PRE-ANTIBIOTIC ERA

SANATORIUM REGIMENS & REST

CAVITARY DISEASE & COLLAPSE THERAPY

FRESH AIR, SUNSHINE-ROOFTOPS SOLARIA

HISTORY

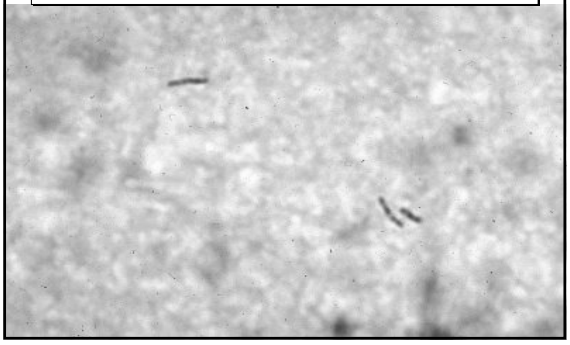
EGYPTIAN MUMMIES: SPINAL TB

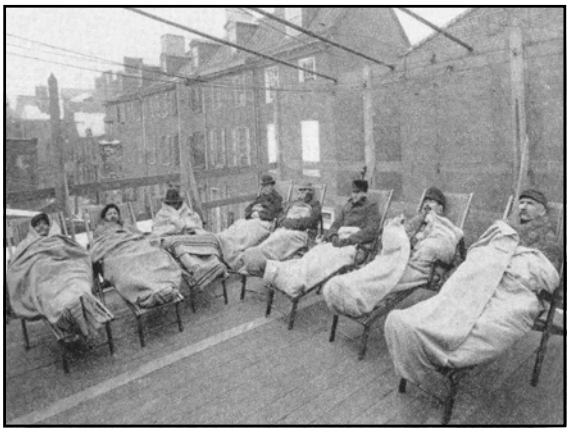
17th-18th CENTURIES- URBANIZATION

19th CENTURY INDUSTRIALIZATION

TB = 25% ADULT DEATHS

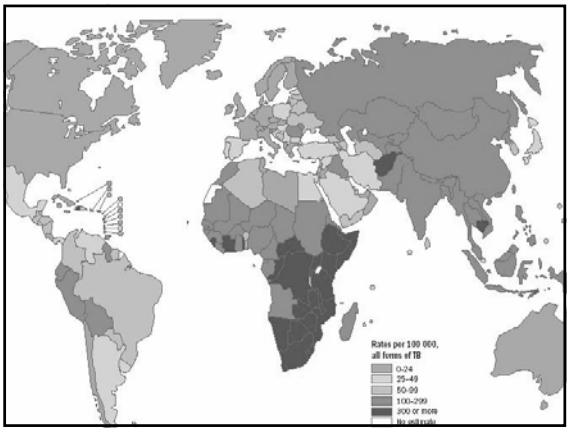
GERM THEORY OF DISEASE KOCH'S BACILLUS-1883





EPIDEMIOLOGY

- M. TUBERCULOSIS INFECTS 1/3 WORLD'S POPULATION
- 8 MILLION NEW CASES ANNUALLY
- 2 MILLION DEATHS
- 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

