Twenty-first Century Threats
Tuberculosis

William Ayliffe
Gresham College
April 2012

Thanks

Patients

Teachers
Izzy Glick
Malcolm Partridge
Malcolm Green
Tony Bron
Stephen Foster

Staff of Gresham

Doctors

The White Death
Thomas Dormandy

23 yr old **John Keats** travelled home to Hamstead

His mother had d.TB 18 yrs previously

Had nursed his brother Tom

“Bring me a candle Brown”

x2 more hmm, surgeon bleeds regularly starvation

Dr. Robert Bree second opinion, no organic disease

Good diet and exercise.

"I have two luxuries to brood over in my walks "...your loveliness, and the hour of my death"

John Gibson Lockhart Blackwood's Magazine, described Endymion as "imperturbable drivelling idiocy".

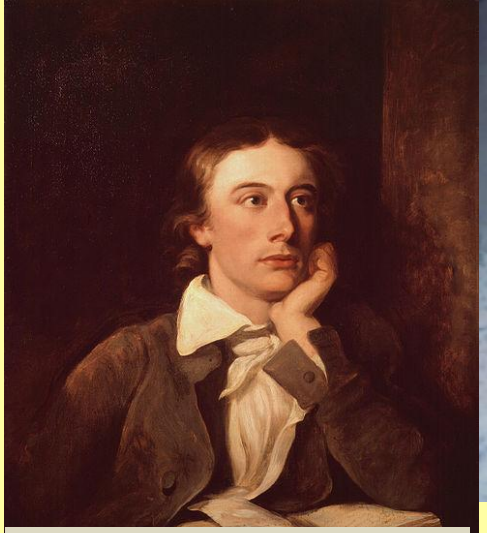
"It is a better and a wiser thing to be a starved apothecary than a starved poet; so back to the shop Mr John, back to plasters, pills, and ointment boxes

Dreadful journey to Rome, quarantined in Naples

Dr. James Clark; “lungs appear to be sound” dainty diet and bleeding. 1 anchovy and antimony

Terrible suffering

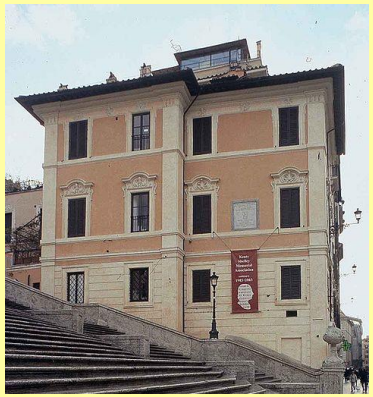
To Fanny Brawne Feb 1820, "I have left no immortal work behind me – nothing to make my friends proud of my memory – but I have lov'd the principle of beauty in all things, and if I had had time I would have made myself remember'd."



John Keats, William Hilton

Fanny Brawne taken circa 1850

Charles Brown, *Portrait of John Keats, 1819.*



Byron:

'Tis strange the mind, that very fiery particle Should let itself be snuffed out by an article.

Shelly: Adonais

The loveliest and the last, The bloom, whose petals nipped before they blew Died on the promise of the fruit

A type of beauty

Kathleen Kelly born to impoverished Retired East India Army officer. Aged 17 marriage arranged to Isaac Newton, surgeon Indian Civil Service.

On outward, seduced by Captain Palliser.

Confesses on wedding night

sent back to England, becoming mistress of Palliser and has his baby.

1872 meets **James Tissot** most commercially successful painters of the day, (Oscar Wilde referred to his subjects as ‘common’)

Pregnant.

She started to cough and Tissot moved the Irish divorcee and 2 illegitimate children into his house!

As tuberculosis gripped, she was unable to bear his grief and overdosed on laudanum in November 1882. Tissot sat by her coffin for four days.

Buried in unconsecrated ground in Kensal Green Cemetery.

A Type of Beauty.

“something strangely perverse in an imagination which souses Ophelia in a weedy ditch, and robs the drowning struggle of that lovelorn maiden of all pathos and beauty"

Elizabeth Siddal: b1829 Hatton Garden married Rossetti

Posed for Millais an hour a time in cold bath

Hogsmill River Ewell: "The flies of Surrey are more muscular, and have a still greater propensity for probing human flesh. I am threatened with a notice to appear before a magistrate for trespassing in a field and destroying the hay ... and am also in danger of being blown by the wind into the water. Certainly the painting of a picture under such circumstances would be greater punishment to a murderer than hanging."

Ruskin paid for her to go to France

Suicide with laudanum

Mycobacterium tuberculosis

So-called because of growth pattern

Mycobacterium tuberculosis

A group of genetically-related organisms

Can cause a disease called tuberculosis

M. bovis: (Cows/badgers, pateurisation)

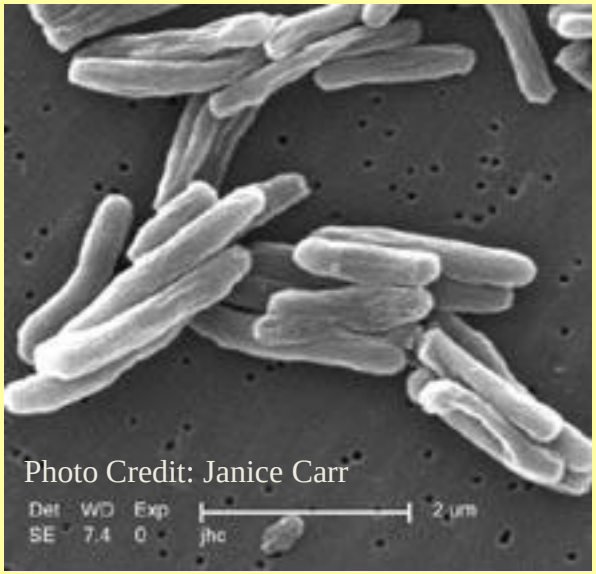
M. bovis BCG;

M canettii, (Horn of Africa)

M. africanum, (W. Africa opportunistic HIV)

Seals

Voles

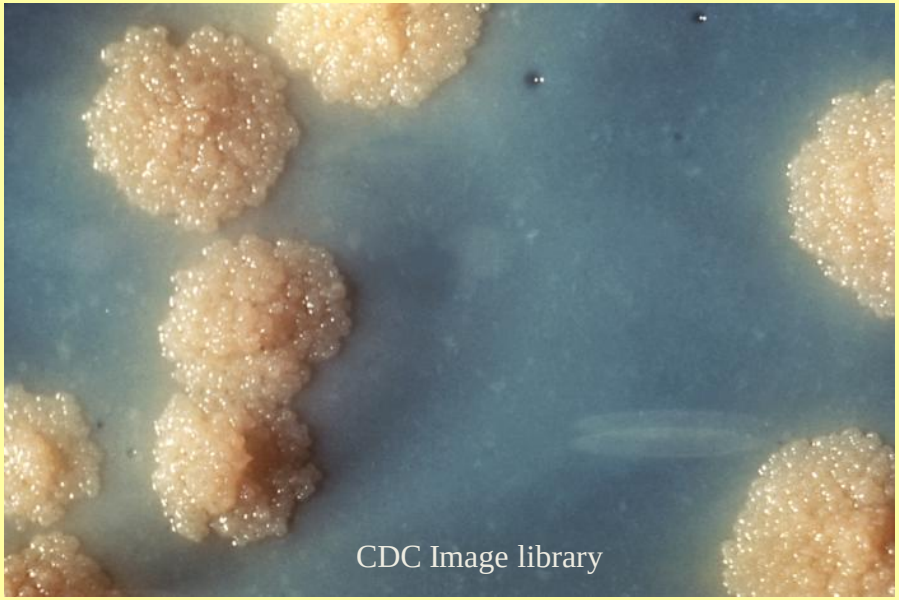


Non-tuberculous mycobacterium

Over 125 species. In environment

Human disease from environmental exposures. Fish tanks

Unlike tuberculosis or leprosy, no human-to-human transmission.



Humans infected their livestock not the other way around

Mycobacterium tuberculosis complex (MTBC)

Clonal, no gene exchange

genetic markers tandem repeat sequences, MTBC emerged c40,000 years ago from *M. **prototuberculosis*** progenitor pool.

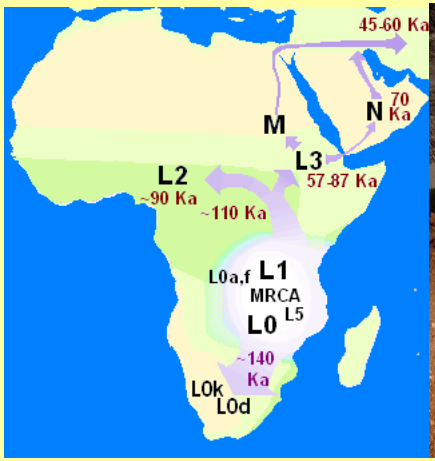
Migrated with modern humans out of Africa

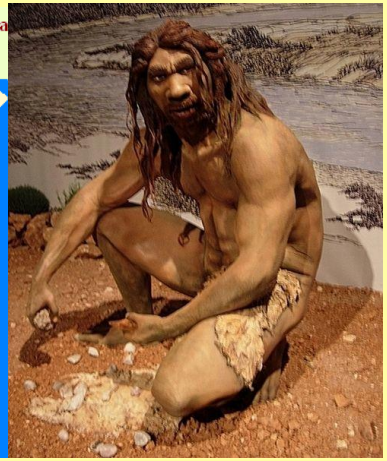
2 lineages arose 20,000 to 30,000 years ago from the common MTBC ancestor,

One infected only humans, disseminating with waves of migration

Second lineage includes *M. bovis and M. caprae;* probable source of animal tuberculosis

Transition from human to animal hosts co-incides animal domestication 13,000 years ago



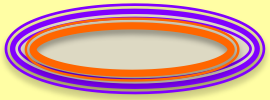


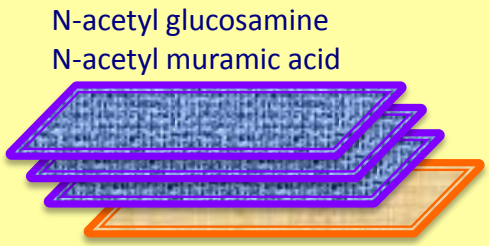
Origin, Spread and Demography of the *Mycobacterium tuberculosis Complex* Thierry Wirth, Konstanz

Resistant, slow growing, tough

Unique cell wall,

additional layer beyond the peptodiglycan layer, unusual lipids, glycolipids, and polysaccharides.





Over 60% of cell wall is lipid.

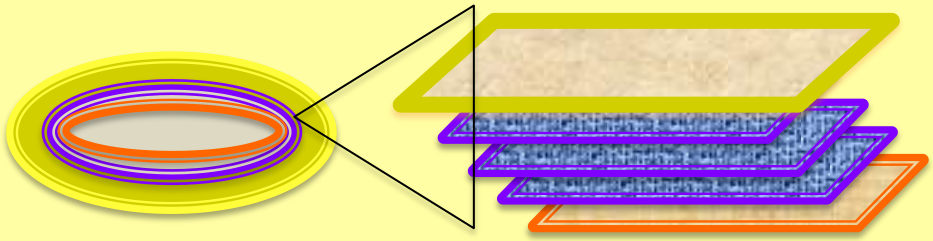
3 components,

mycolic acids, cord factor, and wax-D.

Mycolic acids are unique alpha-branched lipids found in cell walls of *Mycobacterium*

Impermeable to stains and dyes Resistance to many antibiotics Resistance to killing by acids and alkali Resistance to osmotic lysis via complement Resistance to lethal oxidations

Survival inside of macrophages



Global impact of TB

WHO: 2009 report

9.27m cases of TB (8.3m2000, 6.6m 1990)

TB killed 1.32m HIV-ve people in 2007

Asia 55% (India 2m, China 1.3m, Indonesia 0.53m)

Africa 31% (Nigeria 0.46m, SA 0.46m)

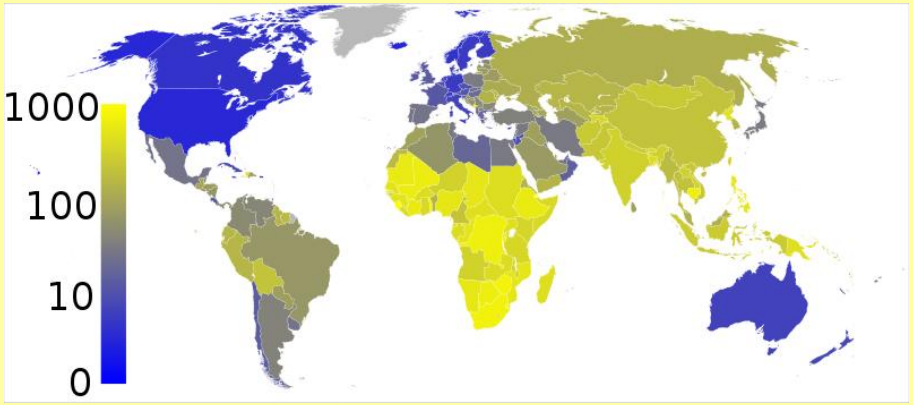
Eastern Med 5%

15% 1.37m were HIV+, most of these in Africa. TB is responsible for 23% of HIV deaths.

In 2010 there were 8,587 cases of TB in the UK (13.9 per 100,000),

After rising for a decade now 6% reduction on the previous year

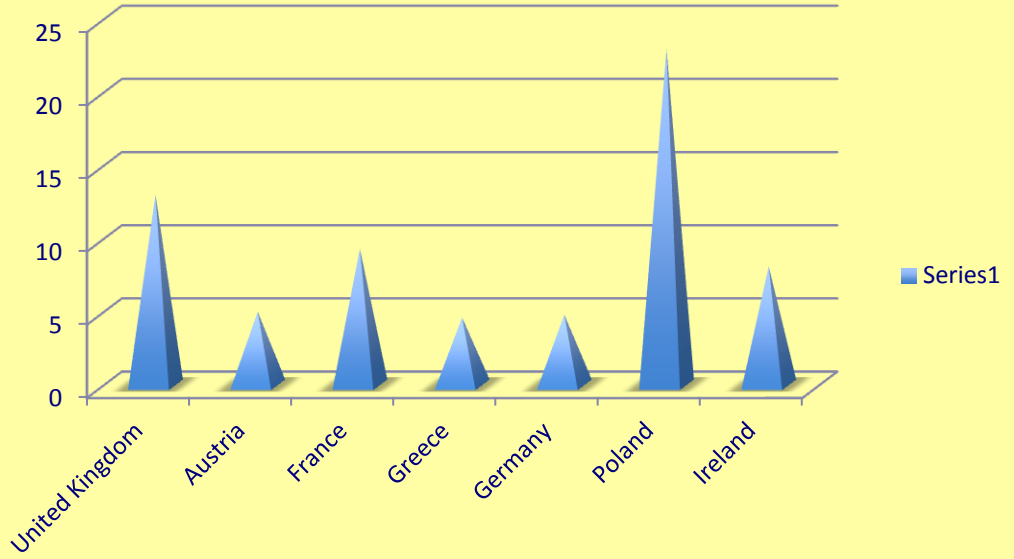
areas with incidence greater than 40/100,000 have different immunisation policies to prevent spread.1 Pulmonary TB accounts for 60% of TB in the UK

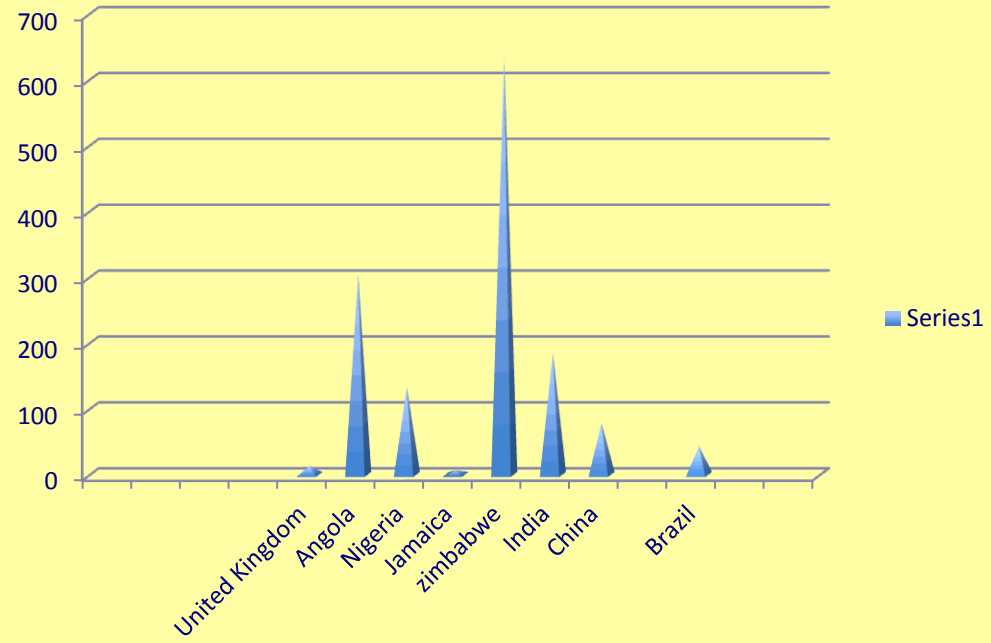


Estimated prevalence of tuberculosis per 100,000 people in 2007

WHO 2011 Report

In UK: 73% cases born abroad





What is Tuberculosis

Infection by a bacterium

Mycobacterium tuberculosis & cousins

The leading cause of death in the world from a bacterial infectious disease.

