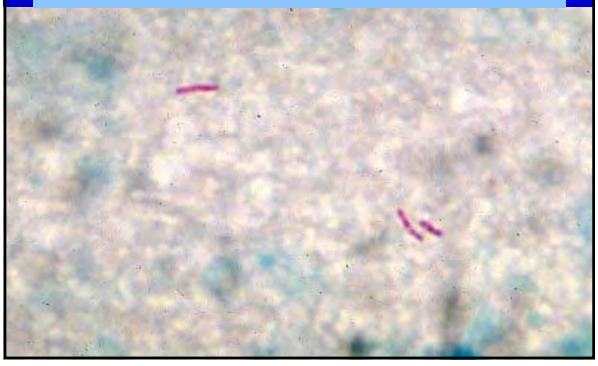
PRE-ANTIBIOTIC ERA

- SANATORIUM REGIMENS & REST
- CAVITARY DISEASE & COLLAPSE THERAPY
- FRESH AIR, SUNSHINE-ROOFTOPS SOLARIA

HISTORY

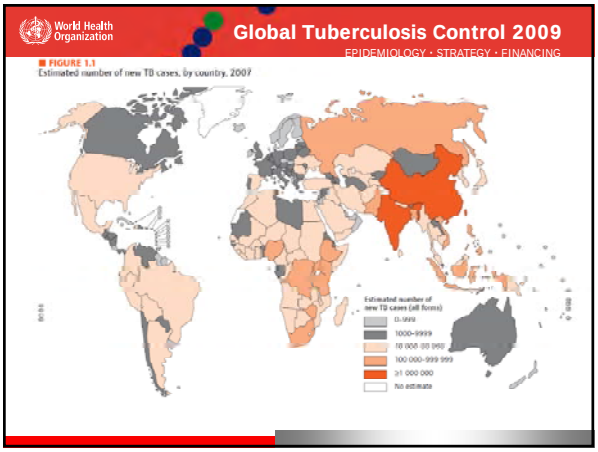
- EGYPTIAN MUMMIES: SPINAL TB
- 17th-18th CENTURIES- URBANIZATION
- 19th CENTURY INDUSTRIALIZATION
- TB = 25% ADULT DEATHS

