PRE-ANTIBIOTIC ERA

SANATORIUM REGIMENS & REST

CAVITARY DISEASE & COLLAPSE THERAPY

FRESH AIR, SUNSHINE-ROOFTOPS SOLARIA

HISTORY

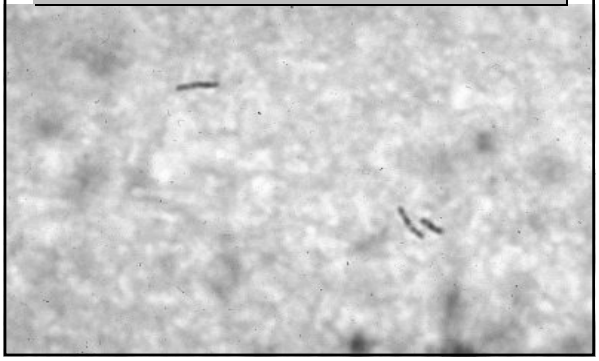
EGYPTIAN MUMMIES: SPINAL TB

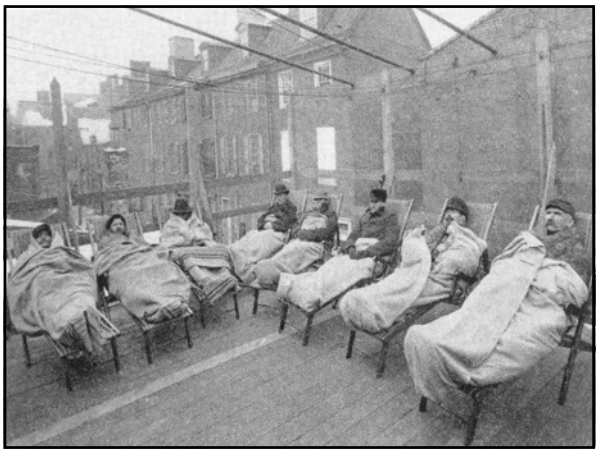
17th-18th CENTURIES- URBANIZATION

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
- 1.7 MILLION DEATHS 2006
- 2ND TO HIV AS CAUSE OF DEATH FROM INFECTIOUS DISEASE
- 14.4 MILLION PREVALENT CASES

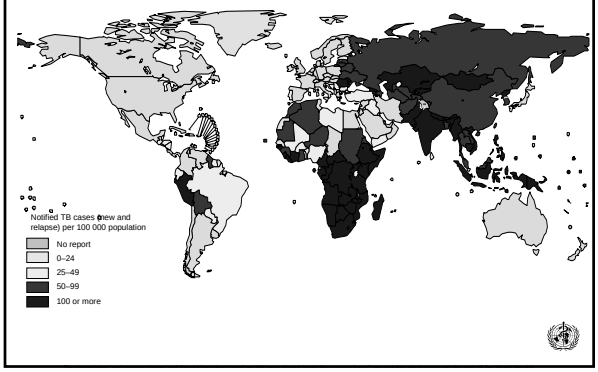
Estimated numbers of new cases, 2006

ANTIBIOTICS

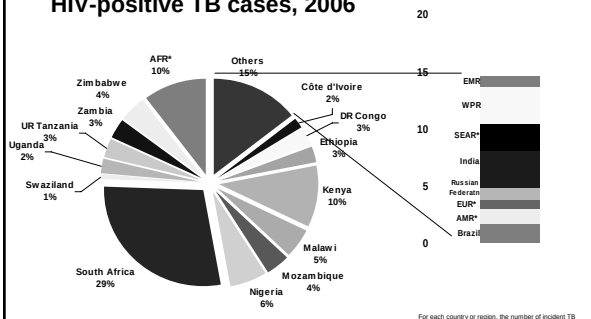
- 1946- STREPTOMYCIN
- RAPID DEVELOPMENT OF FAILURE WITH MONOTHERAPY
- INH =MAGIC BULLET- 1952
- RIFAMPIN & SHORT COURSE RX- 1970

