HISTORY OF TUBERCULOSIS

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INTRODUCTION

Outline:
1. Earliest discovery of the evidence of Tuberculosis in animals and humans - by genotype.
2. TB in the Ancient, Medieval and early Renaissance periods.
3. Early treatment and understanding of TB - 17-19th centuries.
5. TB Sanatorium era.
6. TB drugs and medical advances.
7. TB in Wisconsin.
8. Conclusion.
Earliest discovery of the evidence of Tuberculosis in animals and humans - by genotype

Let’s Take a Trip

-To the Big Horn Mountains of Wyoming.

-To the blue seas of the Mediterranean off the coast of Israel.
Natural Trap Cave is located near the Montana and Wyoming border in Bighorn Canyon National Recreation Area.
NATURAL TRAP PIT CAVE – WYOMING

- 80 feet deep with a 15 foot opening

Unique pit cave that:
- is located along ancient migratory route.
- has a climate that preserves fossils and bone.

Archeological site – at bottom
“This study involved the use of molecular DNA techniques to identify the presence of M. tuberculosis complex in Skeletal specimen with lesions suggestive of tuberculosis. From Natural Trap Cave (Wyoming)...results provide the first definitive diagnosis of M. tuberculosis complex in a fossil. They suggest that bovids were the vectors that transported the primordial organism....”

Pleistocene bison of North America -16,000 - 15,000 BC

Rothschild BM et al., (2001) Mycobacterium tuberculosis Complex DNA from an Extinct Bison Dated 17,000 years before the Present. *Clinical Infectious Diseases* vol. 33 page 306
Atlit (pop. 5,797)

Off Israel’s coast 10 miles south of Haifa and 43.7 miles north of Tel Aviv

Close to Mt Carmel
- Originally an outpost of the Crusaders which fell in 1291.

- Modern city founded in 1903.

- Shipwrecks common but divers found archeological site in 1984.

- This site is only 25-39 feet below the surface of the water in the Bay of Atlit.

- Human remains of a woman and child were found (2008).
-stone megaliths of the pre-pottery Neolithic site of Atlit-yam.

date of 6900-6300 BCE.

-Earliest evidence of agro-pastoral marine system on coast.
“...we examined one of the earliest villages with evidence of both animal domestication and agriculture, Atlit-Yam...for the presence of tuberculosis in human remains with characteristic lesions. M. tuberculosis was confirmed in the skeletal remains of a woman and child, using both ancient DNA and bacterial cell-wall specific lipid markers. Detection analysis indicates that the modern M. tuberculosis lineage characterized by the TbD1 deletion existed 9000 years ago.”

"The direct detection of ancient Mycobacterium tuberculosis molecular biomarkers has profoundly changed our understanding of the disease in ancient and historical times. Initially, diagnosis was based on visual changes to skeletal human remains, supplemented by radiological examination. The introduction of bimolecular methods has enabled the specific identification of tuberculosis in human tissues, and has expanded our knowledge of the palaeopathological changes associated with the disease. We now realize that the incidence of past tuberculosis was greater than previously estimated...."

TB in the Ancient, Medieval and early Renaissance periods
"The patient coughs frequently, his sputum is thick and sometimes contains blood. His breathing is like a flute. His skin is cold, but his feet are hot. He sweats greatly and his heart is much disturbed. When the disease is extremely grave, he suffers from diarrhea."

From clay tablet in library of Assyrian King Assurbanipal (668-626 BC)
Hippocrates (c.460-c.370 BCE)

3 kinds of phthisis
- Excess phlegm (lived 1 year)
- Exhaustion (lived 3 years)
- Black and swollen followed by sputum, cough, fever and wasting (lived for many years)

Galen (129-210 CE)

- Hectic fevers could become phthisis
- Bloodletting to cure
- First to see tubercles (phûma)
- Described struma on neck (scrofula)

Isaac Judaus (c.840-932 CE)

- Wrote five books on fevers
- Codified consumption (cool, moist and sooth)
- Not bloodletting

Phthisis (Φθίνω) - Greek word used to describe many conditions including what we would call tuberculosis. It means to waste away, decline, decay, atrophy, or literally wasting of the body.
Ancient treatment for Phthisis – consumption: diet, lifestyle

Diet - to replenish the wasting, to strengthen respiration, heal lungs.

- Pomegranate
- Plantain
- Nuts
- Honey
- Alternative milks like goat milk

Lifestyle - sea voyages often believed to have a healing effect (nausea would purge waste and air was humid and aided expectoration).