GERM THEORY OF DISEASE
KOCH'S BACILLUS-1883



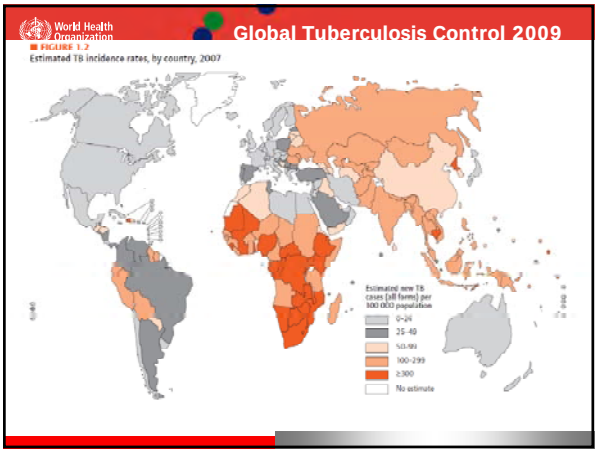
EPIDEMIOLOGY

- 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



ANTIBIOTICS

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



World Health Organization

Global Tuberculosis Control 2009

FIGURE 1.3
Estimated HIV prevalence in new TB cases, 2007

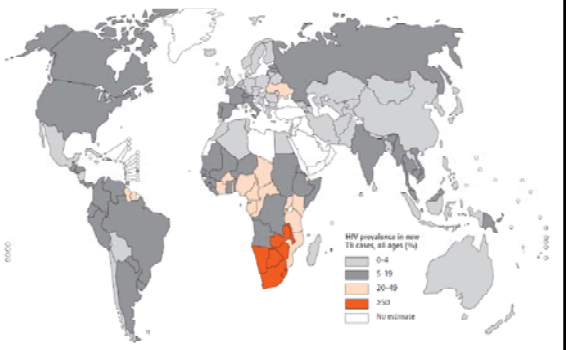


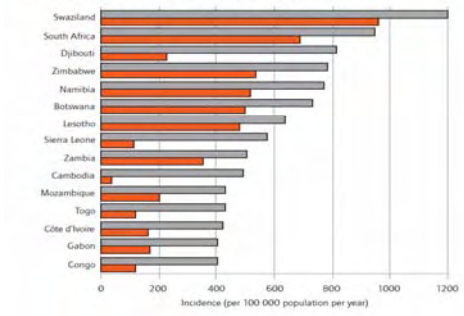
TABLE 1.2
Estimated epidemiological burden of TB, 2006

	POPULATION (1000)	INCIDENCE: ALL FORMS NUMBER (1000)	INCIDENCE: ALL FORMS PER 100 000 POP. PER YEAR	INCIDENCE: SMEAR-POSITIVE NUMBER (1000)	INCIDENCE: SMEAR-POSITIVE PER 100 000 POP. PER YEAR	PREVALENCE: ALL FORMS NUMBER (1000)	PREVALENCE: ALL FORMS PER 100 000 POP.	MORTALITY: ALL FORMS NUMBER (1000)	MORTALITY: ALL FORMS PER 100 000 POP. PER YEAR	HIV PREV IN INCIDENT TB CASES[b] %
1 India	1 161 731	1 933	169	837	73	3 416	299	336	29	1.2
2 China	1 320 864	1 511	99	590	45	2 658	201	221	15	3.3
3 Indonesia	228 864	534	234	240	105	578	253	68	33	1.6
4 South Africa	48 282	454	940	184	382	432	998	136	218	44
5 Nigeria	144 720	459	311	198	137	830	615	117	81	3.5
6 Bangladesh	155 991	351	223	158	101	610	391	70	45	3.0
7 Ethiopia	81 021	306	378	136	168	520	641	58	83	5.3
8 Pakistan	150 943	292	181	131	82	423	263	55	34	3.3
9 Philippines	96 264	248	287	111	129	373	432	39	45	3.1
10 DR Congo	60 644	237	392	105	173	391	645	51	84	4.2
11 Russian Federation	143 221	151	107	68	48	179	126	24	17	3.8
12 Viet Nam	86 206	149	173	66	77	194	225	20	23	3.0
13 Kenya	36 555	141	384	56	153	122	334	26	72	52
14 UR Tanzania	39 460	123	312	53	136	151	469	26	65	13
15 Uganda	29 896	106	356	46	154	158	661	25	84	15
16 Brazil	188 855	94	50	40	21	174	93	7.5	4.0	15
17 Mozambique	20 971	93	443	39	186	131	624	24	117	30
18 Thailand	63 444	98	142	40	62	125	197	19	23	11
19 Myanmar	48 379	83	171	37	76	92	189	6.1	13	2.6
20 Zimbabwe	13 225	74	557	30	227	79	597	17	131	43
21 Cambodia	14 197	71	500	31	226	94	669	13	92	9.5
22 Afghanistan	26 004	42	161	19	73	50	191	8.0	32	3.0
High-burden countries	4 150 713	7 334	177	3 265	79	11 849	286	1 330	32	11

World Health Organization

Global Tuberculosis Control 2009

FIGURE 1.4
Fifteen countries with the highest estimated TB incidence rates per capita (all forms; grey bars) and corresponding incidence rates of HIV-positive TB cases (red bars), 2007