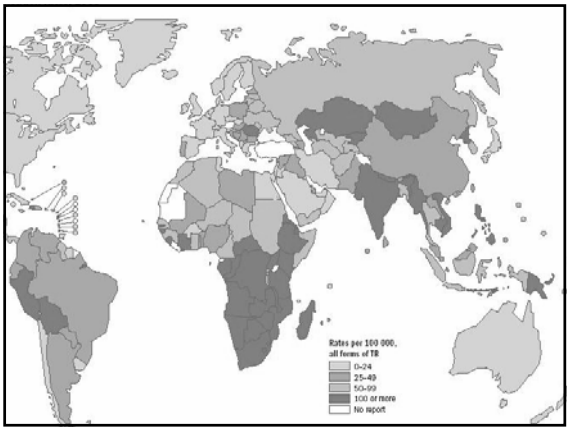
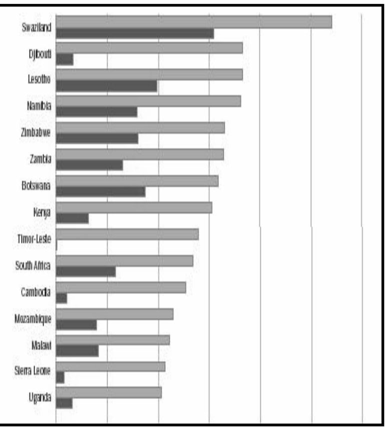
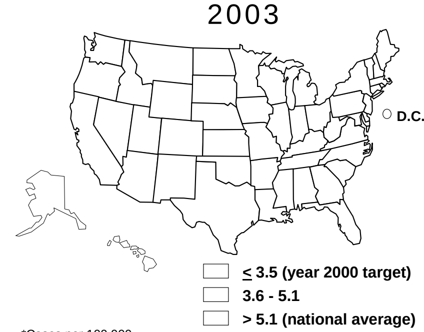


FIGURE 3

Fifteen countries with the highest estimated TB incidence rates per capita (all ages, all forms; grey bars) and corresponding incidence rates of HIV-infected TB (among adults aged 15–49 years; blue bars), 2003



TB Case Rates,* United States, 2003



*Cases per 100,000

stimated TB burden, 2003

		INCIDENCE				PREVALENCE		MORTALITY	
		ALL CASES		SMEAR-POSITIVE CASES		ALL FORMS OF TB, INCLUDING IN HIV-INFECTED PEOPLE			
	POPULATION 1000s	NUMBER 1000s	RATE PER 100 000 POP.	NUMBER 1000s	RATE PER 100 000 POP.	NUMBER 1000s	RATE PER 100 000 POP.	NUMBER 1000s	RATE PER 100 000 POP.
1 India	1 065 462	1 788	168	798	75	3 086	290	352	33
2 China	1 304 196	1 334	102	600	46	3 203	246	236	18
3 Indonesia	219 883	627	285	282	128	1 484	675	143	65
4 Nigeria	124 009	363	293	156	126	677	546	105	85
5 Bangladesh	146 736	361	246	162	111	719	490	84	57
6 Pakistan	153 578	278	181	125	82	551	359	67	43
7 Ethiopia	70 678	252	356	109	155	377	533	56	79
8 South Africa	45 026	242	536	98	218	206	458	33	73
9 Philippines	79 999	237	296	107	133	366	458	39	49
0 Kenya	31 987	195	610	84	262	283	884	43	133
1 DR Congo	52 771	195	369	85	160	298	564	43	81
2 Russian Federation	143 246	161	112	72	50	229	160	29	20
3 Viet Nam	81 377	145	178	65	80	195	240	19	23
4 UR Tanzania	36 977	137	371	58	157	194	524	32	86
5 Brazil	178 470	110	62	49	28	164	92	15	8
6 Uganda	25 827	106	411	46	179	168	652	25	96
7 Thailand	62 833	89	142	40	63	130	208	12	19
8 Mozambique	18 863	86	457	36	190	120	636	24	129
9 Zimbabwe	12 891	85	659	34	265	85	660	20	153
0 Myanmar	49 485	85	171	38	76	92	187	12	25
1 Afghanistan	23 897	80	333	36	150	160	671	22	93
2 Cambodia	14 144	72	508	32	225	108	762	13	95
igh-burden countries	3 942 338	7 027	178	3 112	79	12 896	327	1 423	36
AFR	687 405	2 372	345	1 013	147	3 487	507	538	78
AMR	867 768	370	43	165	19	503	58	54	6
EMR	518 063	634	122	285	55	1 120	216	144	28
EUR	878 902	439	50	196	22	577	66	67	8
SEAR	1 614 648	3 062	190	1 370	85	5 662	351	617	38

