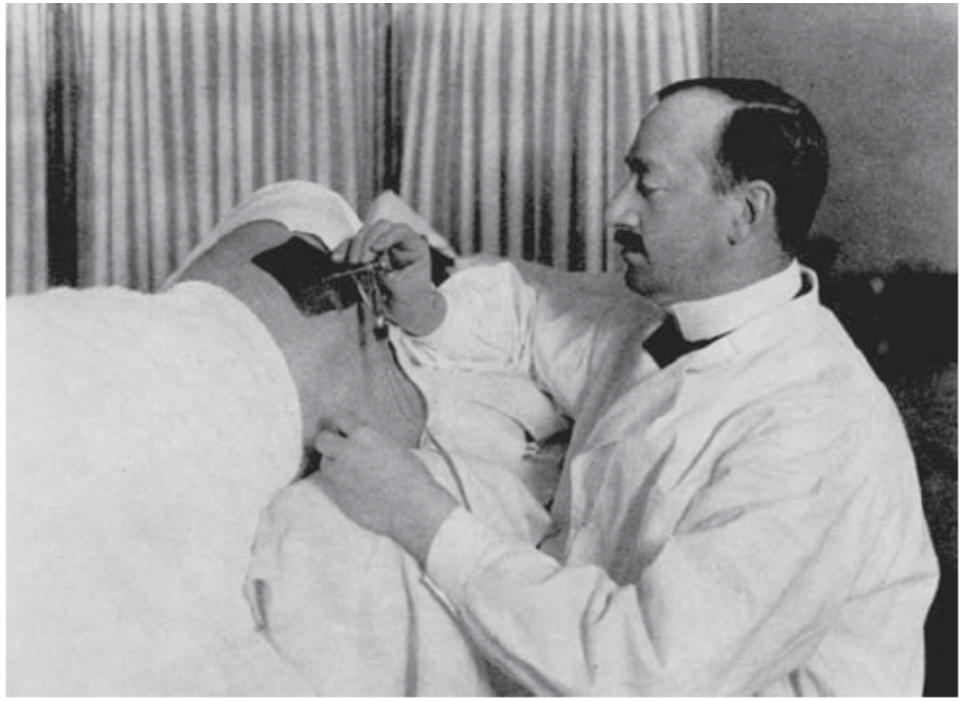
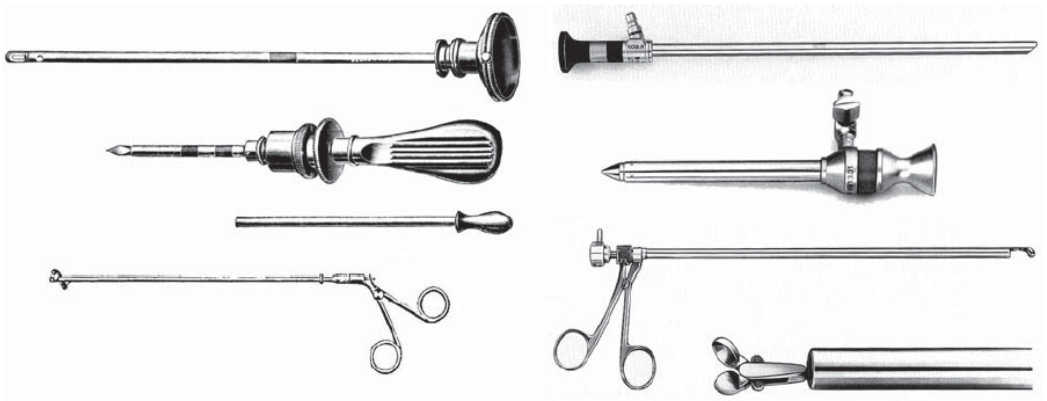
Internal Pneumolysis

- The Swedish internist Hans

  Christian Jacobaeus (1879-1937)
- Initiated thoracoscopy to lyse pleural adhesions