RISING INCIDENCE WORLDWIDE

FAILURE OF PUBLIC HEALTH

FAILURE OF POLITICAL WILL

RX TO CURE COSTS $12/PT

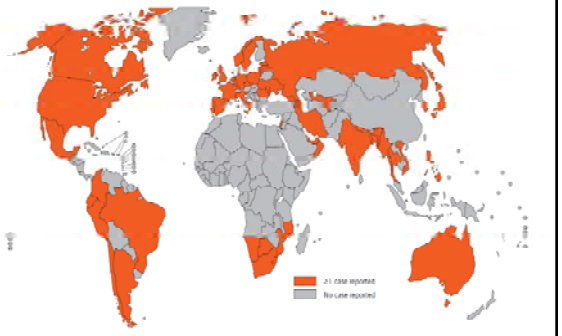
>95% TB IS IN RESOURCE POOR CONTRIES

MONEY & INFRASTRUCTURE

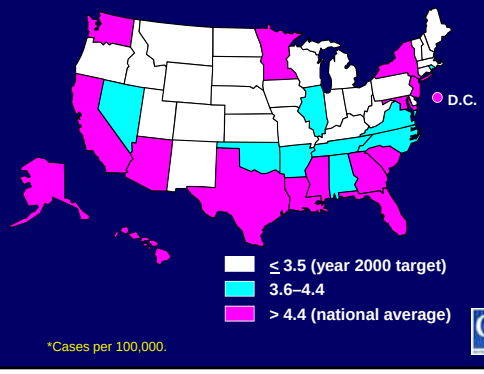
World Health Organization

Global Tuberculosis Control 2009

FIGURE 2.12
Countries that had reported at least one case of XDR-TB by the end of 2008



TB Case Rates,* United States, 2007



*Cases per 100,000.

DEVELOPED WORLD TB

DOWNWARD TREND BEFORE ANTIBIOTICS: WHY?

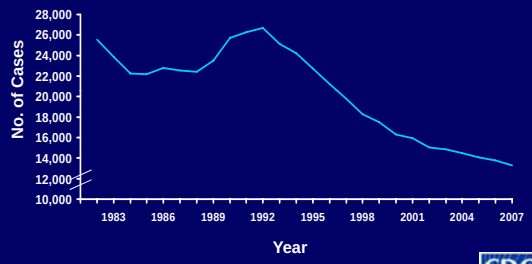
1900-WW2: ANNUAL DECREASE 4-6% IN DEVELOPING COUNTRIES

Higher natural resistance

Better living conditions-less crowding

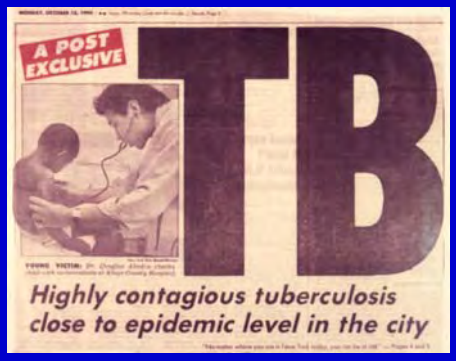
Effect of sanatoriums

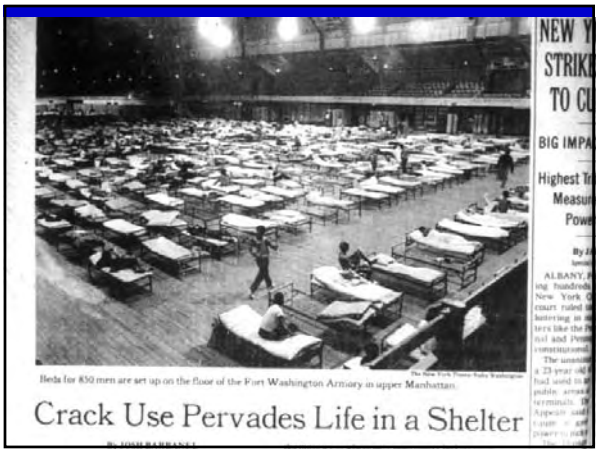
Reported TB Cases* United States, 1982–2007



*Updated as of April 23, 2008.