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

RISING INCIDENCE WORLDWIDE

FAILURE OF PUBLIC HEALTH

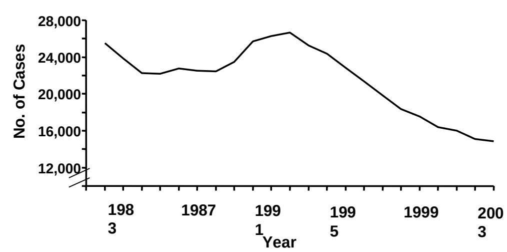
FAILURE OF POLITICAL WILL

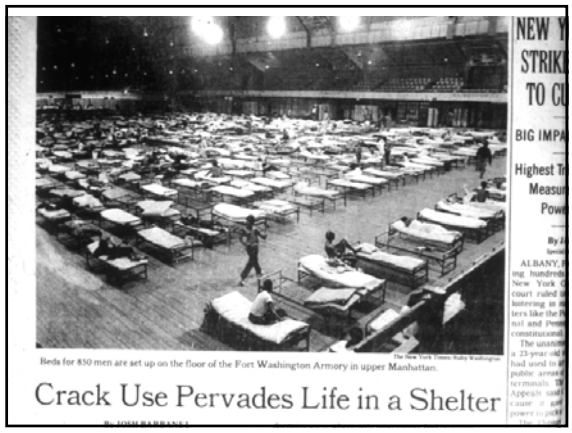
RX TO CURE COSTS $12/PT

>95% TB IS IN RESOURCE POOR CONTRIES

<2% $$ GOES TO THEM

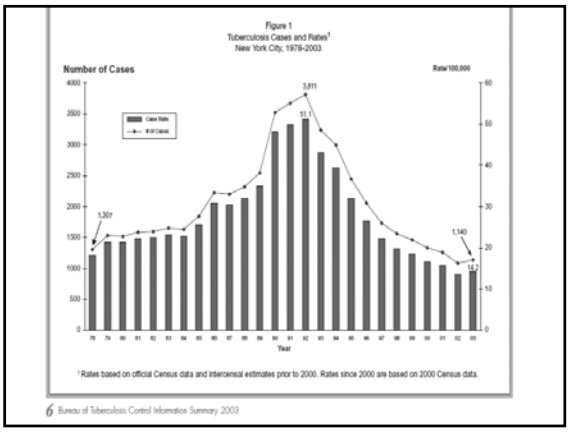
Reported TB Cases United States, 1982-2003