Estimated TB incidence rate, 2006

Tuberculosis notification rates, 2006



Geographical distribution of HIV-positive TB cases, 2006

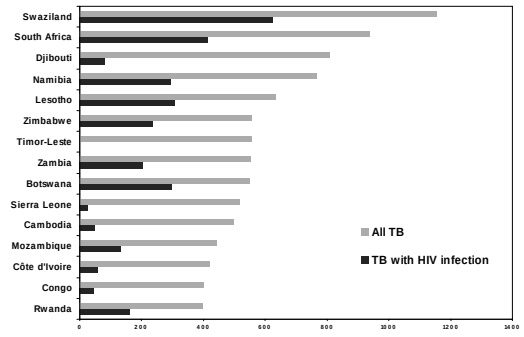


For each country or region, the number of incident TB cases arising in people with HIV is shown as a percentage of the global total of such cases. AFR* is all countries in the WHO African Region except those shown separately; AMR* excludes Brazil; EUR* excludes the Russian Federation; SEAR* excludes India.

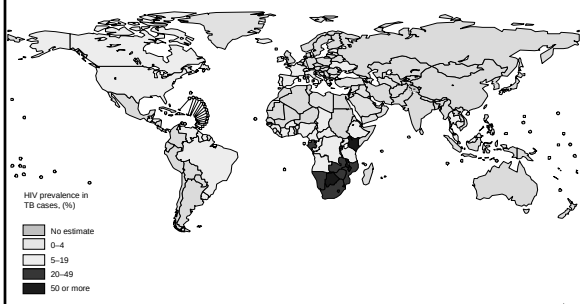
TABLE 1.2
Estimated epidemiological burden of TB, 2006

		INCIDENCE[1]				PREVALENCE		MORTALITY		HIV PREV. IN INCIDENT TB CASES[2]
		ALL FORMS		SMEAR-POSITIVE		ALL FORMS		ALL FORMS		
	POPULATION 1000s	NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP	NUMBER 1000s	PER 100 000 POP PER YEAR	%
1 India	1 151 751	1 933	168	867	75	3 445	299	325	28	1.2
2 China	1 320 864	1 311	99	590	45	2 658	201	201	15	0.3
3 Indonesia	228 864	534	234	240	105	578	253	88	38	0.6
4 South Africa	48 282	454	940	184	382	482	998	105	218	44
5 Nigeria	144 720	450	311	198	137	890	615	117	81	9.6
6 Bangladesh	150 991	351	229	158	101	610	391	70	45	0.0
7 Ethiopia	81 021	306	378	136	168	520	641	68	83	6.3
8 Pakistan	160 943	292	181	131	82	423	263	55	34	0.3
9 Philippines	86 264	248	287	111	129	373	432	39	45	0.1
10 DR Congo	60 644	237	392	105	173	391	645	51	84	9.2
11 Russian Federation	143 221	153	107	68	48	179	125	24	17	3.8
12 Viet Nam	86 206	149	173	66	77	194	225	20	23	5.0
13 Kenya	36 553	141	384	56	153	122	334	26	72	52
14 UR Tanzania	39 459	123	312	53	135	181	459	26	66	18
15 Uganda	29 899	106	355	46	154	168	561	25	84	16
16 Brazil	189 323	94	50	59	31	104	55	7.6	4.0	12
17 Mozambique	20 971	93	443	39	186	131	624	24	117	30
18 Thailand	63 444	90	142	40	62	126	197	13	20	11
19 Myanmar	48 379	83	171	37	76	82	169	6.1	13	2.6
20 Zimbabwe	13 229	74	557	30	227	79	597	17	131	43
21 Cambodia	14 197	71	500	31	220	94	665	13	92	9.6
22 Afghanistan	26 088	42	161	19	73	60	231	8.3	32	0.0
High-burden countries	4 150 313	7 334	177	3 265	79	11 889	286	1 330	32	11

Fifteen countries with the highest estimated TB incidence rates per capita and corresponding incidence rates of HIV-positive TB cases, 2006