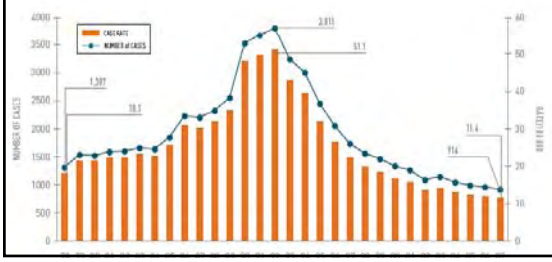
CDC

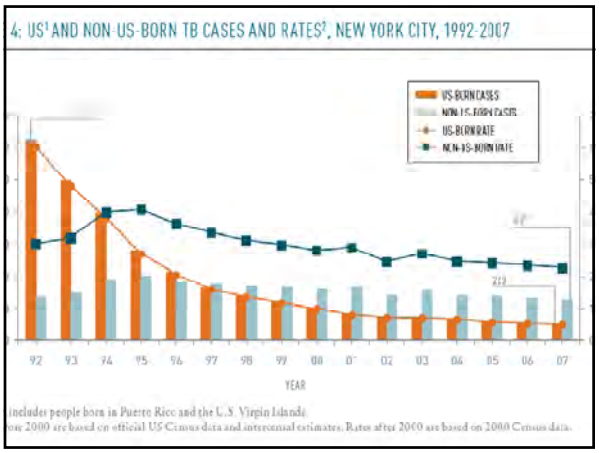


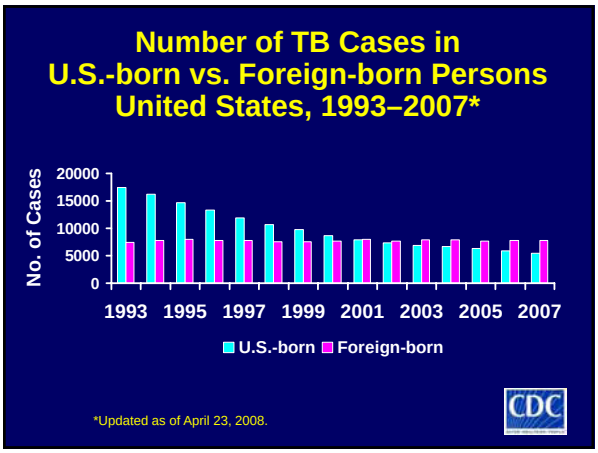


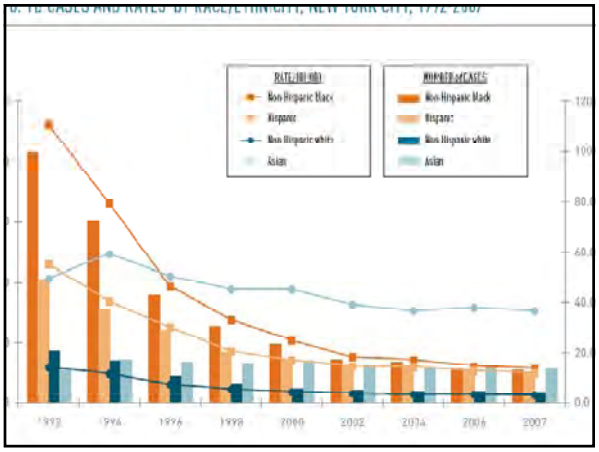
In 2007, New York City (NYC) recorded 914 confirmed tuberculosis (TB) cases; the lowest number since TB became reportable in 1897.

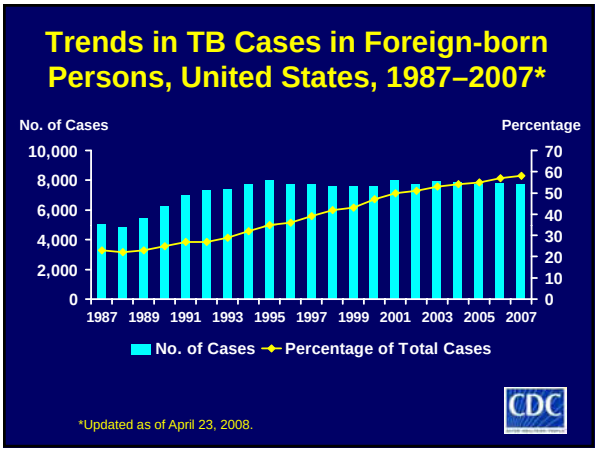
FIGURE 1: TB CASES AND RATES,[1] NEW YORK CITY, 1978-2007

