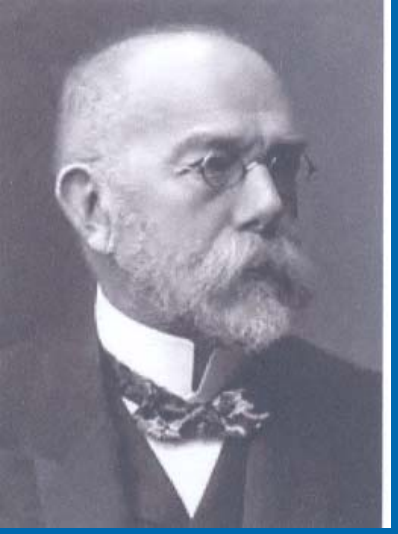

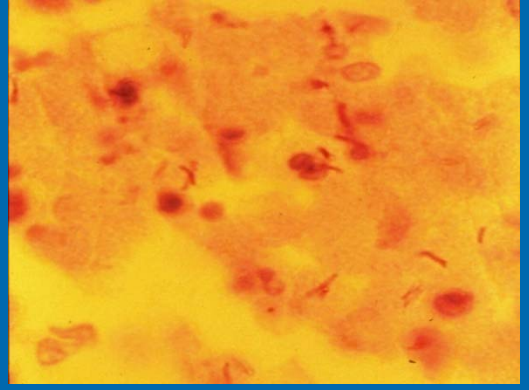

Tuberculosis & co-morbidities

12/9/2011

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HISTORY OF TUBERCULOSIS

- TB: Major Cause of Suffering and Death
- **First human case 3400 BC**
- **Consumption, White Plague, scrofula, King's Evil, pthisis**
- **England 1815: 1 in 4 deaths**
- **France 1918: 1 in 6 deaths**
- **During 20thC, TB killed ~100 million**

Timothy Cratchit aka Tiny Tim

- **Tiny Tim known based on invalid son of Dicken's friend**
- **1997 Excavation at St. Andrew's Church found 19C gravesite**
- **"*In Memory. Timothy Cratchit. 1839–1884, Beloved Husband of Julia, Father of Robert, and Son of Robert and Martha*."**
- **Skeletal remains of 40yo man wearing metal frame and leather on legs and back**
- **PCR confirmed TB***

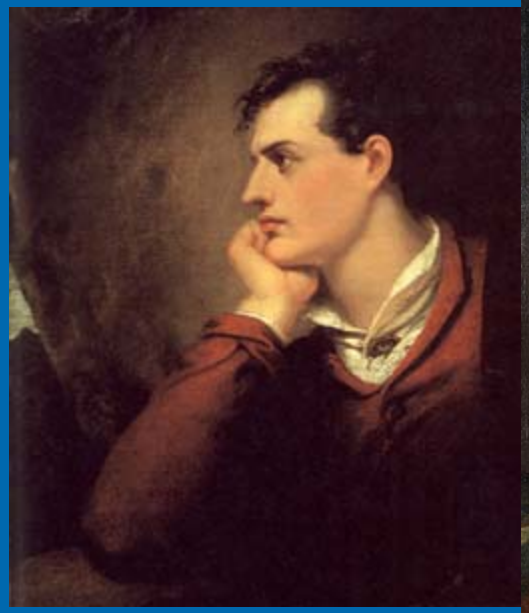
*CW Callahan. JID 1997;176:1653–4

HISTORY OF TUBERCULOSIS

- At the height of the Romantic movement tuberculosis was declared to be:
- "The mark of spirituality or the wages paid by those seemingly touched by a burning creativity."