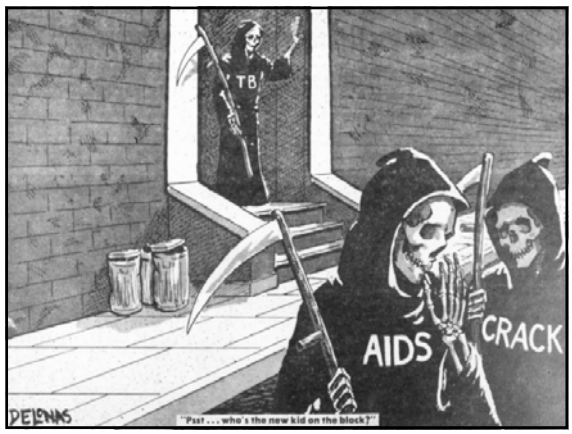


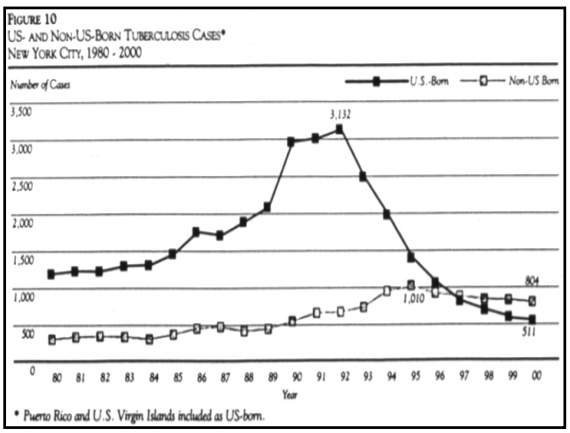


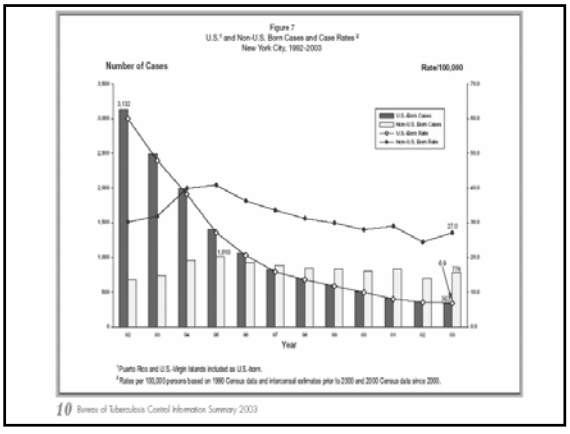
Beds for 850 men are set up on the floor of the Fort Washington Armory in upper Manhattan.

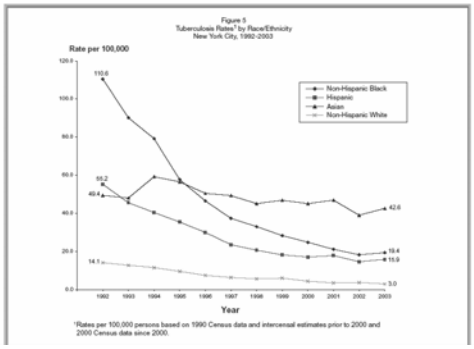
Crack Use Pervades Life in a Shelter



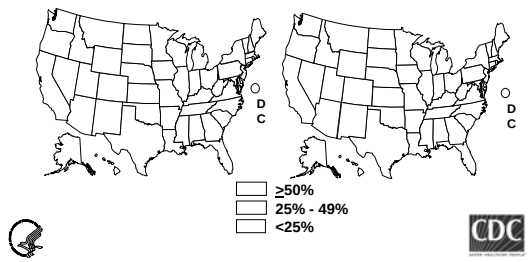




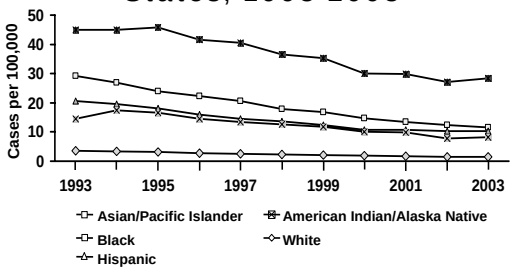




Percentage of TB Cases Among Foreign-born Persons, United States

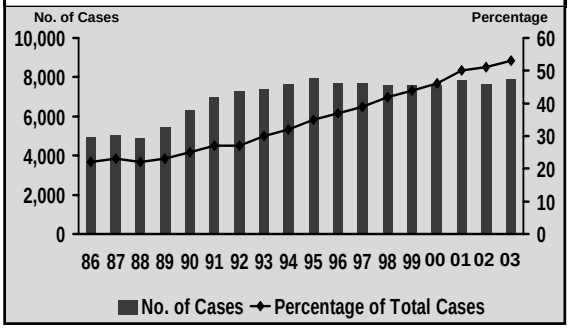


TB Case Rates* by Race/Ethnicity** United States, 1993-2003

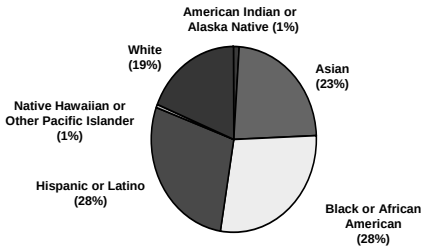


*Cases per 100,000.
**All races are non-Hispanic. In 2003, Asian/Pacific Islander category includes persons who reported race as Asian only and/or Native Hawaiian or Other Pacific Islander only.

