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.


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.

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 \textit{M. tuberculosis} and \textit{Mycobacterium africanum}, a phylogenetic variant of MTBC limited to West Africa

Sebastien Gagneux \textit{Phil. Trans. R. Soc. B} 2012 \textbf{367}

Robert Koch

- Discoverer of \textit{Mycobacterium tuberculosis}
- 1882

Mycobacterium tuberculosis

- Difficult to stain (concentrated carbol fuchs 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

Mycobacterium differ from other routinely isolated Bacteria

- \textit{Slow-growing} with a generation time of 12 to 18 hours (c.f. 20-30 minutes for \textit{Escherichia coli})
- \textit{Hydrophobic} with a high lipid content in the cell wall. Because the cells are hydrophobic and tend to clump together, they are impermeable to the usual stains, e.g. \textit{Gram’s stain}
Route of infection

Pulmonary tbc – a result of bacilli inhalation
  Untreated active cases
    – Sputum droplets
    – Dust

Intestinal tbc – milk infected with M. bovis

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

• Most infections are inquiries by direct person-to-person transmission of airborne droplets of organisms from an active case to a susceptible host. (Robbins)

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

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
Tuberculosis

1993 WHO had declared tuberculosis a global emergency! (multidrug resistant strains)

WHO Global Tuberculosis report 2015

- Globally, TB prevalence in 2015 was 42% lower than in 1990.
- Of the 9.6 million new TB cases in 2014, 58% were in the South-East Asia and Western Pacific regions. The African Region had 28% of the world’s cases in 2014, but the most severe burden relative to population: 281 cases for every 100 000 people, more than double the global average of 133

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.

- 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

• TST involves an intradermal injection of 5 tuberculin units (5-TU) of PPD-S (purified protein derivative) or 2 TU of PPD RT23. A delayed-type hypersensitivity reaction might occur within 48 to 72 hours. This reaction will cause erythema (redness) and induration of the skin at the injection site. Only the transverse induration is measured as shown above.

• 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!

• 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.

• They are considered more specific for M. tuberculosis than PPD because they are not produced by BCG vaccine strains.

Interferon Gamma Release Assay (IGRA) testing

<table>
<thead>
<tr>
<th>weeks</th>
<th>Morphological changes</th>
</tr>
</thead>
</table>
| 0-3   | •Small amount of exudate  
       | •Neutrophils           |
|       | •Macrophages collect and ingest most of the bacilli |
| 0-3   | •Macrophages aggregate and form nodules ("epithelioid")  
       | •Macrophages fuse to form multinucleate cells of Langhans type  
       | •CD4 (helper) (secrating IFN-gamma) and CD8 (cytotoxic) lymphocytes are mixed with macrophages  
       | •A mantle of B lymphocytes |
Tuberculous granuloma

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

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

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
- Caseation
- Calcification
- Scarring

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
  - or
- 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

Aneurysms
TBC complications

- Secondary infection of the cavity
  - bacterial – purulent, lung abscess
  - fungal colonization
- Epithelial lining – squamous metaplasia – carcinoma
- Fibrosis of the lung and pleura

Squamous metaplasia

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 (primay, secondary)
- Meninges (tuberculobus meningitis)
- Kidneys (renal tbc)
- Adrenals (Addison disease)
- Fallopian tube (salpingitis)
- Bones (Vertebrae – Potts 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 Guérin’ (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.


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.