HISTORY OF TUBERCULOSIS

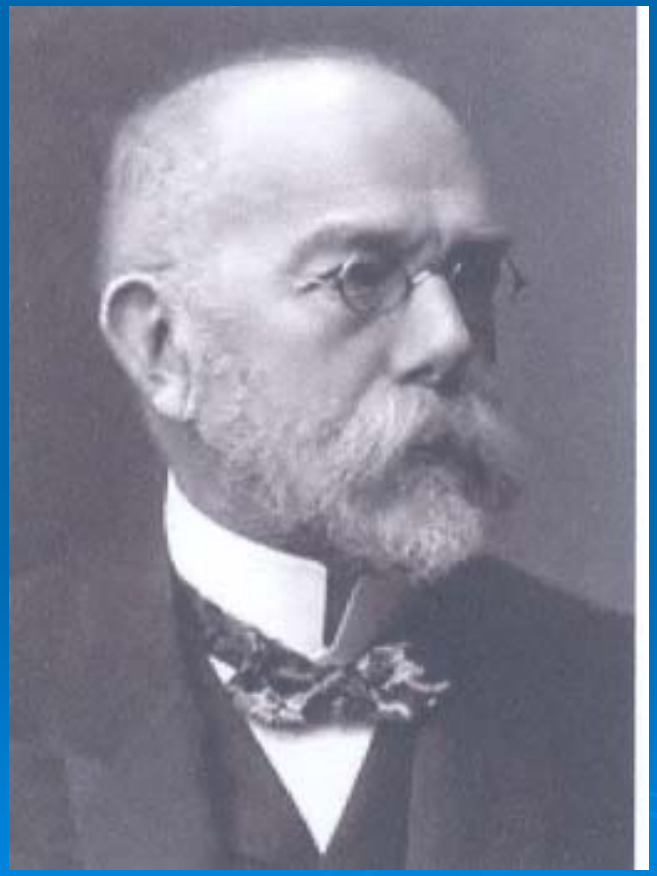
- Mark of beauty-pale consumptive look
  - 1858 painting of Queen Guinevere by William Morris
- La Boheme- Mimi
- La Dame aux Camelias- Margrerite



“I look pale . . . I should like to die of consumption – because the ladies would say ‘Look at poor Byron, how interesting he looks in dying’.”

Lord Byron (1788-1824)

HISTORY OF TUBERCULOSIS



- Robert Koch(1843-1910)
- Discovery Tuberculosis bacillus
- April 10, 1882
  - Berlin Physiological Society

HISTORY OF TUBERCULOSIS

- Sanatorium Movement

- National association for the study and prevention of tuberculosis 1904.
- Rapid growth.
  - 11,953 beds in 1908
  - 30,000 beds in 1915
  - 97,726 beds in 1942 (peak)

HISTORY OF TUBERCULOSIS

- Tuberculosis Nursing

Nurse crossing roofs to visit patients

With no drug therapies, past TB suffers like these in 1953 were isolated in sanatoriums.

Tuberculosis today

Still a Major Cause of Suffering and Death

- One third of the worlds population are infected with TB
- 9 million people worldwide become sick with TB each year
- 2 million will die each year of TB related disease
- TB is the leading killer of people who are HIV infected.