Trends in TB Cases in Foreign-born Persons, United States, 1986-2003

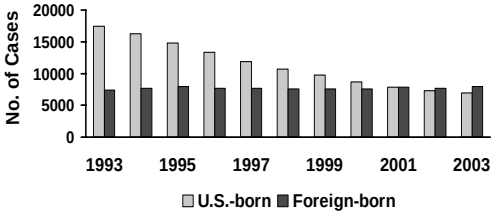


Reported TB Cases by Race/Ethnicity* United States, 2003



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

Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993-2003



M. Tuberculosis complex

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

TRANSMISSION ENHANCERS

INOCULUM SIZE:

- AUTOPSY SUITE TRANSMISSIONS

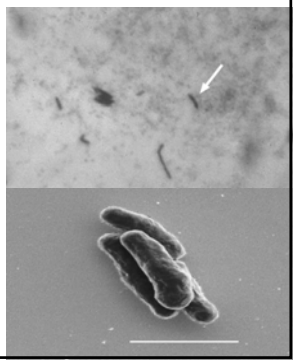
STRAIN VARIABILITY/VIRULENCE:

- KENTUCKY OUTBREAK

VENTILATION: BACILLUS LONGEVITY & INFECTIVITY IN AIR

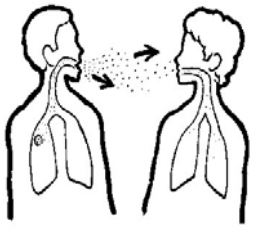
THE BACILLUS

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



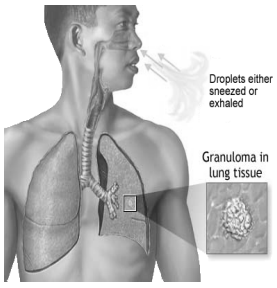
Primary Infection: BEFORE IMMUNE RESPONSE

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



TRANSMISSION

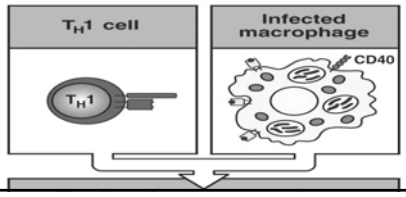
- Lungs=entry portal
- Inhalation of droplet nuclei
- Coughing: 3000 droplet nuclei/cough
- Talking: 5 minutes
- Sneezing: BEST



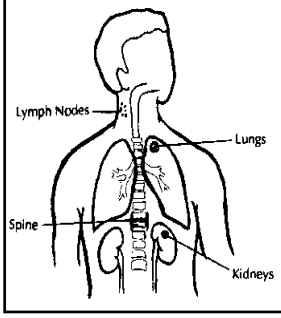
REPLICATION

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

AND



DISSEMINATION



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

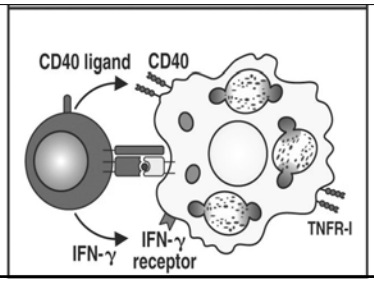
INTERFERON GAMMA

- 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)

Development of Immune Response: 6-12 weeks

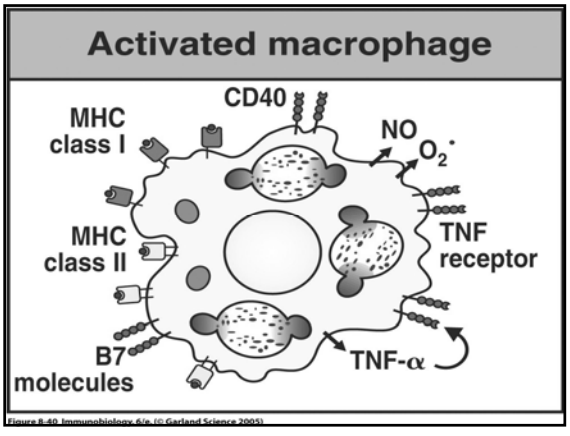
- Alveolar macrophage infected with TB secretes Interleukins 12 & 18
- These attract CD 4 cells
- CD 4 cells meet TB antigen macrophage presents to them
- Transformation of CD 4 cells

