Mycobacterium

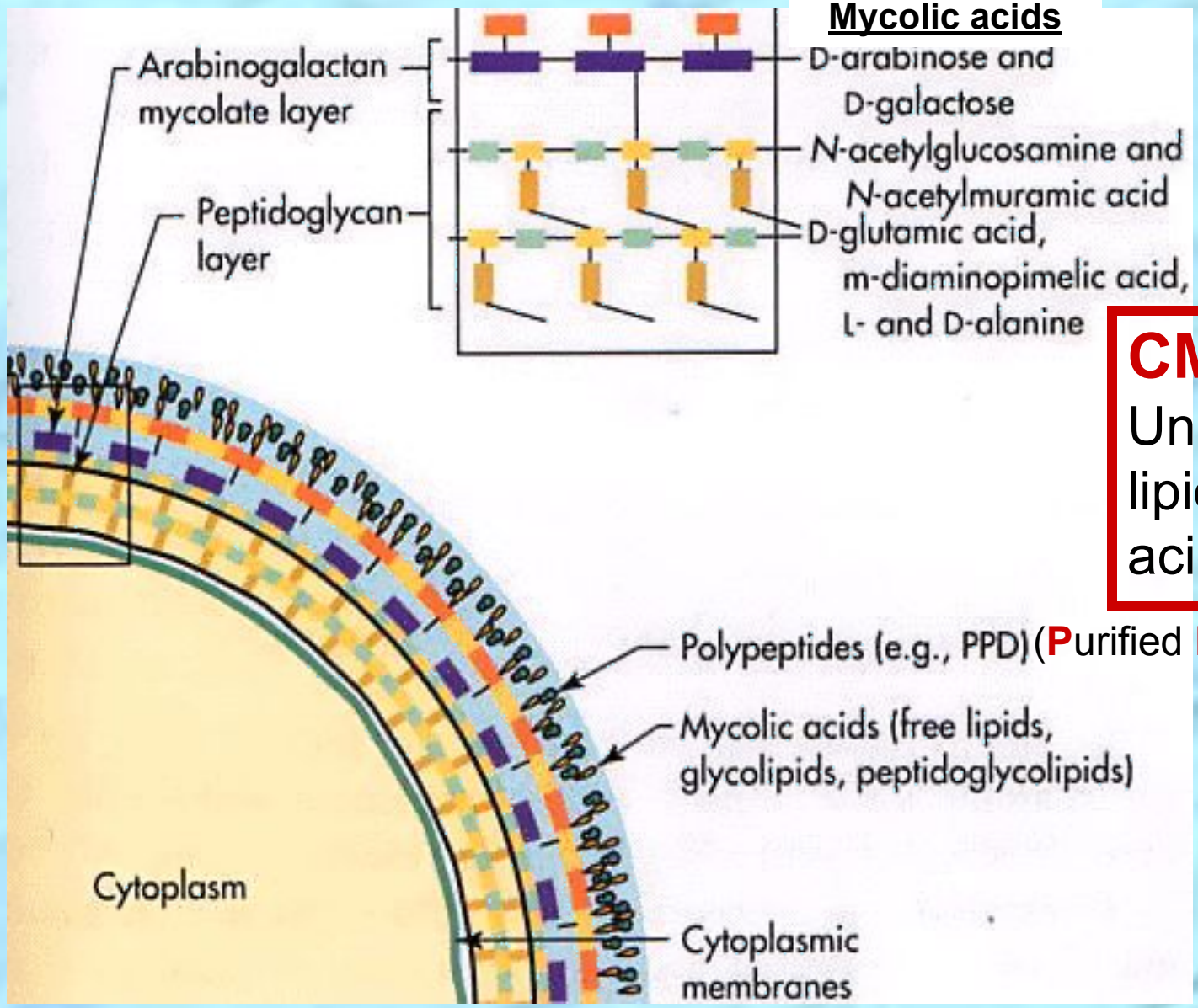
Important Human Pathogens

Mycobacterium tuberculosis

Mycobacterium leprae (uncommon)

Mycobacterium avium-intracellulaire Complex (MAC) or (M. avium)

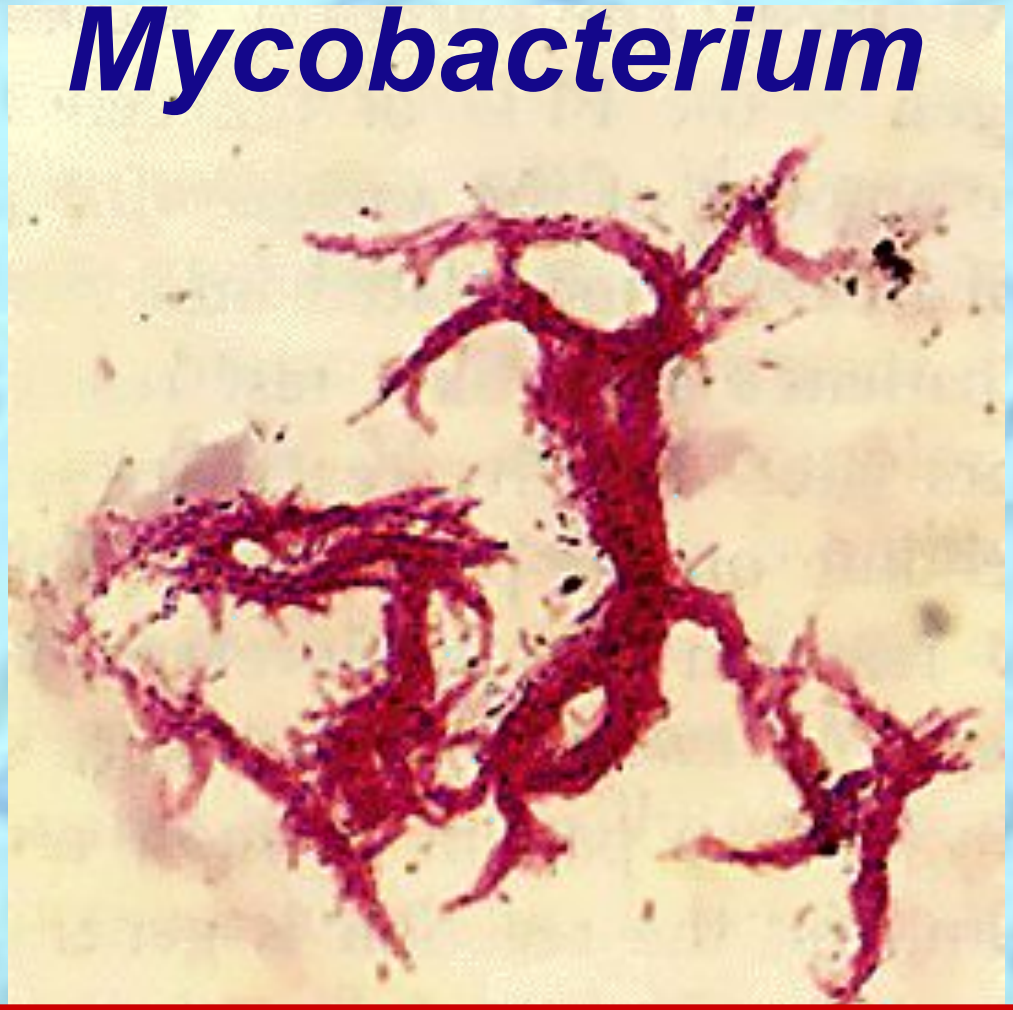
Lipid-Rich Cell Wall of Mycobacterium



CMN Group:
Unusual cell wall lipids (mycolic acids,etc.)

(**P**urified **P**rotein **D**erivative)

