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
- 9.2 MILLION NEW TB CASES 2006
- 14.4 MILLION PREVALENT TB CASES 2006
- 1.5 MILLION TB DEATHS IN HIV-NEG  2006
- 200,000 TB DEATHS IN HIV-POS 2006
- 2ND TO HIV AS CAUSE OF DEATH FROM INFECTIOUS DISEASE
TABLE 1.2
Estimated epidemiological burden of TB, 2006

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High-burden countries 6,189,313 7,334 177 3,265 19 11,819 286 1,350 32 11
RISING INCIDENCE WORLDWIDE
FAILURE OF PUBLIC HEALTH
FAILURE OF POLITICAL WILL
RX TO CURE COSTS $12/PT
>95% TB IS IN RESOURCE POOR COUNTRIES
MONEY & INFRASTRUCTURE

TB Case Rates,* United States, 2007

- ≤ 3.5 (year 2000 target)
- 3.6–4.4
- > 4.4 (national average)

*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, 1982–2007

*Updated as of April 23, 2008.
Crack Use Pervades Life in a Shelter

By JOYCE BARRAN

Beds for 850 men are set up on the floor of the Fort Washington Armory in upper Manhattan.

NEW YORK STRIKE TO COVER BIG IMPACT

Highest Tax Measure Passes

By GEORGE HANSEN

ALBANY, N.Y. — Hundreds of New York State court ruled in favor of citizens who questioned the constitutionality of the statute of a 25-year-old law that had been used to bar public access to terminals of the state's public transportation system. The Appeals court upheld the state's use of the law to control public affairs.
In 2007, New York City (NYC) recorded 914 confirmed tuberculosis (TB) cases; the lowest number since TB became reportable in 1897.

**Figure 1: TB Cases and Rates, New York City, 1978-2007**

includes people born in Puerto Rico and the U.S. Virgin Islands.

rates after 2000 are based on official US Census data and ministerial estimates. Rates after 2000 are based on 2000 Census data.

5: TB CASES AND RATES BY RACE/ETHNICITY, NEW YORK CITY, 1992-2007
Reported TB Cases by Race/Ethnicity*
United States, 2007

- American Indian or Alaska Native (1%)
- Asian (25%)
- White (17%)
- Alaska Native (1%)
- Native Hawaiian or Other Pacific Islander (<1%)
- Hispanic or Latino (23%)
- Black or African-American (26%)

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

Number of TB Cases in U.S.-born vs. Foreign-born Persons
United States, 1993–2007*

- U.S.-born
- Foreign-born

*Updated as of April 23, 2008.
Trends in TB Cases in Foreign-born Persons, United States, 1987–2007*

*Updated as of April 23, 2008.

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

*Updated as of April 23, 2008.
Countries of Birth of Foreign-born Persons Reported with TB
United States, 2007

Mexico (24%)
Philippines (12%)
Viet Nam (7%)
India (5%)
China (5%)
Haiti (2%)
Rep. Korea (3%)
Other Countries (39%)

Primary Anti-TB Drug Resistance
United States, 1993–2007*

% Resistant

Isoniazid  MDR TB

1993 1995 1997 1999 2001 2003 2005 2007

*Updated as of April 23, 2008.

Note: Based on initial isolates from persons with no prior history of TB.
Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
Primary MDR TB
United States, 1993–2007*

*Updated as of April 23, 2008.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

XDR TB Case Count defined on Initial DST† by Year, 1993–2007*

†Drug susceptibility test.
*Reported incident cases as of April 23, 2008.
Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
**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

REPLICATION

- 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

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)
**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

**PATHOLOGY OF A GRANULOMA**

Macrophages secrete lytic enzymes which cause tissue necrosis

Epithelioid cell=highly stimulated macrophage

Langhans Giant Cell=fused macrophages with multiple nuclei
GRANULOMA = SUCCESSFUL TISSUE REACTION & HEALING

- Small antigen load & high hypersensitivity = Epithelioid cells, giant cells etc.
- Large antigen load & high hypersensitivity = Necrosis & Caseation
- Small or large antigen load & no hypersensitivity = few cells
- No granuloma & huge #s of bacilli: AIDS patients

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
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

• HYPERSENSITICITY REACTION

• EXUDATIVE PLEURAL EFFUSION

• CULTURE NEGATIVE FEW BACILLI

• WW II STUDIES: 65% RELAPSE TO ACTIVE TB IF UNTREATED
PRIMARY INFECTION - ADOLESCENCE/YOUNG ADULTS

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

PRIMARY INFECTION: 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

Can also be axillary
BONES

- ONE THIRD INVOLVE SPINE From:
  - Hematogenous spread from initial infection
  - Lymphatic spread from pleural disease
  - Contiguous disease

POTTS DISEASE

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

- **HEMATOGENOUS SPREAD AFTER PRIMARY INFECTION**
  SEEDS GLOMERULI & FORMS GRANULOMAS
- **LATER, CASEOUS NECROSIS, FIBROSIS & CALCIFICATION**
- **ASYMPTOMATIC UNTIL CALYX/PELVIS ULCERATED**
- **STERILE PYURIA: MUST SEND FOR MTB CULTURE**
- **USUALLY EVIDENCE OF PULMONARY TB PRESENT**
- **25% MILIARY HAVE POSITIVE URINE CULTURE FOR MTB**

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

Available in most of world in WHO reference labs

- SOLID MEDIA=Slow growth =3-8 weeks; Lowenstein Jensen (LJ slant) =egg based or Middlebrook 7H11=agar based

- LIQUID MEDIA=Rapid growth = 1-3 weeks; Middlebrook 7H12
CULTURE CONT’D

- LIQUID: RAPID GROWTH:
  1-3 weeks in Middlebrook 7H12 broth media

- IDENTIFICATION FROM CULTURE
  - DNA PROBES – MTB complex, *M. avium* complex, *M. kansasii*, *M. gordonae*
  - BIOCHEMICAL TESTS – Niacin, Nitrate, Catalase, etc. to identify other mycobacteria

WHAT IS MTB COMPLEX?

*M. tuberculosis* Complex (MTBC) can include:
- *M. tuberculosis*
- *M. bovis, M. bovis BCG*
- *M. africanum*
- *M. microti*
- *M. canetti*

BIOCHEMICAL TESTS NECESSARY TO DISTINGUISH THESE

*M. bovis* ALMOST ALWAYS RESISTANT TO PYRAZINAMIDE
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

RFLP=Restriction fragment Length Polymorphism

Restriction endonuclease makes DNA fragments
Separate fragments by electrophoresis
IS 6110 as DNA probe=
Insertion sequence occurring repeatedly at highly variable locations on MTB chromosome
DNA FINGERPRINTING

- Molecular epidemiologic tool to identify different TB strains
- First used by Dutch in early 1990s to quantify source of local TB strains
- Used to identify nosocomial outbreaks in AIDS wards, shelters
- 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**
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, Chest XRay evidence of old disease
- 10 mm: everyone else
ELISPOT (Enzyme-linked immunospot)

- T-cell based assay from blood: Need 1 tube of blood
- *M. tuberculosis* genes NOT present in *M. bovis BCG*
- Early secretory antigen target-6 (ESAT-6)=gene product specifically produced by *M. tuberculosis* and not by *M. bovis BCG* or any other mycobacteria

Will this replace PPD?

- T cells specifically target this antigen (ESAT-6) and can be detected by ELISPOT obtaining 1 tube of blood
- TB outbreak in high school in UK showed ELISPOT higher sensitivity and specificity than PPD skin test
- Licensed & available as Quantiferon Gold but discordance with PPD in numerous studies; significance not yet clear
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

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