Hygiene* - bath with oils

Travel to warmer climate – preferably warmer and drier like Egypt
Ancient treatment for Phthisis – consumption: medicine

myrrh  frankincense  black pepper  acacia  Eucalyptus

Blood-letting

hyssop

Asian medicine – moxibustion use of mugwort burned on skin

opiates
Theory of humors

Body is filled with four humors:
1. Black bile (spleen) = warm and moist.
2. Yellow bile (gal bladder) = warm and dry.
3. Phlegm (lungs) = cold and moist.
4. Blood (liver) = cold and dry.

All are in balance when healthy but any excess or deficit results in illness

Theory dominated Western thinking until the scientific age and displaced by cellular pathology (Rudolf Virchow -1858) and germ theory (Koch 1882).

Remedies for phthisis - type of illness:
Respiratory illness = dry warm foods, dry warm climate
Excess phlegm = purge, expectorate, cough
Fever = bloodletting
Blood-letting throughout the ages

Ancient

Medieval

Renaissance
-12th Century English historian and monk, William of Malmesbury wrote about isolated reports of cures after visiting royal tombs and from the king’s touch.

-English and French kings established and continued the practice (touched thousands each year and passed out a coin – talisman)

-Queen Anne was the last English royal to use the practice (1712) George I put an end to it in 1714. However, it continued in France up to 1825.
Early Treatment and Understanding of TB
Seventeenth-Nineteenth centuries
Anatomists: with new ideas emerging in chemistry, physics and anatomy

Franciscus Sylvius (1614-1672)

Sylvius (Dutch) anatomist, chemist who specified phthisis and a relationship with the lungs and tubercles

Richard Morton (1637-1698)

Morton (English) described a relationship between glands, tubercles and consumption of the lungs
Baillie described lung tubercles (1793) and made a connection between the description and symptoms.

He found scrofulous tubercles more widespread than thought.

Later - Anatomists (1)

Italian Giovanni Battista (John Baptist) Morgagni - the father of modern anatomy:
- Wrote about the causes of disease by anatomy (1761).
- Described tubercles and noted similarity between tubercles and glands.

Matthew Baillie (1761-1823)

JB Morgagni (1722-1809)

Treatment: (humor theory with some added chemistry and physiology including: bloodletting, breathing treatments and fever control.)
Later – Anatomists (2)

-Delineated a spinal pathology as consumptive.
-Hence Pott’s disease.

Percivall Pott (1714-1788)

-Austrian physician who invented percussion as a diagnostic tool.

-later work devoted to consumption.

-wrote on how to detect cavities in the lung by percussion and noted use of hand on chest to detect vibrations and identify a cavity.

-someone followed-up on this idea.

Leopold von Auenbrugg (1722-1809)
René Laennec (1781-1826)

- French physician and scholar
- He unified pathologies of lung and lesions within the body
- Claimed that the tubercle must be present in phthisis
- Died of tuberculosis (age 45)

Laennec appointed to a Royal hospital in Paris where he studied tuberculosis and invented the stethoscope (below)

Method of inspection
- palpation (feeling).
- percussion (tapping).
- auscultation (listening) using rolled up paper and later the wooden tube.

Treatise on Mediate Auscultation (1819)
Eighteenth Century treatment - Consumption

Pills, liquor, draught mixed with herbs:

- pills
- Cinchona (quinine)
- licorice
- goldenrod
- veronica
- hyssop

Rest and good sleep with aids:

- poppy
- opium

Bloodletting
Hydrotherapy

- People living near the sea were less consumptive

- Bath, England (opposite)

Tobias Smollett (1721-1771) doctor and novelist

Visited Bath to recover from TB

Travelled to warmer climate for TB as well
Thomas Beddoes (1760-1808)
Professor at Oxford

Philanthropic Pneumatic Institute

-inhaling gases

Cow houses – lower levels of oxygen Beddoes believed was beneficial to the consumptives

Hotwells water spa – to treat consumption (1799)
Exercise to loosen body fluids and strengthen lungs:

Sea travel for consumption promoted by Scot Ebenezer Gilchrist in 1769

Horse riding was believed to promote some form of respiratory exercise and like sea travel the rolling or rocking promoted strength to chest muscles.
“Do you see how necessary a world of pains and troubles is to school an intelligence and make it soul?” – letter to brother

John Keats (1795-1821) d.25

Uncle and mother died young – probably from TB

Dr. James Clark (1788-1870)

Dr James Clark – physician to young Victoria and prince Albert and the Nightingale family among others.