Acid-Fast (Kinyoun) Stain of Mycobacterium

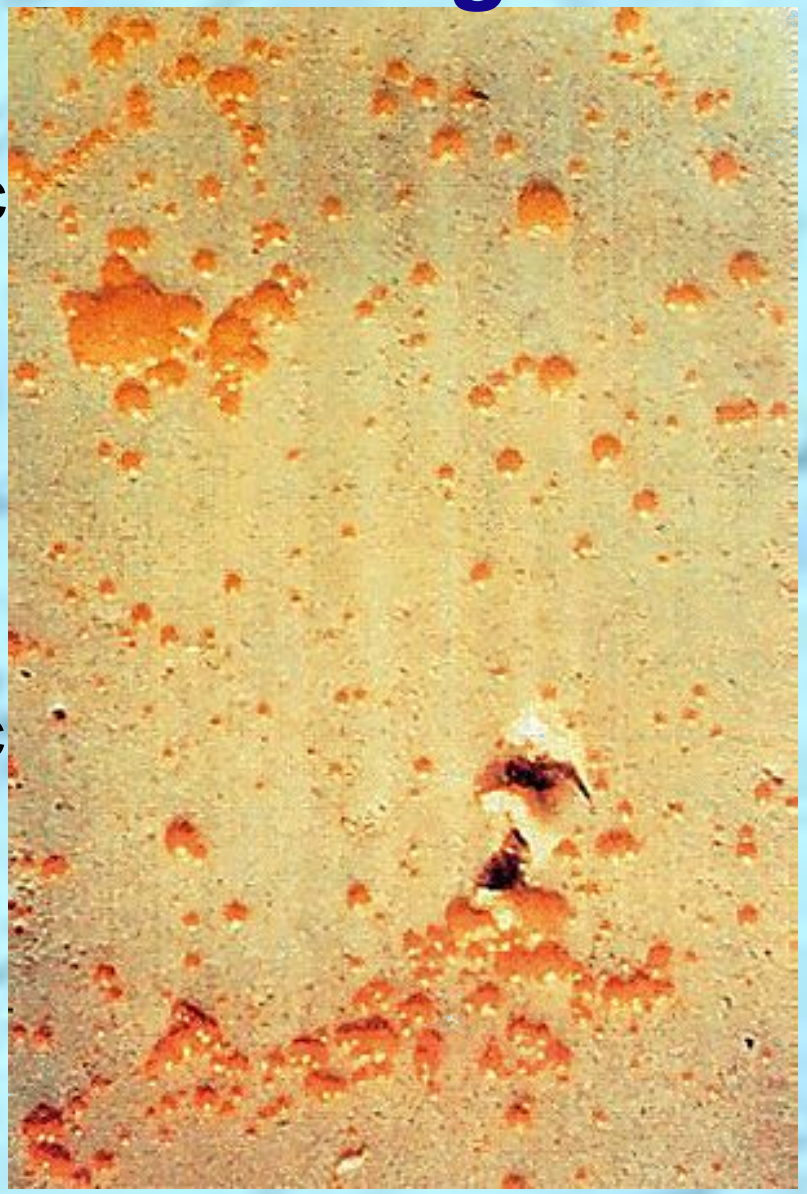


NOTE: cord growth (serpentine arrangement) of virulent strains

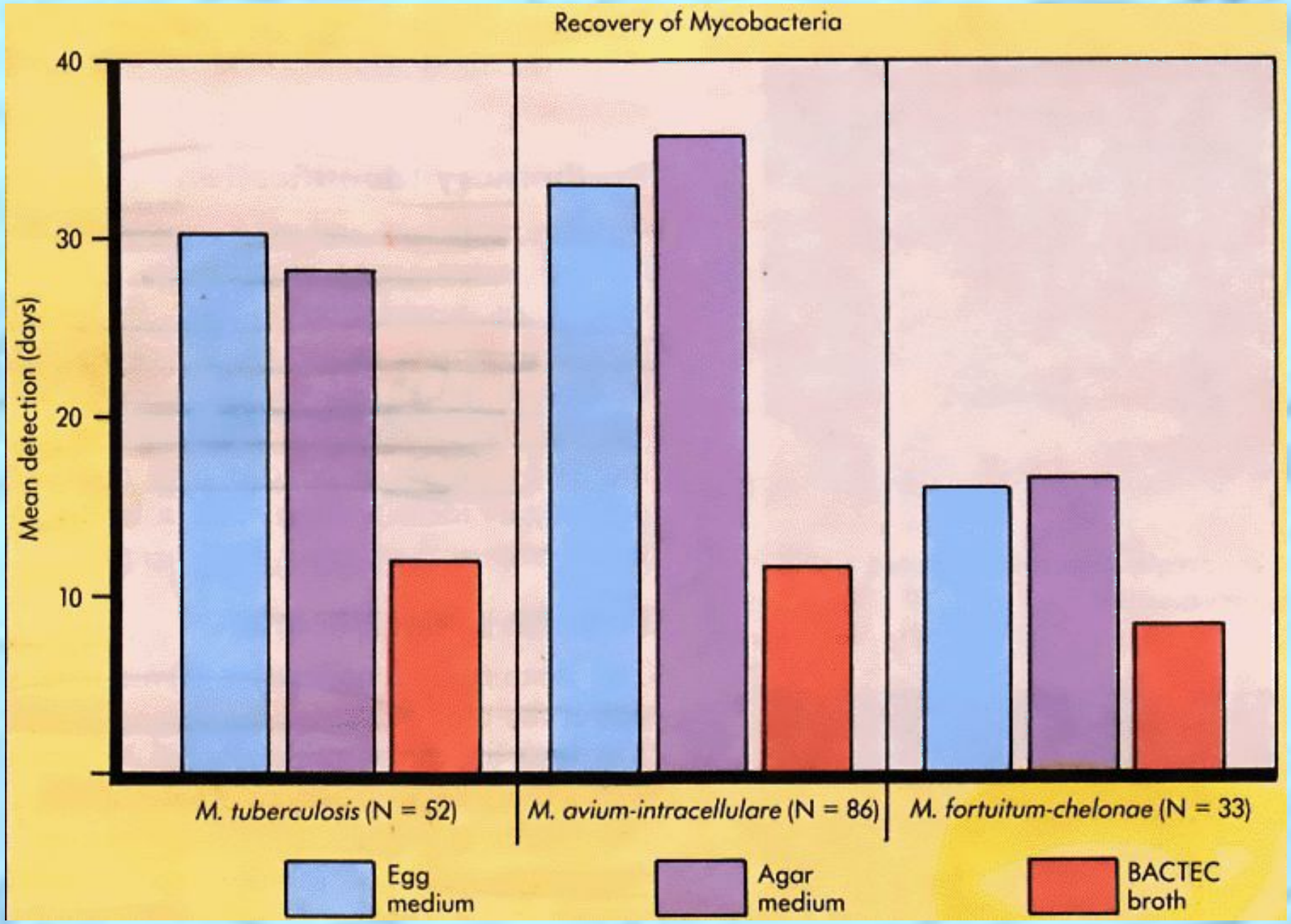
Photochromogenic Mycobacterium kansasii on Middlebrook Agar

NOTE: Mycobacteria pathogenic for humans can be differentiated (**Runyon Groups**) by:

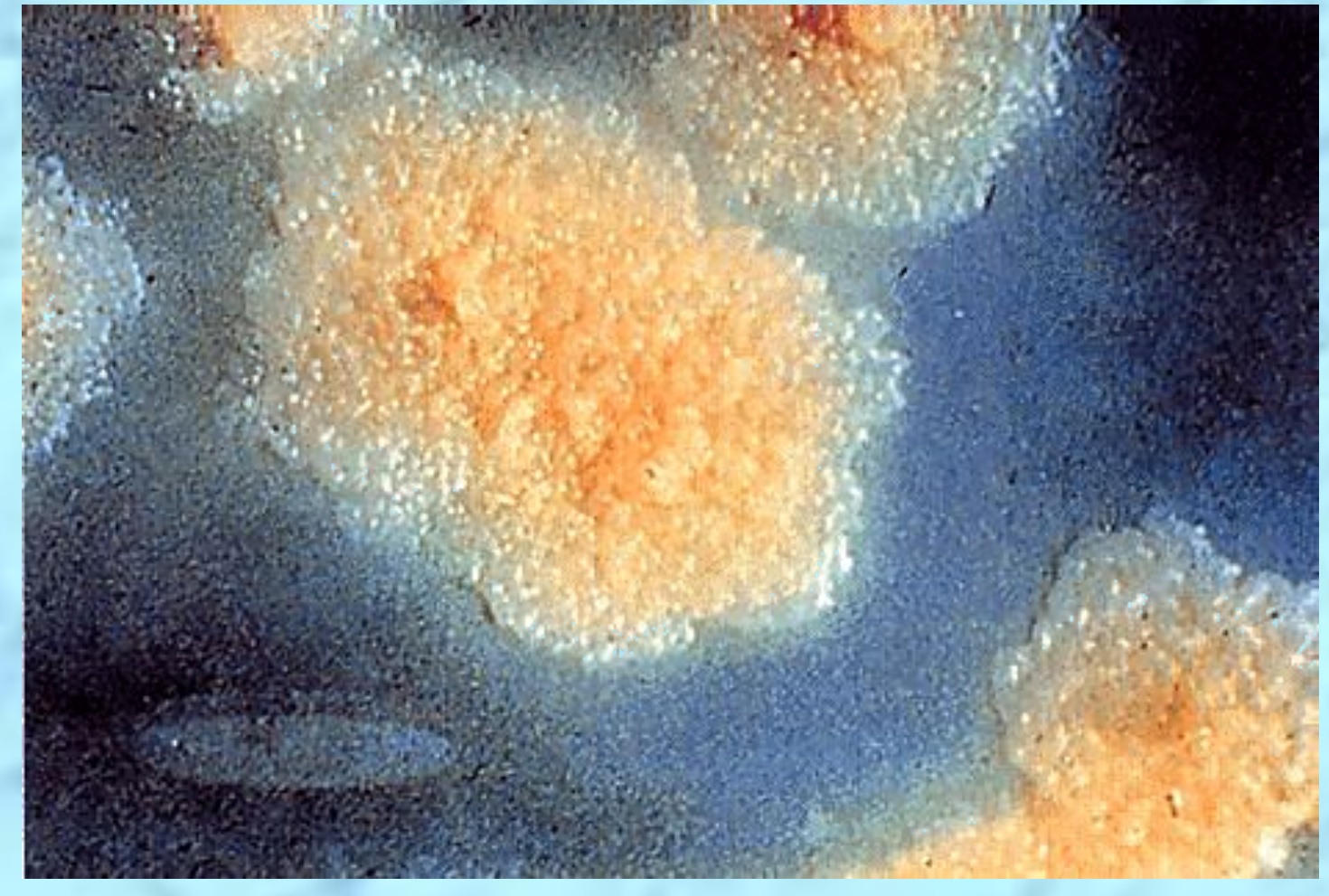
- ✔ **speed of growth** (all are slower than most other pathogens) and by
- ✔ production of **chromogenic pigments** (in light, in dark, or none)



Improved Mycobacterial Isolation Medium



Eight Week Growth of Mycobacterium tuberculosis on Lowenstein-Jensen Agar



Pathogenic Mycobacterium spp.

BCG

AIDS patients

Organism	Pathogenicity	Frequency in United States
M. tuberculosis *Complex*		
M. tuberculosis	Strictly pathogenic	Common
M. leprae	Strictly pathogenic	Uncommon
M. africanum	Strictly pathogenic	Rare
M. bovis	Strictly pathogenic	Rare
M. ulcerans	Strictly pathogenic	Rare
Runyon Group I (Slow-Growing Photochromogens)		
M. kansasii	Usually pathogenic	Common
M. marinum	Usually pathogenic	Uncommon
M. simiae	Usually pathogenic	Uncommon
Runyon Group II (Slow-Growing Scotochromogens)		
M. szulgai	Usually pathogenic	Uncommon
M. scrofulaceum	Sometimes pathogenic	Uncommon
M. xenopi	Sometimes pathogenic	Uncommon
Runyon Group III (Slow-Growing Nonchromogens)		
M. avium complex	Strictly pathogenic	Common
M. genavense	Strictly pathogenic	Uncommon
M. haemophilum	Usually pathogenic	Uncommon
M. malmoense	Usually pathogenic	Uncommon
Runyon Group IV (Rapid Growers)		
M. fortuitum	Sometimes pathogenic	Common
M. chelonae	Sometimes pathogenic	Common
M. abscessus	Sometimes pathogenic	Uncommon
M. mucogenicum	Sometimes pathogenic	Uncommon

Mycobacterial Clinical Syndromes

Mycobacterium tuberculosis
- Pulmonary tuberculosis
- Extrapulmonary tuberculosis
- Tuberculosis in HIV-infected patients