Estimated HIV prevalence in new TB cases, 2006



RISING INCIDENCE WORLDWIDE

FAILURE OF PUBLIC HEALTH

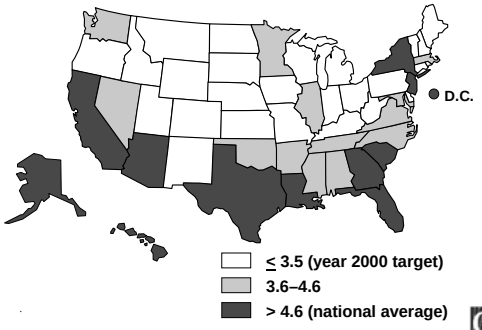
FAILURE OF POLITICAL WILL

RX TO CURE COSTS $12/PT

>95% TB IS IN RESOURCE POOR CONTRIES

MONEY & INFRASTRUCTURE

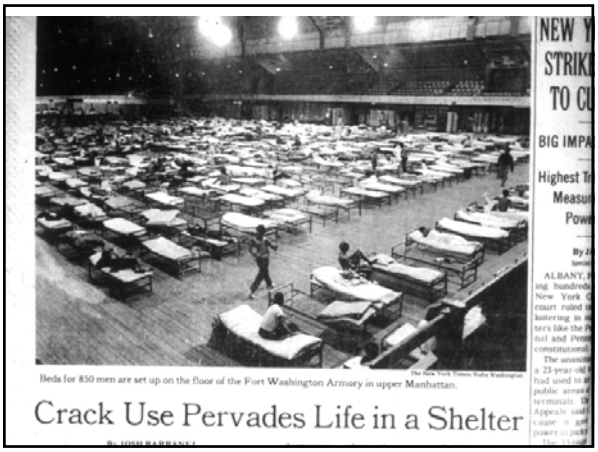
TB Case Rates,* United States, 2006



≤ 3.5 (year 2000 target)
3.6–4.6
> 4.6 (national average)

*Cases per 100,000.

CDC



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

Crack Use Pervades Life in a Shelter

DEVELOPED WORLD TB

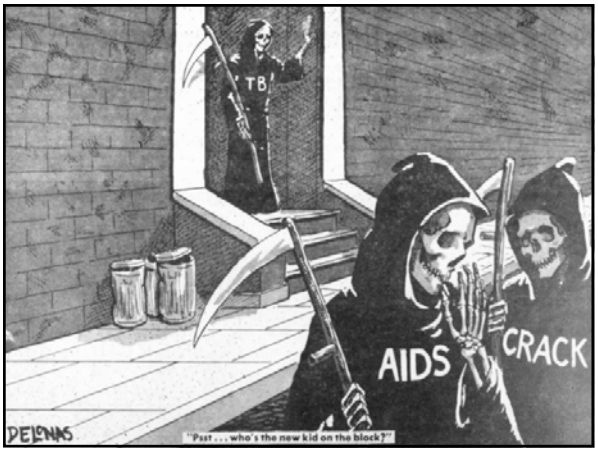
DOWNWARD TREND BEFORE ANTIBIOTICS: WHY?

