Tuberculosis – Past

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no financial disclosures
Tuberculosis – past 20% of all deaths in Western world between 17th and 19th centuries
Every second, someone is newly infected
Every twenty seconds, there is one death
Disease of poverty – low and middle income countries

Tuberculosis
‘the white plague’ – wasting
Obligate human pathogen – no reservoir but man
Hallmark of disease: tubercles
Natural state is one of resistance
‘they shall lay hands on the sick, and they shall recover’ Mark 16:18

Tuberculosis

the ‘royal touch’ for ‘the King’s evil’

scrofula

Mary I of England

Clovis I
1819 René Laennec – “De l’auscultation médiate”
pathology of tuberculosis – autopsies Hôpital Necker, Paris
physical signs of pulmonary disease

1865 Jean Antoine Villemin – Etudes sur la Tuberculosis
infectious nature of tuberculosis (inoculated rabbits)

1882 Robert Koch – Die Aetiologie der Tuberculose
demonstrated tubercle bacillus

1890 Robert Koch – Heilmittel gegen der Tuberculose
tuberculin as treatment, but quickly discredited

1907 Clemens von Pirquet (1908 Charles Mantoux)
tuberculin as diagnostic: latent tuberculosis discovered

Tuberculosis - past

hereditary disease
bacterial etiology
infectious disease – circumstances
1819 René Laennec – “De l’auscultation médiate”
pathology of tuberculosis – autopsies Hôpital Necker, Paris
physical signs of pulmonary disease

1865 Jean-Antoine Villemin – “Etudes sur la Tuberculose”
infectious nature of tuberculosis (inoculated rabbits and cows)
1819 René Laennec – “De l’auscultation médiate”
pathology of tuberculosis – autopsies Hôpital Necker, Paris
physical signs of pulmonary disease

1865 Jean-Antoine Villemin – “Etudes sur la Tuberculose”
infectious nature of tuberculosis (inoculated rabbits)

1882 Robert Koch – “Die Aetiologie der Tuberculose”
in vitro growth of tubercle bacillus
posited Henle-Koch postulates

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tuberculin as diagnostic: latent tuberculosis discovered

Tuberculosis

- past

hereditary disease
bacterial etiology
infectious disease – circumstances
1882 – etiology of tuberculosis
   Henle-Koch postulates
1890 – tuberculin treatment
<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Cured</th>
<th>Improved</th>
<th>No Improvement</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung TB</td>
<td>1%</td>
<td>34%</td>
<td>55%</td>
<td>4%</td>
</tr>
<tr>
<td>Joint-Bone TB</td>
<td>2%</td>
<td>54%</td>
<td>42%</td>
<td>1%</td>
</tr>
</tbody>
</table>

1,061 patients - Lung TB
708 patients - Joint-Bone TB

Robert Koch's Mitteilungen über ein Heilmittel gegen Tuberculose.
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latent tuberculosis discovered
Tuberculosis - past

- hereditary disease
- bacterial etiology
- infectious disease – circumstances
Mycobacterium tuberculosis out of the soil - not a zoonotic disease
Mycobacterium tuberculosis out of Africa origin, migration, expansion

186+34+39 isolates whole genome sequencing 34,167 polymorphic sites (SNP) 4,955 mitochondrial genomes

Population structure is clonal originated in Africa infected humans for at least 70,000 yrs evolved in parallel with human host
Neolithic Demographic Transition: population density facilitates transmission

Mycobacterium tuberculosis out of Africa origin, migration, expansion

Comas et al, Nature Genetics 2013
Mycobacterium tuberculosis
Beijing lineage
origin, migration, expansion

6 major CCs and basal lineage originated in East Asia/Far East infected humans for at least ~6,000 yrs expanded in parallel with human host

Merker et al, Nature Genetics 2015

110 out of 4,987 isolates
24 tandem repeats (VNTR)
whole genome sequencing
6001 polymorphic sites (SNP)

CC = clonal complex
6 major CCs and basal lineage originated in East Asia/Far East infected humans for at least ~6,000 years expanded in parallel with human host

Merker et al, Nature Genetics 2015

Molecular clock set at $1 \times 10^{-7}$ mutations per nucleotide per year

110 out of 4,987 isolates 24 tandem repeats (VNTR) whole genome sequencing 6001 polymorphic sites (SNP)

Mycobacterium tuberculosis Beijing lineage origin, migration, expansion
a crowd disease: high population density maximizes transmission

Mycobacterium tuberculosis
origin, migration, expansion
a chronic disease: latency and reactivation allow repletion of susceptibles individuals

Mycobacterium tuberculosis
origin, migration, expansion
Mycobacterium tuberculosis human T cell epitopes are hyperconserved

Comas et al, Nature Genetics 2010

21 representative diverse Tb isolates comparative analysis sequences of essential, non-essential and 491 T cell epitope genes

little genetic variability of genes that interact with T cells, a strong purifying selection on T cell epitopes?

no diversifying selection to evade host immunity

M. tub benefits from T cell recognition – transmission?
Mycobacterium tuberculosis
immune evasion, latency, reactivation

Kaufmann, FEMS Microbiol Rev 2013

a strong purifying selection on T cell epitopes?
no diversifying selection to evade host immunity
24-y-old man