Mycobacterium avium-intracellulare complex
- Asymptomatic colonization
- Pulmonary disease
- Disseminated disease in HIV-infected patients

Mycobacterium leprae
- Tuberculoid leprosy
- Lepromatous leprosy

Other mycobacteria
- Pulmonary disease (e.g., *M. kansasii*)
- Cutaneous disease (e.g., *M. marinum*, *M. ulcerans*, *M. fortuitum-chelonae*)

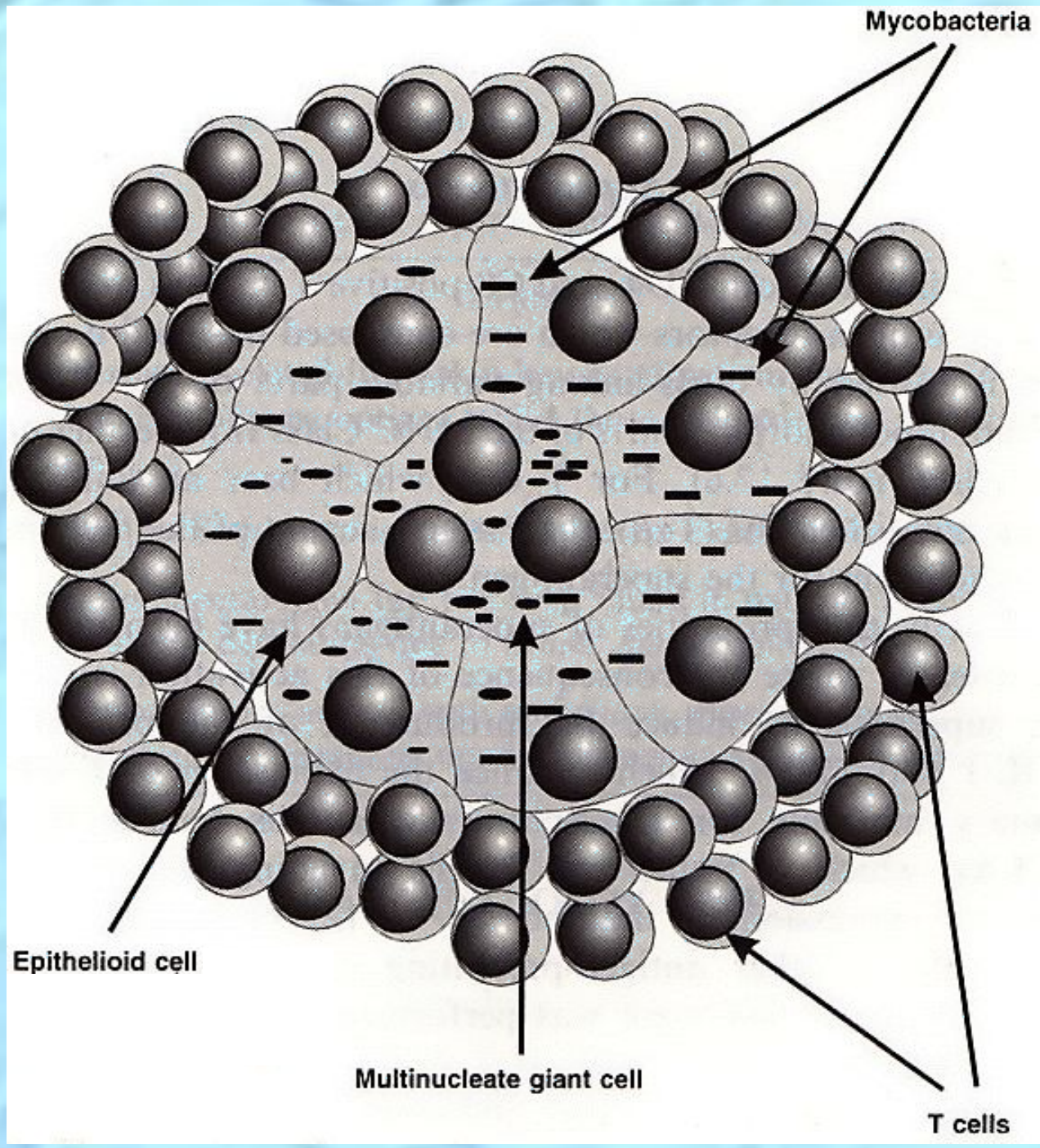


Diagram of a Granuloma

NOTE: ultimately a fibrin layer develops around granuloma **(fibrosis)**, further "walling off" the lesion.

Typical progression in pulmonary TB involves **caseation**, **calcification** and **cavity formation**.

Laboratory Diagnosis of Mycobacterial Disease

Detection

Skin test

Microscopy

- Carbolfuchsin acid-fast stain
- Fluorochrome acid-fast stain
- Direct nucleic acid probes

Culture

- Solid agar-based or egg-based media
- Broth-based media

Identification

Morphologic properties

Biochemical reactions

Analysis of cell wall lipids

Nucleic acid probes

Nucleic acid sequencing

Differential Characteristics of Commonly Isolated Mycobacterium spp.

Organism	Niacin	Nitrate Reductase	Heat-Stable Catalase	Tween-80 Hydrolysis	Iron Uptake	Arylsulfatase	Urease
M. tuberculosis	+	+	−	−		−	+
M. kansasii	−	+	+	+		−	+
M. avium complex	−	−	+/−	−		−	−
M. fortuitum	−	+	+	V	+	+	+
M. chelonae	V	−	V	V	−	+	+

Mycobacterium tuberculosis

Mycobacterium tuberculosis Infections

Physiology and Structure

Weakly gram-positive, strongly acid-fast, aerobic bacilli.

Lipid-rich cell wall, making the organism resistant to disinfectants, detergents, common antibacterial antibiotic, and traditional stains.

Virulence

Capable of intracellular growth in unactivated alveolar macrophages.

Disease primarily from host response to infection.

Epidemiology

Worldwide; one third of the world population is infected with this organism.

Sixteen million existing cases of disease and 8 million new cases each year.

Disease most common in Southeast Asia, sub-Saharan Africa, and Eastern Europe.

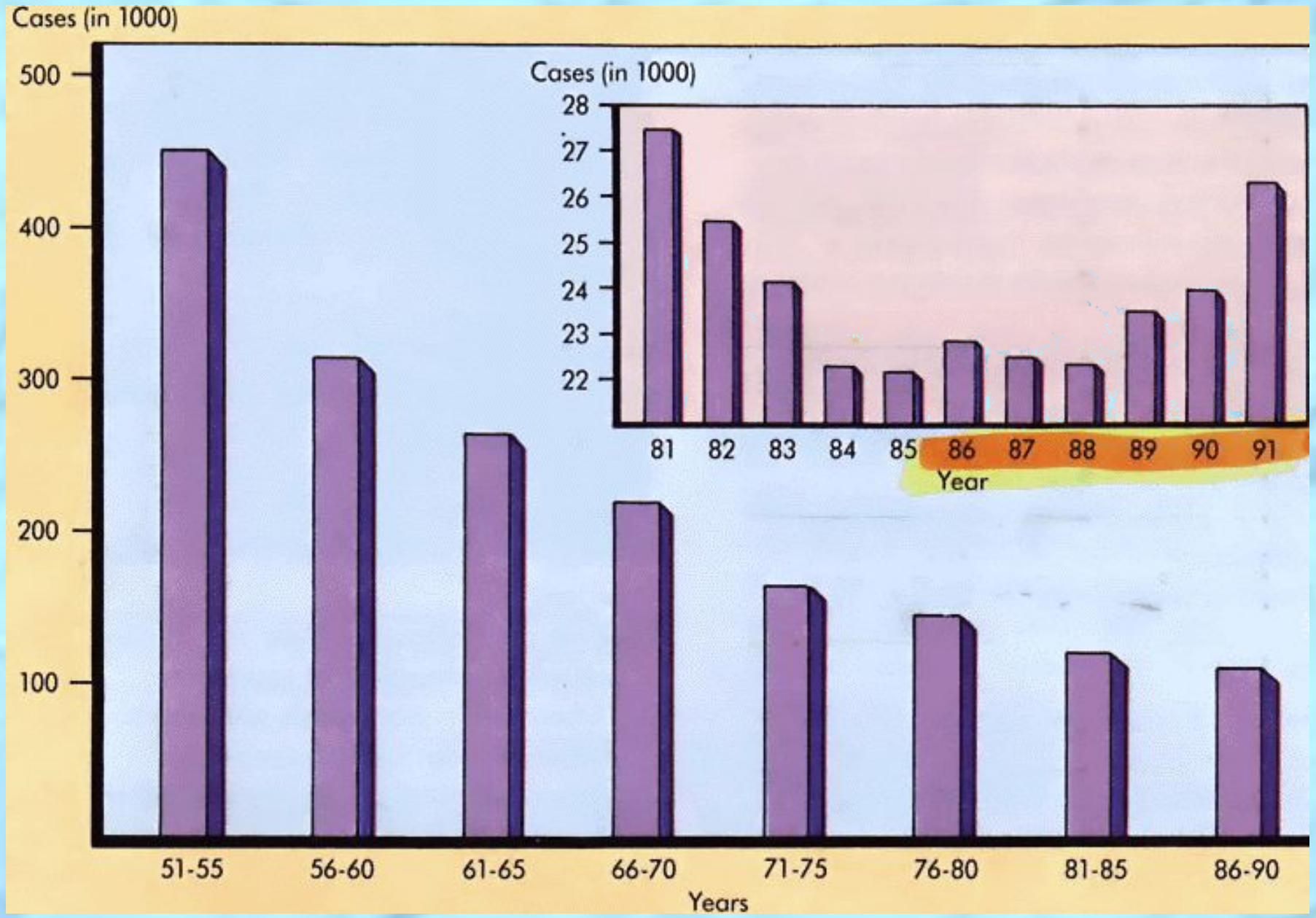
Approximately 20,000 new cases in United States annually.

Populations at greatest risk for disease are immunocompromised patients (particularly those with HIV infection), drug or alcohol abusers, homeless, and individuals exposed to diseased patients.

Humans are the only natural reservoir.

Person-to-person spread by infectious aerosols.

Incidence of Tuberculosis in USA



Mycobacterium tuberculosis Infections *(cont.)*

Positive PPD + Chest X-Ray +

MDR-TB a serious global health threat

BCG (bacille Calmette-Guerin) = attenuated ***M. bovis***

Diseases

Primary infection is pulmonary.