Practiced in Rome (1819) and later in London (1826).

Clark wrote a treatise on Consumption the cause and treatment of which he believed that it was too late for Keats who had prolonged consumption.

–a morbid condition of the whole system which he called “tubercular cachexy” and means there is too much blood in one place. The opposite is ‘galloping consumption’ which kills quickly.

The treatment was rest, starvation (low food intake), no opiates and bloodletting.
Charlotte (1816-1855) d.38
Emily (1818-1848) d.30
Anne (1820-1849) d.29
Patrick Branwell (1817-1848) d.31

Maria Bronte (1814-1825) died of TB at age 11
Elizabeth Bronte (1815-1825) died of TB at age 10

Six in the Bronte family died of TB; some thought TB hereditary

Clergy Daughter’s School – Cowan Bridge, Lancashire

Three writers in the family:
Charlotte – Jane Eyre
Emily – Wuthering Heights
Anne – The Tenant of Wildfell Hall

Patrick Bronte (1777-1861) d. 84
Maria Branwell (1783-1821) d.38
Elizabeth (aunt)Branwell (1776-1842) d.66

Emily (1818-1848) d.30
Charlotte (1816-1855) d.38
Anne (1820-1849) d.29

Patrick Branwell (1817-1848) d.31
Robert Koch (1843-1910)

First to visualize a mycobacterium was Gerhard Hansen (1873) *Mycobacterium leprae* – couldn’t prove cause

- Used new technology (microscope).
- Invented a method to prove cause (Koch’s postulates).
- Lesion is secondary to infection by a germ.
- Consumption redefined as the presence of a germ.
- ‘On the etiology of tuberculosis’ March 24, 1882.

TB still remained at the top of the mortality tables in the 19th Century.
TB became a public health concern – and social problem

TB charities formed alongside National TB Programs

TB dispensary

How to treat?
TB Prevention

-Vaccine for TB - (BCG) 1921
-tested on cows then own children
-some success (on 116,000 children at l'Hospital de la Charité in Paris, 1928)

Slowly adopted across Europe (Scandinavia, Germany, Japan & Africa)
Still recommended by WHO for childhood vaccination
TB Prevention

Preventorium - to prevent TB in children of TB patients (France)

Jacques-Joseph Grancher (1843-1907)

Preventorium for children in New Jersey

Pioneer of prevention of TB in children
Various chemical or natural agents like copper, coal and gold (1925-1940).

- Turpentine
- Arsenic
- Coal-tar
- Creosote
- Iodine
- Seaweed
- Cod liver oil
- Calcium
- Mercury
- Tannin (wine)
TB Treatment (2)

Sulphanilamide, promin (all sulpha drugs)
Fatty acid and derivatives
Aromatic compounds
Dyes
Others:
Synthetic detergents
Urea
Nicotinamide (b-3 niacin)
Calciferol - Vitamin D
8-hydroxyquinoline sulphate (ointment today)

Wilhelm Röntgen (1845-1923)

Niels Ryberg Finsen (1860-1904)

Charles Mantoux (1877-1947)

Clemens von Pirquet (1874-1929)
- German physician and the founder of the TB Sanatorium movement.
- Diagnosed with tuberculosis which he said was cured after moving to the Himalayas.
- Opened first TB sanatorium in Prussian Silesia at Görbersdorf (now in Poland)
Treatment:
- High altitude - increased heart size
- Fresh air -
- Good nutrition
- Individually designed medical treatment

**TB Sanatorium**

*Treatment in the sanatorium:*
- In the beginning complete rest or fever required complete bed rest.
- Daily treatment and examination (temperature, disinfectants, x-rays, pulse and weight).
- Exercise (moderate) and time outdoors (not direct sun - which caused fevers).
- Teaching on hygiene, disease, diet.
- He had tuberculosis and moved to mountains after learning of Brehmer’s work.
- Established the first TB sanatorium in the United States (1892).
- Opened a laboratory where he tested TB treatments on rabbits (nutrition and fresh air).
Hermann Biggs (1859-1923)

- Developed Plan to systematically battle TB – leading cause of death in NYC (10,000/year at rate of 280/100,000).
  1. Mandatory notification.
  2. Sputum microscopy.
  3. Case management.
  4. Public education.
  5. Political will.