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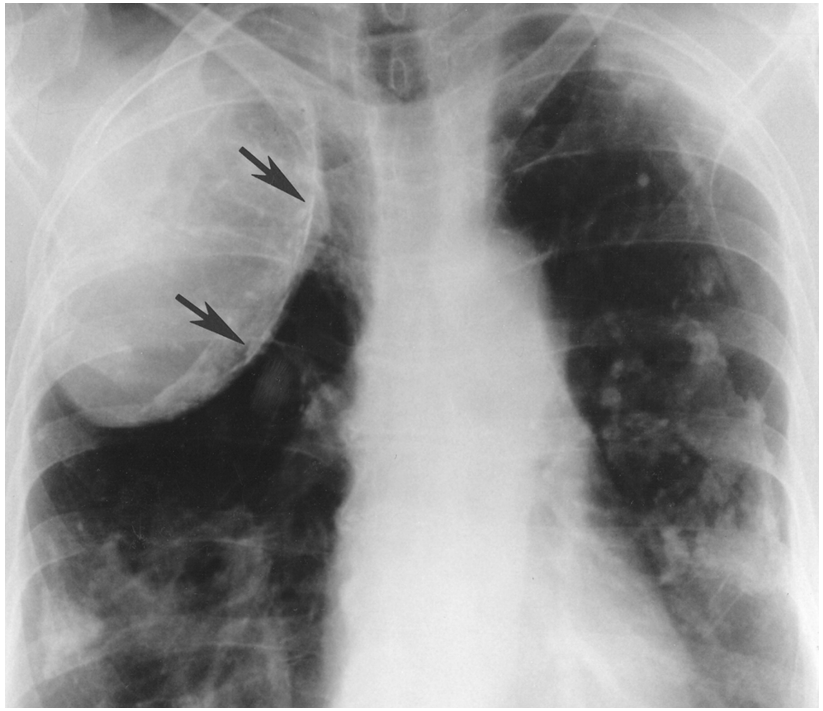
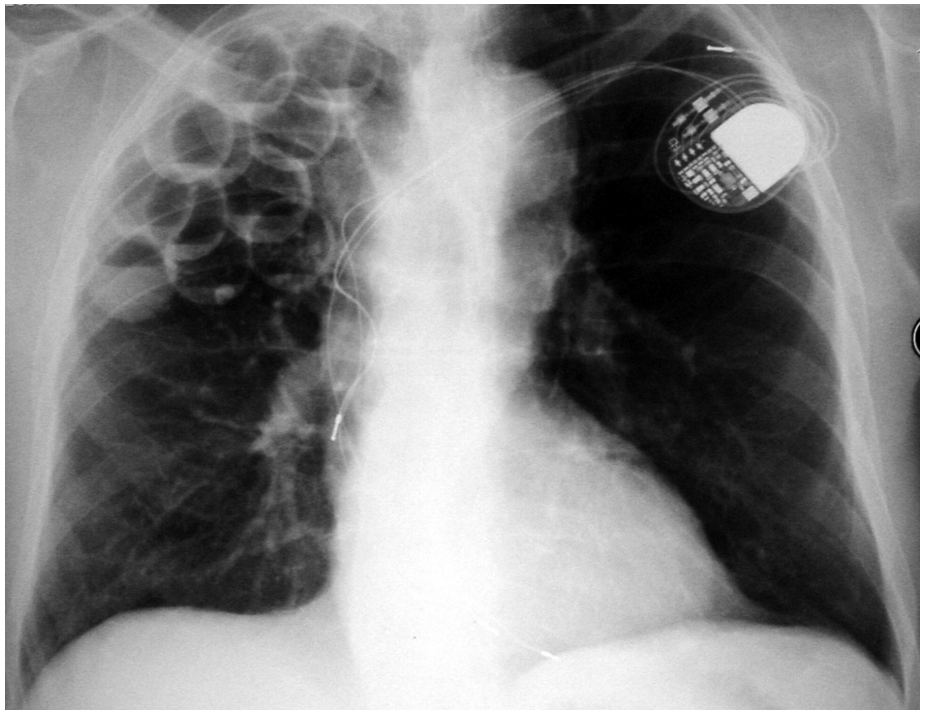
Plombage