1.8 billion people/year
one-third of the entire world population.

Lungs, lymph glands, skin, bones, gut, lining of brain, reproductive organs

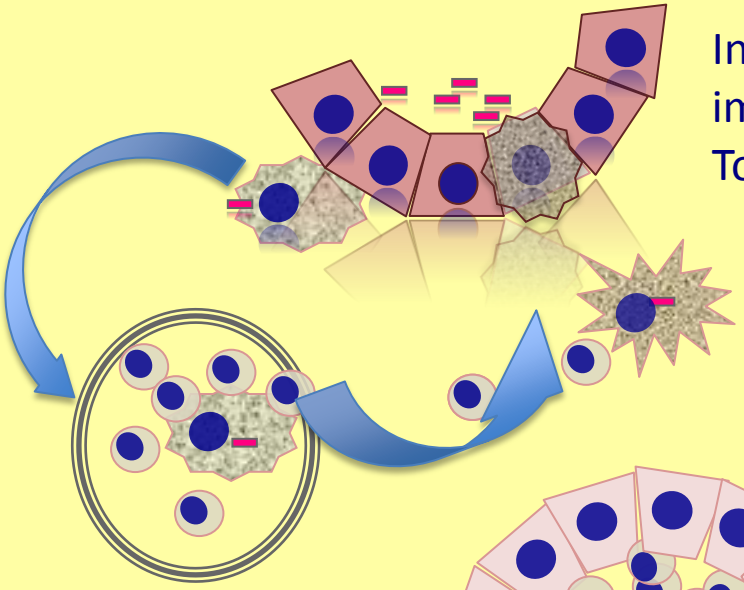
Immune system walls off the organism forming a lump (tubercle)

Most don't get sick (Latent infection)

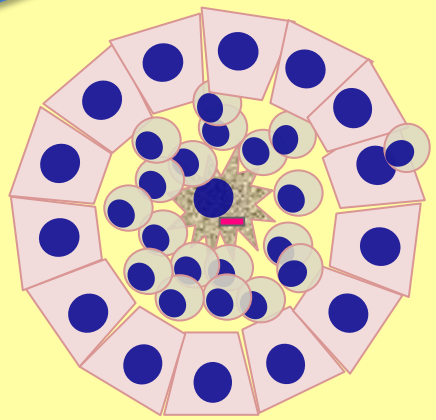
Others get sick

Some very sick

Some die.

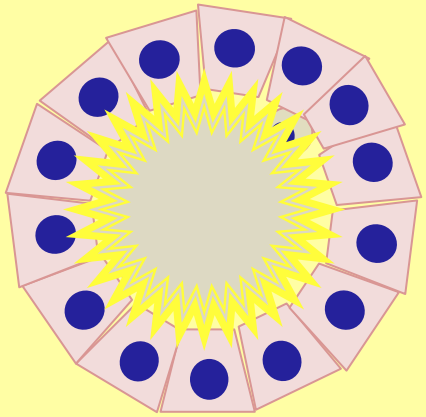


Innate immunity
TollLR, γδ



Adaptive Immunity
T-cells, cytokines
SPECIFIC

Caseation



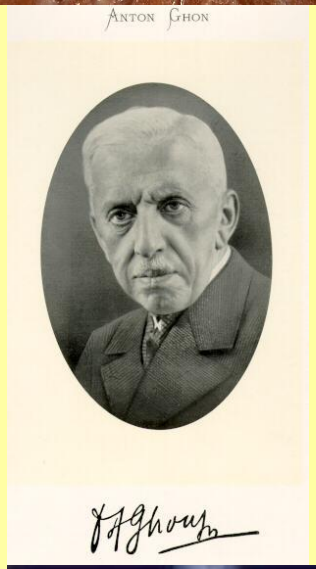
Pulmonary disease

Inhaled bacilli implant in the lung.

Body defence 1.5-cm inflammatory lesion

Joseph Marie Jules Parrot (1829-1883)

Describes primary focus 1876



Ghon focus.

Anton Ghon 1866-1936: Pathologist;

q. Graz, Prof Prague, dies of TB pericarditis

Caseation; bacilli, free or within Mϕ, drain to the regional LN, also caseate.

Ghon complex: lung lesion and node

Ranke's complex: The calcified end stage

Extra-Pulmonary disease

Milliary: 1-3% cases: result of erosion of the infection into a pulmonary vein

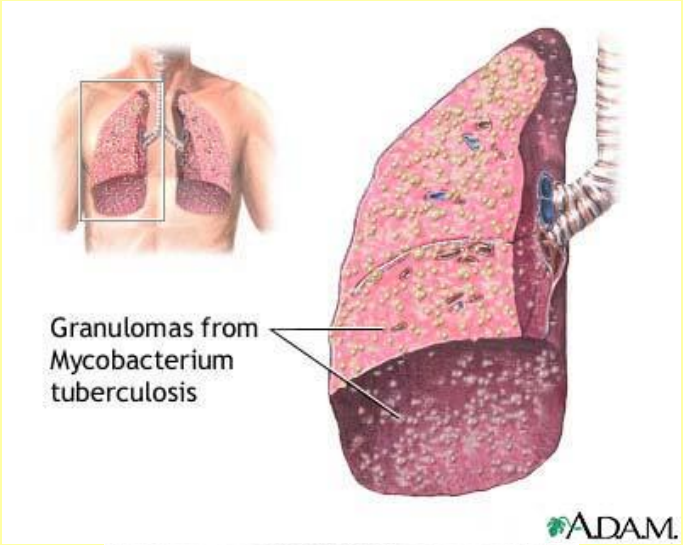
Thomas Wolfe:

North Carolignian writer; Fell ill travelling in Seattle.

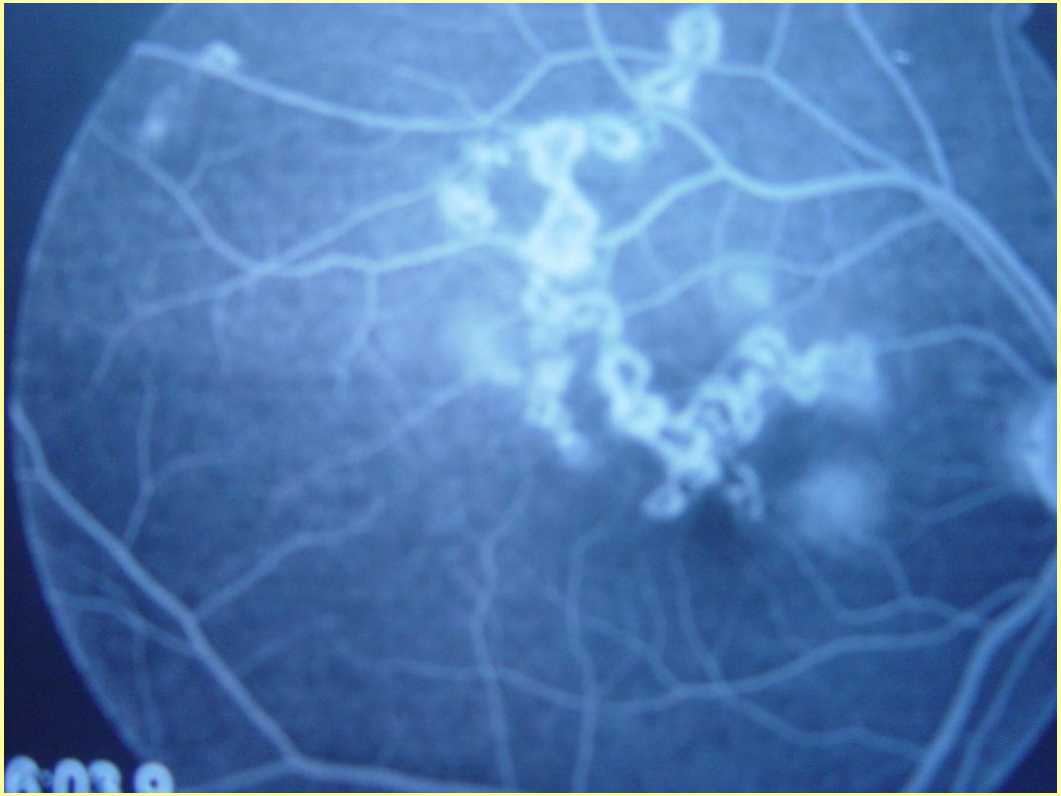
Walter Dandy: Baltimore's Johns Hopkins Hospital neurosurgeon , attempts life-saving operation

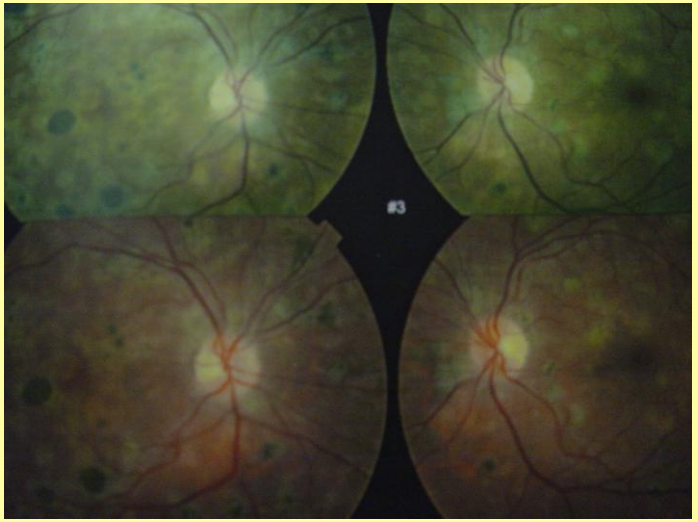
however disease had overrun the entire right side of his brain.

Without regaining consciousness, dies



Even affects the eyes





TB of Lymph nodes

TB of neck

cervical tuberculous lymphadenopathy

Adults: **M. Tb**

Children: **Mycobacterium scrofulaceum**

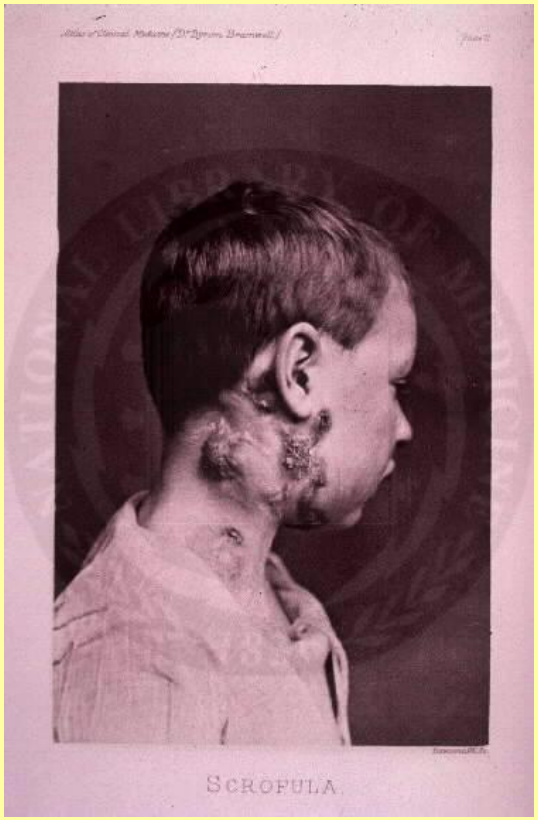
"cold abscess", because there is no accompanying local color or warmth and the overlying skin acquires a violaceous (bluish-purple) color

"Swine Evil”

"King's or Queen's Evil”

"Morbus Regius."

In France it was called the *Mal De Roi*



The Kings Touch

Strangely visited people,
All swoln and ulcerous, pitiful to the eye
The mere despair of surgery,
he cures,
Hanging a golden stamp about their necks,
Put on with holy prayers: and 'tis spoken,
To the succeeding royalty he leaves
The healing benediction—*Macbeth, Act 4, Scene 3, 171-7*

France:

Robert the Pious or Robert II of France was the first to practise the ritual in the 11th century.

Philip I (1052-1108)

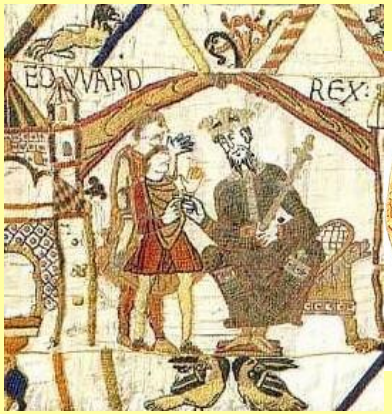
King Henry IV of France is often touching and healing as many as 1,500 individuals at a time.

Louis XIV (Sun King 1638-1715 longest reigning King), placards indicating the days and times the King would be available for royal touches were posted

Louis XV touched more than 2000 scrofula victims and the last French monarch to do this was **Charles X** in 1825.

King Henry IV of France touching
Engraving; André Du Laurens (1558-1609)

Touching in England



King Edward the Confessor (1003-1066)

Henry II, **Mary I**, **Elizabeth I,** cured all *ranks and degrees. ”.*

Charles I touched around 100 people shortly after his coronation at Holyrood in 1630

James II and **James Francis Edward Stuart**, the Old Pretender, performed the ceremony.

Charles Edward Stuart, the "Young Pretender,” 1745 at Glamis Castle.

Henry Benedict Stuart, the brother of Charles, performed the ceremony until his death in 1807.

All the Jacobite Stuarts produced special touch-piece medalets

William III (Dutch) refused to believe in the tradition and did not practice the ceremony. Following his death courtesy of the little gentleman in the black velvet waistcoat (vole burrow) His sister-in-law as **Queen Anne** did.

William Tooker 1557-1621***“Charisma; sive Donum Sanationi****s* historical vindication of the power inherent in the English sovereign of curing

Sainte Ampoule

St. Remigius ordered two empty vials be placed on an altar and as he prays before them these two vials miraculously filled respectively with the necessary Oil of the Catechumens and Chrism.