TUBERCULOSIS AND MEDICAL SCIENCE

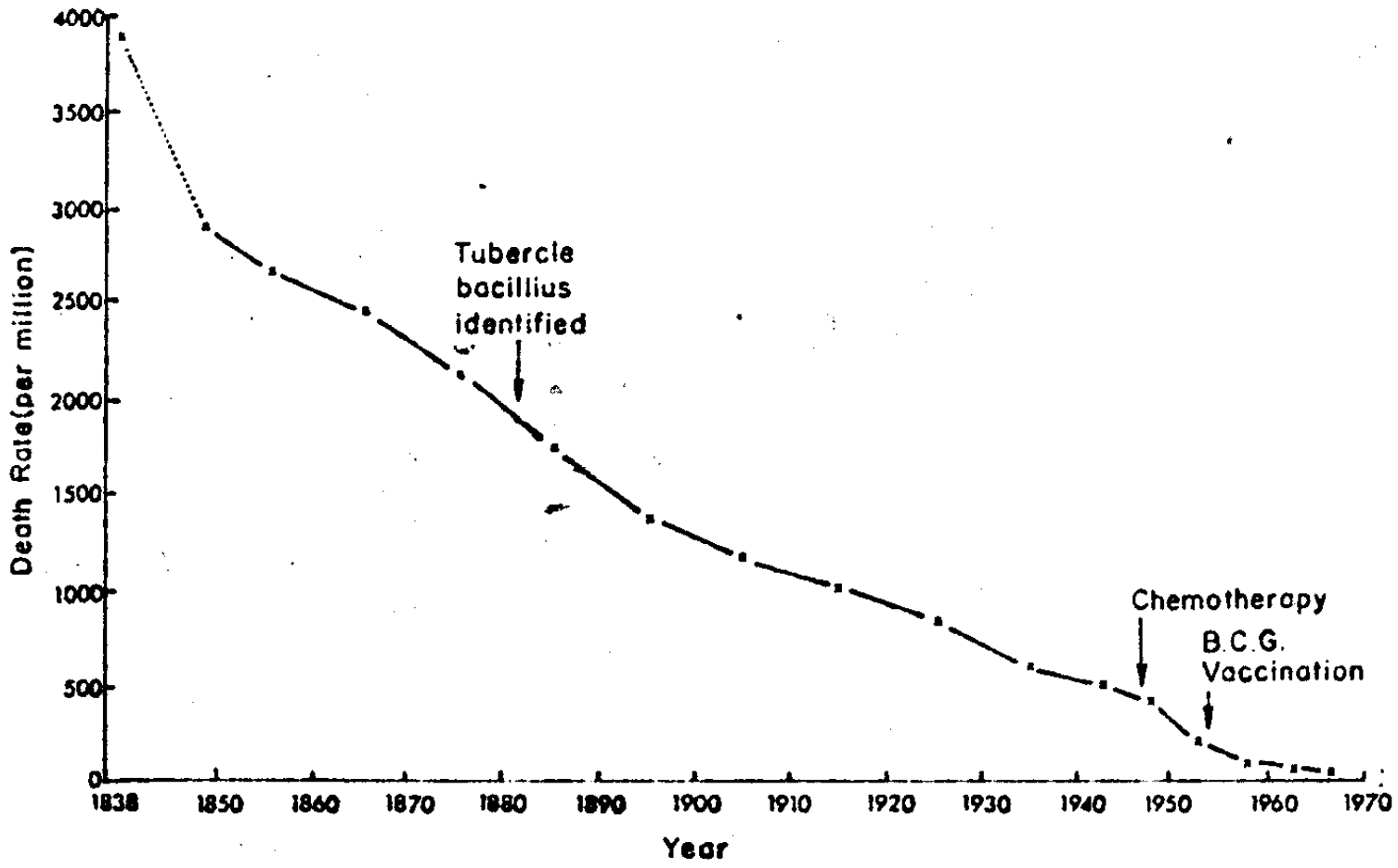