Oleothorax



Lucite Balls



Sputum negative in 30-60%

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Thoracoplasty

- 1885 – de Cerenville 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%

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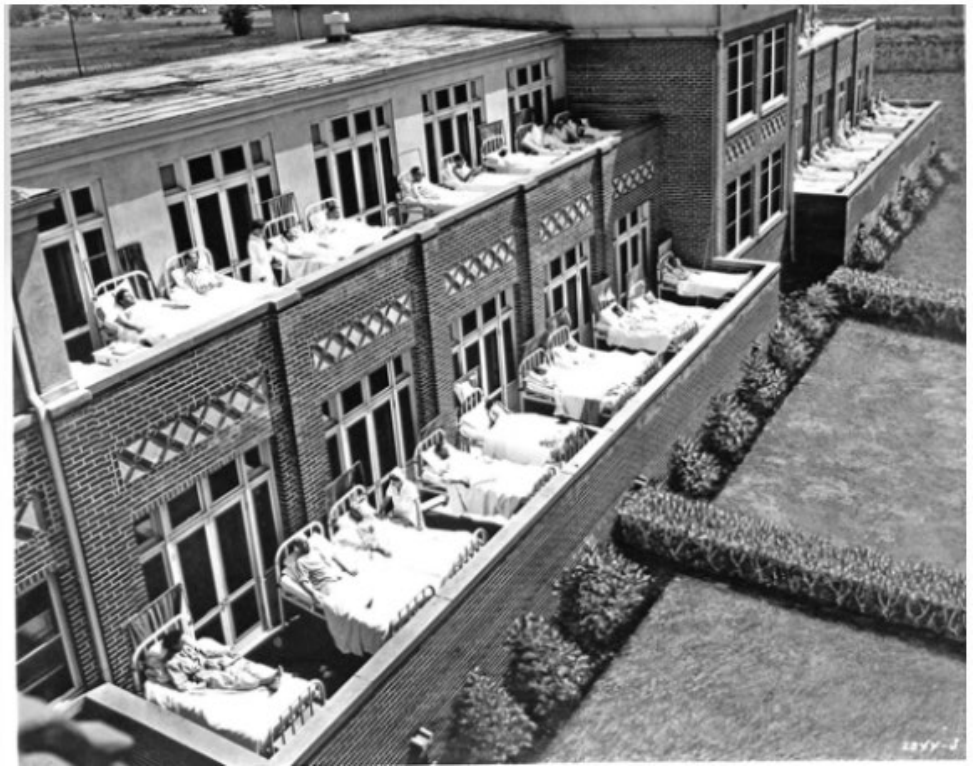
Early National Jewish (continued)



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

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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

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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-aminosalicyclic 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"

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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

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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

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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.

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PAS + SM Decreased Development of Resistance