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

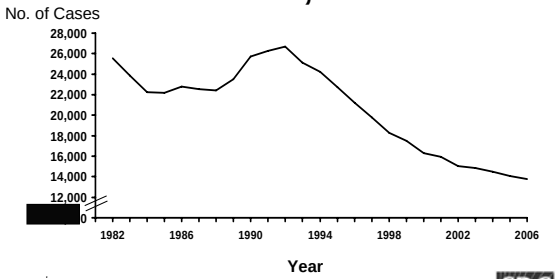
Higher natural resistance

Better living conditions-less crowding

Effect of sanatoriums

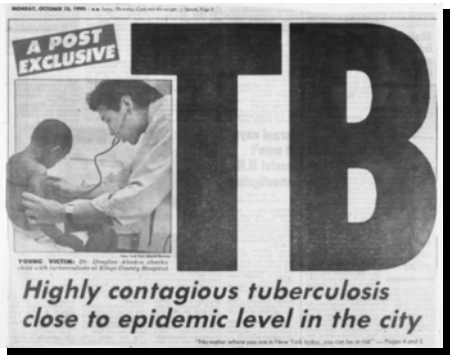


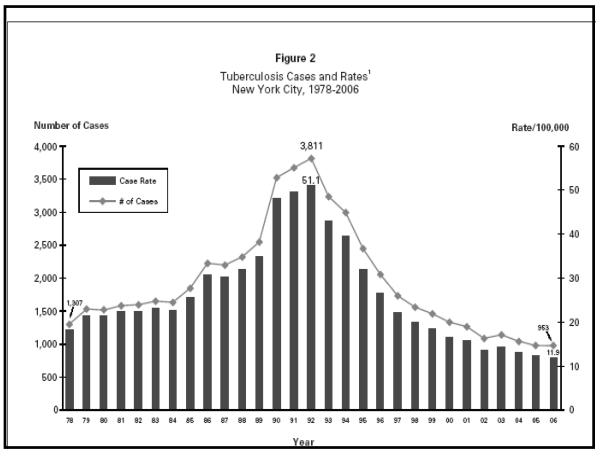
Reported TB Cases* United States, 1982–2006



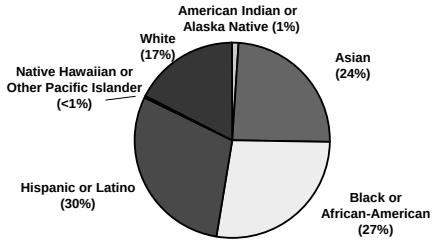
*Updated as of April 6, 2007.

CDC

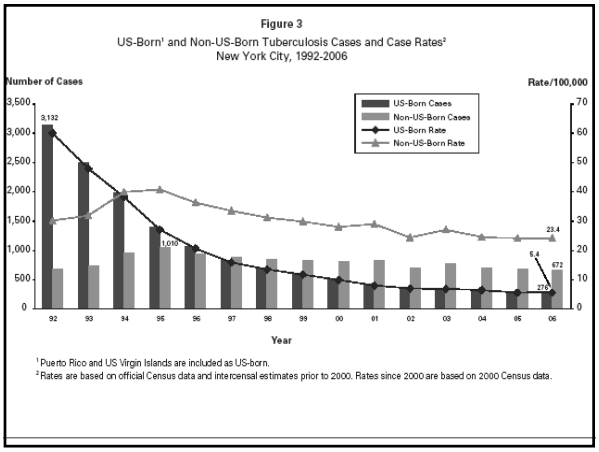




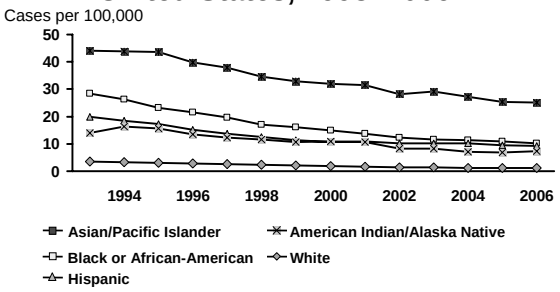
Reported TB Cases by Race/Ethnicity* United States, 2006



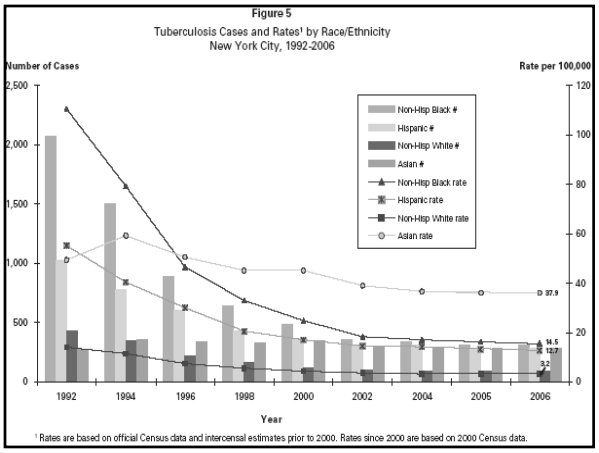
*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.