St. Remi grave opened by Hincmar Archbishop of Reims, 2 scented vials. perfumery unknown in the Carolingian empire

Originally unguents used to cover the scent of decay of corpse during his funeral

Hincmar creates the legend of the **Holy Ampoule (*Sainte Ampoule)***

1131: First documented use: coronation of Louis VII (married Eleanor of Aquitaine) by Pope Innocent II

The coronation regalia of the Kings of England includes an ampulla used for Henry IV in 1399. contain the oil presented by the Virgin Mary in a vision of St Thomas of Canterbury. It is accompanied by C13th golden spoon

Late Carolingian ivory binding, c. 870
Musée de Picardie Amiens
miracles from the life of St Remi.
Top: dying pagan asks Saint Remi for baptism,
Centre: the Hand of God fills the two vials,
Bottom: the dove of the Holy spirit delivering the *Sainte Ampoule at the Baptism of Clovis.*

The baptism of Clovis by St Remigius in Rheims
Master of St Giles c1500
Washington
The first Frankish King to be converted

TB in ancient times
Possible TB in early Homo species

"Workers at a travertine factory near Denizli, Turkey, were startled recently when they sawed a block of the limestone for tiles and discovered part of a human skull."

500,000 yrs old

Tiny lesions 1-2 mm in size found along the rim of bone just behind the right eye orbit. characteristic of Leptomeningitis tuberculosa

Possible TB in H. Erectus

Homo erectus, first human species to migrate out of Africa.

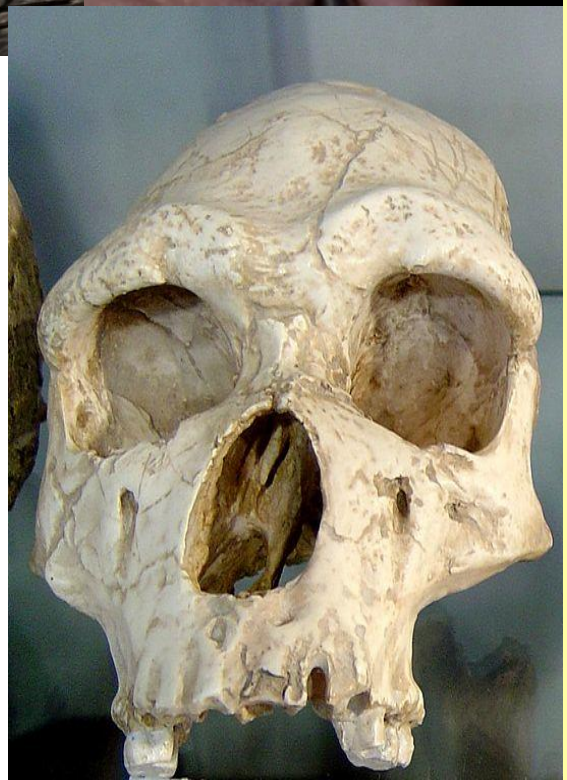
Dark skin inhibits vitamin D production in Northern latitudes

New bone forms on inside surface of skull

Found on occipital, parietal and frontal bones, venous drainage.

Caused by haemorrhage or inflammation, precise aetiology controversial.

(Credit: Marsha Miller, the University of Texas)



TB in ancient times

1950's TB affects skeleton in 3-5% cases. Spine and wt bearing joints

Stone age: Angulation found in neolithic skeletons from Heidleberg.

Rib lesions: destructive vs new bone on inner surface from spread via pleura

1550 BCE **Ebers papyrus**, Egyptian medical treatise,

Describes pulmonary consumption associated with neck lymph nodes.

Recommends treatment with surgical draining and application of a mixture of acacia seyal, peas, fruits, animal blood, insect blood, honey and salt.

Tomb of Ipy 19thDynasty
Humped back gardener

Pott's disease (tuberculosis of the spine) in an Egyptian mummy from the time of the 21. Dynasty (about 1000 BC) Nepaharan, a 25 yr old priest of Amun.
Drawing by Mrs Cecil Firth 1910

What killed ‘Dr Granville's mummy’

First scientific autopsy of ancient Egyptian mummy. Royal Society 1825

Irtyersenu, 50yr old F, from the necropolis of Thebes c600 BC.

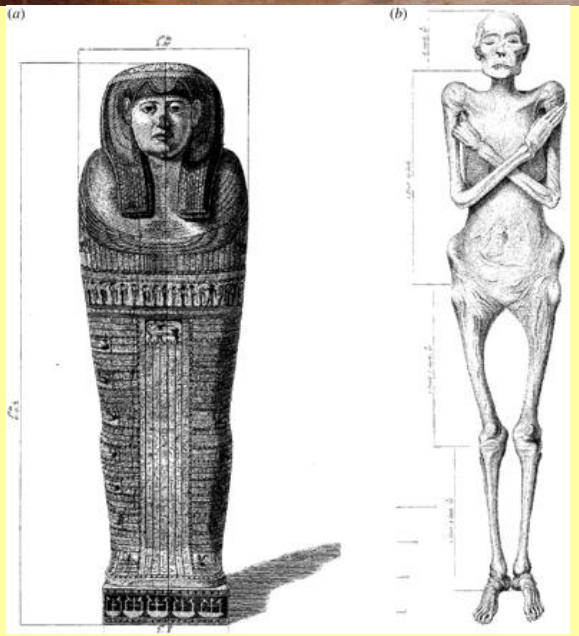
Augustus Bozzi Granville (1783-1872), obstetrician, described many organs still in situ cause of death to a tumour of the ovary.

However, subsequently benign cystadenoma

Histology of the lungs demonstrated a potentially fatal pulmonary exudate

Donoghue, HD: 2010 Proceedings of the Royal Society B , 277

MTBC DNA: lung and gall bladder samples. Lung and femurs +ve MTB cell-wall mycolic acids, pyrenebutyric acid-pentafluorobenzyl mycolates.



Iron age TB

The earliest known case of human tuberculosis in Britain dates to the middle period of the Iron Age, approximately 2,200 years before present.

Male skeleton 30 yrs old; excavated at Tarrant Hinton in Dorset

Vertebral lesions strongly suggest infection.

60° angular kyphosis of the spine.

Pott's disease

Molecular evidence of ***M. tuberculosis complex*** *DNA not M.Bovis*

Michael Taylor Imperial College 2005

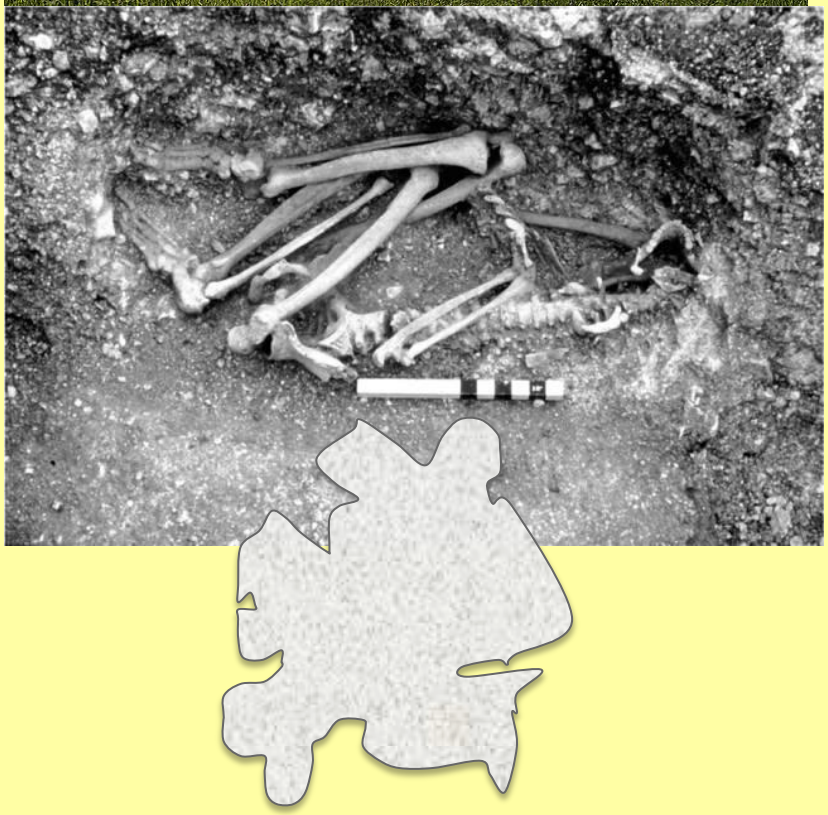
Iron Age population recovered from the cemetery of Aymyrlyg, Tyva (Tuva), South Siberia.

molecular study presence of MTBC DNA in four of 5 cases.

M. bovis rather than *M. tuberculosis* and first identification of the bovine TB in archaeological human remains

Tuberculosis among Iron Age individuals from Tyva, South Siberia: Palaeopathological and biomolecular findings Eileen Murphy 2009.

Journal of Archaeological Science 36, 2029-38.



TB in written history

Rigveda, 1500 BCE: calls the disease *yaksma*

Emperor Shennong (2700 BCE). Credited for introducing farming and herbal medicines

Yellow Emperor (2696 BC) Initiator of Chinese Civilization and credited with many inventions.

200BC***: Huangdi Neijing***, medical text, dialogue of Emperor describes xulao bing (weak consumptive disease), persistent cough, abnormal appearance, fever, a weak and fast pulse, chest obstructions, and shortness of breath

Hippocrates, Book 1 ***Of the Epidemics***; fever, colorless urine, cough resulting in a thick sputa, and loss of thirst and appetite. delirium before death;

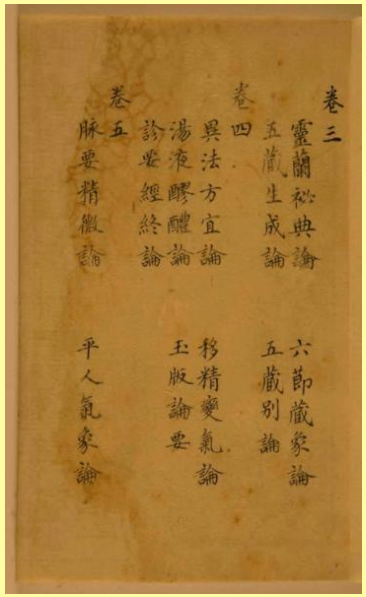
Phthisis thought to be hereditary

Aristotle believed it was contagious.

Galen treatments: opium; blood letting; a diet of barley water, fish, and fruit.

Aretaeus first systematic description: ***De causis et signis diuturnorum morborum****: Voice hoarse; neck slightly bent, tender, not flexible, somewhat extended; fingers slender, but joints thick; of the bones alone the figure remains, for the fleshy parts are wasted; the nails of the fingers crooked, their pulps are shrivelled and flat...Nose sharp, slender; cheeks prominent and red; eyes hollow, brilliant and glittering; swollen, pale or livid in countenance; the slender parts of the jaws rest on the teeth as, as if smiling; otherwise of cadaverous aspect...*

The Farmer God taught agriculture
mural painting from Han dynasty AD150



C17th TB

Paracelsus: TB failure of an organ in its alchemical duties. In the lungs, stony precipitates develop; the *tartaric process*

Franciscus de la Boe (Sylvius i.e. of the woods)

Not the inventer of Gin (a C16th Sylvius de Bouve)

tubercles often seen in lungs of consumptives:

'I found more than once larger and smaller tubercles in the lungs, which on section were found to contain pus. From these tubercles I hold that not infrequently phthisis has its origin. Only the wasting originated by an ulcer in the lung is to be called phthisis

"phthisis is the scrofula of the lung" in his book *Opera Medica published posthumously 1679*

Francois de le Boë (Sylvius) and his Wife. 1672 Frans van Mieris Dresden, Gemäldegalerie

17th Century TB

Pulmonary TB rife in London,

Locke *De Phthisica,* estimated 20% of all deaths in London

Christopher Bennet (1617-55) Dr and victim age 38.

1655: ***Theatri Tabidorum***. the nature and cure of consumptions, whether a phthisick, an atrophy, or an hectick; four images and a description of inhaler for administering fulmigations.

Self experimented on himself remedies, including balsam.

Case histories not repetitions of ancient authors.

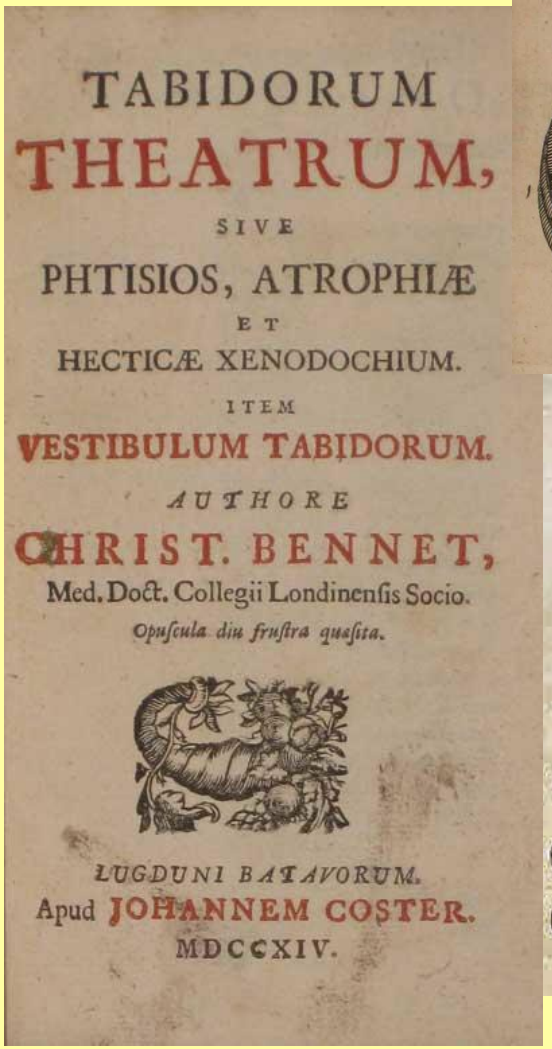
Aim comprehensive short text Popular

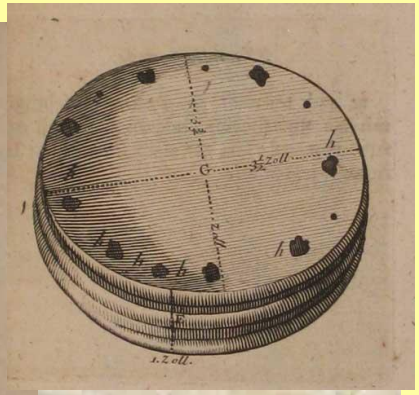
Treatment of fumigation, type of clothing, type of exercise and the best body postures.

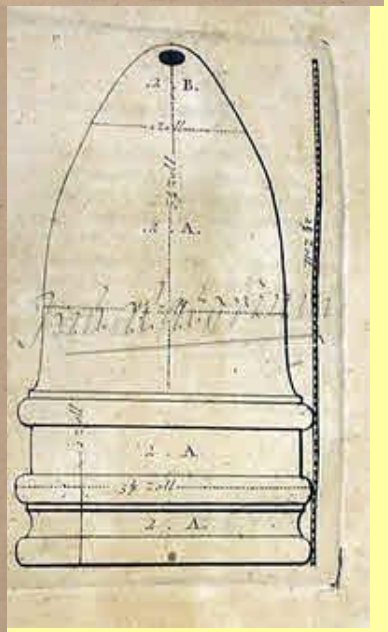
Thomas Willis (1621-75)

Practise of Physick has a chapter on Phthisis. Consumption arising from a Fault of the Lungs, a withering away of the whole body from an ill formation of the lungs. concluded that all diseases of the chest must ultimately lead to consumption

Thomas Sydenham (1624-89): Brief fragment in papers after his death: Points out that something in London caused young people 15-25yrs to get the disease. De Phthisi, recommended horse riding.


TABIDORUM
THEATRUM,
SIVE
PHTISIOS, ATROPHIÆ
ET
HECTICÆ XENODOCHIUM.
ITEM
VESTIBULUM TABIDORUM.
AUTHORE
CHRIST. BENNET,
Med. Doct. Collegii Londinensis Socio.
Opuscula diu frustra quæsita.
LUGDUNI BATAVORUM.
Apud JOHANNEM COSTER.
MDCCXIV.





