Tuberculosis

TB is an ancient disease

- The human TB appears to be significantly older than 10,000 years: a recent study from Turkey reported a 500,000-year-old fossil of *Homo erectus*, which shows lesions characteristic of TB.
  

- *Homo erectus*, Natural History Museum, Ann Arbor, Michigan

Tuberculosis

- Greeks named the disease *phthisis* because of its characteristic wasting

  (Latin, from Greek, from *phtinein* - to waste away)

18th Century Hungarian Mummies

- Over 200 mummies were found in a closed-off area of the Dominican church.
- Buried between 1731 and 1838 in the crypt church in the northern Hungarian town of Vac, the naturally-preserved mummies were forgotten for decades and discovered in 1994 during the church's renovation.
- The mummification process happened thanks to the favorable microclimate inside the crypt

89% of the mummies, ranging in age from newborns to over 65, had been infected with tuberculosis and around 35 percent were suffering from the disease at the time of death. The strains of tuberculosis found in the people buried in Vac offer a unique chance to study the pathogens from a time before the development of antibiotics.

Tuberculosis (TB) today

- TB remains a major global health problem.
- Ten million new TB cases and 3 million deaths are estimated to occur each year, more than any time in history.
- Almost 2 billion people are thought to be latently infected, providing a large reservoir for active TB that will last for decades.

WHO 2010 Global tuberculosis control—surveillance, planning, financing. Geneva, Switzerland
MTBC

- TB is caused by a group of phylogenetically closely related bacteria, collectively known as the Mycobacterium tuberculosis complex (MTBC)
- TB in humans is primarily caused by *M. tuberculosis* and *Mycobacterium africanum*, a phylogenetic variant of MTBC limited to West Africa

Sebastien Gagneux, Phil. Trans. R. Soc. B 2012 367

Robert Koch

- Discoverer of *Mycobacterium tuberculosis*
- 1882

Mycobacterium tuberculosis

- Difficult to stain (concentrated carbol fuchsin in the Ziehl–Neelsen stain)
- Difficult to kill (can survive within the host’s phagocytes)
- Difficult to identify in tissue section (failure to demonstrate does not exclude a diagnosis)
**Resistance of Mycobacterium**

- Mycobacterium are killed at 60°C in 15 – 20 min
- In sputum they survive for 10 – 30 min
- Relatively resistant to several chemicals including Phenol 5%
- Sensitive to Glutaraldehyde and Formaldehyde
- Ethanol is suitable application to superficial surfaces and skin gloves

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**Route of infection**

Pulmonary tbc – a result of bacilli inhalation

Untreated active cases
- Sputum droplets
- Dust

Intestinal tbc – milk infected with M. bovis

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**Epidemiology of tuberculosis**

**Europe**

- In 2010, 73,996 TB cases were reported by the 27 EU Member States, Iceland and Norway.
- The overall notification rate in 2010 was 14.6 per 100,000 population, with a mean annual decline in the case notification rate of 4.4% during the period 2006 to 2010.

**Epidemiology of tuberculosis**

- For the first time, all EU Member States had notification rates below 100 per 100,000 population and one additional country, Poland, joined the 22 countries already in the elimination phase defined as below 20 cases per 100,000

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**Epidemiology of tuberculosis**

- In most developed countries – considerable fall in the incidence and mortality over last 100 years
  - but in 1990
  - almost 1/3 of the world’s population were infected with *Mycobacterium tuberculosis* with 8 millions new cases
WHO Global Tuberculosis report 2017

- In 2016, 6.3 million new cases of TB were reported (up from 6.1 million in 2015)
- In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 576,000 deaths among HIV-positive people.
- An estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries: India, Indonesia, China, the Philippines and Pakistan

- In 2017, WHO has developed a TB-SDG monitoring framework of 14 indicators that are associated with TB incidence.
  - Coverage of essential health services;
  - Percentage of total health expenditures that are out-of-pocket;
  - Health expenditure per capita;
  - HIV prevalence;
  - Prevalence of smoking;
  - Prevalence of diabetes;
  - Prevalence of alcohol use disorders

HIV & tbc

- Worldwide over 6 millions people are dually infected (Africa)
- Particularly aggressive form with widespread dissemination and poor host response

Risk factors

- Elderly
- Infants
- Low socioeconomic status
- Crowded living conditions
- Weak immune system
- Alcoholism, malnutrition
- Recent tbc infection within 2 years
- Diabetes, Hodgkin, silicosis, renal failure

Epidemiology

- MTBC can infect virtually any organ. However, from a public health point of view, classical pulmonary TB is the most important form of the disease because of its infectious nature.
- Lung cavities tend to harbour large numbers of bacteria, which is why cavitary TB tends to be the most infectious form of the disease.