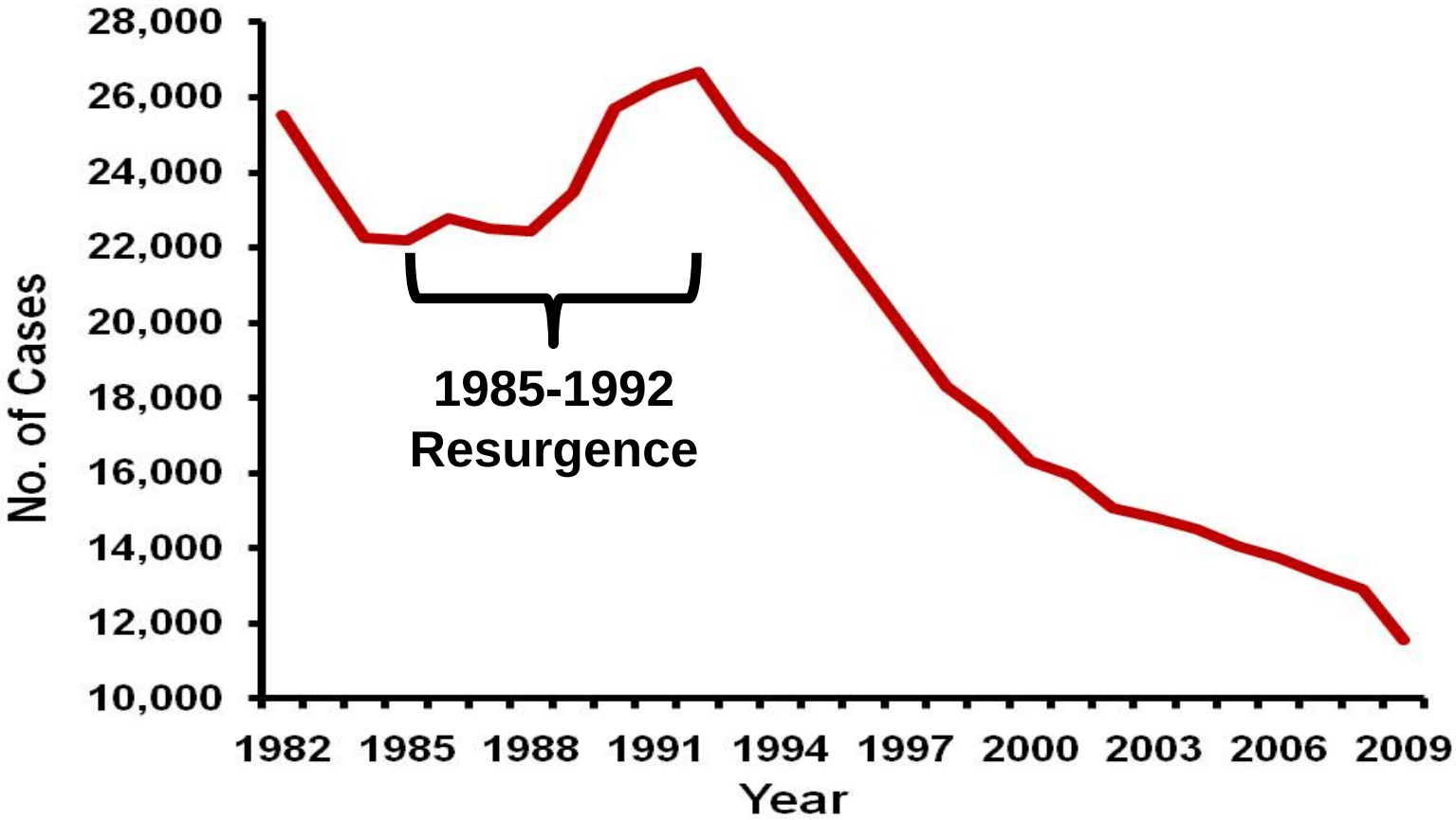