C17th England

Richard Morton (1637–1698)

Oxford trained Vicar. Unable to comply with Act of Uniformity ousted.
?Leyden, Holland. Reappears with patronage of Prince Orange, FRCP 1678.

1689: ***Phthisiologica, seu exercitationes de phthisi libris comprehensae. Totumque opus variis histories illustratum***

Different types of wasting disease

Tubercles were always present in the wasting disease affecting the lungs; **consumption, phthisis**.

'Consumptive Cough proceeds from a Glandulous Swelling, or Tubercule of the Lungs themselves,

Galenic influence interprets tubercles as glandular degenerations

Recommends fresh air free from "smoak of coals"

over 18% all deaths in the City of London in 1700.

"Therefore in the preventing of a Consumption the Great Business"

TB caused by an imbalance of the humours, 'a vitiated disposition of the Mass of Blood, and of the Spirits in the Nerves, contracted gradually from several Procatartick or predisposing causes'.

Which 'polluted and distemper'd' the blood:

1) 'the stopping of some usual and necessary Evacuations';
2) 'troublesome passions of the Mind';
3) 'a too plentiful, and unseasonable gorging of Meat and Drink';
4) 'the neglect of due Exercise';
5) 'Night-studies, and long Watchings';
6) 'a foggy and thick Air';
7) 'An Hereditary Disposition;
8) 'an ill formation of the Breast';
9) 'Infection';
10) 'Chalky Stones';
11) 'also some particular Diseases, which corrupt and overthrow the Nature of the Blood and Spirits do occasion this Distemper'.

Sir Richard Blackmore

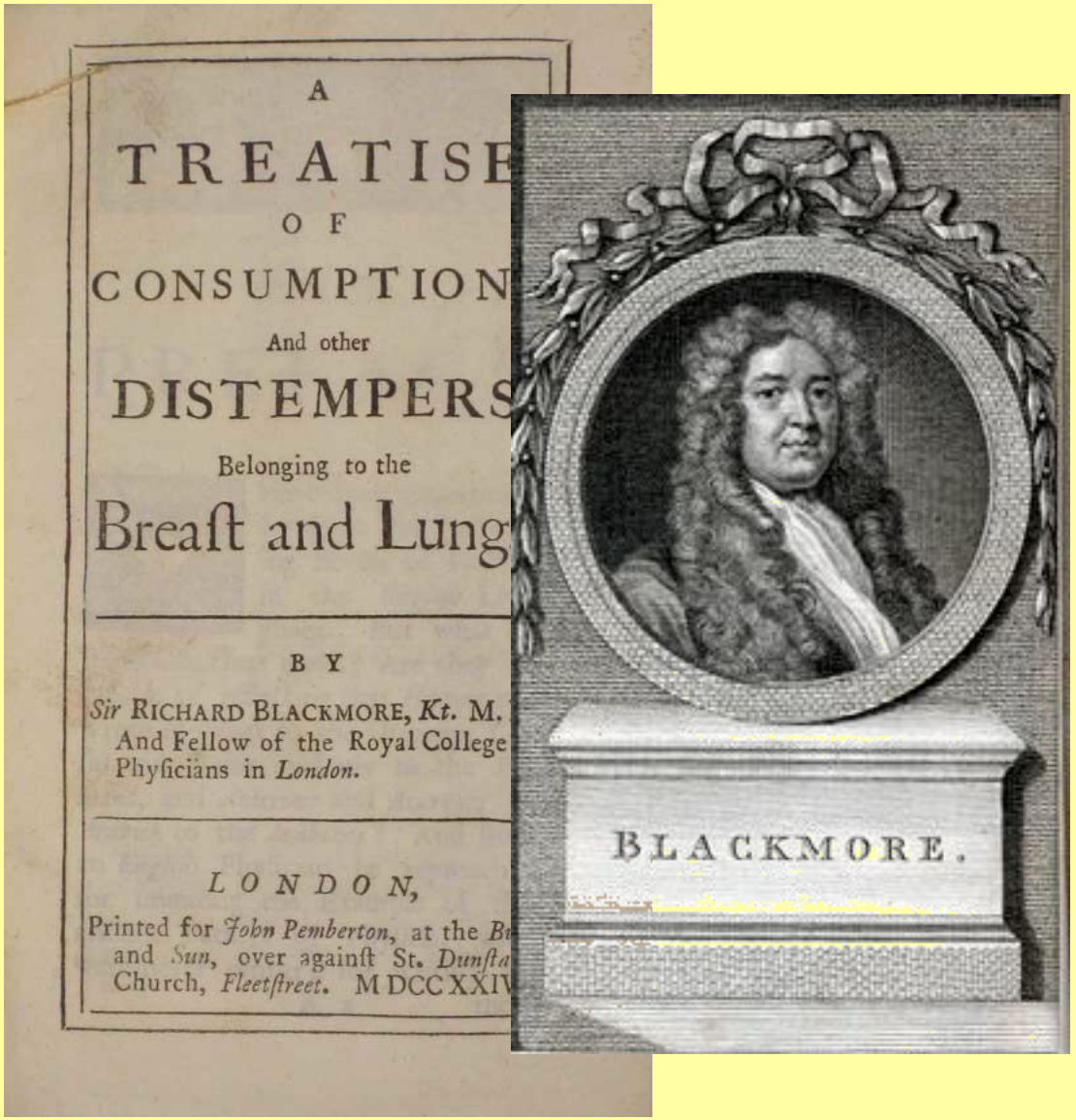
Q. Padua

Alexander Pope: “avatar of dulness”

‘The Disease that in *English we call a Consumption, is in the Latin Tongue called Tabes, and in the Greek, Pthisis,*

essential and distinguishing Character of a confirm’d Consumption is, A Wasting of the Body, by Reason of an ulcerated State of the Lungs, attended with a Cough, a Discharge of purulent Matter, and a Hecktick Fever. These are the necessary and inseparable Symptoms that belong to this Distemper, at the first Formation of an Ulcer there, though many others arise in this Progress;

A Treatise of Consumptions and other Distempers belonging to the Breast and Lungs *(London, 1724)*



Industrial Revolution

Coalbrookdale by Night, 1801, Philipp Jakob Loutherbourg the Younger

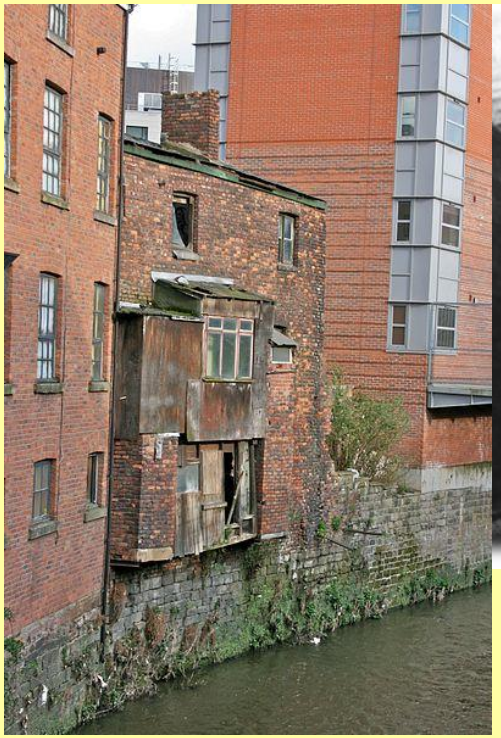
Hell on Earth

1808, **Robert Southey:** "The dwellings of the labouring manufacturers are in narrow streets and lanes, blocked up from light and air, crowded together because every inch of land is of such value that room for light and air cannot be afforded them. Here in Manchester, a great proportion of the poor lodge in cellars, damp and dark, where every kind of filth is suffered to accumulate

1830: **Alexis de Tocqueville** "From this foul drain, the greatest stream of human industry flows out to fertilize the world. From this filthy sewer pure gold flows. Here humanity attains its most complete development and its most brutish; here civilization works its miracles, and here civilized man is turned back almost into a savage."

Such is the Old Town of Manchester.. and the frightful condition of this Hell upon Earth. Everything here arouses horror and indignation.

Friedrich Engels, The Condition of the Working Class in England, 1844



LONG MILLGATE: old part of Manchester where Engels found some of the worst slum dwellings

C19th epidemic

TB exploded 1790-1840

Overcrowding, alcoholism, poverty and vice

1769; Children collected from workhouses transported to factories to die

1833: Factory Act: Lord Althorp limited hours of children to 10!

Split the parties

Palmerston For, Melbourne (liberal)against

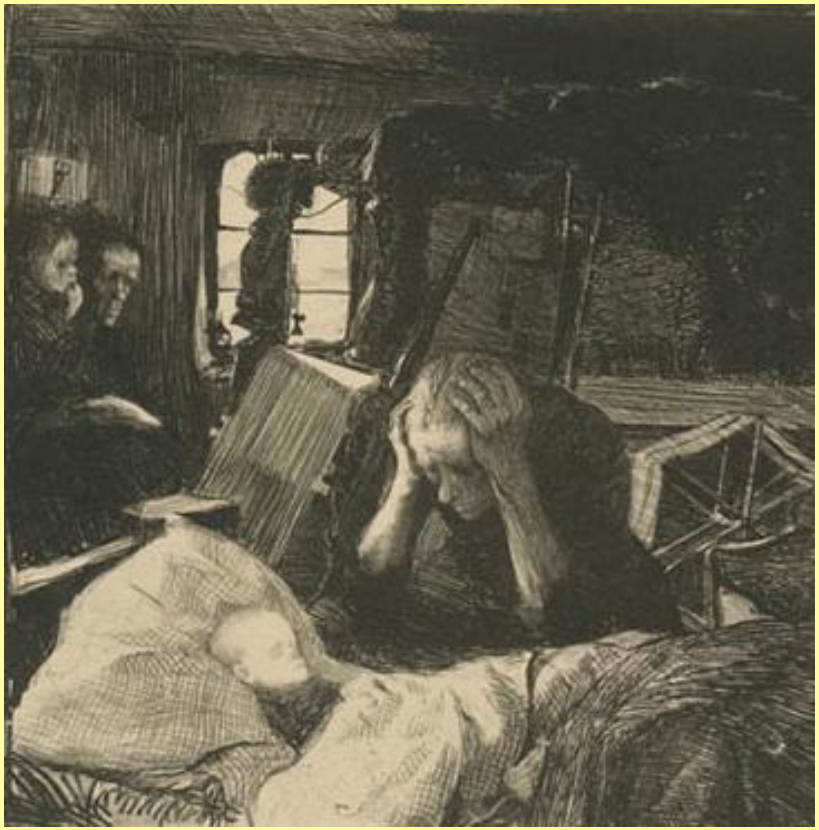
Manchester 1829-35 1:$ still births, half of these to consumptives or scofulous

London: Poor parishes x4 mortality than rich

Dublin: 36% dwellings one room, housing 5 or more.

Prisons

Nunneries: After admission life expectancy 3 years.



Poverty1893-94
Kathe Kollwitz
etching and drypoint
Statliche Kunstsammlungen Dresden

Marie Duplessis: Model for violetta

Lover of Dumas fils

Married wealthy Englishman d. TB

Armand falls in Love, father forbids it so in atonement for her sins makes him believe she has lost her love.

La Traviata: Verdi

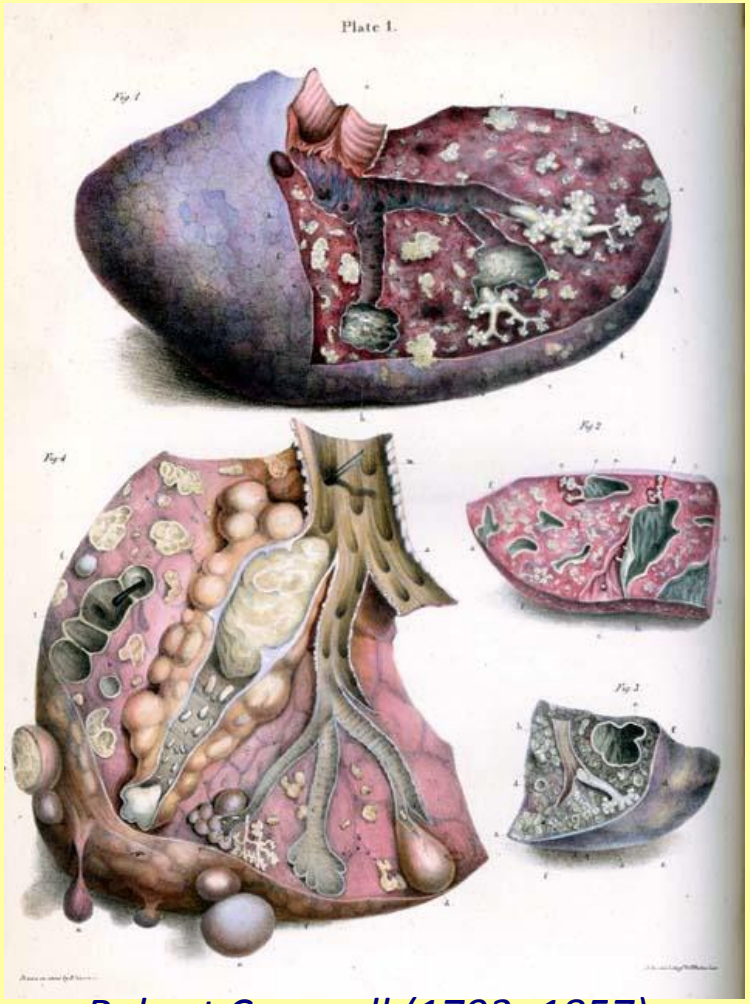
Napoleeon II:

Rostand's play, Sarah Bernhardt.

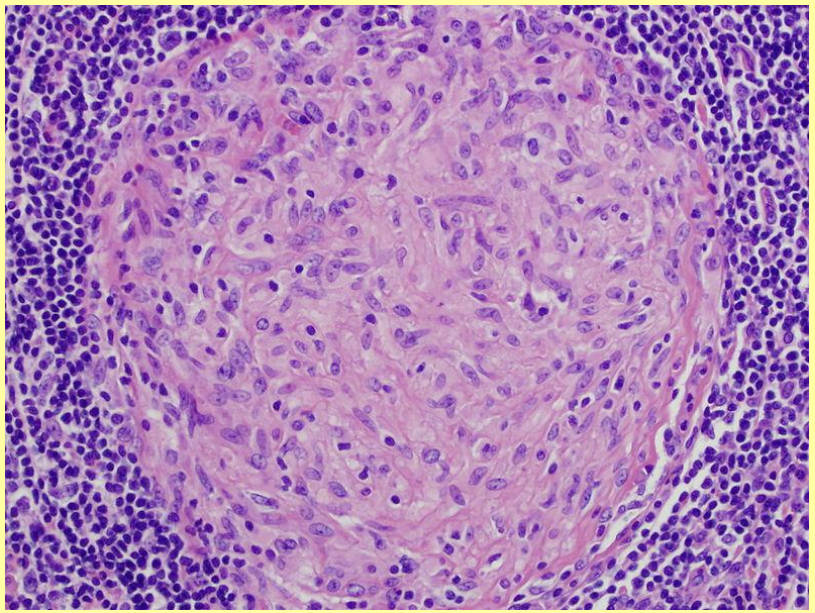
"Woman with Dead Child" by Kathe Kollwitz, etching, 1903 National Gallery of Art,D.C

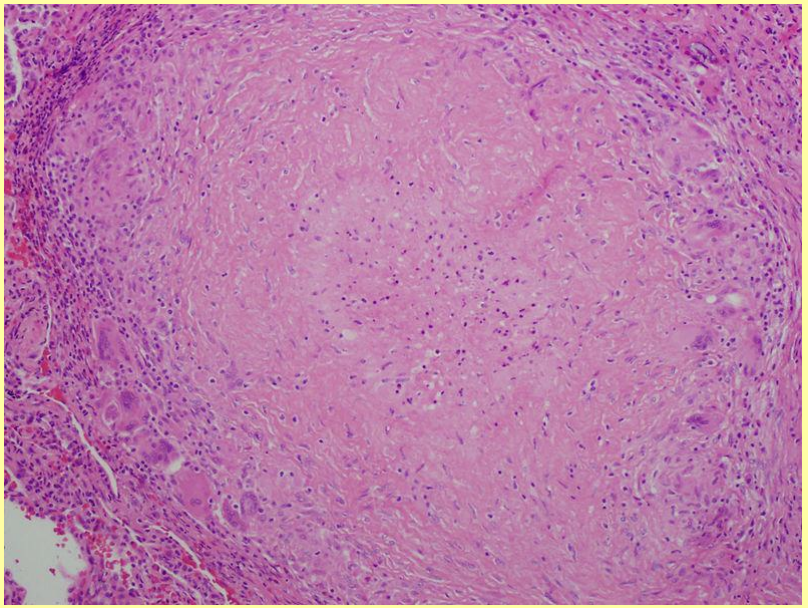
Tubercle

A nodule



Robert Carswell (1793–1857)





Diagnosis: Percussion

Leopold von Auenbrugg (1722, Graz, Austria; died May 17, 1809)

Inn-keeper father, studies Vienna, q22yrs enters Spanish Military Hospital of Vienna

comparison with post-mortem specimens, researches on corpses, injected fluid into the pleural cavity, and showed percussion to tell exactly the limits of the fluid present

Jean-Nicolas Corvisart (1755–1821). Translates Auenbrugg's ***Inventum Novum****:* Perfects percussion in Collège de France, 1804, Corvisart became the primary physician of Bonaparte, until exile to St. Helena Island October 1815

Refuses to wear wig so not promoted until after revolution.

