EGYPTIAN MUMMIES: SPINAL TB
17th-18th CENTURIES- URBANIZATION
19th CENTURY INDUSTRIALIZATION

TB = 25% ADULT DEATHS
GERM THEORY OF DISEASE
KOCH’S BACILLUS-1883

PRE-ANTIBIOTIC ERA
SANATORIUM REGIMENS & REST
CAVITARY DISEASE & COLLAPSE THERAPY
FRESH AIR, SUNSHINE-ROOFTOPS SOLARIA
### ANTIBIOTICS

- 1946- STREPTOMYCIN
- RAPID DEVELOPMENT OF FAILURE WITH MONOTHERAPY
- INH = MAGIC BULLET - 1952
- RIFAMPIN & SHORT COURSE RX - 1970

### EPIDEMIOLOGY

- M. TUBERCULOSIS INFECTS 1/3 WORLD’S POPULATION
- 8 MILLION NEW CASES ANNUALLY
- 2 MILLION DEATHS
- 2ND TO HIV AS CAUSE OF DEATH FROM INFECTIOUS DISEASE
RISING INCIDENCE WORLDWIDE

FAILURE OF PUBLIC HEALTH

FAILURE OF POLITICAL WILL

RX TO CURE COSTS $12/PT

>95% TB IS IN RESOURCE POOR COUNTRIES

<2% $$ GOES TO THEM

TB Case Rates,* United States, 2003

*Cases per 100,000
DEVELOPED WORLD TB

DOWNWARD TREND BEFORE ANTIBIOTICS: WHY?

1900-WW2: ANNUAL DECREASE 4-6% IN DEVELOPING COUNTRIES

Higher natural resistance

Better living conditions-less crowding

Effect of sanatoriums

Reported TB Cases
United States, 1982-2003

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Cases</th>
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<td>1983</td>
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<td>1999</td>
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Crack Use Pervades Life in a Shelter

By JOSH BARRANIEL

Beds for 550 men are set up on the floor of the Fort Washington Armory in upper Manhattan.
Figure 1
Tuberculosis Cases and Rates\(^1\)
New York City, 1978-2003

\(^1\) Rates based on official Census data and Interim estimates prior to 2000. Rates since 2000 are based on 2000 Census data.
TB Case Rates* by Race/Ethnicity** United States, 1993-2003

*Cases per 100,000
**All races are non-Hispanic. In 2003, Asian/Pacific Islander category includes persons who reported race as Asian only and/or Native Hawaiian or Other Pacific Islander only.
Reported TB Cases by Race/Ethnicity*  
United States, 2003

- Hispanic or Latino (28%)
- Black or African American (28%)
- Asian (23%)
- White (19%)
- Native Hawaiian or Other Pacific Islander (1%)
- American Indian or Alaska Native (1%)

*All races are non-Hispanic. Persons reporting two or more races comprised less than 1% of all cases.

Percentage of TB Cases Among Foreign-born Persons, United States

1993 2003

- ≥50%
- 25% - 49%
- <25%
M. Tuberculosis complex

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*: unpasteurized milk/cheese
- *Mycobacterium africanum & canetti*
- *Mycobacterium microti*: rodents

THE BACILLUS

- **CELL WALL CONTENT=LIPIDS**
- **SLOW GROWTH:**
  - 20 hours vs. 20 minutes for E.Coli
- Length of RX
TRANSMISSION

- Lungs=entry portal
- Inhalation of droplet nuclei
- Coughing: 3000 droplet nuclei/cough
- Talking: 5 minutes
- Sneezing: BEST

TRANSMISSION ENHANCERS

INOCULUM SIZE:
- AUTOPSY SUITE TRANSMISSIONS

STRAIN VARIABILITY/VIRULENCE:
- KENTUCKY OUTBREAK

VENTILATION: BACILLUS LONGEVITY & INFECTIVITY IN AIR
Primary Infection: Before Immune Response

- TB reaches alveoli
- Replicates extracellularly and intracellularly
- Lack of immediate host immune response

Reproduction

- Intracellularly = within alveolar macrophage
- MTB prevents acidification of phagosome
- MTB multiplies for weeks in alveolar macrophages

And
**DISSEMINATION**

- Metastatic foci established in regional nodes
- Seed blood
- Travel to tissues favoring multiplication

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**Development of Immune Response: 6-12 weeks**

- Alveolar macrophage infected with TB secretes Interleukins 12 & 18
- These attract CD 4 cells
- CD 4 cells meet TB antigen macrophage presents to them
- Transformation of CD 4 cells
TRANSFORMED CD 4 CELLS:

- **PROLIFERATE**: production of clones of similarly reactive CD 4 cells
- **CUTANEOUS HYPERSENSITIVITY**: big enough population of transformed CD4 allows delayed rxn to tuberculin
- **RELEASE INTERFERON GAMMA**

INTERFERON GAMMA

- CD4 cells release interferon gamma
- Interferon gamma stimulates additional macrophage phagocytosis of M. tuberculosis
- Interferon gamma stimulates macrophage to release tumor necrosis factor alpha (TNF Alpha)
Interferon Gamma activates macrophage:
- Stimulates macrophage to phagocytose MTB
- Makes macrophage secrete TNF alpha