Fig. 1. Respiratory tuberculosis: mean annual death rate, England and Wales. (*Reproduced with permission from McKeown T, Lowe CR. An Introduction to Social Medicine. Oxford: Blackwell, 1974.*)

Tuberculosis Cases in the United States, 1953–2010

year	Tuberculosis Cases	Rate/100,000 population	Tuberculosis Deaths	Death /100,000 population
1953	84,304	52.6	19,707	12.4
1960	55,494	30.7	10,866	6.0
1970	37,137	18.1	5,217	2.6
1980	27,749	12.2	1978	0.9
1990	25,701	10.3	1810	0.7
2000	16,309	5.8	776	0.3
2010	11,182	3.6	------	-------

Reported TB Cases, United States, 1982–2009



*Updated as of July 1, 2010.

Tuberculosis in WV

Year	Active cases	New cases	Deaths
1950	6,107	2,099	428
1960	4,563	676	105
1970	3,077	329	65
1980	----	203	10.4
1990	----	87	4.9
2010	----	14	1

Tuberculosis- disease

- Primary *(10%infected in youth will develop disease in their lifetime)*
  - *20/1 risk in 1st year*
- Secondary/postprimary
  - *1/3 of all new adult cases in US are due to recent transmission & not reinfection*

Tuberculosis- disease

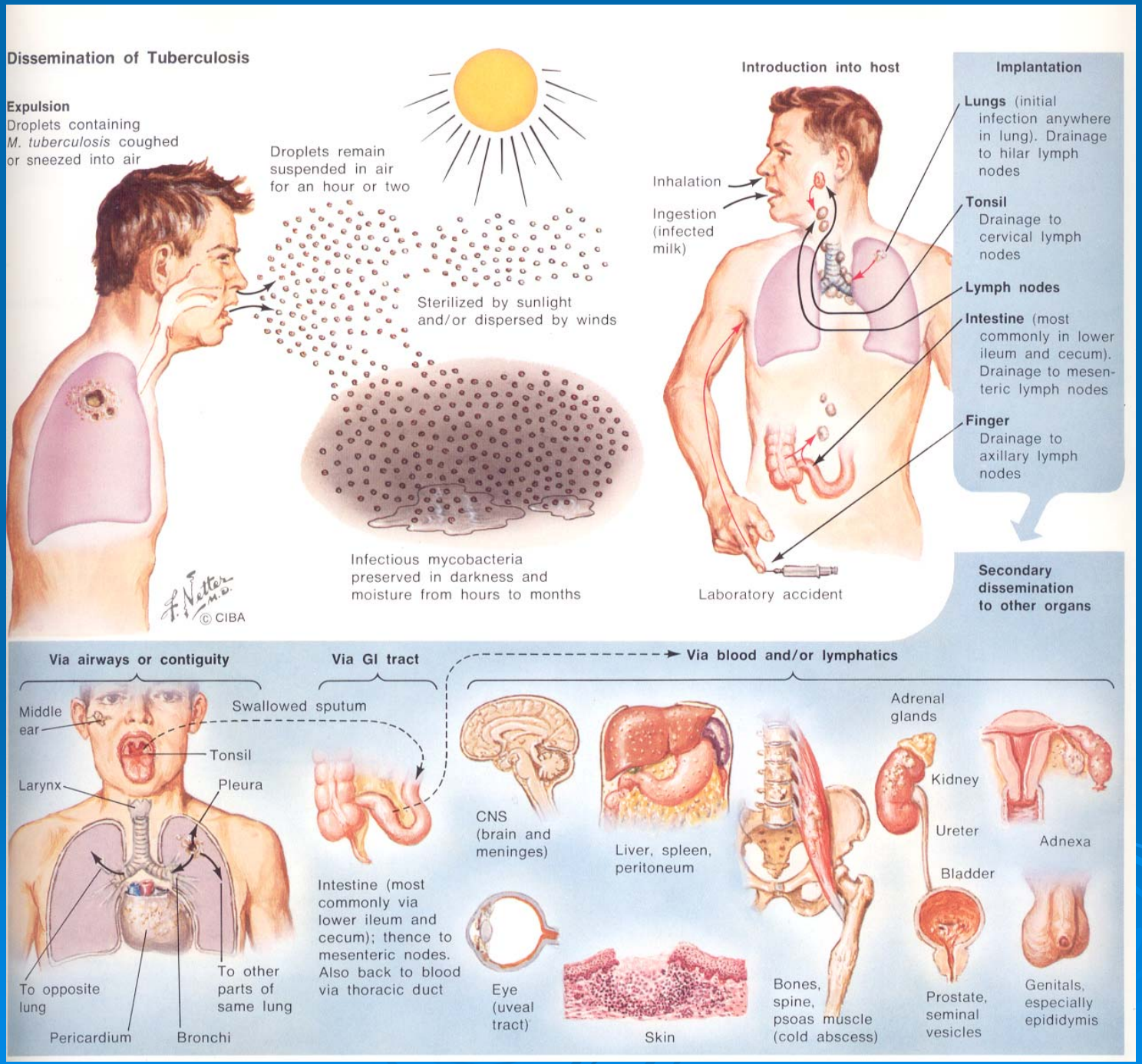
- Without treatment:
  - 5% if those infected with M.TB will develop disease in the 1st 2 years after infection
  - Another 5% will develop it in their lifetime
    - (a lifetime risk after infection of 10%)

Tuberculosis Infection
exogenous factors

- Crowding
- Poor ventilation
- Disease site cavity/larynx
- Co-morbidities HIV/IDD infected individual
- Delay in seeking care
  - by infected individual

Crowding

- *M.T B is spread by* droplet nuclei expelled when person with infectious TB coughs, sneezes, shouts, or sings
- Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi
- Rate of infection affected by proximity, frequency, and duration of exposure
- Major of MTB is human