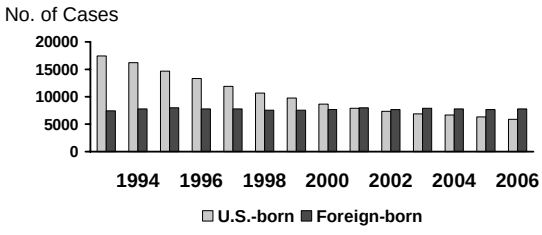
TB Case Rates by Race/Ethnicity* United States, 1993–2006**



*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.
**Updated as of April 6, 2007.

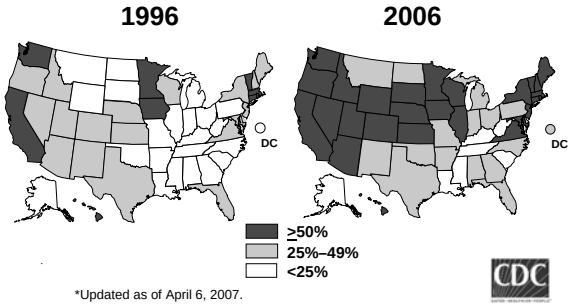


Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2006*



*Updated as of April 6, 2007.

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

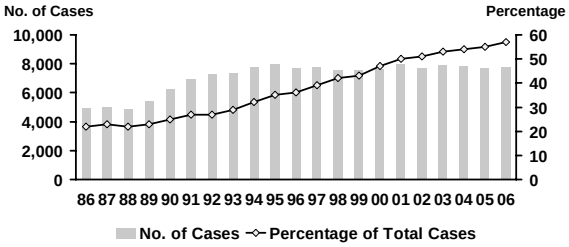


*Updated as of April 6, 2007.

M. Tuberculosis complex

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

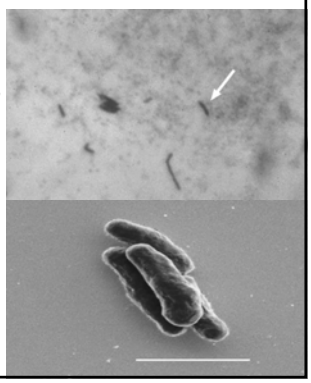
Trends in TB Cases in Foreign-born Persons, United States, 1986–2006*



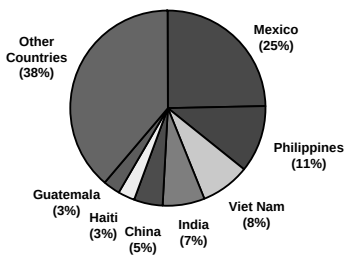
*Updated as of April 6, 2007.

THE BACILLUS

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

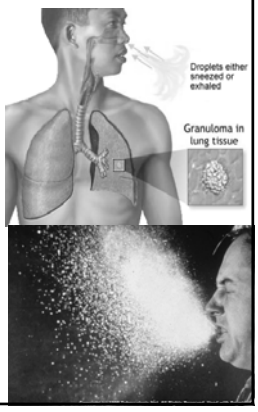


Countries of Birth of Foreign-born Persons Reported with TB United States, 2006



TRANSMISSION

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



TRANSMISSION ENHANCERS

INOCULUM SIZE:

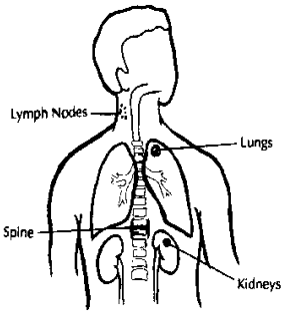
- AUTOPSY SUITE TRANSMISSIONS

STRAIN VARIABILITY/VIRULENCE:

- KENTUCKY OUTBREAK

VENTILATION: BACILLUS LONGEVITY & INFECTIVITY IN AIR

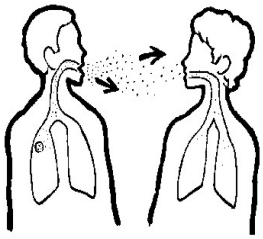
DISSEMINATION



- 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



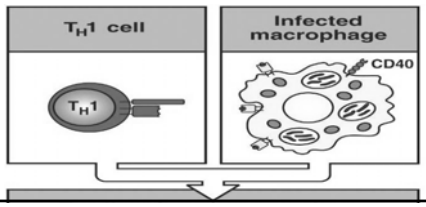
Development of Immune Response: 6-12 weeks

- 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

REPLICATION

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

AND



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

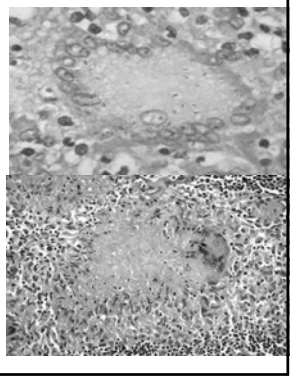
- CD4 cells release interferon gamma
- Interferon gamma stimulates additional macrophage phagocytosis of M. tuberculosis
- Interferon gamma stimulates macrophage to release tumor necrosis factor alpha (TNF Alpha)

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

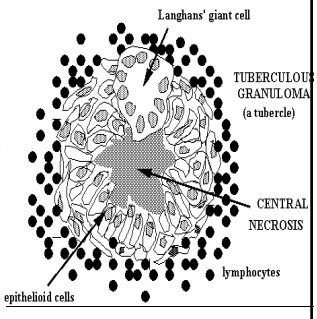
- Murine experiments:
  - Blockade of TNF alpha resulted in reactivation, high bacillary burden, persistent tuberculosis and death
  - TNF alpha knock-out mice infected with *M. tuberculosis* followed similar course

PATHOLOGY OF A GRANULOMA

Macrophages secrete lytic enzymes which cause tissue necrosis

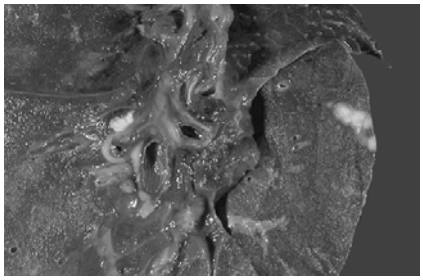
Epithelioid cell=highly stimulated macrophage

Langhans Giant Cell= fused macrophages with multiple nuclei



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-ADOLESCENCE/YOUNG ADULTS

Develop cavitary disease:

23% age 15-19

13% age 20-24

4% 25-29

Primary Infection with Progression

Progressive Primary Disease

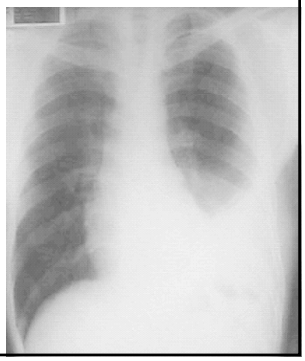
- Young children <5- cannot resolve initial infection :Progression to active disease, miliary or disseminated, CNS involvement
- Almost always developing world where TB is endemic

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

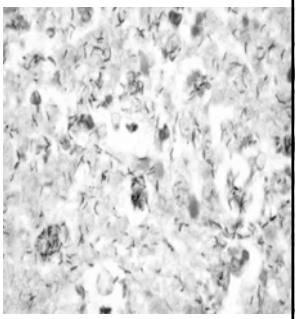
TUBERCULOUS PLEURISY

- **HYPERSENSITICITY REACTION**
- **EXUDATIVE PLEURAL EFFUSION**
- **CULTURE NEGATIVE-FEW BACILLI**
- **WW II STUDIES: 65% RELAPSE TO ACTIVE TB IF UNTREATED**