Dissemination to any body site occurs most commonly in immunocompromised patients and untreated patients.

Diagnosis

Microscopy and culture are sensitive and specific. Direct detection by molecular probes is relatively insensitive.

Treatment, Prevention, and Control

Multiple-drug regimens and prolonged treatment are required to prevent development of drug-resistant strains.

Regimens recommended for treatment include isoniazid and rifampin for 9 months, with pyrazinamide and ethambutol or streptomycin added for drug-resistant strains.

Prophylaxis for exposure to tuberculosis can include isoniazid for 9 months, rifampin for 4 months, or rifampin and pyrazinamide for 2 months. Pyrazinamide and ethambutol or levofloxacin are used for 6 to 12 months following exposure to drug-resistant *M. tuberculosis*.

Immunoprophylaxis with BCG in endemic countries.

Control of disease through active surveillance, prophylactic and therapeutic intervention, and careful case monitoring.

Typical Progression of Pulmonary Tuberculosis

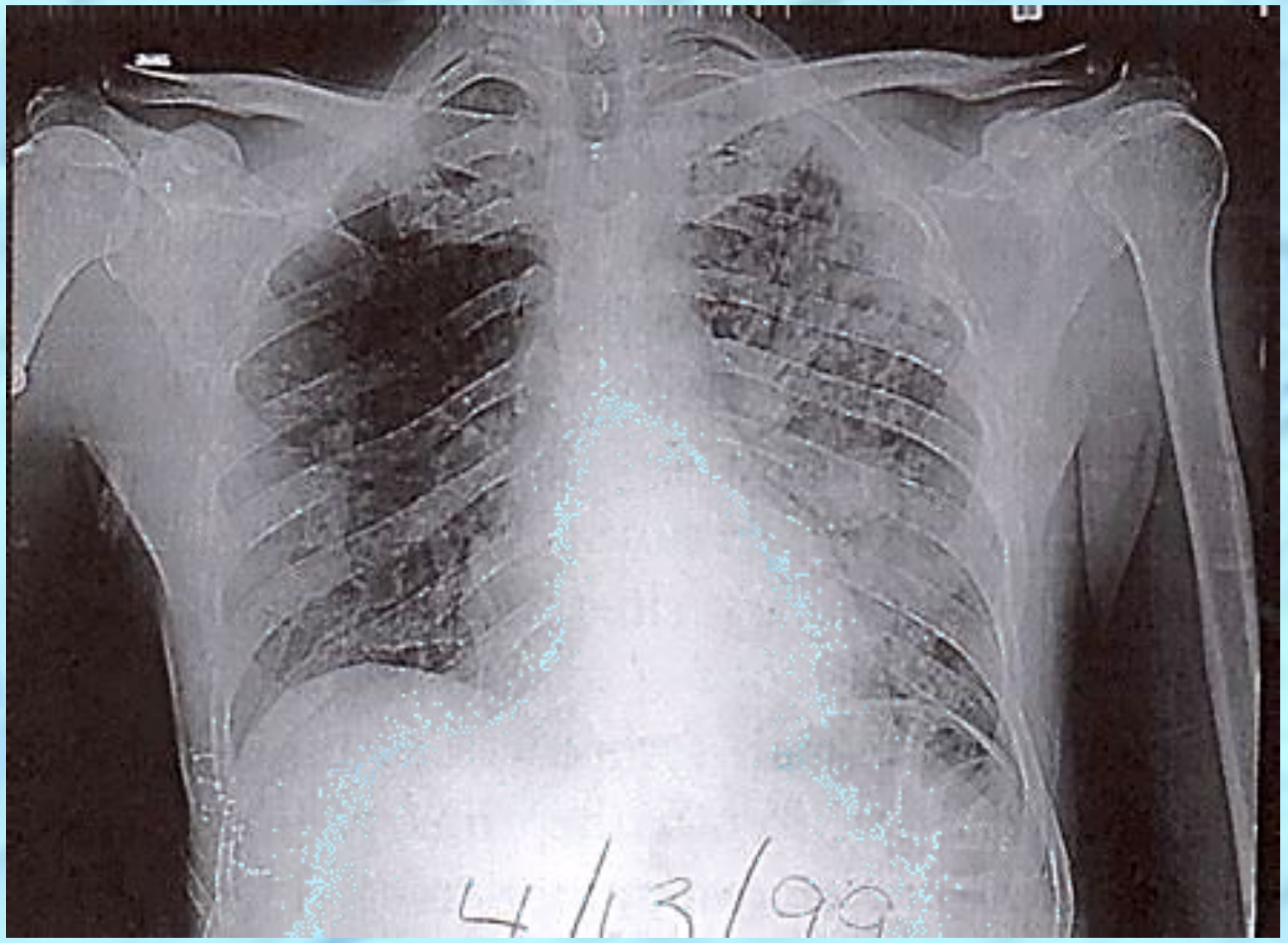
- **Pneumonia**
- **Granuloma formation with fibrosis**
- **Caseous necrosis**
  - Tissue becomes dry & amorphous (resembling cheese)
  - Mixture of protein & fat (assimilated very slowly)
- **Calcification**
  - Ca^{++} salts deposited
- **Cavity formation**
  - Center liquefies & empties into bronchi

PPD Tuberculosis Skin Test Criteria

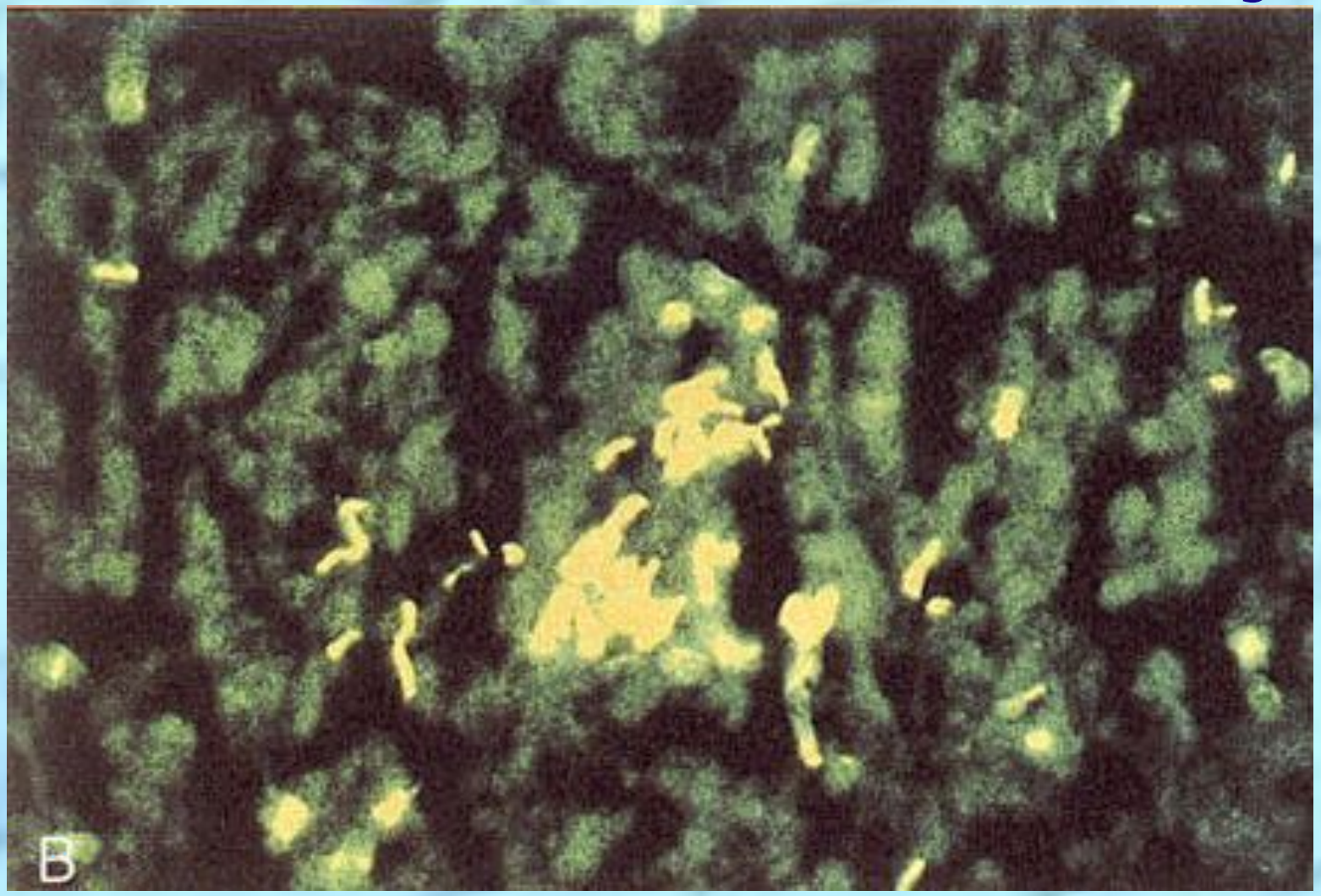
Reactivity to PPD	Populations
≥5 mm of induration	HIV-positive patients; patients receiving immunosuppressive therapy; recent contacts of patients with tuberculosis; patients with abnormal chest radiographs consistent with prior tuberculosis
≥10 mm of induration	Recent immigrants from high-prevalence countries; injection drug users; residents and employees of high-risk settings (e.g., prisons; residential facilities for the elderly, patients with AIDS, and the homeless; health care facilities; mycobacteriology laboratory); persons with conditions of high risk (e.g., silicosis, diabetes, chronic renal failure, hematologic disorders, significant weight loss, gastrectomy, jejunoileal bypass); children younger than 4 years or exposed to adults at high risk
≥15 mm of induration	Persons at low risk for tuberculosis

PPD = **P**urified **P**rotein **D**erivative from *M. tuberculosis*

Chest X-Ray of Patient with Active Pulmonary Tuberculosis



Mycobacterium Tuberculosis Stained with Fluorescent Dye



Mycobacterium leprae

Mycobacterium leprae Infections

Physiology and Structure

Weakly gram-positive, strongly acid-fast bacilli.

Lipid-rich cell wall.