Interferon Gamma activates macrophage:
-Stimulates macrophage to phagocytose MTB
-Makes macrophage secrete TNF alpha



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**

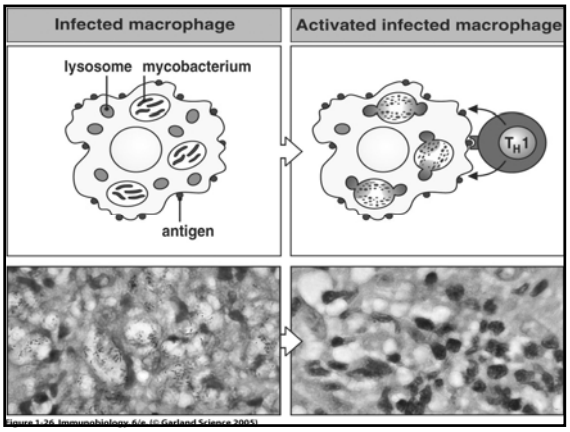


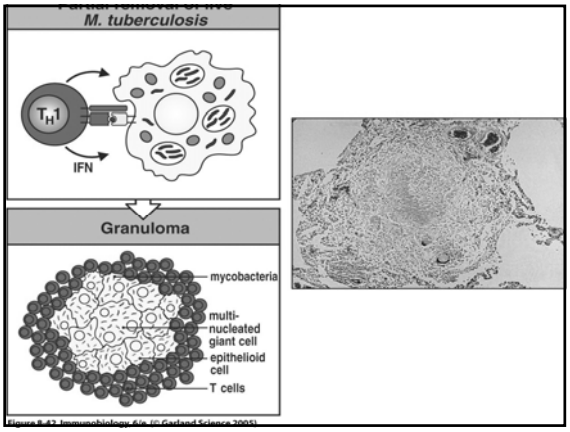
Tumor Necrosis Alpha (TNF alpha)

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

PATHOLOGY

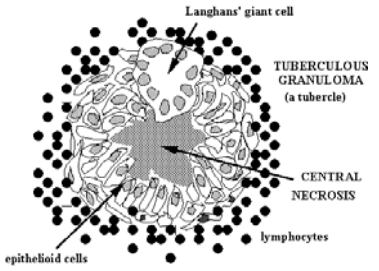
- Macrophages secrete lytic enzymes which cause tissue necrosis
- Epithelioid cell=highly stimulated macrophage
- Langhans Giant Cell= fused macrophages with multiple nuclei





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-ADOLESCENCE

Develop cavitary disease:

23% age 15-19

13% age 20-24

4% 25-29

Primary Infection with Progression

Progressive Primary Disease

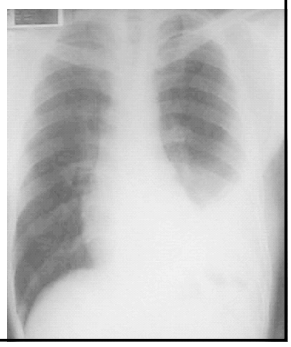
- Young children <5- cannot resolve initial infection :Progression to active disease, miliary or disseminated, CNS involvement
- Almost always developing world where TB is endemic