OVERWHELMING TB

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



Reactivation: 10-15% of those infected

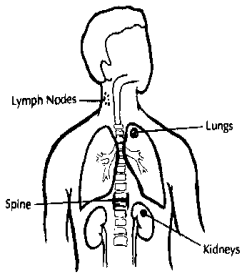
- **Persistence of viable organisms**
- **Containment of infection, lack of active disease**
- **Viable organisms remain alive, dormant for years**
- **Disease occurs when cellular immune system can no longer contain MTB**

- **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**

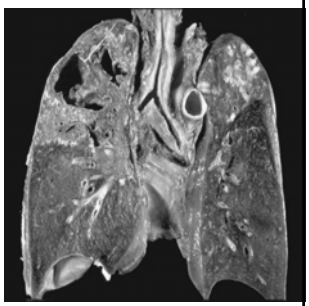
EXTRAPULMONARY TB



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

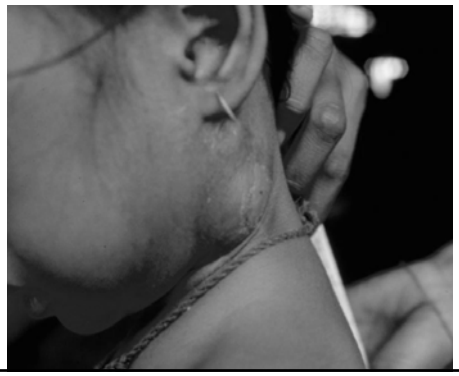
85% Reactivation=Lungs

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



LYMPH NODES: SCROFULA
Most frequent form of extrapulmonary TB

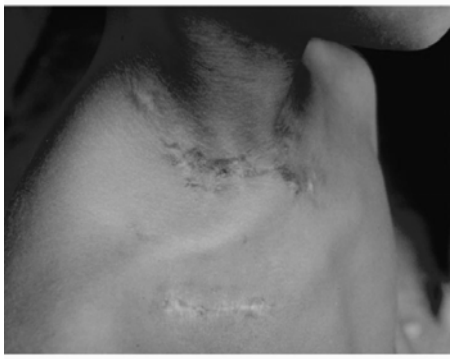
Usually Cervical



BONES

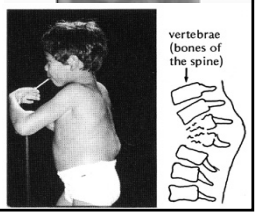
- **ONE THIRD INVOLVE SPINE From:**
- **Hematogenous spread from initial infection**
- **Lymphatic spread from pleural disease**
- **Contiguous disease**

Or Supraclavicular



POTTS DISEASE

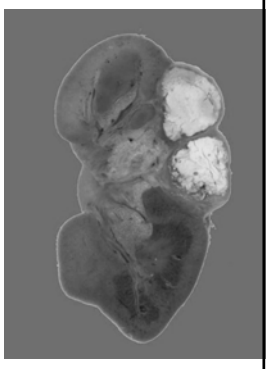
- Earliest focus: Anterior superior or inferior angle of vertebral body
- Spreads to interverteberal disk & adjacent vertebra



Can also be axillary

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

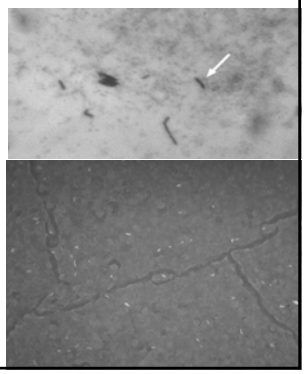
CULTURE CONT'D

- **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

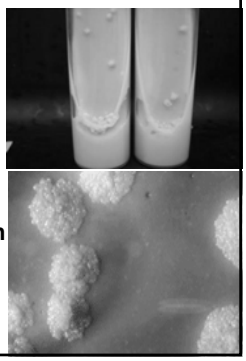
***M. bovis* ALMOST ALWAYS RESISTANT TO PYRAZINAMIDE**