Activated macrophage

Figure 8.40: Immune Biology, 6th ed. (© Garland Science 2005)
**Tumor Necrosis Alpha (TNF alpha)**

- TNF alpha increases macrophage ability to kill *M. tuberculosis*
- TNF alpha required for granuloma formation
- Granulomas sequester mycobacteria and prevent uncontrolled dissemination

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**Infected macrophage**

- lysosome
- mycobacterium
- antigen

**Activated infected macrophage**

- TH1

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Figure 1-36. *Immunobiology, 6/e, (C) Garland Science 2005*
Lack of TNF Alpha

• Murine experiments:
  – Blockade of TNF alpha resulted in reactivation, high bacillary burden, persistent tuberculosis and death
  – TNF alpha knock-out mice infected with *M. tuberculosis* followed similar course

PATHOLOGY

• Macrophages secrete lytic enzymes which cause tissue necrosis
• Epithelioid cell = highly stimulated macrophage
• Langhans Giant Cell = fused macrophages with multiple nuclei
Primary Infection with Resolution: 85% of Cases

- Patient asymptomatic/viral syndrome
- Enlargement of hilar/peri-bronchial nodes
- Ghon complex: hilar node calcification
- Positive PPD 6-12 weeks

Primary Infection with Progression

Progressive Primary Disease

- Young children <5 cannot resolve initial infection: Progression to active disease, miliary or disseminated, CNS involvement
- Almost always developing world where TB is endemic
TUBERCULOUS PLEURISY

• HYPERSENSITIVITY REACTION
• EXUDATIVE PLEURAL EFFUSION
• CULTURE NEGATIVE—FEW BACILLI
• WW II STUDIES: 65% RELAPSE TO ACTIVE TB IF UNTREATED

PRIMARY INFECTION—ADOLESCENCE

Develop cavitary disease:
23% age 15-19
13% age 20-24
4% 25-29
AIDS NOSOCOMIAL OUTBREAKS

- Multiple nosocomial outbreaks of TB in AIDS wards, homeless shelters and prisons in late 1980s-1990s
- Undiagnosed patient with active TB in AIDS ward where all patients CD4<50
- No CD4s to mobilize so no interferon gamma & no macrophages stimulated to phagocytose or secrete interferon gamma

OVERWHELMING TB

- No immunologic control of bacillus
- Rapid dissemination
- MDR strains killed scores in AIDS wards
Reactivation: 10-15% of those infected

- Persistence of viable organisms
- Containment of infection, lack of active disease
- Viable organisms remain alive, dormant for years
- Disease occurs when cellular immune system can no longer contain MTB

CAUSES OF REACTIVATION

- Iatrogenic immunosuppression
  - Transplant; Rheumatologic Rx
- Immunocompromising diseases
- Malnutrition
- Old Age
- Unknown: ?hormonal ?stress
85% Reactivation=Lungs

• Caseating necrosis, liquefaction, drainage into the bronchial tree
• Cavity formation

• Cavity favors bacillary multiplication to huge #s: $10^9$-$10^{10}$ organisms / GM tissue
• 5-6 logs greater than # organisms in non-cavitary disease= MOST CONTAGIOUS
• Implications for development of drug resistance
EXTRAPULMONARY TB

- Viable organisms remain alive for years
- Most common organs to which disseminated during primary infection

LYMPH NODES: SCROFULA
Most frequent form of extrapulmonary TB
Usually Cervical

Or Supraclavicular
BONES

• ONE THIRD INVOLVE SPINE From:

• Hematogenous spread from initial infection

• Lymphatic spread from pleural disease

• Contiguous disease

Can also be axillary
**POTTS DISEASE**

- Earliest focus: Anterior superior or inferior angle of vertebral body
- Spreads to intervertebral disk & adjacent vertebra

**RENAL TUBERCULOSIS**

- ASYMPTOMATIC
- STERILE PYURIA
- USUALLY EVIDENCE OF PULMONARY TB PRESENT
- 25% MILIARY HAVE POSITIVE URINE
**Diagnosis:**

**Symptoms**

- Systemic symptoms non-specific: fever, fatigue, night sweats, weight loss
- Pulmonary symptoms: cough, productive or dry
- Hemoptysis: can be emergency
  - Suggests bronchial wall erosion

**DIAGNOSTIC PROCEDURES**

- **SPUTUM SMEAR:**
  - Acid fast=all mycobacterial species
  - Ziehl-Neelsen stain
  - Auramine
  - SMEAR POSITIVE MEANS AT LEAST 10,000 ORGS/ML
CULTURE=GOLD STANDARD

Now available in most of world via WHO reference labs

-SOLID MEDIA: 3-8 weeks
  - Lowenstein Jensen=egg based
  - Middlebrook 7H11=agar based