TB – lung cavities
• Infection: seeding of a focus with organisms, which may or may not cause clinically significant tissue damage – disease

• There is no diagnostic test that resolves the various stages within the spectrum of Mycobacterium tuberculosis infection.

• The Mantoux tuberculin skin test (TST) is the standard method of determining whether a person is infected with *Mycobacterium tuberculosis*

• (IGRAs) are diagnostic tools for latent tuberculosis infection (LTBI); cannot distinguish between latent infection and active tuberculosis

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**Tuberculin skin testing**

• The Mantoux tuberculin skin test (TST) is the standard method of determining whether a person is infected with *Mycobacterium tuberculosis*.

• The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm.

• The TST is an intracutaneous injection.

• The skin test reaction (palpable induration, not redness) should be read between 48 and 72 hours after administration.

• It does not differentiate between infection and disease!

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**Interferon-Gamma Release Assays (IGRAs)**

• IGRAs are ex vivo blood tests of T-cell immune response; they measure T-cell release of interferon-gamma (IFN-gamma), following stimulation by antigens specific to the *M. tuberculosis* complex.

• (IGRAs) are diagnostic tools for latent tuberculosis infection (LTBI), cannot distinguish between latent infection and active tuberculosis (TB) disease and should not be used for diagnosis of active TB, which is a microbiological diagnosis.

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**Primary tbc – Ghon focus**

<table>
<thead>
<tr>
<th>Patients infected for the first time</th>
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<tbody>
<tr>
<td><strong>weeks</strong></td>
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<tr>
<td>0-3</td>
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<td></td>
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<tr>
<td>&gt;3</td>
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</table>
Tuberculous granuloma

<table>
<thead>
<tr>
<th>weeks</th>
<th>Morphological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3</td>
<td>• Granuloma is visible to naked eye (&lt;2cm)</td>
</tr>
<tr>
<td></td>
<td>• Granuloma undergoes central caseous necrosis</td>
</tr>
<tr>
<td></td>
<td>• Development of satellite tubercles that fuse together, so</td>
</tr>
<tr>
<td></td>
<td>• Granuloma increases in size</td>
</tr>
</tbody>
</table>

Pathogenesis

- Mycobacterial antigens are presented to CD4 T cells, they secrete IFN-gamma monocytes became activated and differentiate into the “epithelioid histiocytes”
- Activated macrophages in turn secrete TNF and chemokines (recruitment of more monocytes)

Granuloma

Pathologic features of TBC

- Caseating granulomas and cavitation are the result of the destructive tissue hypersensitivity that is part of the host immune response

Primary tbc

Peripheral primary Ghon focus

+ caseation in the regional lymph node

= primary Ghon complex

With radiologically detectable calcification - Ranke complex
Reparative changes of the primary complex
- Development of a fibrous capsule
- Deposition of calcium salts (dystrophic calcification)
- Calcified foci and lymph nodes may undergo resorption

The major consequences of primary TBC
- Induced hypersensitivity and increased resistance
- The foci of scarring may harbor viable bacilli for years (possible reactivation when host defences are compromised)
- Uncommonly, it may lead to progressive primary tuberculosis

Progressive changes of the primary complex
- Caseation of the central area with the peripheral extension of granulation tissue
- If the lesion erodes into a bronchus
  - Cavity
  - Dispersion to the other parts of the lung
  - Bacilli, being swallowed, infect the intestine
- If the lesion erodes the pleura
  - Pleural effusion
  - Secondary pyogenic infection

Chronic tuberculous cavity

Fibrinopurulent pleuritis
- Lung is covered by thick layer of pus and fibrin (pleural effusion due to secondary pyogenic infection)

Miliary tuberculosis
Massive haematogenous dissemination with involvement of liver, spleen, bone marrow and CNS (tuberculous meningitis)
Miliary pulmonary tuberculosis

- Small yellowish lesions visible in subpleural location

Secondary tbc

- Reactivation of dormant primary lesion or
- Exogenous, fresh infection
- Bloodborne dissemination
- Near the apex of the upper lobes (commonly with cavitation that occurs readily)

Secondary tbc

- Exudate
- Cavity
- Calcification
- Scarring
- Caseation
- Necrosis
- Tuberculosis