Unable to be cultured on artificial media.

Diagnosis made with specific skin test (tuberculoid form of disease) or acid-fast stain (lepromatous form).

Virulence

Capable of intracellular growth.

Disease primarily from host response to infection.

Epidemiology

Rare in United States but common in other countries (e.g., Asia, Africa).

Armadillos are naturally infected and represent an indigenous reservoir.

Lepromatous form of disease, but not the tuberculoid form, is highly infectious.

Person-to-person spread by direct contact or inhalation of infectious aerosols.

People in close contact with patients who have lepromatous disease are at greatest risk.

Mycobacterium leprae Infections (cont.)

Diseases

Tuberculoid form of leprosy.

Lepromatous form of leprosy.

Intermediate forms of leprosy.

Diagnosis

Microscopy is sensitive for the lepromatous form but not the tuberculoid form.

Skin testing required to confirm tuberculoid leprosy. Culture cannot be used.

Treatment, Prevention, and Control

Dapsone with or without rifampin is used to treat the tuberculoid form of disease; clofazimine is added for the treatment of the lepromatous form. Therapy is prolonged.

Dapsone is recommended for long-term prophylaxis in treated patients.

Disease is controlled through the prompt recognition and treatment of infected people.

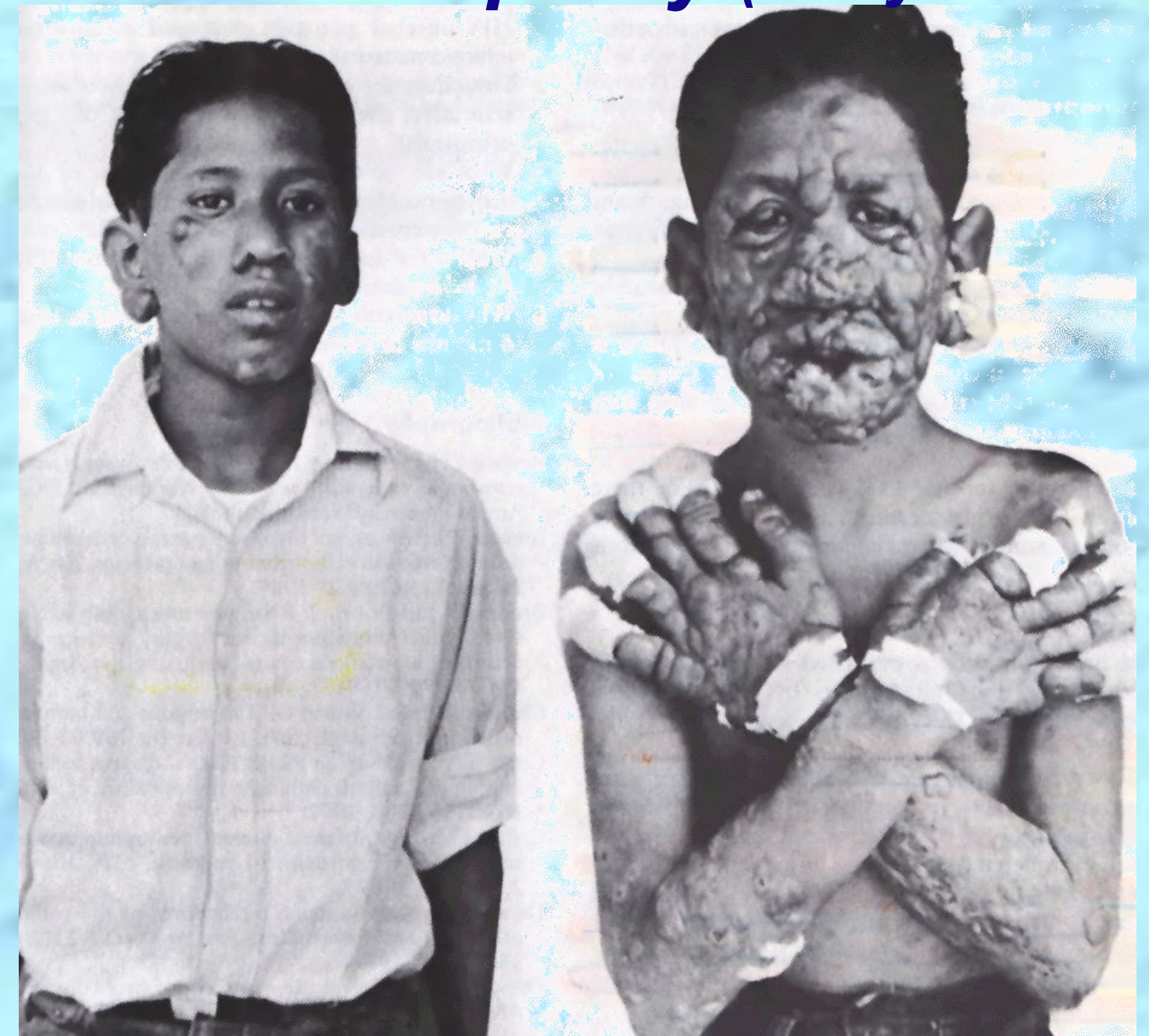
Tuberculoid vs. Lepromatous Leprosy

Clinical Manifestations and Immunogenicity

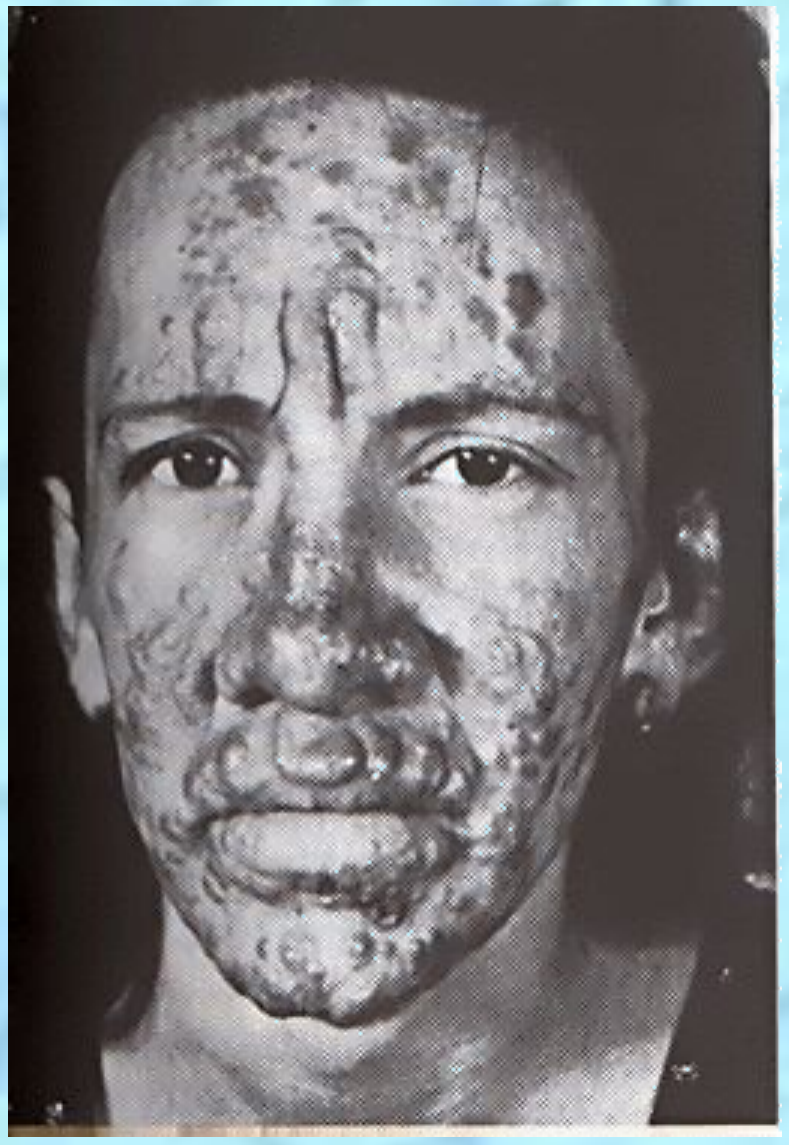
Features	Tuberculoid Leprosy	Lepromatous Leprosy
Skin lesions	Few erythematous or hypopigmented plaques with flat centers and raised, demarcated borders; peripheral nerve damage with complete sensory loss; visible enlargement of nerves	Many erythematous macules, papules, or nodules; extensive tissue destruction (e.g., nasal cartilage, bones, ears); diffuse nerve involvement with patchy sensory loss; lack of nerve enlargement
Histopathology	Infiltration of lymphocytes around center of epithelial cells; presence of Langhans' cells; few or no acid-fast bacilli observed	Predominantly "foamy" macrophages with few lymphocytes; lack of Langhans' cells; numerous acid-fast bacilli in skin lesions and internal organs
Infectivity	Low	High
Immune response		
Delayed hypersensitivity	Reactivity to lepromin	Nonreactivity to lepromin
Immunoglobulin levels	Normal	Hypergammaglobulinemia
Erythema nodosum leprosum	Absent	Usually present