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



Nucleic Acid Amplification: Can detect MTB in fresh sputum

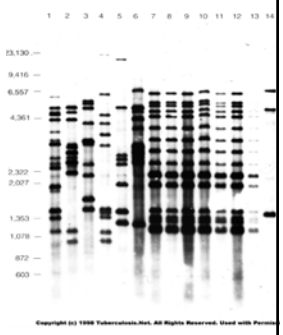
- Sensitivity intermediate between acid fast smear and culture
- AFB smear negative, nucleic acid amplification=40-77% sensitive
- AFB smear positive, nucleic acid amplification=95% sensitive & 100% specific
- **LUXURY OF DEVELOPED WORLD**

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



UPPER LOBE INFILTRATE

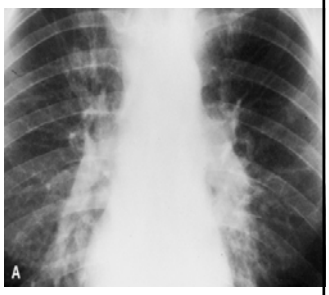
- Apical or sub-apical
- Most common in reactivation disease if immune system intact
- Radiologic extent of disease reflects tissue damage
- Tissue damage reflects host's ability to have hypersensitivity reaction

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



Chest X-Ray

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

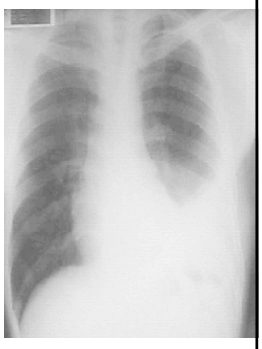
PLEURAL EFFUSION

Seen in post-primary as above: scant orgs

Smear negative but culture positive 25%

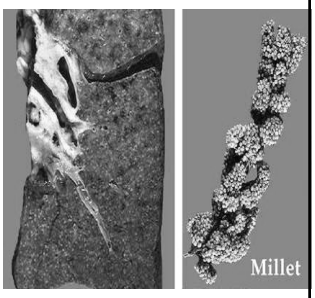
Seen as complication of reactivation TB: more likely to have orgs

Smear positive 50% & culture positive 60-70%



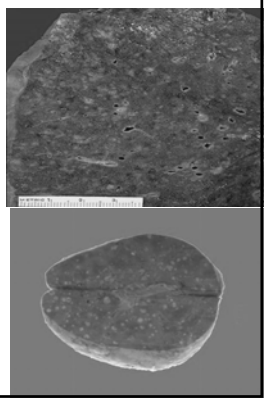
MILIARY PATTERN

- 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

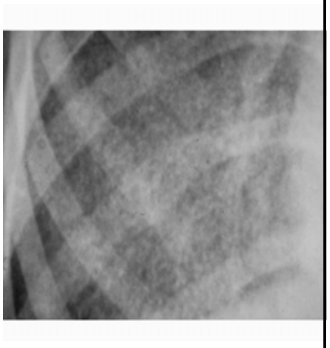
Immunocompromising diseases:

-alcoholism

-cirrhosis

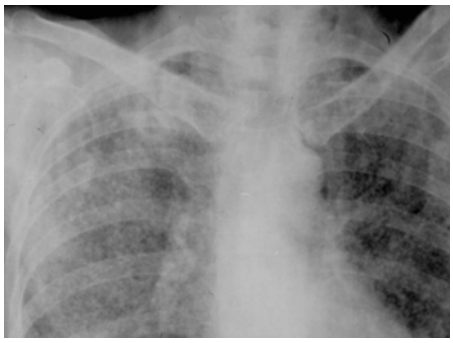
-rheumatologic diseases

-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

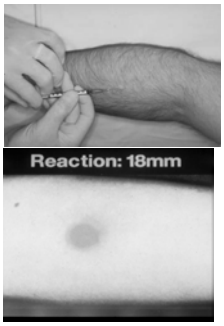
Targeted Testing: **PPD is NOT a general screen**

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**

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**

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 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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