1998  Inflammatory bowel disease, multiple regimens of immunosuppressive drugs

2005\textsuperscript{4} Start prednison + infliximab (TNF-alfa blocking agent)

2005\textsuperscript{7} Car sharing to work: driver with sputum smear positive lung tuberculosis

develops fever, cough, weight loss

ESR 14 $\rightarrow$ 114

chest X-ray ‘completely normal’
Mycobacterium tuberculosis
immune evasion, latency, reactivation

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chest X-ray ‘completely normal’
Mantoux skin test negative
BAL: ZN, auramine and PCR negative
Starts on quadruple therapy (HRZE)
Mycobacterium tuberculosis
immune evasion, latency, reactivation

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chest X-ray ‘completely normal’
Mantoux skin test negative
BAL: ZN, auramine and PCR negative

Starts on quadruple therapy (HRZE)
Culture (at 3 wks): \textit{M. tuberculosis}

Symptoms worsen, mediastinal lymphadenopathy
Mycobacterium tuberculosis
immune evasion, latency, reactivation

immune reconstitution inflammatory syndrome
Tuberculosis - past

1857: first sanatorium, 1897: first dispensary, Scotland (UK)
1907: pneumothorax
1882: Koch's discovery of the bacillus
1945–1962: drugs

Sanatoria

BCG vaccination
1950–1980: radiological screening
1968: ambulatory treatment
1978: Styblo model
1991: DOTS
2002: outbreak management, risk-group management
2006: XDR-TB

General screening
Drug therapy

Socioeconomic improvement

hereditary disease
bacterial etiology
infectious disease – circumstances
Tuberculosis - past treatments

1860s sanatorium
1890s pneumothorax
1950s thoracoplasty
The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor G. C. Cameron, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tyler, Professor G. S. Wilson, and Dr. P. D’Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

- **Brompton Hospital, London.**—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital).

- **Colindale Hospital (L.C.C.), London.**—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

- **Harefield Hospital (M.C.C.), Harefield, Middlesex.**—Clinician: Dr. M. B. O’Shea; Pathologist: Dr. G. M. D. Macleod; Radiologist: Dr. J. H. A. H. Ryan.

- **Bangour Hospital, Bangour, West Lothian.**—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

- **Killingbeck Hospital and Sanatorium, Leeds.**—Clinicians: Dr. W. M. Gilmour, Dr. A. M. Rees; Pathologist: Professor J. W. McLeod.

- **Northern Hospital (L.C.C.), Winchmore Hill, London.**—Clinicians: Dr. P. A. Nash, Dr. R. Shoulman; Radiologist: Dr. J. M. Alston, Dr. A. Mohun.

- **Selly Hospital, Selly, Glam.**—Clinicians: Dr. D. M. E.

### Condition on Admission

Each patient was under observation at a centre for at least one week before streptomycin treatment or observation proper for the trial started. Data in Table I reflect the condition on admission.

<table>
<thead>
<tr>
<th>Condition on Admission</th>
<th>Group</th>
<th>Group</th>
<th>Max. Evening Temperature First Week*</th>
<th>Group</th>
<th>Group</th>
<th>Sedimentation Rate</th>
<th>Group</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>8</td>
<td>8</td>
<td>98.5-98.9°F (36.9-37.7°C)</td>
<td>3</td>
<td>4</td>
<td>0-10</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fair</td>
<td>17</td>
<td>20</td>
<td>99.0-99.4°F (37.2-37.5°C)</td>
<td>13</td>
<td>12</td>
<td>11-20</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Poor</td>
<td>30</td>
<td>24</td>
<td>100.0°F (38.0°C)</td>
<td>15</td>
<td>17</td>
<td>21-30</td>
<td>16</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>52</td>
<td>55</td>
<td>52</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

* Temperature by mouth in all but six cases. **Examination not done in one case.

### Radiological Assessment

<table>
<thead>
<tr>
<th>Radiological Assessment</th>
<th>Streptomycin Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerable improvement</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Moderate or slight improvement</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>No material change</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moderate or slight deterioration</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Considerable deterioration</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Deaths</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>52</td>
</tr>
</tbody>
</table>

The overall results given in Table II (extracted from Table IX) show differences between the two series that leave no room for doubt. The most outstanding difference

### Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make

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#PPFE"
• originated in Africa
• infected humans for at least 70,000 years
• evolved and migrated in parallel with human host
• natural state is one of resistance
• impact on concept of ‘specificity of disease’
• Henle-Koch postulates on etiology of infectious disease
• the white plague – until nineteenth century responsible for 20% †
• social and economic factors, public health and curative medicine

• bacterial population structure is clonal
• strong purifying selection on T cell epitopes implying M. tub benefits from immune recognition?
pre-Columbian M. tuberculosis cluster with animal lineage sharing 76 SNPs with M. pinnipedii zoonotic transfer from seals?

Mycobacterium tuberculosis pre-Columbian skeletons zoonotic origin?

Bos et al, Nature 2014

3 of 68 skeletal samples ~1028 – 1280 AD predate European contact signs of bone tuberculosis phylogenetic assessment