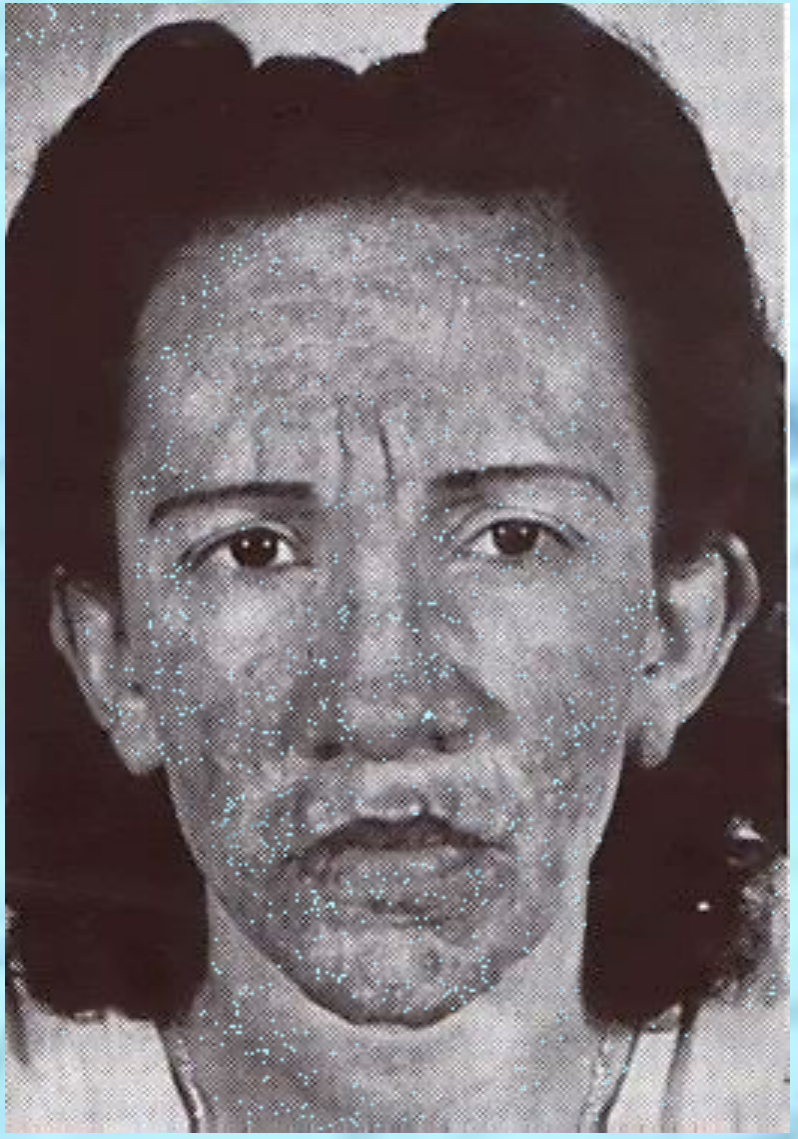
Lepromatous vs. Tuberculoid Leprosy

Lepromatous Leprosy (Early/Late Stages)

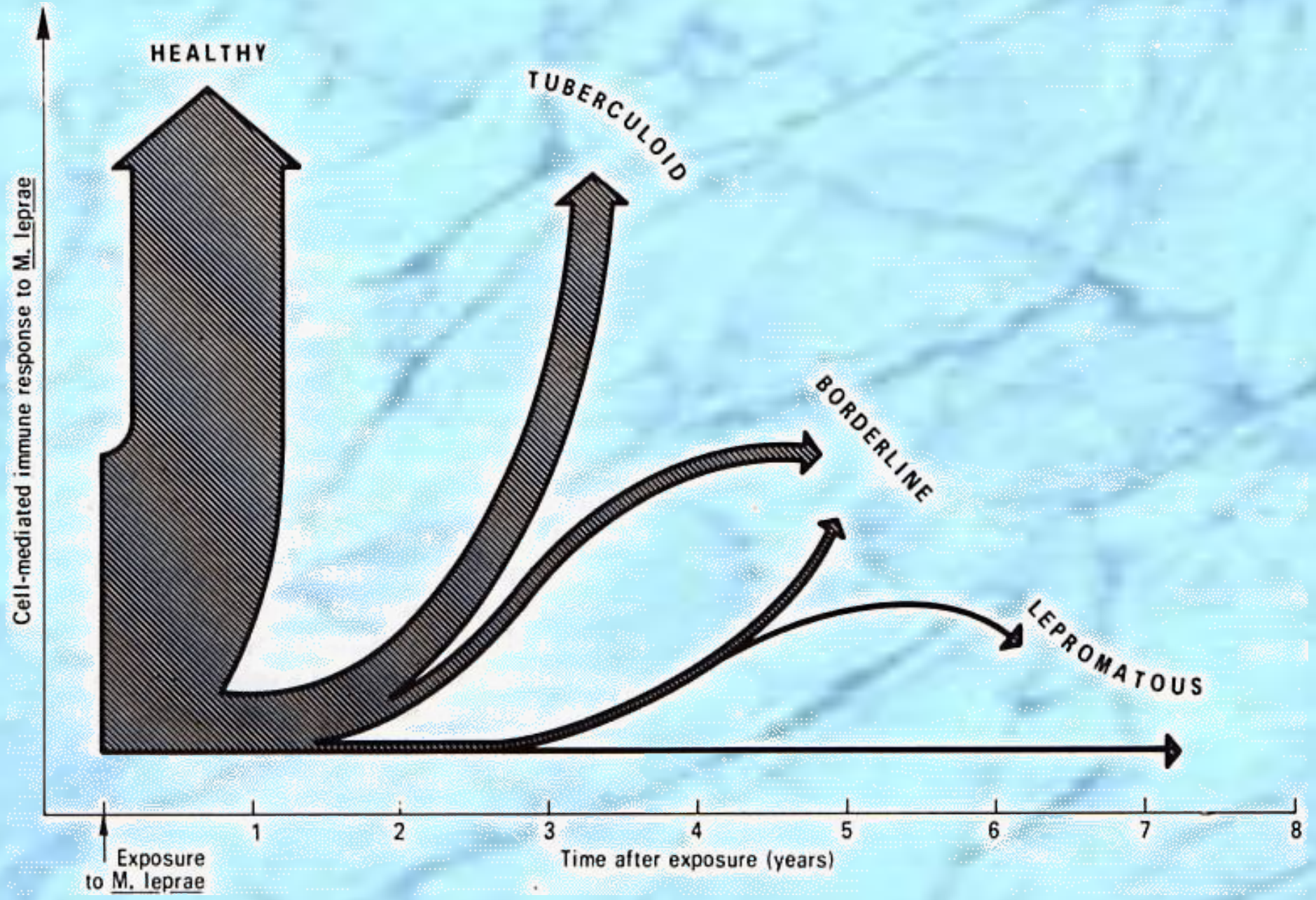


Lepromatous Leprosy Pre- and Post-Treatment

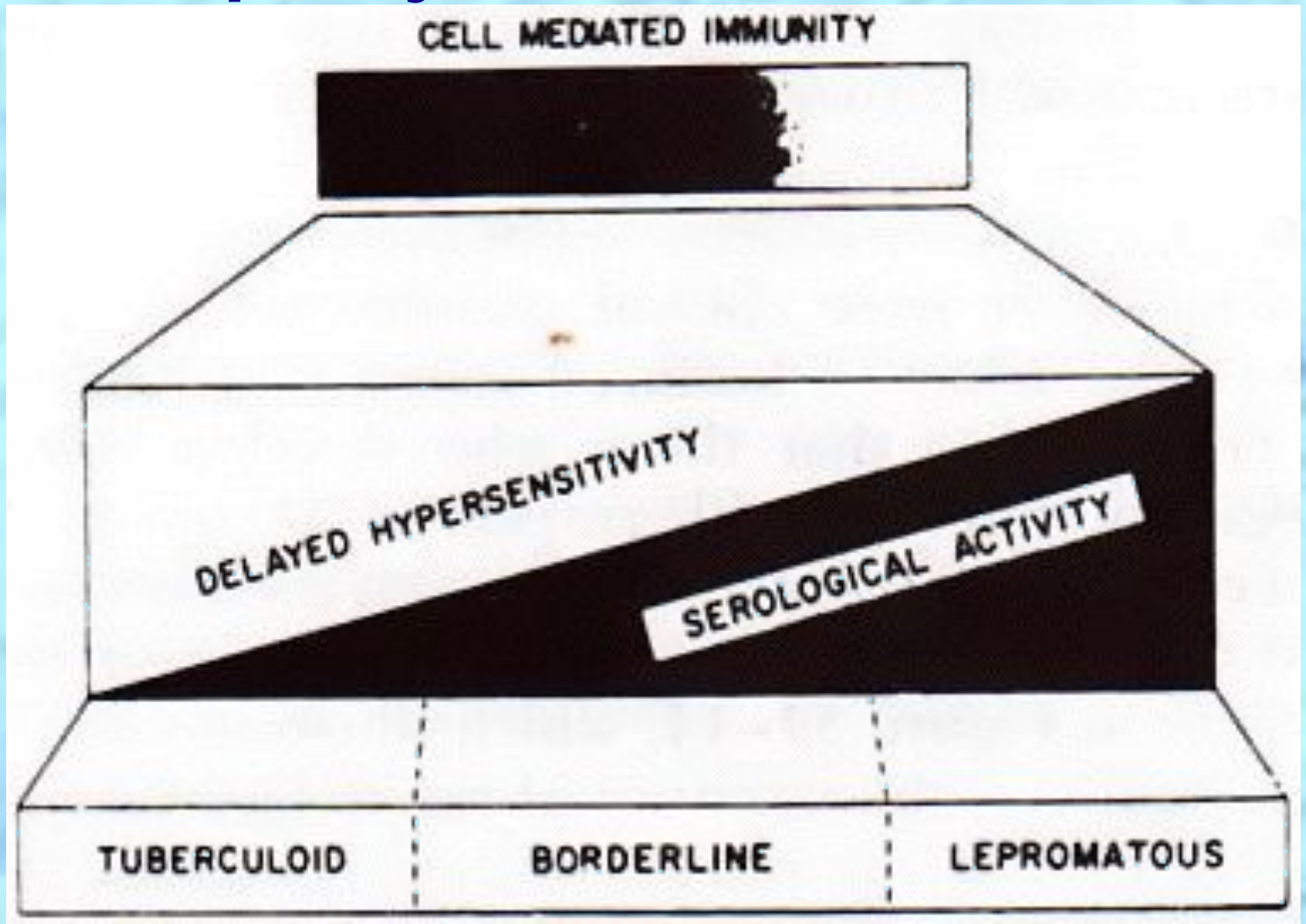




Clinical Progression of Leprosy



Effect of Cell-Mediated Immunity on Leprosy Clinical Outcome



Mycobacterium avium-intracellulaire Complex (MAC)

Mycobacterium avium-intracellulaire Infections

Physiology and Structure

Weakly gram-positive, strongly acid-fast aerobic bacilli.
Lipid-rich cell wall.

Virulence

Capable of intracellular growth.
Disease primarily from host response to infection.

Epidemiology

Worldwide distribution, but disease is seen most commonly in countries where tuberculosis is less common.

Acquired primarily through ingestion of contaminated water or food; inhalation of infectious aerosols is believed to play a minor role in transmission.

Patients at greatest risk for disease are those who are immunocompromised (particularly patients with AIDS) and those with long-standing pulmonary disease.