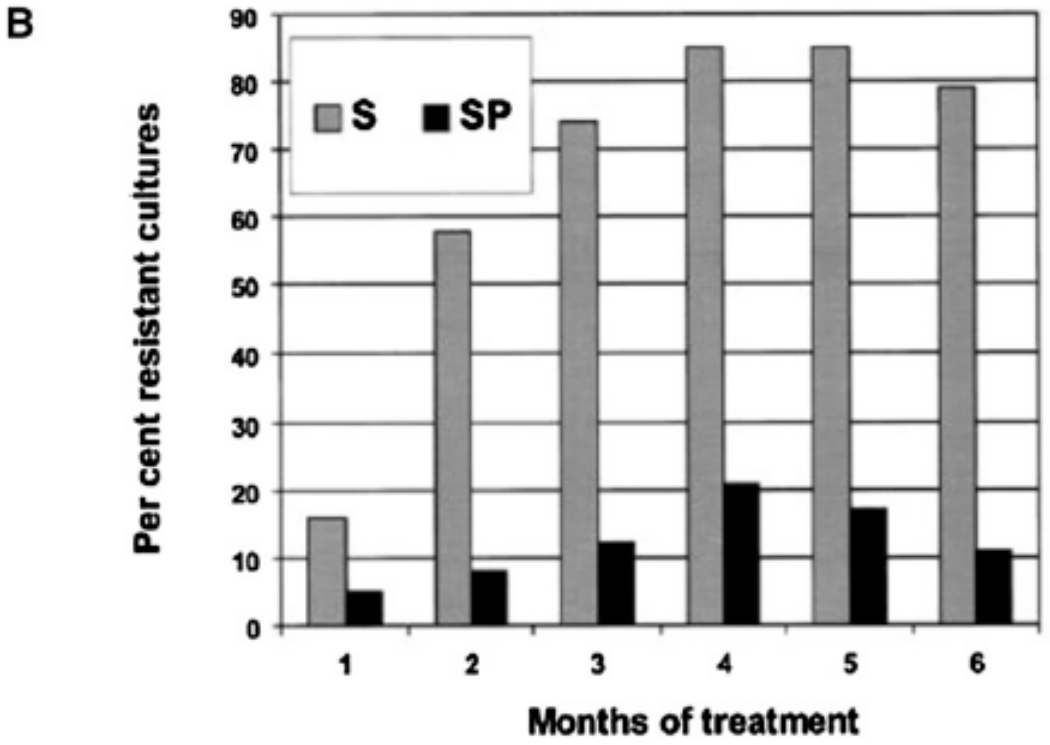

Figure 1. p-aminosalicylic acid (PAS) given with streptomycin (SM) reduces the emergence of SM resistance. The percentage of strains that is SM resistant in the SM series (indicated by S) and the SM plus PAS series (indicated by SP) during 6 months of treatment. Data from Reference 16.

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

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Selective Primary Care

The NEW ENGLAND JOURNAL of MEDICINE

200 NEJM ANNIVERSARY ARTICLE

Tuberculosis, Drug Resistance, and the History of Modern Medicine

Salmaan Keshavjee, M.D., Ph.D., and Paul E. Farmer, M.D., Ph.D.

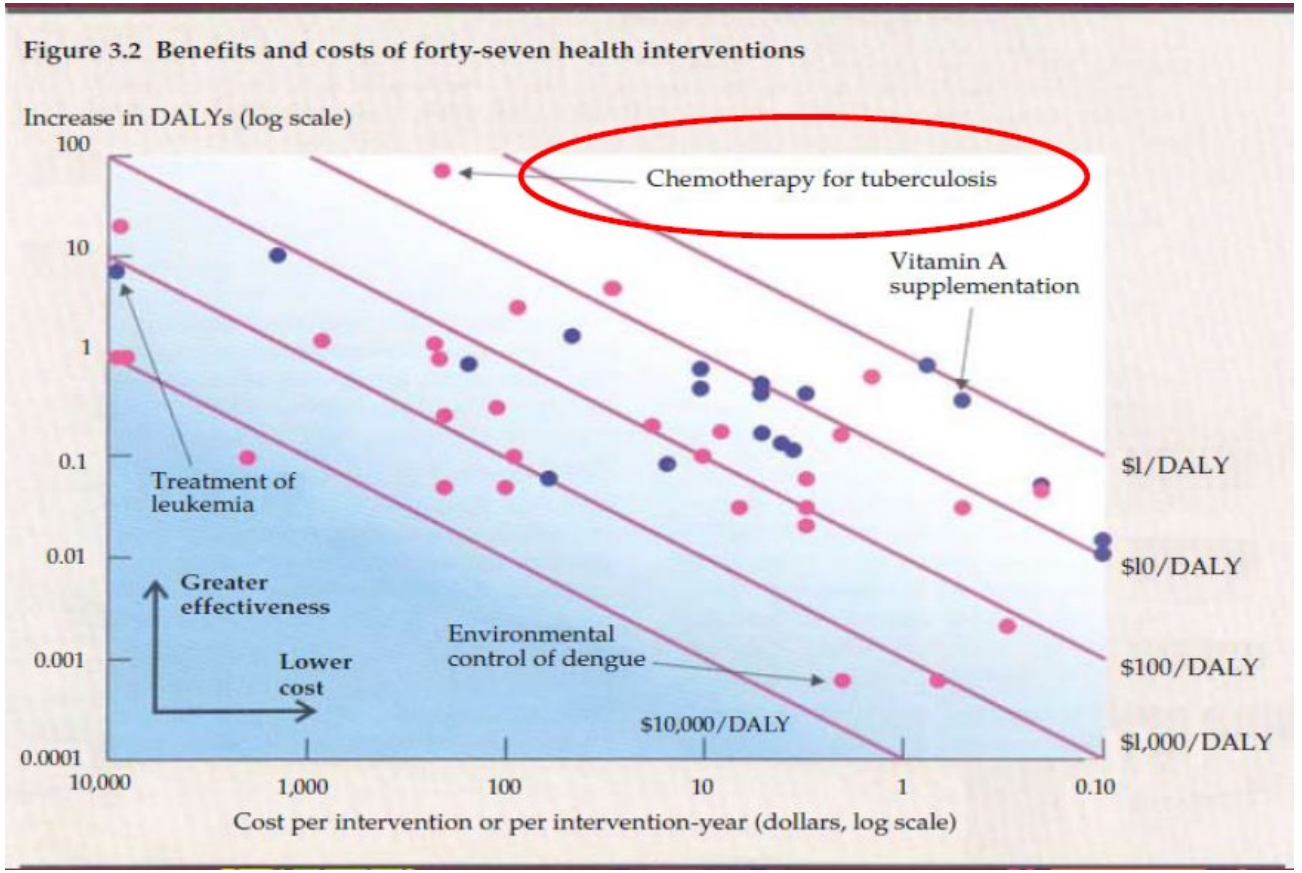
- "Health for all" 1978 Alma-Ata
- However, by 1980s: funding withers, low-income countries are reliant upon loans from the World Bank and similar institutions
- ***Selective primary care*** with clear targets, measurable outcomes, high return on investments
- TB too complex and costly to address in resource-poor countries?