Dissemination of Tuberculosis
Expulsion
Droplets containing
M. tuberculosis coughed
or sneezed into air
Droplets remain
suspended in air
for an hour or two
Sterilized by sunlight
and/or dispersed by winds
Infectious mycobacteria
preserved in darkness and
moisture from hours to months
F. Netter M.D.
© CIBA
Introduction into host
Inhalation
Ingestion
(infected
milk)
Laboratory accident
Implantation
Lungs (initial
infection anywhere
in lung). Drainage
to hilar lymph
nodes
Tonsil
Drainage to
cervical lymph
nodes
Lymph nodes
Intestine (most
commonly in lower
ileum and cecum).
Drainage to mesen-
teric lymph nodes
Finger
Drainage to
axillary lymph
nodes
Secondary
dissemination
to other organs
Via airways or contiguity
Via GI tract
Via blood and/or lymphatics
Middle
ear
Swallowed sputum
Tonsil
Larynx
Pleura
To opposite
lung
To other
parts of
same lung
Pericardium
Bronchi
Intestine (most
commonly via
lower ileum and
cecum); thence to
mesenteric nodes.
Also back to blood
via thoracic duct
CNS
(brain and
meninges)
Liver, spleen,
peritoneum
Adrenal
glands
Kidney
Ureter
Bladder
Adnexa
Eye
(uveal
tract)
Skin
Bones,
spine,
psoas muscle
(cold abscess)
Prostate,
seminal
vesicles
Genitals,
especially
epididymis

Tuberculosis transmission

- Person to person by ***droplet nuclei***
  - ***Aerosolized***
    - Coughing (may be 3000 organisms)
    - Sneezing
    - Signing/speaking

    Those <10 um in diameter may remain suspended for up to several hours

    Cavitary & laryngeal-most organisms

Tuberculosis Infection
exogenous factors

- Crowding
- Poor ventilation
- Disease site cavity/larynx
- Delay in seeking care
  - by infected individual
- Co-morbidities HIV/IDD infected individual

Tuberculosis Infection
exogenous factors

Tuberculosis is a social disease with medical implications.

Tuberculosis- disease

endogenous factors

- Individual's innate susceptibility / Genetics
- Individual's level of functional cell-mediated immunity
  - Less in < 4 yrs
  - Elderly
  - Co-morbidities that effect immunity

Mycobacterium Tuberculosis (around 4000 genes)

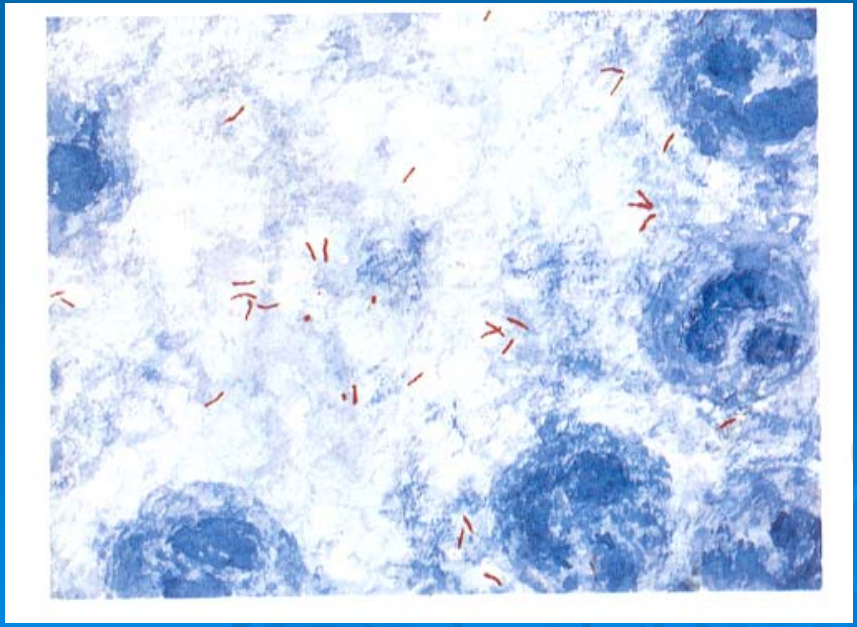
- Mycolic acids in the bacterial cell wall
  - Arabinogalactan
  - Peptidoglycan

  (confers low permeability of the cell wall-

  Reducing the effectiveness of most antibiotics)