Pierre Priory: Pleximeter. English Dr. forgets his and uses middle finger.

Diagnosis: Stethoscope

René-Théophile-Hyacinthe Laennec (178 1826)

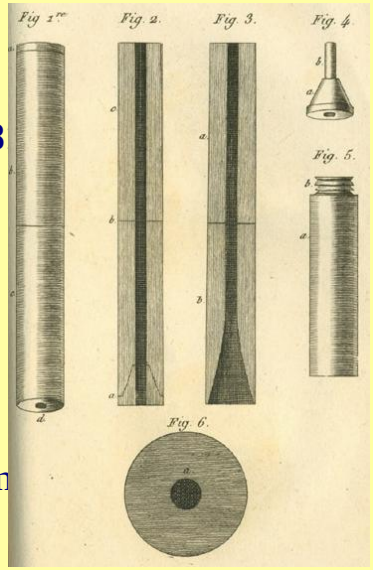
5yrs mother died TB; 12 yrs Nantes uncle, Guillaime-François Laennec, faculty of medicine.

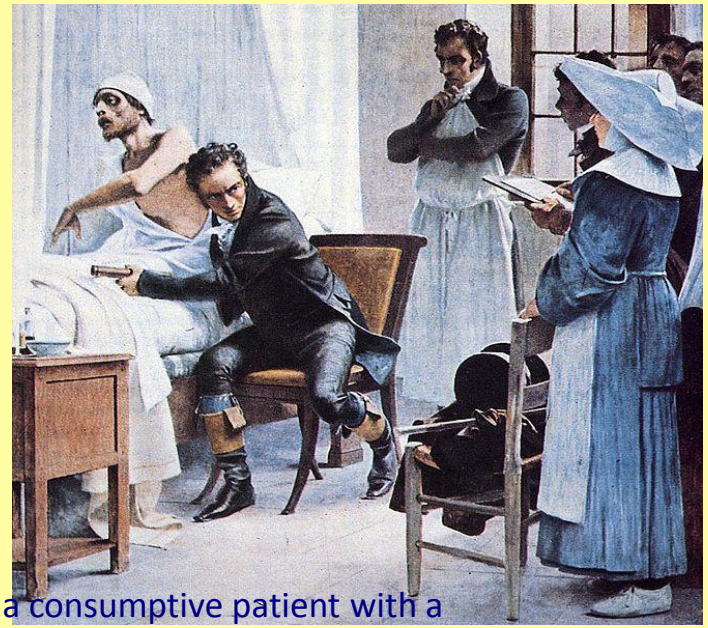
1799: Paris: Under Corvisart, learns sound (percussion) as aid to diagnosis

In 1816, I was consulted by a young woman percussion and the application of the hand were of little avail on account of the great degree of fatness…I rolled a quire of paper into a kind of cylinder and applied one end of it to the region of the heart and the other to my ear, and was not a little surprised and pleased to find that I could thereby perceive the action of the heart in a manner much more clear and distinct than ever

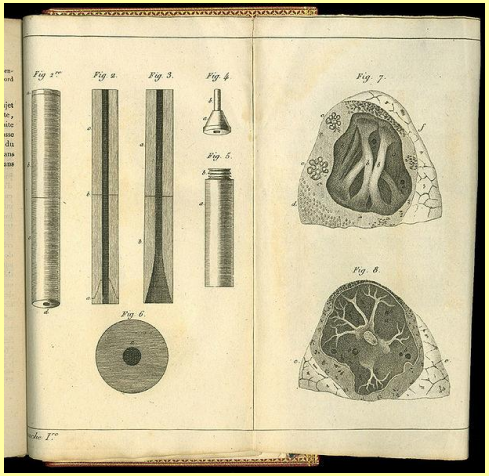
His nephew Mériadec Laennec, is said to have diagnosed tuberculosis in Laennec using Laennec's stethoscope

L. A. Connor, founder of American Heart Assoc 1866–1950) carried a silk handkerchief with him to place on the wall of the chest for ear auscultation

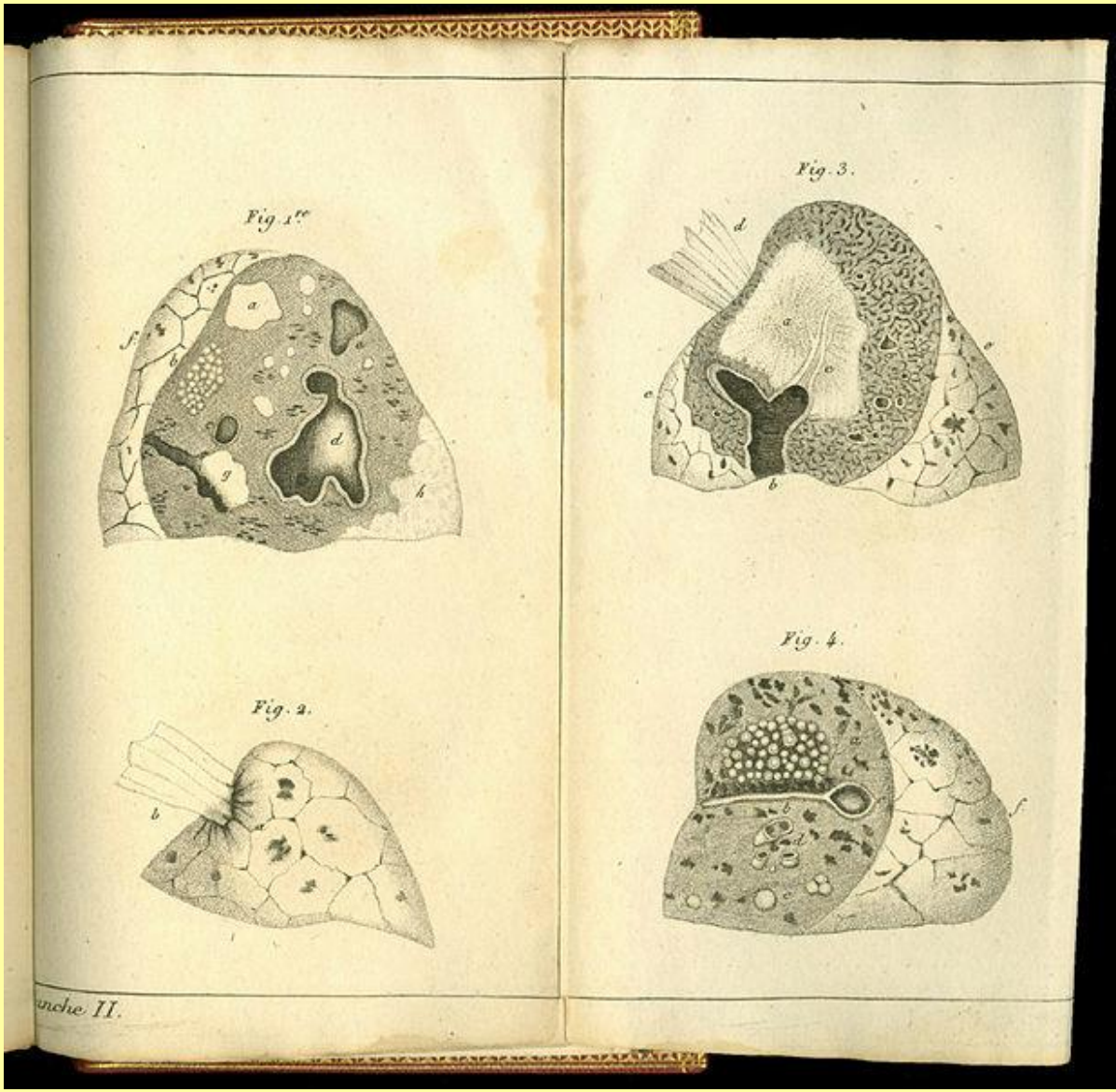




"Laennec examines a consumptive patient with a stethoscope in front of his students at the Necker Hospital". Painting by Théobald Chartran.
Also paints Roosevelt who hated it placed in the darkest corner of the White House before destroying painting



1819: *De l'auscultation médiate.*
René-Théophile-Hyacinthe Laennec (1781-1826)



Wilhelm Conrad Röntgen

1895 discovers X-rays

1897: Francis Williams, Boston Am J Med Soc, describes CXR findings compared to auscultation. Suggests Xray better in picking up disease

Skilled percussionists and auscultators less convinced.

Identifying the cause

Girolamo Fracastoro (1478 –1553) Italian physician, poet, Prof Verona

*1*546 ***De contagione***, epidemic diseases are caused by transferable tiny particles ."I call fomites [Latin *fomes, "tinder"] such things as clothes, linen, etc., which although not themselves corrupt, can nevertheless foster the essential seeds of the contagion and thus cause infection.*

Not a concept of living germs.

The name for syphilis is derived from Fracastoro's 1530 epic poem, ***Syphilis sive morbus gallicus*** ("Syphilis or The French Disease"),

shepherd boy named Syphilus insults sun god of Haiti punished with a horrible disease.

The poem suggests using mercury as a cure

1720, **Benjamin Marten** proposed in ***A New Theory of Consumptions more Especially of Phthisis or Consumption of the* Lungs** cause of TB an animacula—microscopic living beings that are able to survive in a new body (similar to the ones described by Anton van Leeuwenhoek

Identifying the cause

Jean-Antoine Villemin (1827 –1892)

Orphaned age 13, lives with Uncle, rtd soldier,

1848 Conscripted to 14th line

1849: Enrolls as Surgeon

1853: military med school Strasbourg, qualifying as an army doctor .

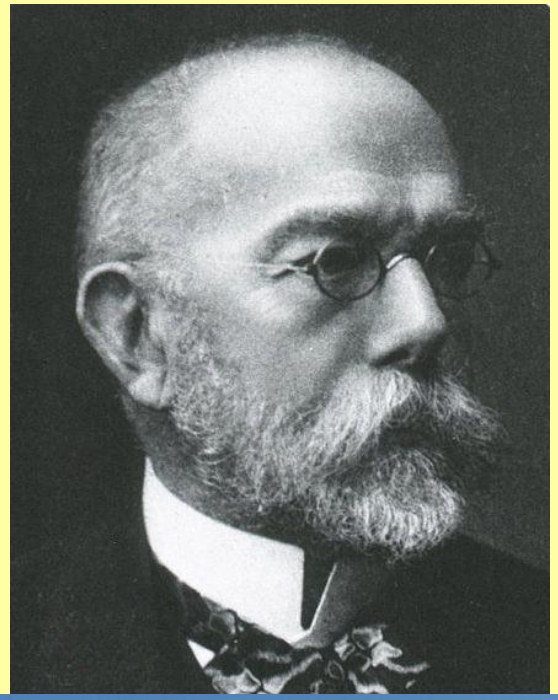
military hospital of Val-de-Grâce in Paris.

1865: proved that tuberculosis was an infectious disease ***Etudes sur la Tuberculosis***.

describes the transmission of tuberculosis from humans to rabbits, from cattle to rabbits, and from rabbits to rabbits. findings were ignored by the scientific community at the time, and Villemin's contributions wouldn't be realized until years later when they were corroborated by other scientists.

1667; designed by François Mansart & Jacques Lemercier, Paris's best example of baroque architecture. Spared ransack Nuns: medical care for injured revolutionaries. Converted to Military Hospital

Identification of the killer



Heinrich Hermann Robert Koch 1843 – 1910

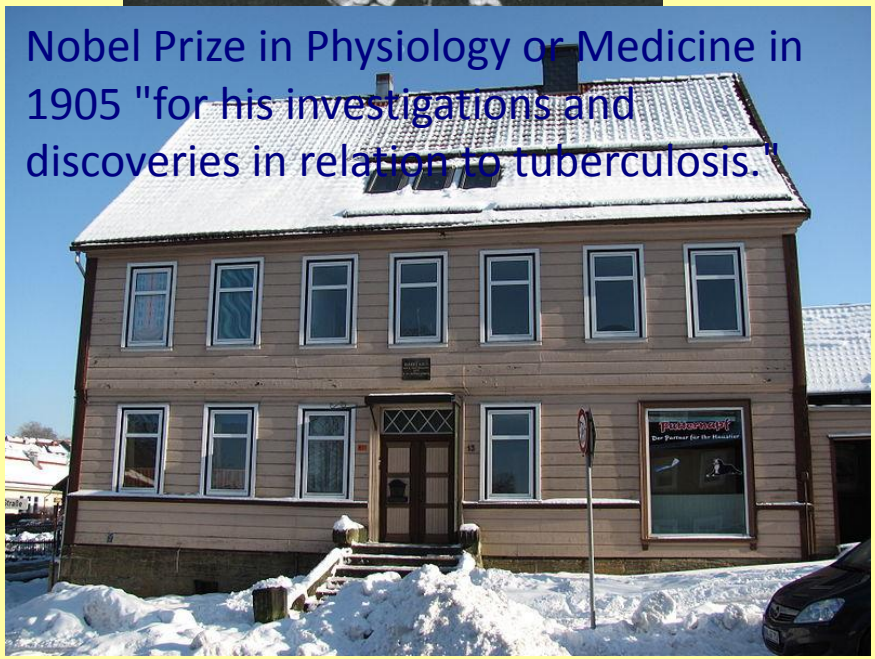
1882: New techniques, discovers *Tubercle Bacilli*

"If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more."

Dissections from guinea pigs experimentally infected with material from pts and cattle infected with TB. The disease was the same, and cultures identical.

When lecture ended there was complete silence. They looked into the microscopes to see the TB bacteria themselves

Paul Ehrlich (Nobel Laureate in 1908), "I hold that evening to be the most important experience of my scientific life."



Identifying the cause

Hans Christian Gram 1850 - 1938

After Medical School worked in the Berlin morgue with **Carl Friedlånder.** Unable to identify bacteria with standard H&E stain.