Standardization but also Divergence in TB Care

Disability-adjusted life years (DALYs)
TB treatment as cost-effective

Directly-Observed Therapy, Short Course (DOTS):

- Diagnosis by smear microscopy only (no culture)
- First-line drugs only
- No infection control



World Development Report 1993

Cost-effective care

“Calculating cost effectiveness has the appearance of rationality and objectivity, but it can be, and has been, transformed into a rigid adherence to the single, cheapest solution at the expense of more nuanced and effective ones.”

- Christian McMillen 2015

- Other examples:
  - Isoniazid preventive therapy
  - Dosing of rifampin (600mg)

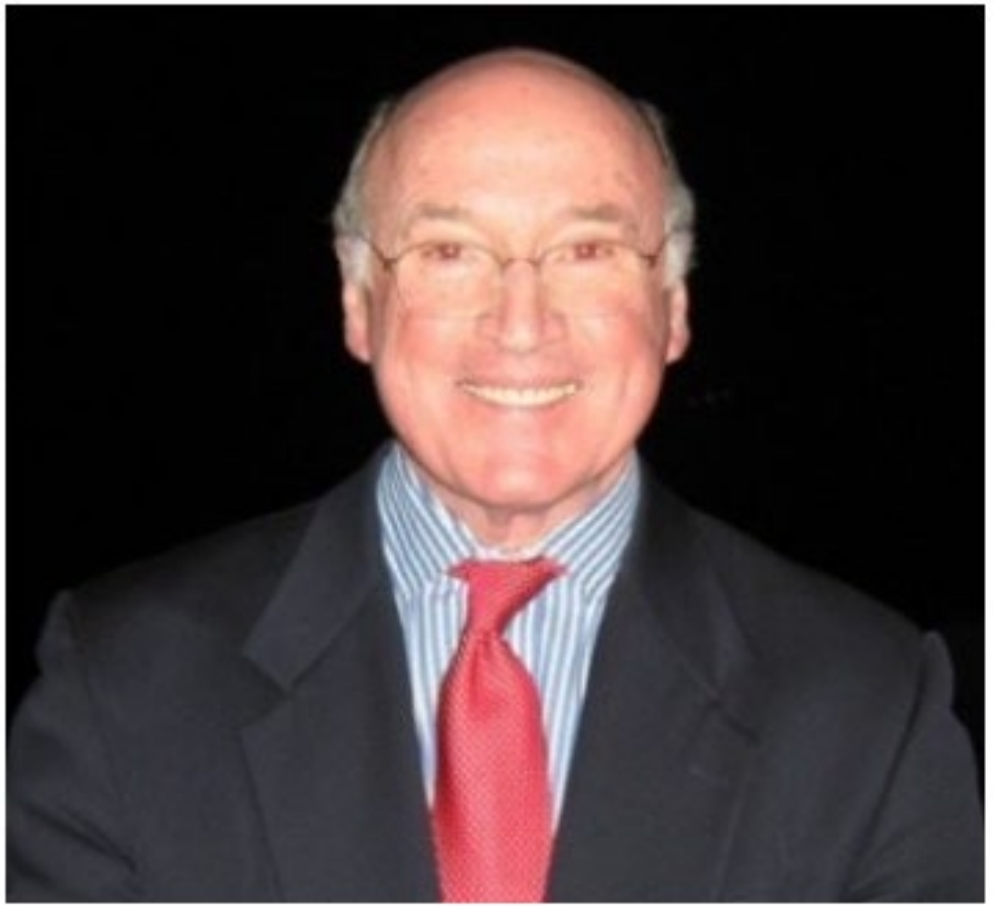
Divergence: Multidrug-resistant (MDR) TB