Mycobacterium avium-intracellulaire Infections

Diseases

Asymptomatic colonization.

Chronic localized pulmonary disease.

Disseminated disease, particularly in patients with AIDS.

Diagnosis

Microscopy and culture are sensitive and specific.

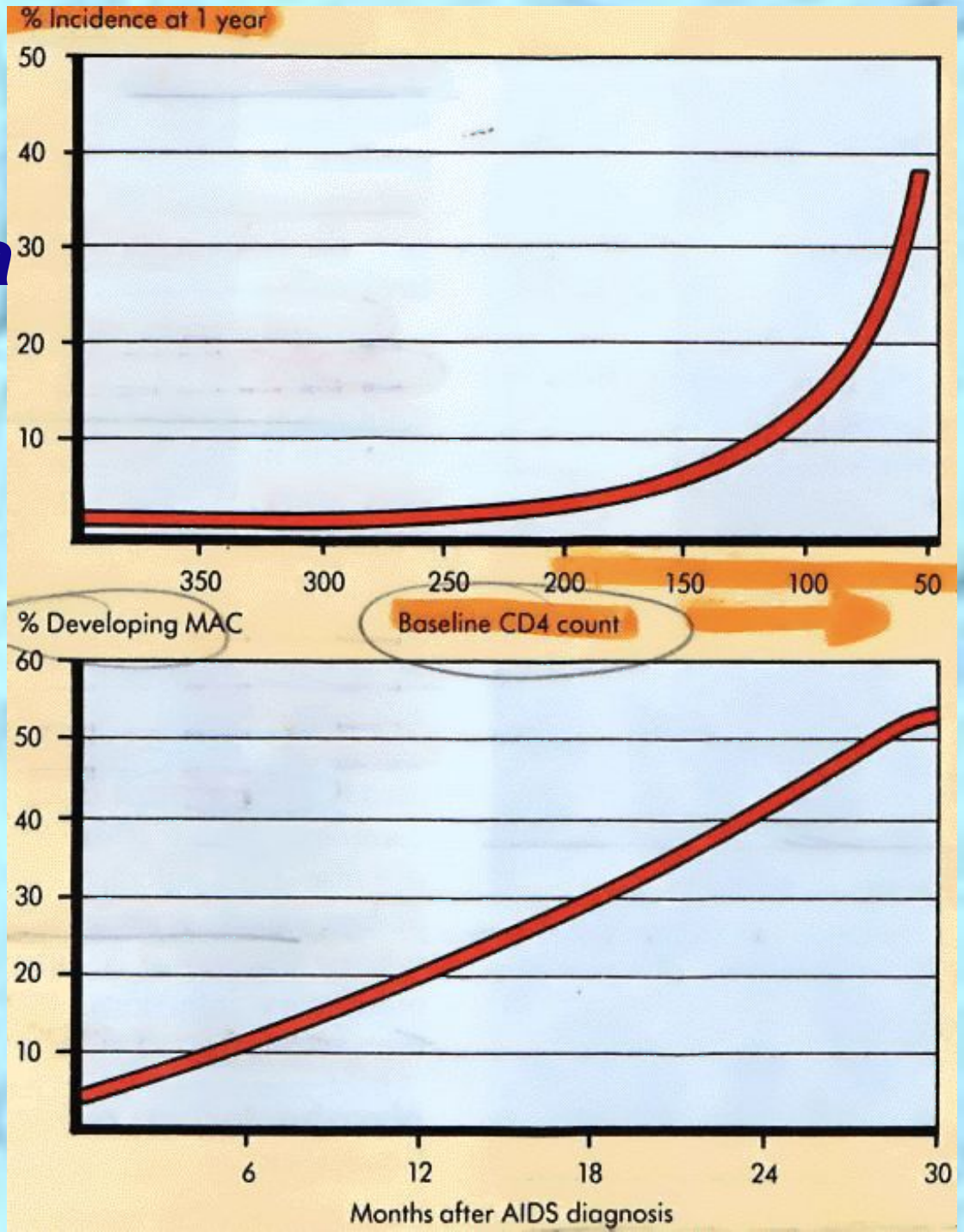
Treatment, Prevention, and Control

Infections treated for prolonged period with clarithromycin or azithromycin combined with ethambutol and rifabutin.

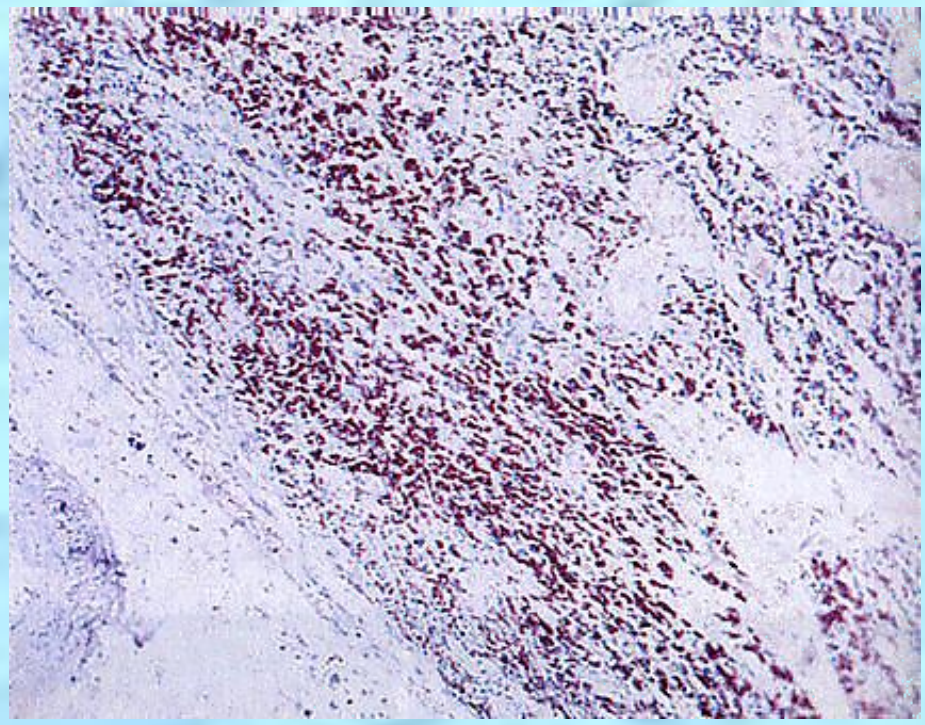
Prophylaxis in patients with AIDS who have low CD4+ cell count consist of clarithromycin or azithromycin or rifabutin.

Prophylaxis has dramatically reduced the incidence of disease in patients with AIDS.

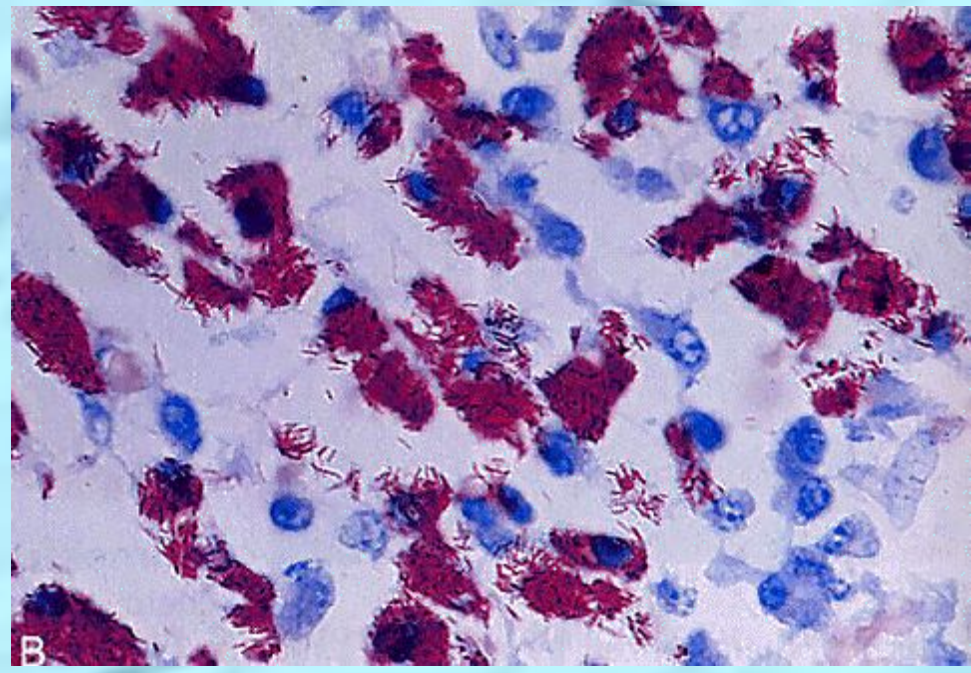
M. avium-intracellulare Complex (MAC) Progression vs. CD4 Count in AIDS Patients