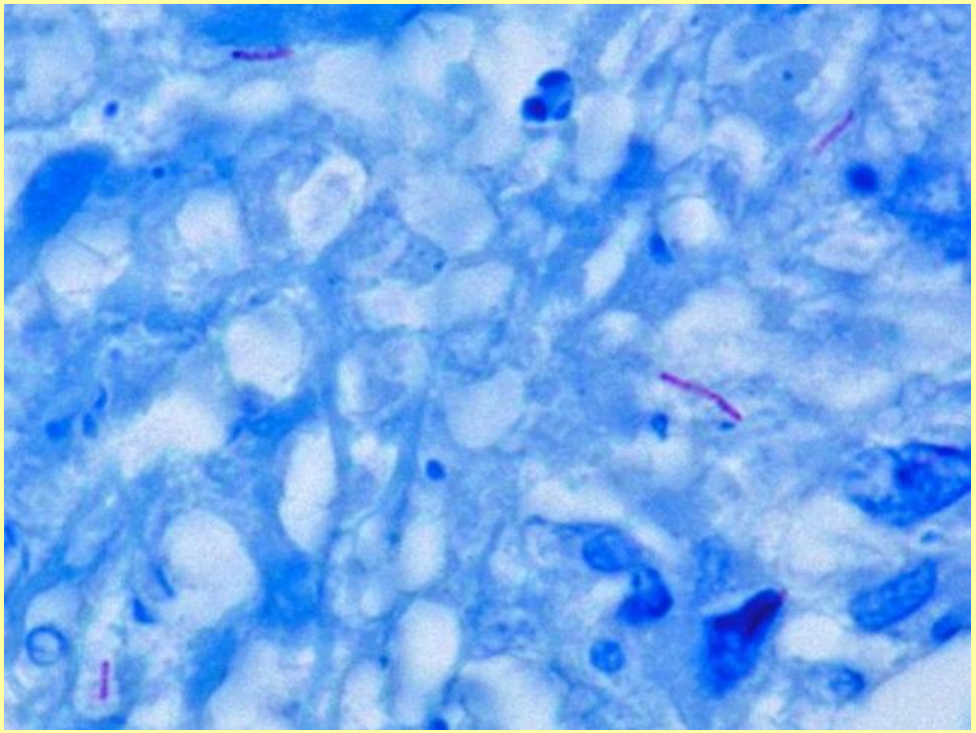
"I have therefore published the method, although I am aware that as yet it is very defective and imperfect; but it is hoped that also in the hands of other investigators it will turn out to be useful."

Gram stain:

based on the chemistry of cell walls. detects peptidoglycan, (amino-acid and sugar polymer mesh) present in a thick layer in Gram positive bacteria

However TB didn't stain consistently

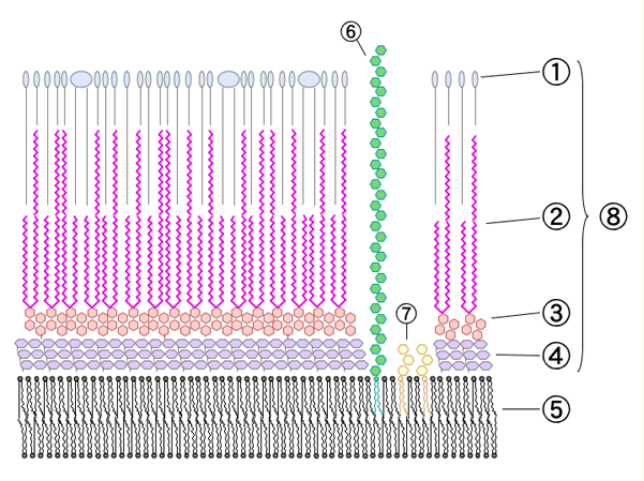
Paul Ehrlich primary stained with Fuchsin then decolourised everything with nitric acid revealing bacterium



The poor absorption of the stain and its strong retention is due to Mycolic Acid.

Dr. Franz Ziehl (1857-1926) professor in Lübeck. introduced the carbolfuchsin (binds mycolic acid) stain for the tubercle bacillus in 1882.

Friedrich C.A. Neelsen: 1854-98: professor Institute of Pathology Rostock, later Dresden University of Technology. Reclusive, d. aged 44, presumably due to pathogen exposure.



outer lipids
mycolic acid
Polysaccharides
peptidoglycan
plasma membrane
lipoarabinomannan
(LAM)phosphatidylinositol mannoside
cell wall skeleton

Not everyone accepted bacilli

Prof. Max Pettenkofer of Munich proclaimed cholera bacillus as the figment of a fevered and uneducated mind

Screams as he downed a flask sent by Koch

It should have killed him

Bovine TB

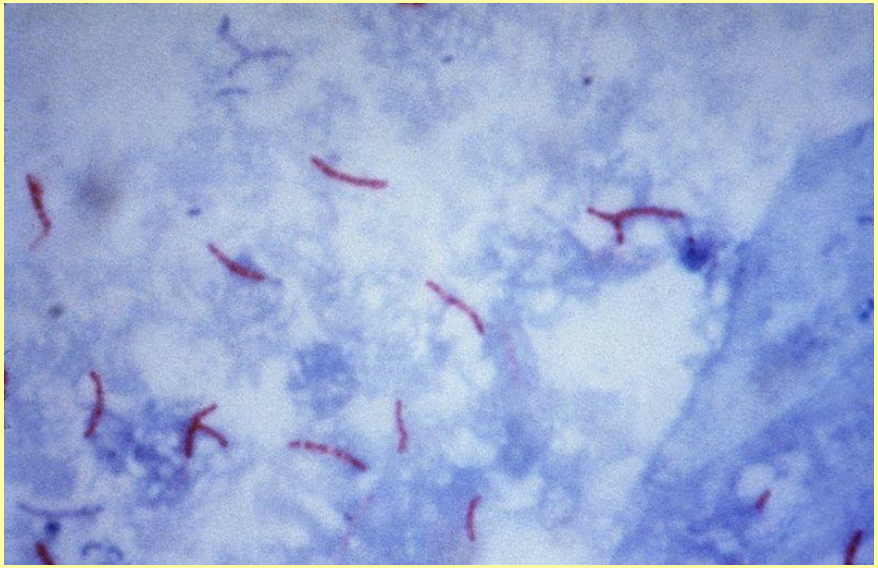
Bovine TB is a chronic infectious disease which affects a broad range of mammals

C18th: wasting disease of cattle in Germany Perlsucht (pearl-like granulomas on lung lining). Considered a variant of syphilis. Safe disposal of corpses.

first half of the 20th century, *M. bovis* is estimated to have been responsible for more losses among farm animals than all other infectious diseases combined.

In the 1930s, 40% of cows in the UK were infected with *M. bovis*

Very rare cases of human to human transmission (Lancet 2007) 6 people night clubbing near Birmingham, contracted bovine tuberculosis (TB). One man has been identified as the source of the outbreak, only one to have ingested unpasteurized products. 5 had had BCG, but one of these A woman died (meningitis).



Bovine TB

Zoonosis

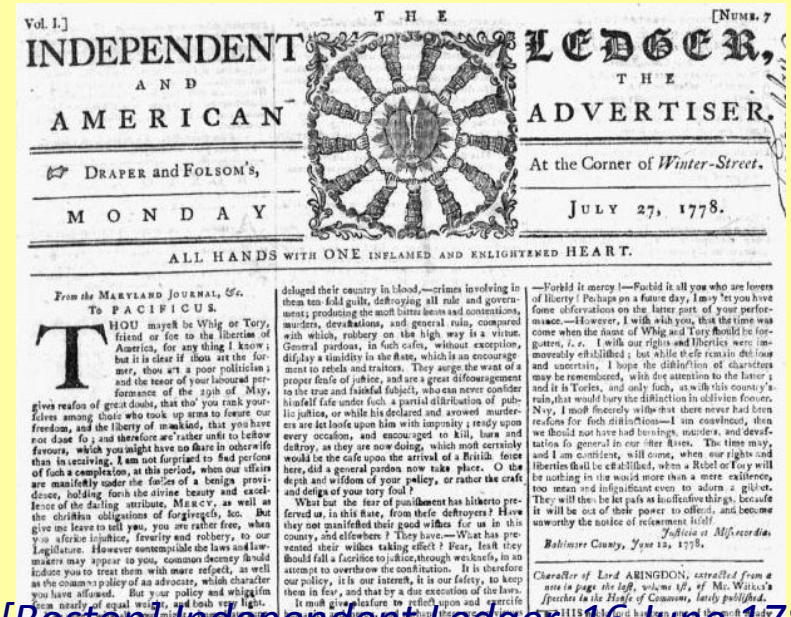
1868: **Villemin** Rabbits inoculated with material from cows or humans developed TB.

1882: **Koch** believed all tubercle bacilli the same

1898: **Theobald Smith** found small differences, also confirmed Villemin that M.Bovis more virulent in rabbits than human bacilli. bTB can infect other species.

1901: British Congress on TB: Koch agreed bTB distinct from TB but stated bTB harmless to humans, audience included Lord Lister and Vets, who disagreed. investigated by Royal Commission,

Led to test and slaughter, the most successful campaign against an infectious disease.



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INDEPENDENT AND AMERICAN LEDGER, THE ADVERTISER.

DRAPER and FOLSOM's, At the Corner of *Winter-Street*.

MONDAY JULY 27, 1778.

ALL HANDS WITH ONE INFLAMED AND ENLIGHTENED HEART.

From the MARYLAND JOURNAL, *&c.*

To PACIFICUS.

THOU myself be Whig or Tory, friend or foe to the liberties of America, for any thing I know; but it is clear if thou art the former, thou art a poor politician; and the tenor of your laboured performance of the 29th of May, gives reason of great doubt, that tho' you rank yourselves among those who took up arms to secure our freedom, and the liberty of mankind, that you have not done so; and therefore are rather unfit to bestow favours, which you might have no share in otherwife than in receiving. I am not surprised to find persons of such a complexion, at this period, when our affairs are manifestly under the smiles of a benign providence, holding forth the divine beauty and excellence of the darling attribute, MERCY, as well as the christian obligations of forgiveness, &c. But give me leave to tell you, you are rather free, when you afcribe injuftice, fevarity and robbery, to our Legiflature. However contemptible the laws and lawmakers may appear to you, common decency fhould induce you to treat them with more refpect, as well as the common policy of an advocate, which character you have affumed. But your policy and whigaifm [illegible] deluged their country in blood,—crimes involving in them ten fold guilt, deftroying all rule and government; producing the moft bitter hatreds and contentions, murders, devaftations, and general ruin, compared with which, robbery on the high way is a virtue. General pardons, in fuch cafes, without exception, difplay a timidity in the ftate, which is an encouragement to rebels and traitors. They purge the want of a proper fenfe of juftice, and are a great difcouragement to the true and faithful fubject, who can never confider himfelf fafe under fuch a partial diftribution of public juftice, or while his declared and avowed murderers are let loofe upon him with impunity; ready upon every occafion, and encouraged to kill, burn and deftroy, as they are now doing, which moft certainly would be the cafe upon the arrival of a Britifh force here, did a general pardon now take place. O the depth and wifdom of your policy, or rather the craft and defign of your tory foul!

What but the fear of punifhment has hitherto preferved us, in this ftate, from thefe deftroyers? Have they not manifefted their good wifhes for us in this county, and elfewhere? They have.—What has prevented their wifhes taking effect? Fear, leaft they fhould fall a facrifice to juftice, through weaknefs, in an attempt to overthrow the conftitution. It is therefore our policy, it is our intereft, it is our fafety, to keep them in fear, and that by a due execution of the laws.

—Forbid it mercy!—Forbid it all you who are lovers of liberty! Perhaps on a future day, I may let you have fome obfervations on the latter part of your performance.—However, I with with you, that the time was come when the name of Whig and Tory fhould be forgotten, *i. e.* I with our rights and liberties were immoveably eftablifhed; but while thefe remain doubtful and uncertain, I hope the diftinction of characters may be remembered, with due attention to the latter; and it is Tories, and only fuch, as with this country's ruin, that would bury the diftinction in oblivion forever. Nay, I moft fincerely with that there never had been reafons for fuch diftinctions—I am convinced, then we fhould not have had burnings, murders, and devaftations fo general in our after ftates. The time may, and I am confident, will come, when our rights and liberties fhall be eftablifhed, when a Rebel or Tory will be nothing in the world more than a mere exiftence, too mean and infignificant even to adorn a gibbet. They will then be let pafs as inoffenfive things, becaufe it will be out of their power to offend, and become unworthy the notice of refentment itfelf!

Judicia et Mifcoredia.

Baltimore County, June 12, 1778.

Character of Lord ARINGDON, *extracted from a note in page the left, volume 1ft, of* Mr. Wilkes's *fpeeches in the Houfe of Commons, lately publifhed.*

[illegible] HIS [illegible]

[Boston] Independent Ledger, 16 June 1783.

1797: Klencke, Brunswick suggested transmitted to humans via infected milk

C20th 50,000 new cases of human mTB infection every year, 2000 of whom died.

Pasteurization:

1773: England; scalding and straining of cream increased keeping of butter; still a "new" process in American newspapers as late as 1802

Controversy rages: Raw milk a health food claims of preventing Asthma vs a killer (FDA)

1998 and 2005, the Centers for Disease Control identified 45 outbreaks of food borne illness from raw milk. Those outbreaks accounted for 1,007 illnesses, 104 hospitalizations, and 2 deaths.

1960's, cattle TB eliminated in most of UK,

except south-west

Ministry of Agriculture or MAFF (DEFRA) suspected other sources of TB

April 1971, dead badger farm in Gloucestershire recent TB. +ve.

Gloucestershire roadkill bTB in 36/165 badgers.

The few very sick badgers excrete huge numbers of TB bacilli Which can survive in the environment for up to a month depending on the time of year and other conditions.

However 80% of badgers tested negative.

Only a very small percentage of those +ve were infectious.

Culling Badgers to protect Cows

bTB in UK cattle is increasing. Escalating sums of money for disease control.

In 2001 Foot and Mouth struck: Routine TB testing of cattle suspended

Cattle kept together indoors.

infected animals spread TB

Slaughtered replacements from elsewhere, not pre-tested for TB – spreading bTB to areas absent for years, County Durham; Scotland.

Herds infected mostly from cattle purchased from infected areas (80%)

Wildlife reservoir (Badger 20%)

Culling slight reduction in cattle TB - but also an increase in cattle TB around the edges of those areas

Natural ranging depends on population density of badgers. In areas of high density badgers are very territorial and most live in social group.

bTB in cattle mostly healthy animals showing an immunological response to tuberculin. different scenario when national eradication programmes devised, when the protection of public health rather than animal health was the prime motivation

Controversies in Control of Bovine TB

Little justification for the large sums of public money spent on bTB control in the UK. Torgeson & Torgeson

Britain's Randomised Badger Culling Trial

provides robust evidence of the role badgers have in transmission of *M bovis* to cattle. Culling badgers changed social behaviour +ve & -ve effects on TB incidence in cattle,

Culling cannot make a meaningful contribution to disease control

Animal management, removal of known sources of infection, early diagnosis, quarantine, movement control and environmental hygiene are less than enthusiastically promoted and applied. The reality is that where these principles are applied in a sustained manner, the outcome is more likely to be successful

Robbie A. McDonald , Central Science Laboratory, York:

However bTB control in cattle is irrelevant as a public health policy. In the UK, cattle-to-human transmission is negligible.

2007, 279 cases TB in the South West only 2 bTB.

Aerosol transmission, the only probable route of human acquisition, occurs at inconsequential levels when milk is pasteurised, even when bTB is highly endemic in cattle.