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

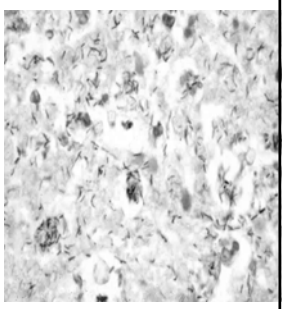
TUBERCULOUS PLEURISY

- 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

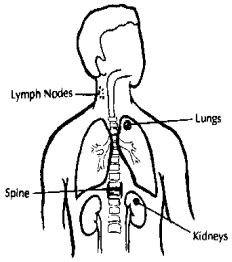
- Persistence of viable organisms
- Containment of infection, lack of active disease
- Viable organisms remain alive, dormant for years
- Disease occurs when cellular immune system can no longer contain MTB

- **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**

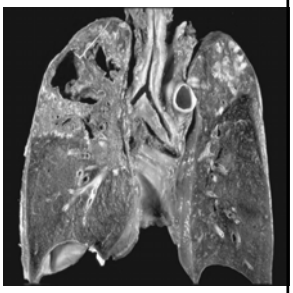
EXTRAPULMONARY TB



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

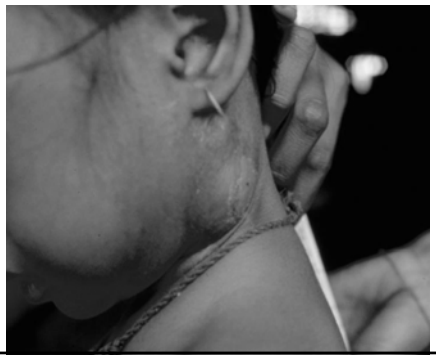
85% Reactivation=Lungs

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



LYMPH NODES: SCROFULA
Most frequent form of extrapulmonary TB

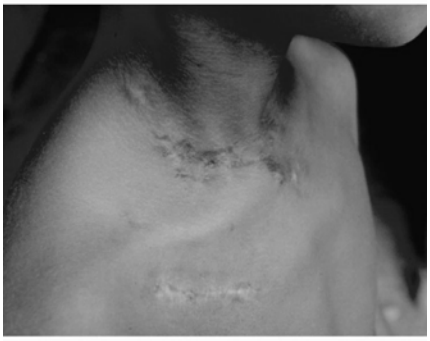
Usually Cervical



BONES

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

Or Supraclavicular



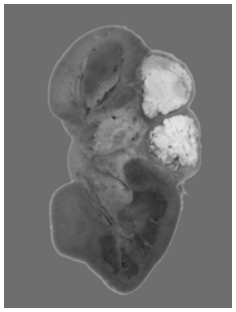
POTTS DISEASE

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

Can also be axillary

RENAL TUBERCULOSIS

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



Diagnosis: Symptoms

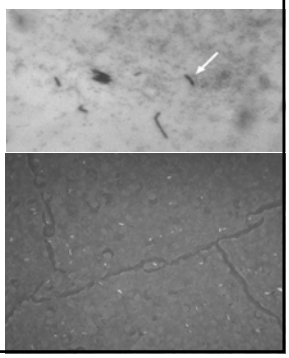
- Systemic symptoms non-specific: fever, fatigue, night sweats, weight loss
- Pulmonary symptoms: cough, productive or dry
- Hemoptysis: can be emergency
  - Suggests bronchial wall erosion

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**

DIAGNOSTIC PROCEDURES

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



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**

CULTURE=GOLD STANDARD

Now available in most of world via WHO reference labs

-SOLID MEDIA: 3-8 weeks

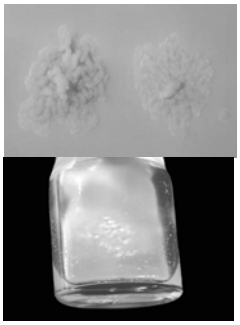
Lowenstein Jensen=egg based

Middlebrook 7H11=agar based

-LIQUID BROTH: 1-3 weeks

Middlebrook 7H12

BACTEC systems



Chest X-Ray

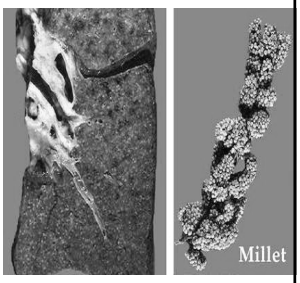
- Upper lobe infiltrate with or without cavity
- Hilar adenopathy with or without infiltrates
- Pleural effusion, exudative
- Lower lobe infiltrate
- Miliary pattern