Tuberculoma

A well defined, rounded mass made up of caseous material surrounded by a capsule
- Stratified tuberculoma (stratified gross appearance as a result of waves of infection and granulomatous reaction)
- Homogenous tuberculoma (arrested tuberculosis following incomplete therapy)
- Conglomerate type tuberculoma (confluent miliary or nodular foci in the absence of cavitation)
- Pseudotuberculoma (a cavity that has been filled with caseous material)

Tuberculoma in section

Progressive postprimary tbc

- Liquefaction of the content of a cavity
- Bacilli became dispersed (gravity, coughing)
- Diffuse areas of caseous pneumonia
- Rapid confluent tuberculous pneumonia
TBC complications

- **Rasmussen’s aneurysm** is a pulmonary artery aneurysm adjacent or within a tuberculous cavity. It occurs in up to 5% of patients.
  - Caseation advances very quickly
  - → destruction of the muscular and elastic coats of an artery
  - → formation of an aneurysm
  - → rupture and fatal haemorrhage

- Obliterative endarteritis and closure of the lumen of the vessel

TBC complications

- Secondary infection of the cavity
  - bacterial – purulent, lung abscess
  - fungal colonization

- Epithelial lining – squamous metaplasia – carcinoma

- Fibrosis of the lung and pleura

Extrapulmonary complications

- Infection and injury (ulceration) to the vocal cords – hoarseness, cough
- Deep ulcers on the margin of the tongue
- Chronic ulcers of the ileum
- Amyloidosis

Extrapulmonary TBC

- [Pulmonary TB (85% of all TB cases)]
- Intestinal TBC (primary, secondary)
- Meninges (tuberculous meningitis)
- Kidneys (renal tbc)
- Adrenals (Addison disease)
- Fallopian tube (salpingitis)
- Bones (Vertebrae – Pott’s disease)

Pott’s disease – tuberculous spondylitis

*(The Hunchback of Notre Dame)*

- Occurs via hematogenous spread
- Lumbar and lower thoracic involvement
- Kyphosis develops from collapse of anterior spine (mainly amongst thoracic vertebrae)
**Tbc in the elderly**

- Activation of old tuberculous foci
- Pancytopenia and leukemoid reaction
- Non-reactive tbc

**Non-reactive tbc**

Elderly, immunodeficiency

- Lacking of the giant cell granuloma (only necrosis)
- Diffuse alveolar damage (ARDS) – oedema, collapse, hyaline membranes

Tissues in this form of tbc are highly infective!!!

**Treatment**

- Left untreated TB kills 50% of patients, with HIV coinfected patients facing an even higher risk of death

**Vaccine**

- The only available vaccine against TB is ‘bacille Calmette Gue’rin’ (BCG), an attenuated form of Mycobacterium bovis, which is a pathogen of cattle
- However, BCG only protects young children against TB meningitis, the most severe form of the disease.
- Why BCG does not protect adults reliably against the classical pulmonary form of TB is unknown

**TB treatment**

- The standard short-course anti-TB regimen of isoniazid, rifampicin, pyrazinamide and ethambutol has been proven to be effective.
- Aside from symptomatic and radiographic improvements, the disappearance of acid-fast bacilli (AFB) from sputum smears and the conversion of culture results for *Mycobacterium tuberculosis* (MTB) are used to assess therapeutic response.
- By five months of the standard anti-TB therapy, most patients will have bacteriologic conversion.

Chien JY: *Chest.* 2013 Jan 3.

**Tuberculosis -treatment**

- The introduction of chemotherapy against TB, which started in the 1940s, has led to increasing levels of drug resistance.
- The global emergence of multi-drug resistance has initiated the post-antibiotic era, making TB essentially incurable in many parts of the world

• 2016 Jan;96:96-101. : Novel mutations conferring resistance to kanamycin in Mycobacterium tuberculosis clinical isolates from Northern India.

• 2016 Jan;96:102-6. Characterization of mutations in streptomycin-resistant Mycobacterium tuberculosis isolates in Sichuan, China

**Multidrug-resistant TB (MDR-TB)**

- Is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs.
- Most people with TB are cured by a strictly followed, 6-month drug regimen that is provided to patients with support and supervision. Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (such as use of single drugs, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings such as prisons and hospitals.

**Drug resistance**

- Resistance to at least the first-line anti-TB drugs isoniazid and rifampicin was reported for (7.8%) new pulmonary TB cases tested for drug susceptibility in the EU

**WHO report**

- In 2015, an estimated 480,000 people worldwide developed MDR-TB, and an additional 100,000 people with rifampicin-resistant TB were also newly eligible for MDR-TB treatment. India, China, and the Russian Federation accounted for 45% of the 580,000 cases.
WHO has devised an ambitious plan to eliminate TB as a global public health problem by 2050