No evidence for cost benefit in terms of animal health of bTB control

The TB epidemic

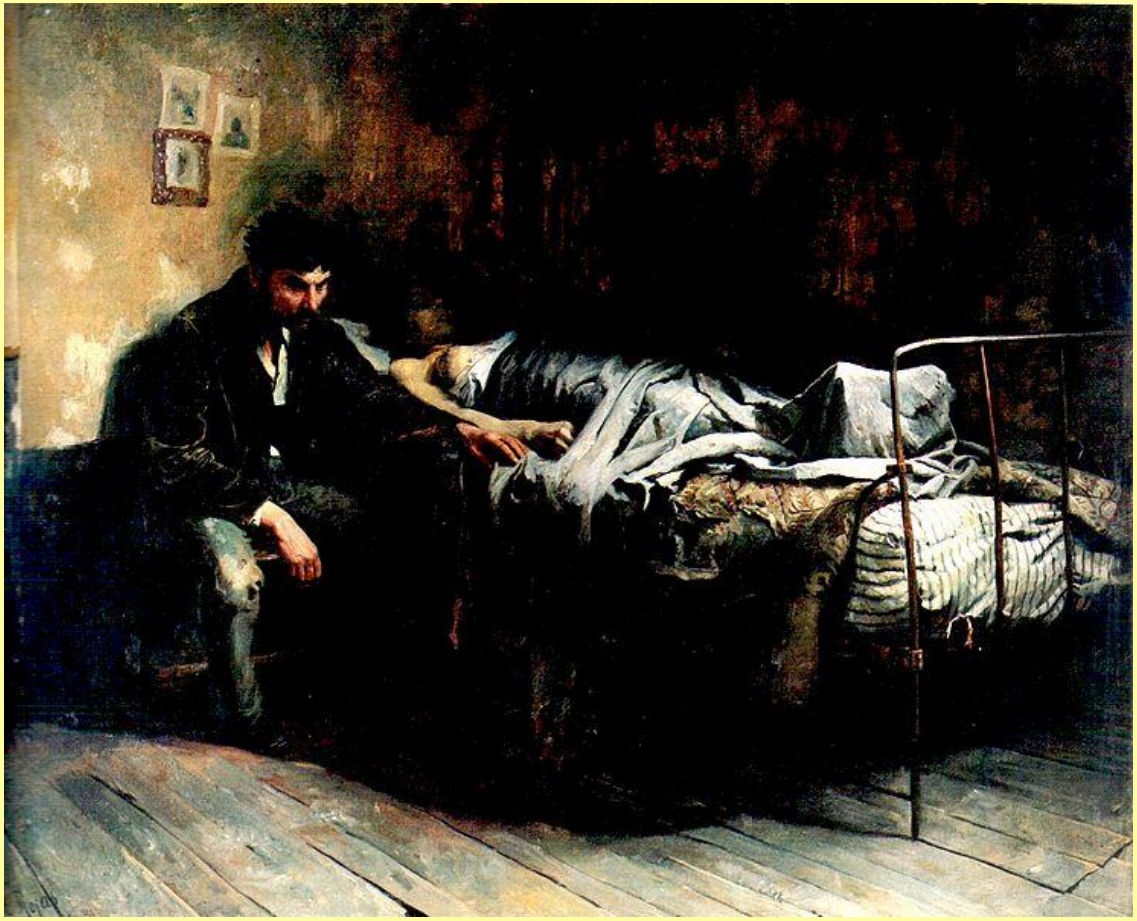
1800s in Britain; no effective treatment.

Even the diagnosis difficulties. Based on symptoms and examination of the chest. The pulse , temperature and weight.

1882 Koch discovered bacillus: the sputum could be examined as decisive test. There were, however, no X-rays

1865: Pollock: 3500 patients attended Brompton Hospital over previous 7 years; 'patients of all classes below the wealthy'. Survival time 4yrs

1887: Williams: 1000 patients 'private practice, upper and middle classes of society' from 1842 to 1864, life expectancy of eight to ten yrs.



La miseria (1886).
Christobal Rojas Veneualan, scholarship Paris, dies of TB aged 32

Prevention
91 years of Bacillus Calmette-Guérin

Vaccination prevented smallpox, ?parallel between bovine tuberculosis and cowpox:

hypothesized that infection with bovine tuberculosis might protect against infection with human tuberculosis.

In the late 19th century, clinical trials using *M. bovis* were conducted in Italy with disastrous results, because M. bovis was found to be just as virulent as M. tuberculosis.

Koch famous for isolating the germs causing fearsome diseases, Cholera, Anthrax and TB

now overtaken by Pasteur, (Anthrax, Rabies)

1890, 10th International Medical Congress Berlin, announces he had "at last hit upon a substance which has the power of preventing the growth of tubercle bacilli,"

excellent results in clinical trials of the agent, prepared and administered by two physicians—E. Pfuhl, his son-in-law, and A. Libbertz, of the Höchst pharmaceutical firm1890: Announces sCURE FOR TB

awarded Grand Cross of the red eagle

1891: Virchow demonstrates 21 innoculated patients who died of miliary TB

Uproar: Koch forced to reveal secret of his miracle cure. Grew bacteria in glycerin broth then heat, but this still left some viable bacteria.

Things fell apart, divorces

Marries 17 yr Hedwig Freiburg, (rumours that he had prematurely used the vaccine to support 2nd marriage)

Leaves for Africa (Malaria) and Bombay (Plague spread by rats)

Returns in triumph, awarded Nobel Prize and dies after an angina attack following strenuous cycle of lectures in Berlin

Prevention
91 years of Bacillus Calmette-Guérin

Camille Guérin 1872-1961, b. Poitiers, father dies of TB (so does his wife). Vet, found immunity to TB associated with living tubercle bacilli in the body.

Léon Charles Albert Calmette 1863 – 1933

brother of Gaston (1858–1914), editor *Le Figaro* who was murdered in 1914 by Henriette Caillaux, socialite mistress and later wife of Finance Minister Joseph Caillaux.

1881 School of Naval Physicians at Brest.

1883 in the Naval Medical Corps in Hong Kong, studied malaria.

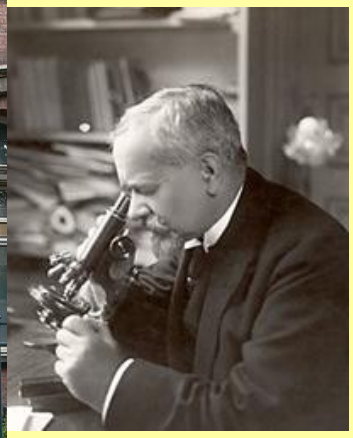
In Paris meets Pasteur, sets up branch in Saigon, dysentary

Returns as director of Pasteur institute Lille

work with Guérin on attenuation by successive cultivation on bile-substrate, idea of Norwegian Kristian Feyer Andvord (1855–1934).

1914 Germans requisition cattle, takes Calmette's wife as hostage to Germany.

1921, 230 passages later, they used BCG to successfully vaccine newborn infant born to a tuberculous mother in the Charité in Paris.



Lübeck disaster:

259 children immunised, 207 contracted TB; 72 died contamination of some batches in Germany. Mass vaccination of children was reinstated in many countries after 1932, when new and safer production techniques were implemented

1850: 500

1950: 50/10,000

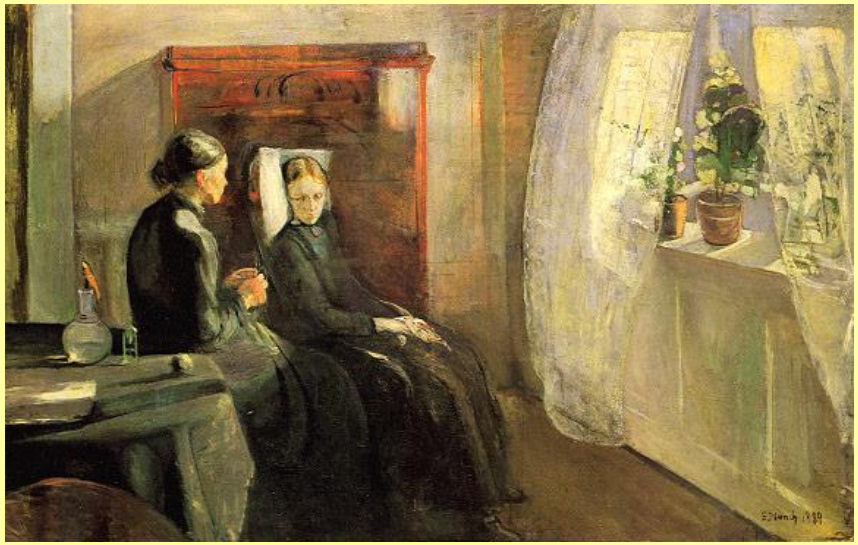
1953: UK universal BCG immunization

2005, policy to immunize all school children at the age of 13, and all neonates born into high risk groups.

Routine immunization with BCG was withdrawn in 2005 because of falling cost-effectiveness:

1953, 94 children would have to be immunized to prevent one case of TB

1988, incidence of TB in the UK had fallen 12,000 children immunized to prevent one case



Spring, 1889 Edvard Munch

Treatment

primarily treated at home. variety of treatments snake oil and wearing a beard

The Sick Child (Det syke barn; 1885) Edvard Munch (1863 – 1944).

favorite sister Sophie dying of TB 1877 age of 15. Munch considered the painting "a breakthrough in my art”

4th version; painted 1907, Tate Gallery, 1928, Gemäldegalerie Dresden.

1930s; National Socialists; Munch's paintings as "degenerate art", and removed his work from German museums

open air treatment in UK

George Boddington 1799-1882; St. Barts open air clinic in Sutton Coldfield.

1836 acquires Driffold House, Maney.

1840: essay, ***On the Treatment and Cure of Pulmonary Consumption***, condemning contemporary treatments and advocating instead dry frosty air, gentle exercise, and a healthy diet

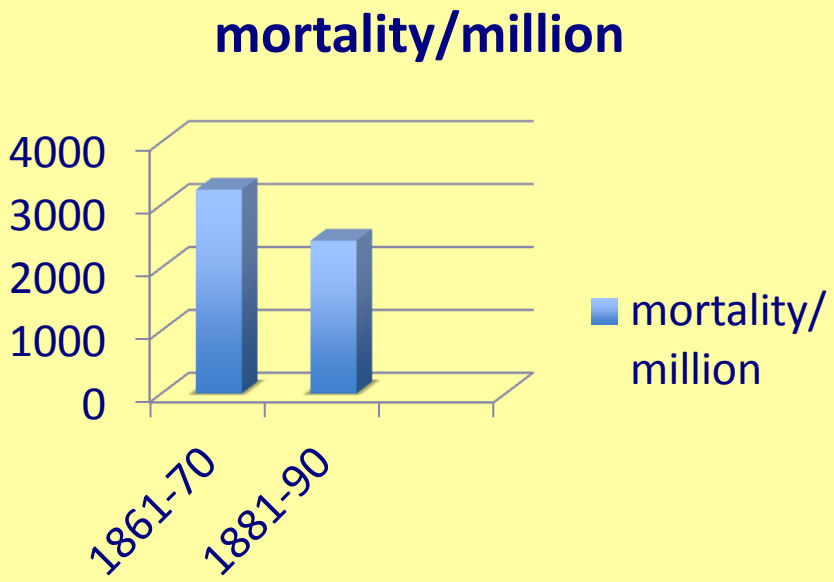
Rubbished in the Lancet ‘very crude ideas and unsupported assertions’

1. fickle British climate being regarded as unsuitable

2. Culture: exaggerated fear of draughts and chills led to closed windows and stuffy, over-heated rooms for patients. ‘All social classes were prejudiced against fresh air, and their prejudices were not without foundation. First, on quasi-medical grounds that are still with us, there was the fear of draughts: the draughts would produce the great British chill, an affliction unknown to the rest of the civilised world3. Mortality from TB was falling

Scale of Need: would fill every hospital bed: 1897 0.25m Phthisis in UK.

(OR McCarthy JRSocMed)



Open air Treatment Europe

Herman Brehmer 1826-1889: Student Berlin;1853 but had contracted TB as a botany student in Silesia. Told to move: Himalayas. Returns 1854 writes his thesis Tuberculosis a curable disease

Sister in law; Countess Maria von Colomb, a niece of Prussian General Gebhard Leberecht von Blücher

1863: **Brehmerschen Heilanstalt für Lungenkranke**, a Sanitorium in a group of cottages in Görbersdorf plentiful altitude fresh air, and good nutrition. Later 300 beds. The results surpassed all previous treatments

1876: **Peter Dettweiler (1837-1904**) patient later assistant—opened **Falkenstein sanatorium**

Alexander Spengler: 1827-1901. Participated in March Revolution. After defeat fled to Switzerland, studied medicine Zurich.

1868 Davos: **Spengler-Holsboer**

1904: National Anti-Tuberculosis Association (Canada), Dr. Ferguson; distinction between health resorts and the new tuberculosis treatment hospitals: new word **not** derived from ***sanitas***, health. Emphasizing the need for scientific healing they used verb root **sano**, to heal, and adopted the new word *sanatorium."*

20th Century sanatoria

1928: Jan Duiker Sanatorium at Zonnestraal (“sunbeam”). Concrete attempted to integrate the patient with his natural surroundings. TB was meant to become extinct so only designed for a life of 30 years.

1932: Alvar Aalto's Sanatorium at Paimio: non-splash basins, so that the patient would not disturb the other while washing. The patients spent many hours lying down, and thus Aalto placed the lamps in the room out of the patients line of vision and painted the ceiling a relaxing dark green

Sun Terraces and sunroof.

Charles Edouard Jeanneret 1887–1965 (**Le Corbusier)** controversial designs show understanding of TB: roof terrace area, whether on a house or a block of flats Unité d'Habitation in Marseilles (1953), used for physical exercise and open-air relaxation

Influence of Sanatoria on Modernist architecture

Early C20th: modernist functional lifestyles that emphasized purity, hygiene, fresh air and sunlight *Licht und Luft*. Coco Chanel suntan:

Modernist architecture takes this on. flat roof, balcony and terrace. Designing buildings to combat TB, for rich and poor.

Flat roof: Davos: Das Flache Dach im Davos': originally to prevent injury from falling icicles in 1851, by Silesian builder, Samuel Haussler.

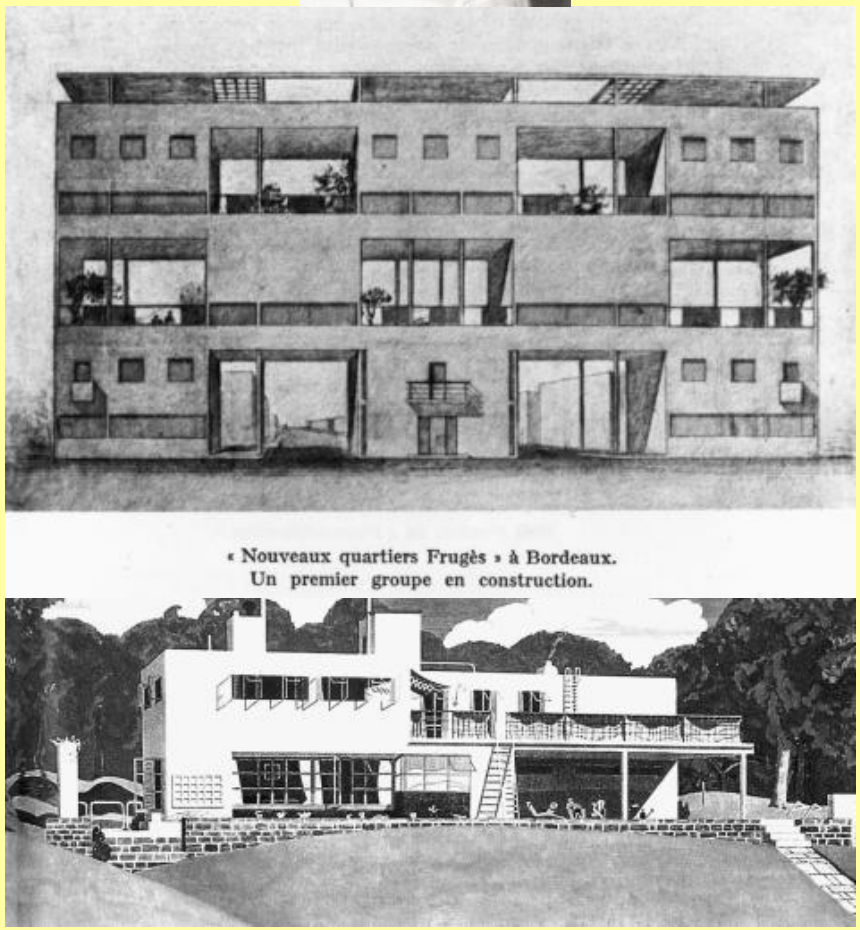
Terrace & Balconies

Allowed fresh air and exposure to sun

(**Le Corbusier:** *Urbanisme (1924), City of tomorrow (1929)*

If you are dying of heart disease or consumption you are not likely to spend time doing five-finger exercises on the piano. Yet such words as Fatherland, Poetry, Ancestor worship, the Ideal, are eloquent phrases flung about by numbers of people occupied in writing for the papers, whose mission is to direct public opinion. But when it comes to a question of demolishing rotten old houses full of tuberculosis and demoralizing, you hear them cry, "What about the iron-work, what about the beautiful old wrought-iron work."