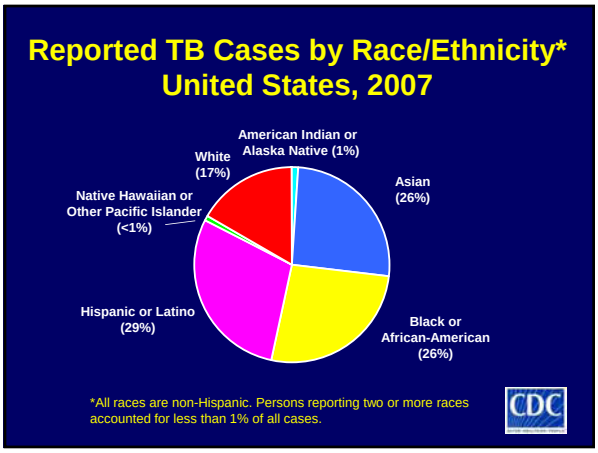


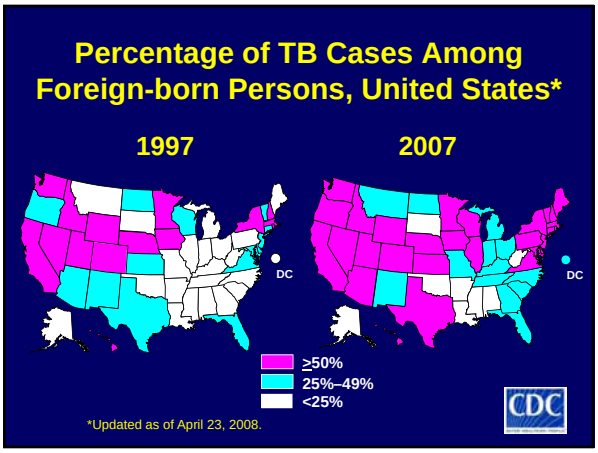

4: US¹ AND NON-US-BORN TB CASES AND RATES², NEW YORK CITY, 1992-2007
US-BORN CASES
NON-US-BORN CASES
US-BORN RATE
NON-US-BORN RATE
YEAR


Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2007*
No. of Cases
20000
15000
10000
5000
0
1993 1995 1997 1999 2001 2003 2005 2007
U.S.-born
Foreign-born
*Updated as of April 23, 2008.
CDC

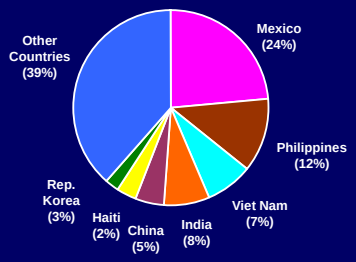

RATE (per 100)
NUMBER of CASES
Non-Hispanic Black
Hispanic
Non-Hispanic white
Asian


Trends in TB Cases in Foreign-born Persons, United States, 1987–2007*
No. of Cases
Percentage
10,000
8,000
6,000
4,000
2,000
0
70
60
50
40
30
20
10
0
1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007
No. of Cases
Percentage of Total Cases
*Updated as of April 23, 2008.
CDC

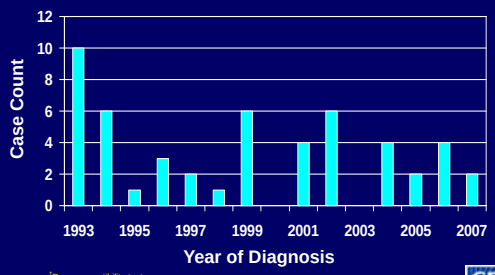

Reported TB Cases by Race/Ethnicity* United States, 2007
American Indian or Alaska Native (1%)
White (17%)
Asian (26%)
Native Hawaiian or Other Pacific Islander (<1%)
Hispanic or Latino (29%)
Black or African-American (26%)
*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.
CDC


Percentage of TB Cases Among Foreign-born Persons, United States*
1997
2007
DC
DC
≥50%
25%–49%
<25%
*Updated as of April 23, 2008.
CDC

Countries of Birth of Foreign-born Persons Reported with TB United States, 2007

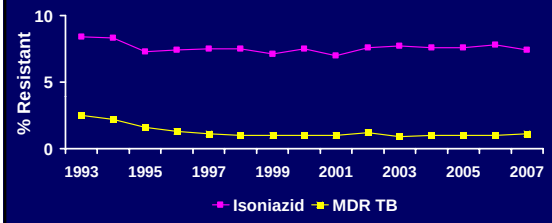


XDR TB Case Count defined on Initial DST† by Year, 1993–2007*



†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.