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

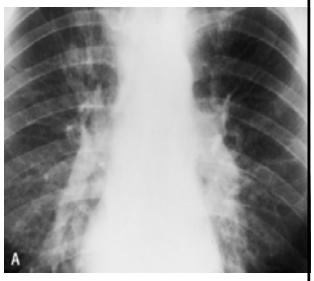
MILIARY PATTERN

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



HILAR ADENOPATHY

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



MILIARY PATTERN

Following childhood infection and progression

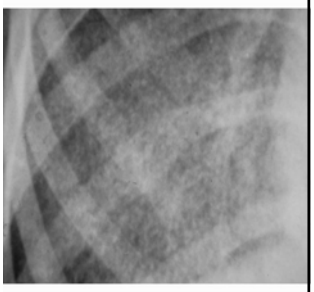
Immunocompromising diseases:

-alcoholism

-cirrhosis

-rheumatologic diseases

-Rx with immunosuppressive



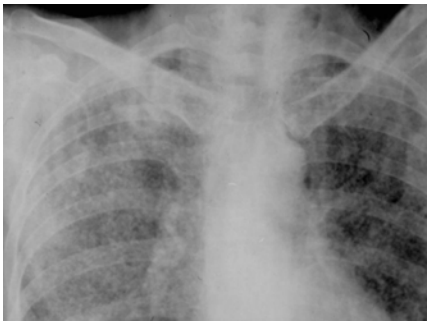
PLEURAL EFFUSION

Seen in post-primary as above: scant orgs

-Smear negative but culture positive 25%

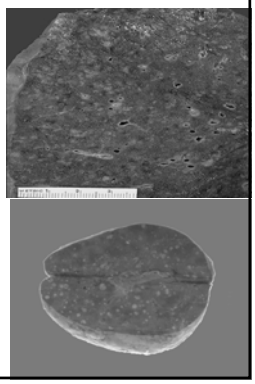
Seen as complication of reactivation TB: more likely to have orgs

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



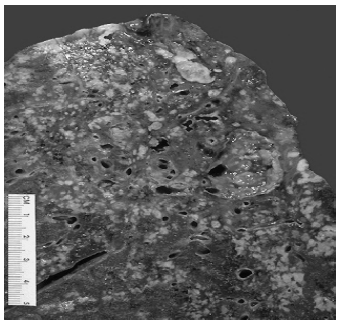
DIAGNOSIS DIFFICULT

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



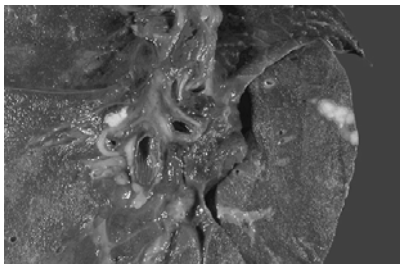
DRUGS: ALL GIVEN ONCE DAILY TOGETHER

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

Protease Inhibitors

Prophylaxis: LTBI

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

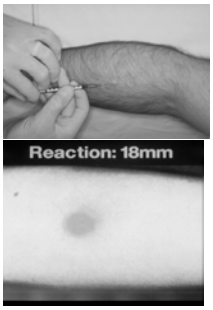
- Immunocompromised patients:
- HIV infected, chemotherapy, organ transplant, immunosuppressive RX for autoimmune diseases
- Close contacts of infectious cases
- Previously untreated patients with Chest x-ray evidence of old disease (NOT just granuloma)
- Recent Immigrants (in US <5 years)
- People who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

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

POSITIVE PPD: DEFINITION

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



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

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