-LIQUID BROTH: 1-3 weeks
  - Middlebrook 7H12
  - BACTEC systems

Nucleic Acid Amplification: Can detect MTB in fresh sputum

• Sensitivity intermediate between acid fast smear and culture

• AFB smear negative, nucleic acid amplification=40-77% sensitive

• AFB smear positive, nucleic acid amplification=95% sensitive & 100% specific

• LUXURY OF DEVELOPED WORLD
DNA Fingerprinting
Molecular epidemiologic tool

- RFLP = Restriction Fragment Length Polymorphism
- Restriction endonuclease produces DNA fragments
- Separate fragments by electrophoresis
- Use probe to DNA sequence IS 6110
- Insertion sequence which occurs repeatedly at highly variable locations on MTB chromosome

- LUXURY OF DEVELOPED WORLD

Chest X-Ray

- Upper lobe infiltrate with or without cavity
- Hilar adenopathy with or without infiltrates
- Pleural effusion, exudative
- Lower lobe infiltrate
- Miliary pattern
UPPER LOBE INFILTRATE

- Apical or sub-apical
- Most common in reactivation disease if immune system intact
- Radiologic extent of disease reflects tissue damage
- Tissue damage reflects host’s ability to have hypersensitivity reaction

HILAR ADENOPATHY

- Most common chest X-ray in patients with AIDS (CD4 <200)
- Reflects minimal cellular immune response
PLEURAL EFFUSION

Seen in post-primary as above: scant orgs

- Smear negative but culture positive 25%

Seen as complication of reactivation TB: more likely to have orgs

- Smear positive 50% & culture positive 60-70%

MILIARY PATTERN

• From description of pathologic lesions as “millet seeds”

• Chest x-ray shows 0.5-1.0 mm nodules
MILIARY PATTERN

Following childhood infection and progression

Immunocompromising diseases:
- alcoholism
- cirrhosis
- rheumatologic diseases
- Rx with immunosuppressive
DIAGNOSIS DIFFICULT

- May have multiple organ involvement
- Millet seed granulomas in tissue
- Transbronchial biopsy=highest yield for diagnosis
TREATMENT: GENERAL PRINCIPLES

• ALWAYS USE AT LEAST 2 DRUGS:
  – Begin with 4 pending sensitivities
  – Natural incidence of spontaneous resistance to any 1 drug = 1 in 10,000 organisms
  – Bacilli resistant to 1 will be killed by others
  – Natural resistance to 2 drugs spontaneously = 1 in $10^{10}$

• Prolonged Length of Rx: 6-9 months

• Directly Observed Therapy
1. Isoniazid = INH
   • Bactericidal against dividing organisms
   • Toxicity=Hepatitis: Chemical vs. Clinical
     -20% patients have rise in transaminases which resolves without stopping INH
     -Age related: <35 = 0.3%; >65 = 4%

2. Rifampin = (RMP)
   • Bactericidal
   • Enables short course treatment: 6-9 months vs. 18-24 months w/out RMP
   • Well tolerated but can cause GI upset, rash
   • Contains red dye excreted in urine sweat, tears-turns them orange
**Rifampin**

- Induces hepatic microsomal enzymes and accelerates metabolism of many drugs making them less effective or ineffective when rifampin is being given:
  - Methadone
  - Coumadin
  - Estrogen
  - Oral Contraceptives
  - Glucocorticoids
  - Digitoxin

**Protease Inhibitors**

- Anti-Arrhythmic Agents
  - Quinidine, Verapamil, Mexiletine
- Theophylline
- Anticonvulsants
- Ketoconazole
- Cyclosporin

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**3. Pyrazinamide (PZA)**

- Main role in sensitive disease is to reduce length of treatment from 9 months to 6 months
- Do not use in pregnancy: no teratogenicity data
4. Ethambutol EMB

- Most important function is prevention of resistance
- Used in drug resistance and when INH or RMP cannot be used (INH hepatotoxicity or RMP drug-drug interactions)
- Blurred vision, red-green color blindness

Prophylaxis: LTBI

Targeted Testing: **PPD is NOT a general screen**

- Immunocompromised patients:
  - HIV infected, chemotherapy, organ transplant, immunosuppressive RX for autoimmune diseases
  - Close contacts of infectious cases
  - Previously untreated patients with Chest x-ray evidence of old disease (NOT just granuloma)
  - Recent Immigrants (in US <5 years)
  - People who work in high exposure institutions
POSITIVE PPD: DEFINITION

- 5 mm: HIV infected, close contacts of infectious cases, CXRay evidence of old disease
- 10 mm: everyone else

ELISPOT (Enzyme-linked immunospot)

- T-cell based assay from blood
- *M. tuberculosis* genes not present in *M. bovis BCG* produce antigen to which T-cell reacts
- 1 tube of blood needed
- Useful in outbreaks for contact investigations: UK school outbreak showed greater sensitivity than PPD
**BCG: Most Widely Used and Most Controversial Vaccine in World**

- M. Bovis strain attenuated through serial passage no standardized strain or procedure to make one largest study: India = no protection from TB infection other studies: England = protection from TB infection prevalence of non-TB mycobacteria may interfere
- All agree: highly effective for infants & small children against dissemination & meningitis

**BCG Used in Countries Where TB Endemic**

- BCG may be indicated for infants and small children continuously exposed to MDR patient
- BCG at birth should not give positive PPD as adult
- Boosting: 2 step testing for all those with BCG