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



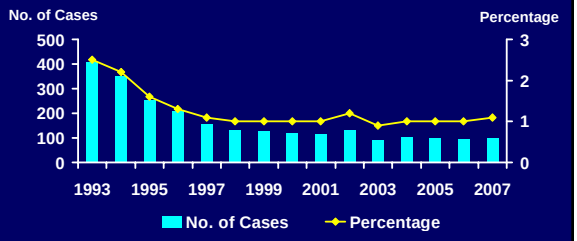
*Updated as of April 23, 2008.

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.

M. Tuberculosis complex

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

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.

THE BACILLUS

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

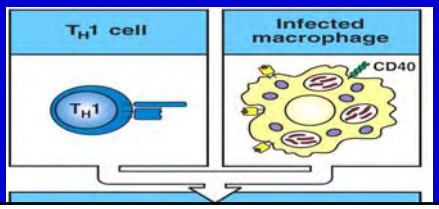
TRANSMISSION

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

REPLICATION

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

AND



TRANSMISSION ENHANCERS

INOCULUM SIZE:

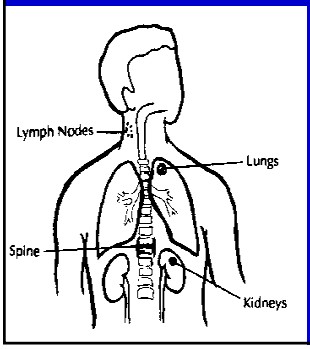
- AUTOPSY SUITE TRANSMISSIONS

STRAIN VARIABILITY/VIRULENCE:

- KENTUCKY OUTBREAK

VENTILATION: BACILLUS LONGEVITY & INFECTIVITY IN AIR

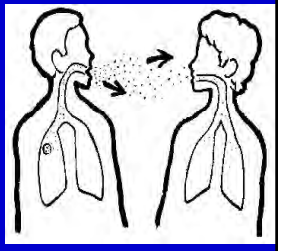
DISSEMINATION



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

Primary Infection: BEFORE IMMUNE RESPONSE

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



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:

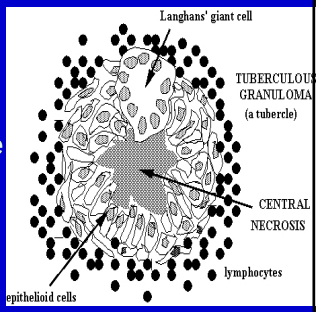
- **PROLIFERATE:** production of clones of similarly reactive CD 4 cells
- **CUTANEOUS HYPERSENSITIVITY:** big enough population of transformed CD4 allows delayed rxn to tuberculin
- **RELEASE INTERFERON GAMMA**

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



INTERFERON GAMMA

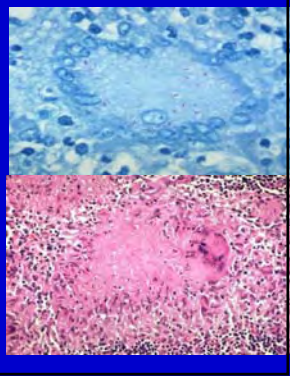
- CD4 cells release interferon gamma
- Interferon gamma stimulates additional macrophage phagocytosis of M. tuberculosis
- Interferon gamma stimulates macrophage to release tumor necrosis factor alpha (TNF Alpha)

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**



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

Lack of TNF Alpha

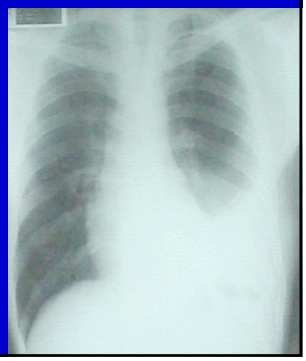
- Murine experiments:
  - Blockade of TNF alpha resulted in reactivation, high bacillary burden, persistent tuberculosis and death
  - TNF alpha knock-out mice infected with *M. tuberculosis* followed similar course