Health Department Rules (1889): To prevent spread of consumption (some of them)
I. Do not permit persons having consumption to spit on the floor...
II. Do not sleep in a room occupied by a person who has consumption...
VI. Do not fail to consult the family physician regarding the social relations of persons suffering from suspected consumption...
Case management, education and prevention through public nurses doing home visits.

“Public health is purchasable. Within natural limitations a community can determine its own death rate.”
- Hermann Biggs

Lillian Wald (1867-1940)
- “public health nurse”
- Visiting Nurse Service in New York
- New York Board of Health to establish first public nursing system in the world
Phrenicotomy

Lucite balls in lungs (also ping pong balls were used)

Lobe of lung to be removed

Thoracoplasty - surgical removal of ribs

Pneumothorax - by artificial means to collapse lung

Lobectomy
Life in a TB sanatorium (a personal experience)

Betty MacDonald (1908-1958)

Firland Sanatorium - Seattle
8 months 1937-38
TB drugs and medical advances

Selman Waksman (1888-1973)

Para-aminosalicylic acid (PAS)

Jørgen Lehmann (1898-1989)

1946 - First clinical study of humans with random allocation compared SM and bed rest alone (British Medical Research Council)

Para-aminosalicylic acid (PAS)

Streptomycin

Salicylsyre

Paraaminosalicylsyre (PAS)
TB drugs and medical advances

Chemotherapy for TB did not really begin until after the Second World War (cira early 1950s)

National Jewish

TB Sanatorium:
- Limited in beginning to a few wealthy people.
- Expanded later (1930’s-1950’s) for general population – especially children.
- By 1938 700 TB sanatoriums in US.
- Abandoned for DOT and chemical quarantine.

Mortality for TB remained relatively high until the advent of the multidrug therapy and mass screening for infection and disease.
1902 First International Conference on TB.

1904 National Tuberculosis Association (NTA) Forerunner American Lung Association (ALA).


1907 Christmas seal raise money for TB.

1944 Public Health Service Act (PH law 78-410).

1947-53 Screening campaign: 20 million x-rayed.

1959 National TB Association and US-Public Health Service Guidelines for Treatment of TB.

1995 NTCA founded.
TB drugs and medical advances

Three companies simultaneously discovered anti-tubercular activity of INH in 1951. Roche launched Rimifon in 1952.

Gerhard Domagk (1895-1964)

Famous for sulfa drugs he also developed INH.

Synthesized in 1912 by two students in their dissertation (Meyer & Malley) in Prague.

A derivative of (pyridine) coal tar.

U.S. first clinical trial of INH begun in 1951 at Sea View Hospital, New York reported in 1952.
**TB drugs and medical advances**

The discovery and synthesis of rifampin changed the treatment of both leprosy and TB.

Piero Sensi (1920) and team discovered the compound of which is derived from rifampicin in soil collected in the French Riviera, which he named after his favorite movie of the time ‘Rififi’.

INH and Rifampin could cure TB patients but with addition of PZA, treatment could be shortened from 9 to 6 months, and with EMB there was less chance of developing resistance to RIF.
TB drugs and medical advances

Clinical trials and development of the perfect regimen to cure TB in the shortest time.

Clinical trials in East Africa, Hong Kong, Singapore

Cornell University studies of TB in mice (important for treatment with PZA).

(1948) First RCT, SM vs. PAS vs. SM & PAS.


(1960s) EMB replaces PAS for 18 months treatment.

(1970s) RIF added to INH/EMB/SM for 9 months treatment.

(1980s) PZA added to INH/RIF for 6 months treatment.

Effect of the addition of thiacetazone (control), PZA or RMP to a basic 6-month SM+INH regimen on the relapse rate in a multicentre East African regimen study.

<table>
<thead>
<tr>
<th>Patients n</th>
<th>Relapses %</th>
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<tbody>
<tr>
<td>SM + INH</td>
<td>112</td>
</tr>
<tr>
<td>SM + INH + Thioacetazone</td>
<td>104</td>
</tr>
<tr>
<td>SM + INH + PZA</td>
<td>153</td>
</tr>
<tr>
<td>SM + INH + RMP</td>
<td>152</td>
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Table from one of the most important BMRC studies - 1971 Lancet vol 299 pp 1079-85 on relapse rates with combined tx
TB drugs and medical advances

Wallace Fox (1920-2010)

These studies allowed the shift from inpatient (sanatoria) to outpatient treatment.