> ***"MDR-TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease"***
>
> - World Health Organization, Groups At Risk, 1996

- Peru 1995 shanty-town MDR outbreak
  - Low-cost standardized regimen advised
  - Hundreds of deaths, documented amplification of drug resistance
- New York 1980s-1990s
  - Mycobacterial culture
  - Fast track drug susceptibility testing
  - Second-line drugs
  - Infection control

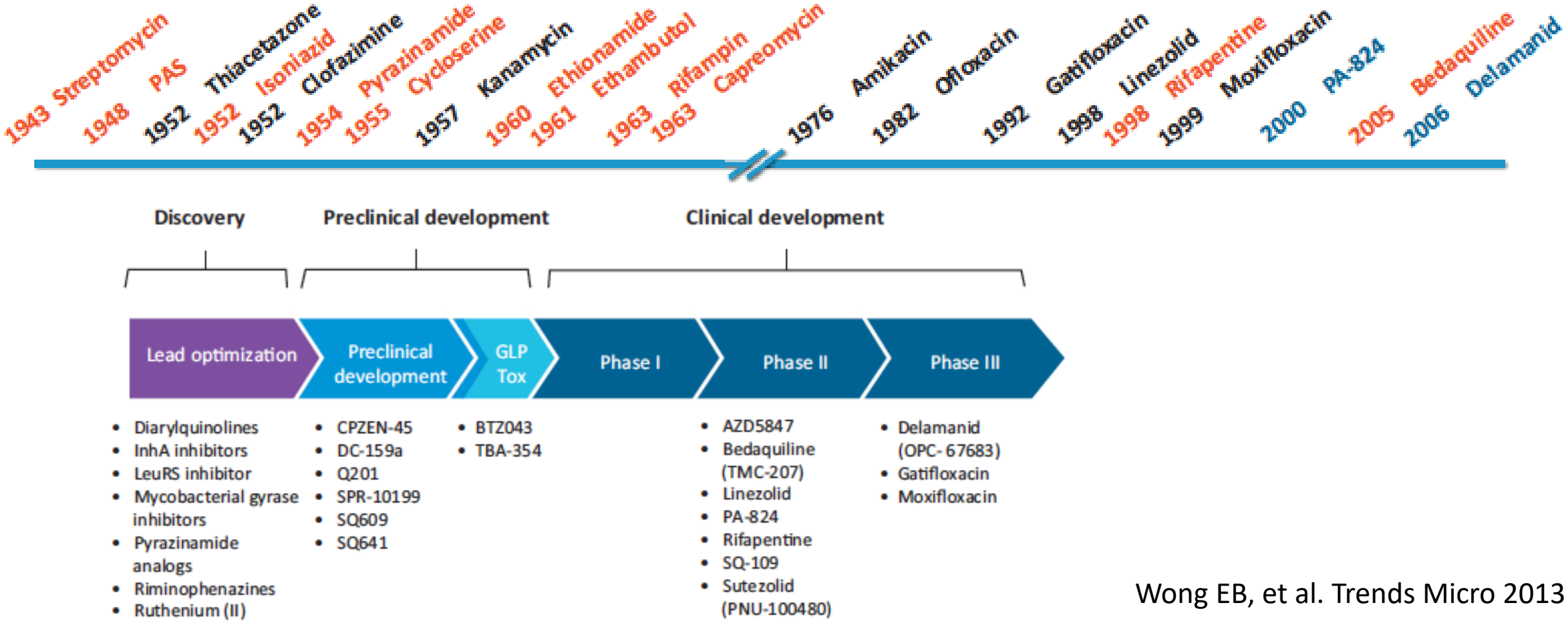
Michael Dee Iseman (1939-2022)