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**

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 with Progression

Progressive Primary Disease

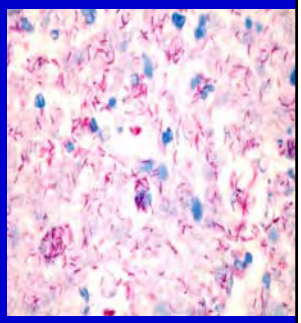
- Young children <5- cannot resolve initial infection :Progression to active disease, miliary or disseminated, CNS involvement
- Almost always developing world where TB is endemic

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

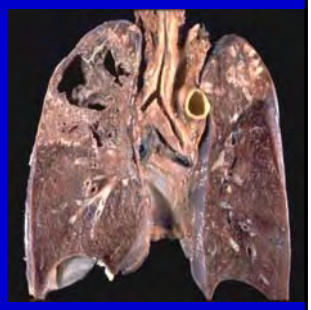
OVERWHELMING TB

- No immunologic control of bacillus
- Rapid dissemination
- MDR strains killed scores in AIDS wards



85% Reactivation=Lungs

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



Reactivation: 10-15% of those infected

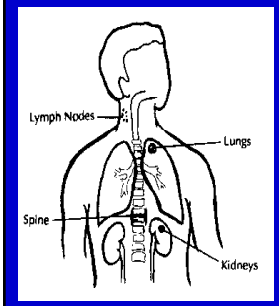
- Persistence of viable organisms
- Containment of infection, lack of active disease
- Viable organisms remain alive, dormant for years
- Disease occurs when cellular immune system can no longer contain MTB

- 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

CAUSES OF REACTIVATION

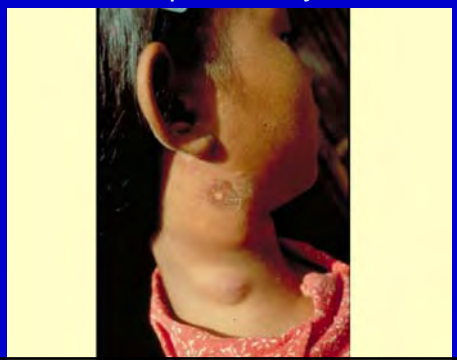
- Iatrogenic immunosuppression
  - Transplant; Rheumatologic Rx
- Immunocompromising diseases
- Malnutrition
- Old Age
- Unknown: ?hormonal ?stress

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



Can also be axillary

Usually Cervical

BONES

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

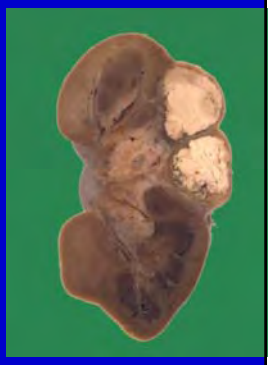
Or Supraclavicular

POTTS DISEASE

- Earliest focus: Anterior superior or inferior angle of vertebral body
- Spreads to interverteberal 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



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

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

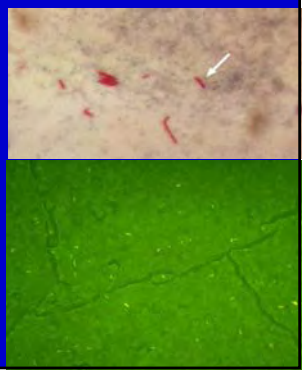
CULTURE CONT'D

- 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

DIAGNOSTIC PROCEDURES

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



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**

Chest X-Ray

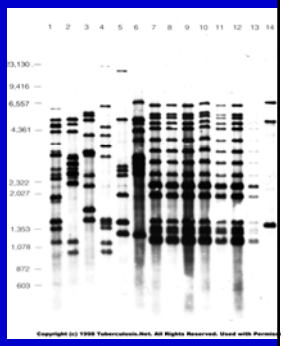
- Upper lobe infiltrate with or without cavity
- Hilar adenopathy with or without infiltrates
- Pleural effusion, exudative
- Lower lobe infiltrate
- Miliary pattern