Margaret Campbell Med Hist 2005



Pen Pits (1936), . House designed by P J B Harland for Sir Arthur Bliss watercolour by Edward Wadsworth (1889–1949 dazzle camouflage WW1`)

Phototherapy

Niels Ryberg Finsen (1860 – 1904)

Faroe Islander, Medical school Copenhagen

Lupus Vulgaris:

chronic and progressive; active 20yrs resistant to all treatment.

"lupus" may derive from the rapacity and virulence of the disease;

1590 "a malignant ulcer quickly consuming the neather parts; ... very hungry like unto a woolfe

Persistent and progressive form of cutaneous TB

Small sharply defined reddish-brown lesions with a gelatinous consistency (called apple-jelly nodules)

Lesions persist for years, leading to disfigurement and sometimes skin cancer

1893: Finsen Om Lysets Indvirkninger paa Huden ("On the effects of light on the skin"),

1895, he was recommending sunbathing for all forms of tuberculosis, not just skin lesions.

Queen Alexandra of Great Britain, (1844–1925), consort to Edward the VII, bronze statue London Hospital

"Introduced to England the Finsen light cure for Lupus, and presented the first lamp to this hospital".

1903: Nobel Prize:

Vitamin D conversion to active hormone Calcitrol

Vitamin D deficiency is a risk factor for tuberculosis

? explain the increased susceptibility of African-Americans to tuberculosis

Provitamin D a precursor of cholesterol; synthesised de-novo in skin

1849: **Williams CJB**, Cod liver oil in Phthisis. Lon J Med. 400 pts Rx

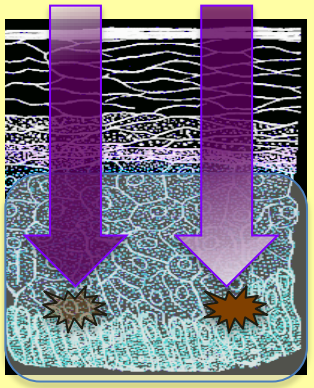
2011: Lancet reported a trial in which Vit D did shorten disease in pts with a subtype of Vit D receptor

In pts with normal levels, Adding Vit D to modern therapy makes no difference.

Cholecalciferol manufacture: irradiation of 7-dehydrocholesterol lanolin sheep's wool.

Alternatively **ergocalciferol** (vitamin D_2) derived from the fungal sterol ergosterol.

220-390nm UVB



SKIN
7-dehydrocholesterol
Pro-vitamin D

vitamin D_3
Cholecalciferol:
Inactive non-hydroxylated form

Parathyroid hormone
low Phosphate

LIVER
25-hydroxyvitamin D_3
Calcifediol:
Pre-hormone

KIDNEY
1,25-dihydroxyvitamin D_3
Calcitriol.
increases blood Ca2+
(>absorption, <excretion, >release from bone)

Collapsing the lung

James Carson, q. Edinburgh 1799.

In Liverpool: experiments Literary and Philosophical Society of Liverpool

On the elasticity of the lungs

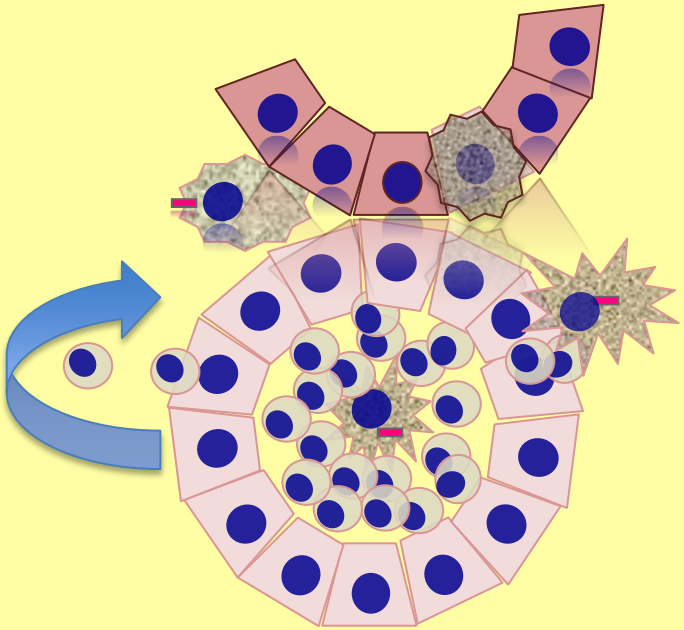
clarified the mechanics of respiration

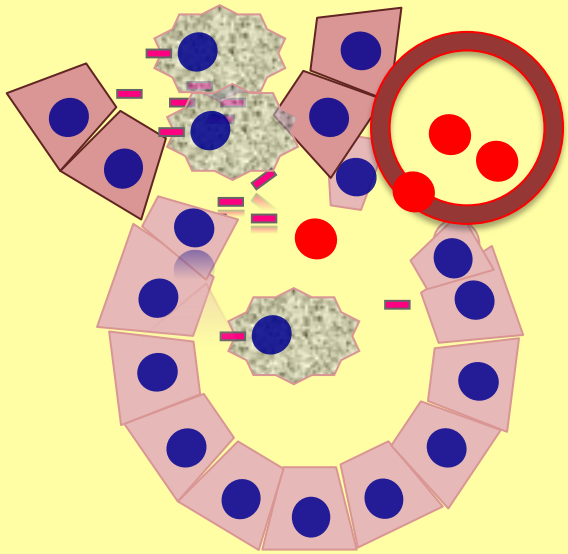
On lesions of the lungs: suggested that this knowledge might be employed to produce temporary collapse of the lung as a therapeutic measure. Two attempts at a clinical trial were defeated by widespread pleural adhesions but the first recorded attempts at artificial pneumothorax had been made

first successful treatments for tuberculosis were all surgical. They were based on the observation that healed tuberculous cavities were all closed. Surgical management was therefore directed at closing open cavities in order to encourage healing

Alice Neel (1900-1984), *T.B. Harlem, 1940*
National Museum of Women in the Arts

TB walled off in granuloma
Kept stable by cytokines
Genetics (Diathesis)
Health of immune system
Vitamin D
Steroids
Anti-TNF
AIDS
Debility
Cavitation access to O_2





Miracle drug

Selman Waksman 1888-1973

Ukrainian born professor of biochemistry at Rutgers University

Coins the term antibiotic

1952: Nobel Prize for discovery of Streptomycin

Streptomyces are found in soil and decaying vegetation. Infrequently pathogenic

Streptomyces griseus

Alfred Schatz isolated a bacterial growth inhibitor from the mould. Post grad student. Lived in the lab.

Fell out with Waksman and bitter about Nobel Prize (similar to Koch's nomination in 1901)

Dr Wm Hugh Feldman from Mayo tested the substance against TB in Guinea Pigs

First pt 21 yr old dying of pulmonary TB. Miraculous cure, goes on to have 3 children.

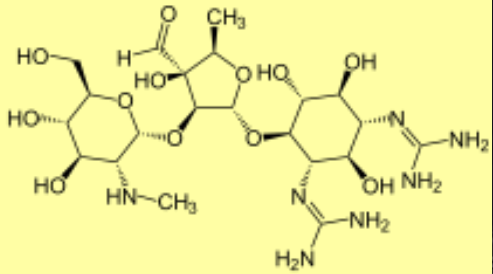
1945: 34 pts

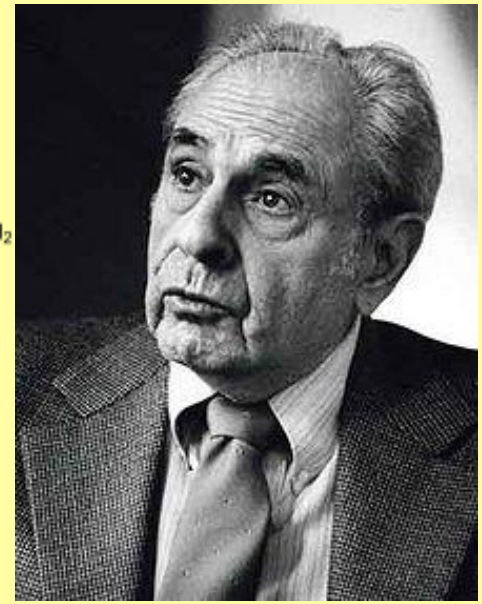
Not all plain sailing:

Eric Blair 1947 being treated with phrenic crush and sub-diaphragm air

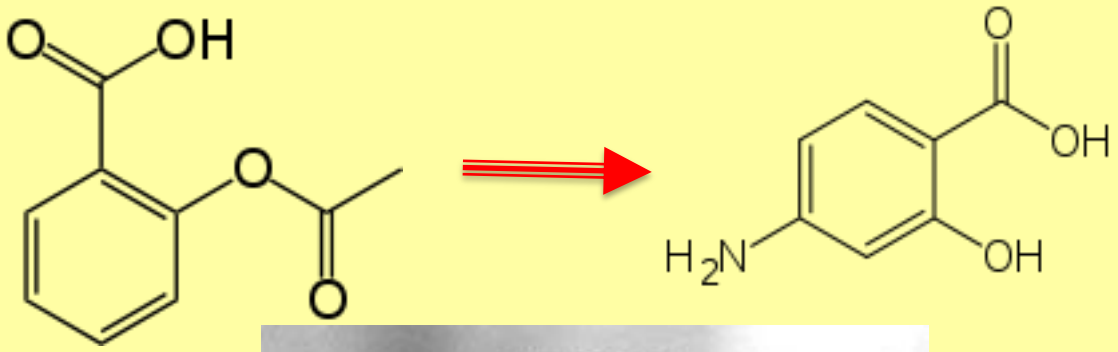
David Astor a rich admirer obtains SM despite dollar-restrictions asking Nye Bevan to allow its import.

Severe hypersensitivity, gives his expensive drug to 2 dying women patients, completes ***1984*** and dies in UCL after marrying Sonia Brownell.





Feldman gets TB himself and is treated with the precious rare drug but gets resistance and would have died but…



Jorgen Lehmann working in Gothenburg.

O_2 uptake by bacillus stimulated by simple organic acids (salycilic, benzoic)

Inhibiting this path with para-aminosalycilic acid (related to aspirin)

20 pts reported in 1946

Would not have caught on if Feldman had not developed drug resistant TB himself.

His life was saved

1948:MRC trials: combined with streptomycin reduced resistent strains of TB

Isoniazid

1912: Hans Meyer & Josef Mally synthesised a chemical

Had antidepressant activities

With race on for new anti-TB, Squibb, Bayers and Hoffman La Roche came up with a chemical active against TB

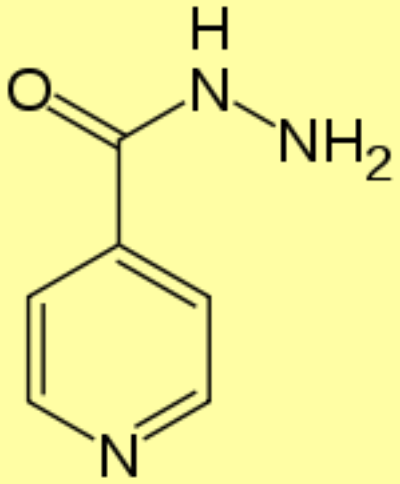
only when patenting was nearly done realised it was isoniazid

Pro-drug activated by enzymes in the bacillus and prevent it making mycolic acid

Trial Sea View Hospital NY. 44 pts

Cheap and effective

Old drugs cost	$3,500/patient
Isoniazid	$100



NICE guidelines

A 6-month, four-drug initial regimen

6 months of isoniazid and rifampicin

supplemented in the first 2 months with pyrazinamide and ethambutol)

‘standard recommended regimen’

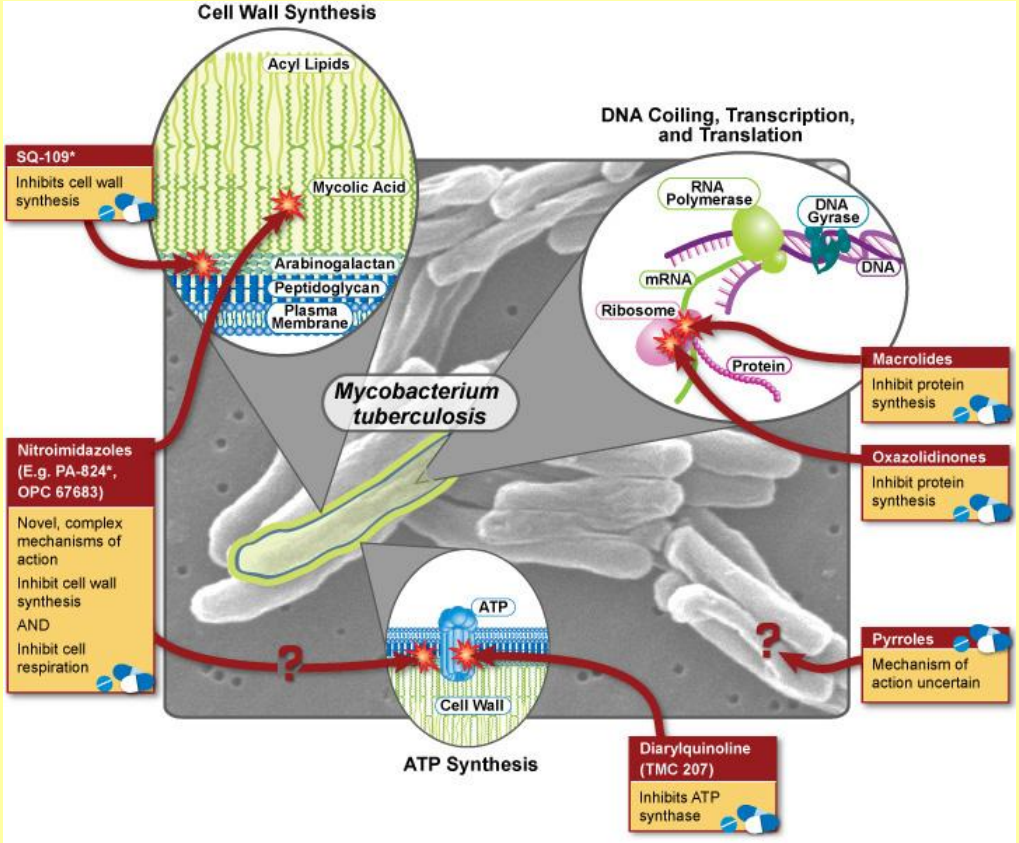
Old TB Sanatoria closed or became specialist Hospitals

Frimley

Papworth

Switzerland: Davos builds ski lifts

HOWEVER…….



THANK YOU