Assured adherence and ‘chemical isolation’ through directly observed therapy (DOT).

Explored the most efficient way to treat TB in the shortest and least expensive way.

Madras Studies:
1958 ambulatory vs sanatoria treatment and the importance of Direct Observation (DOT).

1961 intermittent therapy explored.

Parallel work in Hong Kong (also adopted DOT).

In the end Madras, Hong Kong and a study in London concluded that effective treatment required DOT.
TB drugs and medical advances

DOT not widely accepted in the U.S. until Dr Sbarbaro and others in Denver campaigned and studied its efficacy.

Others had advocated against it due to many factors including: civil right, socioeconomic status, and cost.

“Moreover, there is now overwhelming conclusive evidence that at least 35% of patients will not take their medication and physicians are unable to identify which patients will and will not take their treatment. Therefore, failures and relapses are inevitable among the self-medicated. When the costs associated with these excess relapses and failures are added to this analysis, all of the self-administered regimens become significantly more costly than any directly administered treatment program.”


1993 DOT was adopted as the standard for care for all TB patients in the U.S. by federal policy. It is also the standard of care Internationally (WHO -1993).
United States TB Cases & Rates, 1953-2011

Death from TB In the US:

1786 =300/100,000
1800=1,600/100,000
1904= 188/100,000
1920= 100/100,000
1930=70/100,000
1945=41.1/100,000
1953=12.4/100,000
1965=4.1/100,000
1975=1.6/100,000
2004=0.2/100,000
2010=0.2/100,000
2004=0.2/100,000
TB in Wisconsin

1883 Board of Health urges separation of TB patient from population

Robert M. La Follette
1855-1925
Governor of Wisconsin 1901-1906

1903 Report on Tuberculosis - recommended state TB sanatoria be built.

1905 Mandatory reporting of TB.

1907 State Sanatorium opened.

1920 Two state and 19 county sanatoria in operation.

Assemblymen John C. Karel and Gustav Schmitt advocate for TB sanatoria.

1945 TB Free Care Bill passed (legal diagnosis by exam, x-ray or lab).
TB Sanatorium (Wisconsin)

1950 20 TB sanatoria operating daily census of 1,867.
1960 17 TB sanatoria operating daily census of 779.

1970 13 TB sanatoria operating daily census of 189 (<15 per facility).

1971 TB ad hoc Committee established - address inadequacy of system for treatment of TB.

1975 Free Care Law for TB modified (only 30 days of hospital care), health insurance to cover TB, closure of all sanatoria not meeting standards and saving state budget costs.

1976 All sanatoria closed
1910 TB is the leading cause of death in Wisconsin, (2,404 deaths).

1930 TB is the 7th leading cause of death in Wisconsin (1,514 deaths).

1940 TB is the 9th leading cause of death in Wisconsin (800 deaths).

1960 TB deaths in Wisconsin = 125 deaths.

1986 TB deaths in Wisconsin = 17 deaths.
Declining rates of TB in Wisconsin from 29.2 in 1953 to 1.2 in 2012

1953 = 1,024 cases (29.2/100,000)  
1965 = 560 cases (13.5/100,000)  
1975 = 265 cases (5.8/100,000)  

1995 = 117 cases (2.3/100,000)  
2004 = 117 cases (1.7/100,000)  
2012 = 71 cases (1.2/100,000)
Czech by birth (later Dutch citizen)
Survivor of Nazi concentration camp and TB
Scientific Director of International Union Against TB
Father of TB epidemiology and founder of DOTS program

“…unlike many other infectious diseases... tuberculosis can be controlled... under any socioeconomic condition because the infectious agent is almost exclusively in the diseased man, and simple and inexpensive means to eradicate tuberculosis are available.”

1993 - WHO declares TB a global emergency

TB DOTS-Program (revised since 2002):
1. Political commitment with increased and sustained financing.
2. Case detection through quality assured bacteriology (smear, culture, DST).
3. Standardized treatment with supervision and patient support.
4. M & E system and impact measurement.
Conclusions

Paul Farmer – physician and medical anthropologist highlighted the faults of the DOTS program.

Work in Haiti, Peru and Rwanda

DOTS-Plus programming throughout The world

Estimated 1 billion deaths in the past 200 years (100 million since 1900).
Estimated 27.6 million deaths since 1990.
Estimated 3.7% of all new TB cases are MDR-TB.
Estimated 20% of all previously treated TB cases are MDR-TB.
Selected References


