A Brief History of TB

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Disclosures

• Research grant
  – Insmed: Phase II multicenter randomized placebo controlled clinical trial of inhaled liposomal amikacin in pulmonary NTM infections

• Advisory Board:
  – Insmed
  – Johnson and Johnson
  – Spero Pharmaceuticals
  – Horizon Pharmaceuticals
  – Paratek

• Data Monitoring Committee
  – Otsuka
History of *Mycobacterium tuberculosis*

- The tubercle bacillus, or its prototype, has been present on Earth for ~ 300,000 years (ribosomal analysis)
- *M. tuberculosis* DNA was found in the bones of a Great Plains Bison in Wyoming ~ 20,000 years ago
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• TB seen in the bones of Egyptian mummies, Andean cave remains and Chinese burial grounds ~ 3,000 B.C.

• The Greeks described “Phthisis” (wasting) as an illness 600-700 B.C. (Hippocrates vs Aristotle)
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- Although TB was endemic during “The Dark Ages” (the fall of the Roman Empire to the “Barbarians”) (5th-15th centuries), little information is available about the disease.

- The “Renaissance” (14th-17th centuries), inspired in part by the rediscovery of the Greeks via Islamic scholars in Spain, was marked by the resumption of inquiry and logic.
Question 1

Who was the first scientist to demonstrate transmission of the causative agent of TB?

A. Robert Koch  
B. Rene Laennec  
C. Jean Antoine Villemin  
D. Benjamin Martin
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
Rene Theophile Hyancithe 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
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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Unraveling the Mystery of Phthisis:

• The tools - van Leeuwenhoek and the microscope (1674’s), Pasteur, Lister and culture (1850’s), Erhlich and staining (1860’s)
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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)
The Sanatorium Movement
Hermann Brehmer (1826-1889)

• Hermann Brehmer 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
The Sanatorium Movement
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.
The Sanatorium Movement

- 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

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

Oleothorax  Lucite balls

Sputum negative in 30-60%
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%
Question 2

What was the first drug given to a patient to treat tuberculosis?
A. Streptomycin
B. Para-aminosalicylate acid
C. Isoniazid
D. Penicillin
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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-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"
Selman Waksman (1888-1973)

- Streptomycin was discovered by Selman Waksman, Schatz and Bugie at Rutgers and reported in 1944.

- Isolated from *Streptomyces griseus* isolated from soil
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.
### British Medical Research Council

#### Streptomycin Trial

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Deaths</th>
<th>X-ray Improvement (%)</th>
<th>Culture Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM</td>
<td>54</td>
<td>4</td>
<td>69</td>
<td>3 mo: 10*, 6 mo: 8</td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>14</td>
<td>33</td>
<td>3 mo: 1, 6 mo: 2</td>
</tr>
</tbody>
</table>

*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).
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.

Chronology of TB Drug Discovery