Mycobacterium Tuberculosis

- A neutral or Gram positive, **acid fast**, rod-shaped non-spore forming thin **aerobic** bacterium of the order Actinomycetales



Co-Morbidities

Some effect disease transmission, some progression to disease & others effective treatment

Risk factors for active Tuberculosis

FACTOR	Relative risk/odds
Recent infection (< 1 year)	12.9
Fibrotic lesions (spontaneously healed)	2-20
Malnutrition & severely underweight	2

Risk factors for active Tuberculosis with comorbidity

FACTOR	Relative Risk/odds
HIV infection	100
Silicosis	30
Renal Failure/hemodialysis	10-25
Diabetes	2-4
IV drug use	10-30

Risk factors for active Tuberculosis with comorbidity

FACTOR	Relative Risk/odds
Immunosuppressive treatment	10
Gastrectomy/ Cancers head & neck	2-5
Jujunoileal bypass	30-60
Posttransplantation period (renal & cardiac)	2

History of Tuberculosis

- chemotherapy
  - Streptomycin – 1930s
  - PAS
  - SURGERY
  - INH – 1954 B6
  - Rifampin – early 1970s
  - Myambutal

Tuberculosis-untreated
(before chemotherapy)

- 1/3 died in the first year after Diagnosis
- 1/2 died in 5 years after diagnosis
- If smear +, 65% were dead at 5 years
- 5 year survivors, 60% had undergone spontaneous remission (40% still smear +)

Pathogenesis

- Humoral immunity
  - No role in protection

Pathogenesis

- Cell mediated immunity
  - Partial protection against m. tuberculosis
  - Macrophages-phagocytize tubercle bacilli
  - T cells (CD4+ lymphocytes) release lyphokines (esp. INF gamma)

Risk of Developing Disease

Normal Immune System

- Untreated, 5% of infected persons with normal immunity develop TB in first 1–2 years post infection, another 5% later in life
- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

Risk of Developing Disease

Weak Immune System

- Persons with weak immunity at increased risk of progressing to TB disease
  - Untreated HIV infection highest risk factor: risk of developing TB disease is 7%–10% *each year*;
  - Children <5 years of age also at increased risk

Co-Morbidities with Tuberculosis

- HIV infection
- Renal insufficiency
- Hepatic disease
- Diabetes
- TNF-alpha Antagonists
- Pregnancy & Nursing Mothers
- Mental Health
- Tobacco abuse

Delayed Hypersensitivity in Tuberculosis

- 48 to 72 hours after exposure
- INF alpha, IL-2, &TNF-alpha-secreting TH1-type helper T cells
- CD4+ T cells needed to produce INF alpha response (IL12 needed)

Delayed Hypersensitivity

- Also plays a role in:
  - Rheumatoid arthritis
  - Temporal arteritis
  - Leprosy
  - Chlamydial infections
  - Berylliosis & other organic dusts that produce hypersensitivity reactions

TB & HIV co-infection

- Management of HIV-related TB is complex
- Should be provided in consultation with experts in treatment of both HIV and TB
- Can be treated with standard regimens except:
  - Do not use once-weekly continuation-phase INH and RPT(Rifapentine)
  - In patients with advanced HIV, use daily or 3x weekly therapy

TB & HIV co-infection

- If possible, use a rifamycin for the entire course of therapy, along with ARV therapy (has decreased induction of the cytochrome P450 system)
- A major concern: RIF(rifampin) interacts with some PIs and NNRTIs
- Rifabutin has fewer drug interactions and may be used instead of RIF
- Drug dosages may need adjusting; consult expert

TB & HIV co-infection

- Treatment may need to be prolonged
- DOT should be standard
- Closely monitor drug-drug interactions

HIV-pregnancy:

- treatment is complicated in HIV-infected pregnant women with TB
- Pregnancy alters distribution/metabolism of some drugs, including ARV drugs
- Protease inhibitor concentrations reduced in pregnancy

HIV-TB in Children

- Increased risk of severe life threatening manifestations:
  - Disseminated disease
  - Meningitis

TB & Renal insufficiency

- Renal insufficiency/end-stage renal disease
  - Some TB drugs are cleared by the kidneys; thus the dosing must be altered with renal disease
    - important to monitor drug concentrations
  - Rather than decrease dosage size, increase dosing interval

TB & Hepatic disease

- INH, RIF, and PZA can all produce liver failure
- Monitoring liver function is critical
- If INH & RIF are not used together, then RIF, EMB & PZA may be used for 6 months
- Labs to confirm TB organism is critical

TB & Diabetes

- No alteration of therapy is usually required
  - But liver function & good control of diabetes warrented
- INH, RIF, PZA, EMB standard regime.