RFLP=Restriction fragment Length Polymorphism

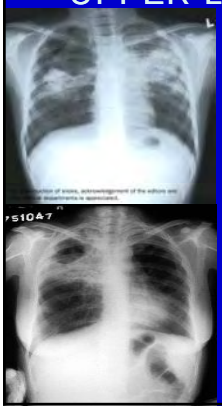
Restriction endonuclease makes DNA fragments

Separate fragments by electrophoresis

IS 6110 as DNA probe= Insertion sequence occurring repeatedly at highly variable locations on MTB chromosome



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

DNA FINGERPRINTING

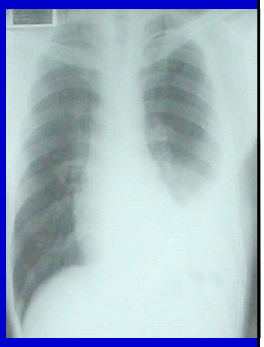
- **MOLECULAR EPIDEMIOLOGIC TOOL TO IDENTIFY DIFFERENT TB STRAINS**
- **FIRST USED BY DUTCH IN EARLY 1990S TO QUANTIFY SOURCE OF LOCAL TB STRAINS**
- **USED TO IDENTIFY NOSOCOMIAL OUTBREAKS IN AIDS WARDS, SHELTERS**
- **LUXURY OF DEVELOPED WORLD**

HILAR ADENOPATHY

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

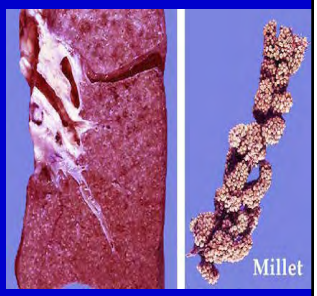
PLEURAL EFFUSION

- 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%



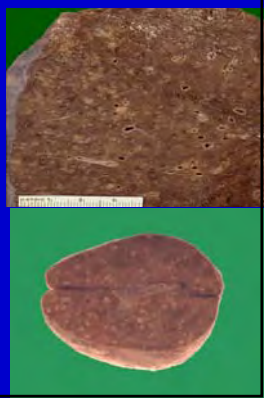
MILIARY PATTERN

- From description of pathologic lesions as “millet seeds”
- Chest x-ray shows 0.5-1.0 mm nodules



DIAGNOSIS DIFFICULT

- **May have multiple organ involvement**
- **Millet seed granulomas in tissue**
- **Transbronchial biopsy=highest yield for diagnosis**



MILIARY PATTERN

Following childhood infection and progression

Immunocompromising diseases:

-alcoholism

-cirrhosis

-rheumatologic diseases

-Rx with immunosuppressive

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
- **D**irectly **O**bserved **T**herapy

Prophylaxis: LTBI

Targeted Testing: PPD is NOT a general screen

Immunocompromised patients:

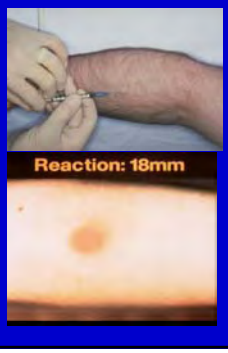
- **HIV infected, chemotherapy, organ transplant, immunosuppressive RX for autoimmune diseases**
- **Close contacts of infectious cases**
- **Previously untreated patients with Chest x-ray evidence of old disease (NOT just granuloma)**
- **Recent Immigrants (in US <5 years)**
- **People who work in high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

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

POSITIVE PPD: DEFINITION

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



BOX 4. Conditions requiring caution in interpreting negative QuantiFERON®-TB Gold test results

- Human immunodeficiency virus infection or acquired immunodeficiency syndrome
- Immunosuppressive drugs, including those used for managing organ transplantation
- TNF*-α
- Diabetes mellitus
- Silicosis
- Chronic renal failure
- Certain hematological disorders (e.g., leukemias and lymphomas)
- Other specific malignancies (e.g., carcinoma of the head, neck, or lung)

* Tumor necrosis factor.

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**

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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