- Professor, NJH
- Former director of the Denver TB Course



National Jewish Health®

Chronology of TB Drug Discovery



Wong EB, et al. Trends Micro 2013

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2024 Global New TB Drug Pipeline[1]

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

Lead Optimization	Early Stage Development	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
Indazole sulfonamides	TBD10 (MK-3854)	OTB-658	TBD09 (MK-7762)	Delpazolid		
Diarylthiazoles	FIM-3002*		TBI-223	Sutezolid, Tedizolid		
DprE1 Inhibitors	CMZ523*		TBAJ-587	TBAJ-876	Sudapyridine (WX-081)	Bedaquiline*
Direct InhA Inhibitors	MPL-447*	TBD11 (CLB-073)*	GSK-286*	Sanfetrinem		
Mtb energy metabolism	JSF-3285*		Macozinone* (PBTZ-169)	BTZ-043*		Delamanid*
Gyrase Inhibitors	CPZEN-45*			TBA-7371*		Pretomanid*
Arylsulfonamides	NTB-3119*			Quabodepistat (OPC-167832*)		
Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP	MBX-4888A (1810)*	GSK-839*		Alpibectir (BVL-GSK098)*		
Oxazolidinones	FNDR-20364*			Ganfeborole (GSK-656*)		
DnaE1 / Nargenicin analogs				Telacebec* (Q203)		
				Pyrifazimine (TBI-166)		
				SQ-109*		

Underline = updates since November 2024

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

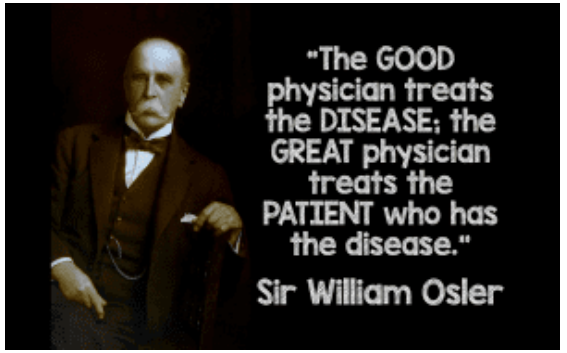
Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2024

“Tuberculosis is a social disease with a medical aspect” – Sir William Osler



Dr Tedros Adhanom Ghebreyesus
Director-General
World Health Organization

WHO Global Tuberculosis Report, 2021

> *Ending this debilitating disease remains a priority for WHO, and in recent years, we have made encouraging progress globally. But the COVID-19 pandemic has put these gains at risk. Not only does the virus pose an increased risk to people with TB, it has also caused severe disruption to services.*
>
> *I want to remind you that the struggle to end TB is not just a struggle against a single disease. It's also the struggle to end poverty, inequity, unsafe housing, discrimination and stigma, and to extend social protection and universal health coverage. If the pandemic has taught us anything, it's that health is a human right, not a luxury for those who can afford it.*
>
> *With solidarity, determination and the equitable use of tools, we will defeat COVID-19. And with the same solidarity, determination and equitable use of tools, we can end TB.*

A Sobering Assessment

"We have had effective treatments for TB for more than a half a century, and yet TB kills more people now than it ever has in the history of [the] world."

"***TB is not newly out of control; it's never been under control***."

S. Lyle Cummins, 1939: "No disease is more likely to escape public notice than pulmonary tuberculosis, because no disease is more insidious or better able to conceal itself behind an appearance of relatively good health."

- Does not elicit the same responses as other pandemics

McMillen 2015