TB & TNF-alpha Antagonists

- Rheumatoid Arthritis:
  - Inflammatory synovitis cellular immune response
  - TNF Binding agents:
    - Etanercept, infliximab, & adalimumab
  - 10/1 Risk of developing progressive TB in LTBI Test before giving the drug & treat where appreciate
- Crohn's Disease
- Other autoimmune diseases

TB & Pregnancy

- Untreated = greater risk to mother & fetus
- Treat immediately for moderate to high suspicion
- Initiate Rx with INH, RIF, & EMB Cross placenta-noteratogenic effects
  - Do not give Streptomycin as it can produce congenital deafness
- Other Antitubculosis drug not to give in pregnancy: Kanamycin, Amikacin,Capreomycin, Fluoroquinolones

TB & Nursing Mothers

- Breast feeding is encouraged for woman on first line drugs.
- Concentrations in breast milk are too small to produce toxicity
- Concentrations also too small to treat TB or LTBI in the infant
- Also give pyridoxine (B6) to mothers on INH

TB & Mental Health

- Always a challenge
  - Understanding & cooperation
  - Drug compliance
- Some second line drugs & steroids can produce psychotic effects
- Substance abuse Alcohol & drugs
  - Treat & monitor

Tobacco abuse

- Increase risk with exposure

Summary

- WV has a high standard for the care of tuberculosis patients.
- We need to embrace the challenge & the complexity of proper treatment in order to eliminate tuberculosis. (DOT & contact investigation)
- We need to treat these patients with respect and compassion with the best chance of success

HISTORY OF TUBERCULOSIS

- Tuberculosis Nursing

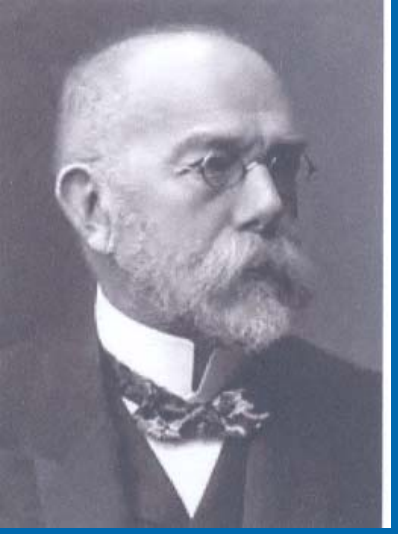
Nurse crossing roofs to visit patients

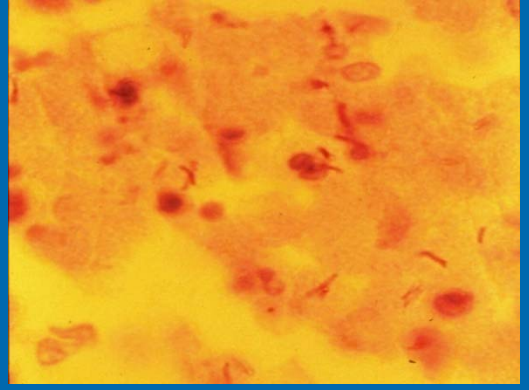
summary

- Great need exists for new drugs/regimens to address the unmet medical needs in TB therapy
- Ultimate success will require still stronger and more robust global TB drug pipeline
- New approach underway for the development of novel anti-TB drug regimens (CPTR initiative)

Eliminate tuberculosis.

- Good contact investigation with proper follow-up & therapy.
- Close monitoring of therapy of active cases with DOT & labs
- Testing all active cases for HIV & MDR & XMD.
- Testing of high risk individuals
- Knowledge of co-morbities





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Questions