Mycobacterium avium-intracellulaire in Tissue Specimens



Low Magnification



High Magnification

REVIEW

of

Mycobacterium

Important Human Pathogens

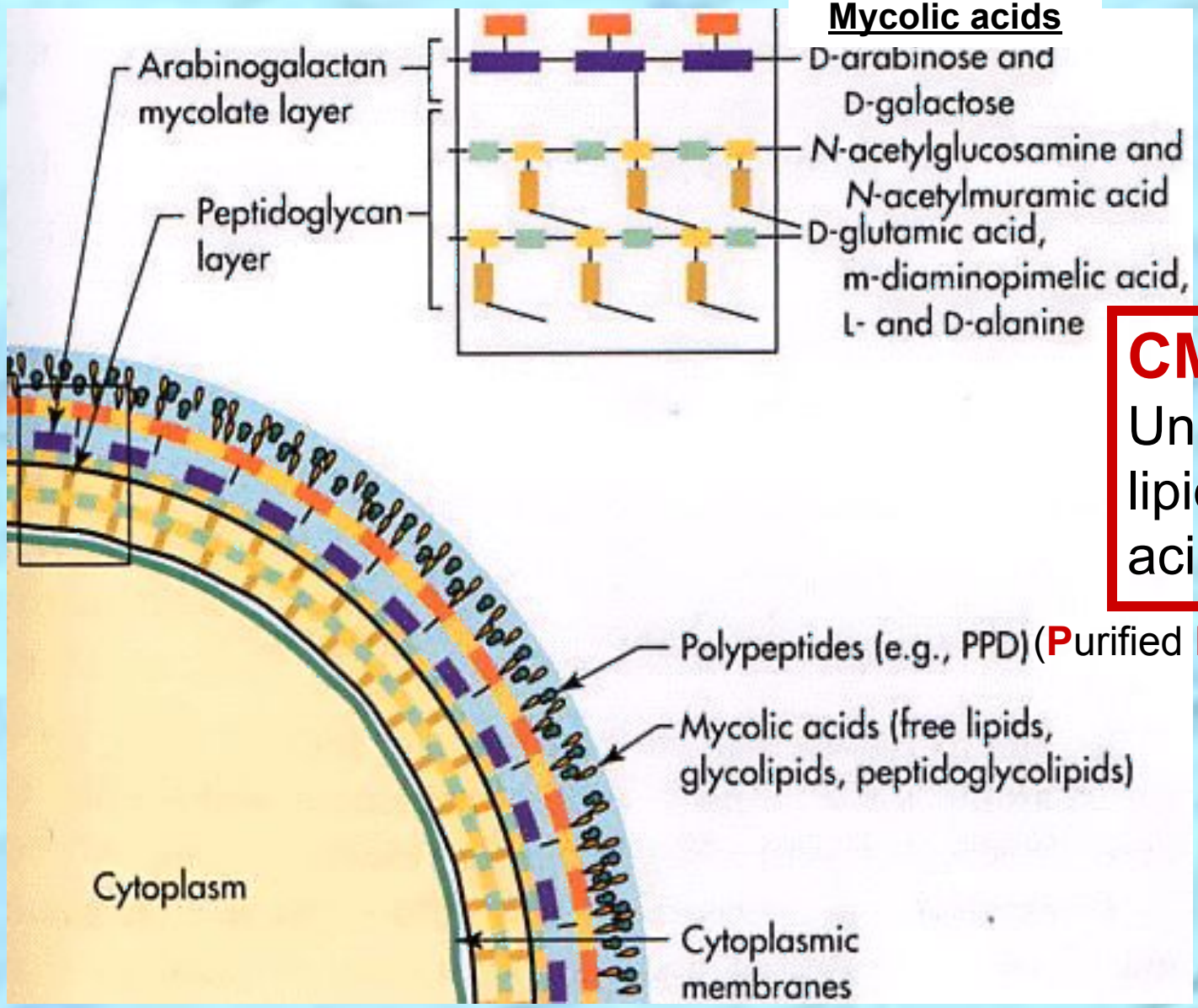
Mycobacterium tuberculosis

Mycobacterium leprae (uncommon)

Mycobacterium avium-intracellulaire Complex (MAC) or (M. avium)

REVIEW

Lipid-Rich Cell Wall of Mycobacterium



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REVIEW

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Runyon Group I (Slow-Growing Photochromogens)		
M. kansasii	Usually pathogenic	Common
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BCG

AIDS patients

REVIEW

Mycobacterial Clinical Syndromes

Mycobacterium tuberculosis
- Pulmonary tuberculosis
- Extrapulmonary tuberculosis
- Tuberculosis in HIV-infected patients

Mycobacterium avium-intracellulare complex
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- Tuberculoid leprosy
- Lepromatous leprosy

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REVIEW

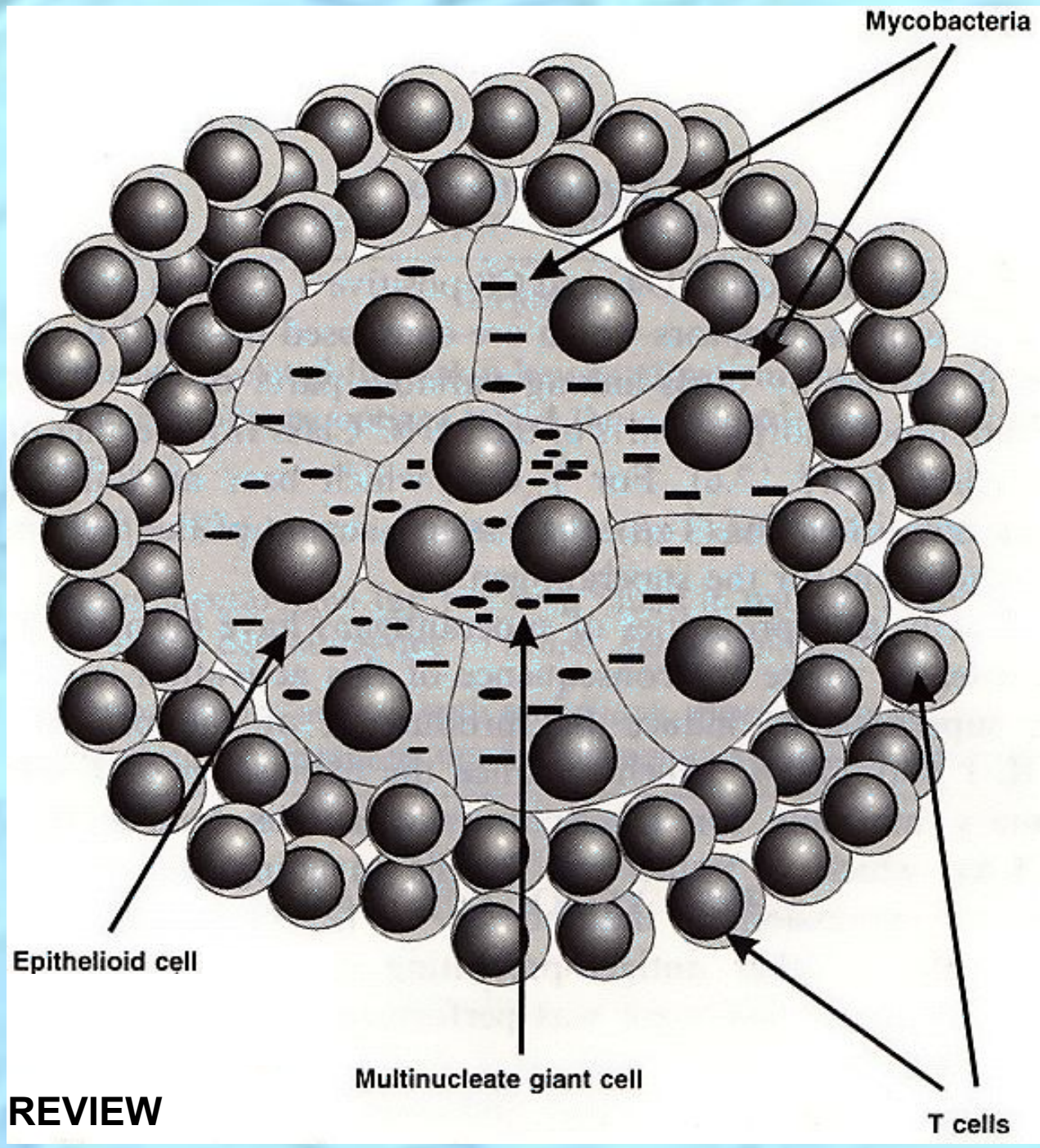

Diagram of a Granuloma

NOTE: ultimately a fibrin layer develops around granuloma **(fibrosis)**, further "walling off" the lesion.

Typical progression in pulmonary TB involves **caseation**, **calcification** and **cavity formation**.

REVIEW

Review of Mycobacterium tuberculosis

Mycobacterium tuberculosis Infections

Physiology and Structure

Weakly gram-positive, strongly acid-fast, aerobic bacilli.

Lipid-rich cell wall, making the organism resistant to disinfectants, detergents, common antibacterial antibiotic, and traditional stains.

Virulence

Capable of intracellular growth in unactivated alveolar macrophages.

Disease primarily from host response to infection.

Epidemiology

Worldwide; one third of the world population is infected with this organism.

Sixteen million existing cases of disease and 8 million new cases each year.

Disease most common in Southeast Asia, sub-Saharan Africa, and Eastern Europe.

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Populations at greatest risk for disease are immunocompromised patients (particularly those with HIV infection), drug or alcohol abusers, homeless, and individuals exposed to diseased patients.

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Person-to-person spread by infectious aerosols.

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Mycobacterium tuberculosis Infections *(cont.)*

Positive PPD + Chest X-Ray +

MDR-TB a serious global health threat

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REVIEW

Diseases

Primary infection is pulmonary.

Dissemination to any body site occurs most commonly in immunocompromised patients and untreated patients.

Diagnosis

Microscopy and culture are sensitive and specific. Direct detection by molecular probes is relatively insensitive.

Treatment, Prevention, and Control

Multiple-drug regimens and prolonged treatment are required to prevent development of drug-resistant strains.

Regimens recommended for treatment include isoniazid and rifampin for 9 months, with pyrazinamide and ethambutol or streptomycin added for drug-resistant strains.

Prophylaxis for exposure to tuberculosis can include isoniazid for 9 months, rifampin for 4 months, or rifampin and pyrazinamide for 2 months. Pyrazinamide and ethambutol or levofloxacin are used for 6 to 12 months following exposure to drug-resistant *M. tuberculosis*.

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Typical Progression of Pulmonary Tuberculosis

- **Pneumonia**
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Review of Mycobacterium leprae

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Disease primarily from host response to infection.

Epidemiology

Rare in United States but common in other countries (e.g., Asia, Africa).

Armadillos are naturally infected and represent an indigenous reservoir.

Lepromatous form of disease, but not the tuberculoid form, is highly infectious.

Person-to-person spread by direct contact or inhalation of infectious aerosols.

People in close contact with patients who have lepromatous disease are at greatest risk.

REVIEW

Mycobacterium leprae Infections (cont.)

Diseases

Tuberculoid form of leprosy.

Lepromatous form of leprosy.

Intermediate forms of leprosy.

Diagnosis

Microscopy is sensitive for the lepromatous form but not the tuberculoid form.

Skin testing required to confirm tuberculoid leprosy. Culture cannot be used.

Treatment, Prevention, and Control

Dapsone with or without rifampin is used to treat the tuberculoid form of disease; clofazimine is added for the treatment of the lepromatous form. Therapy is prolonged.

Dapsone is recommended for long-term prophylaxis in treated patients.

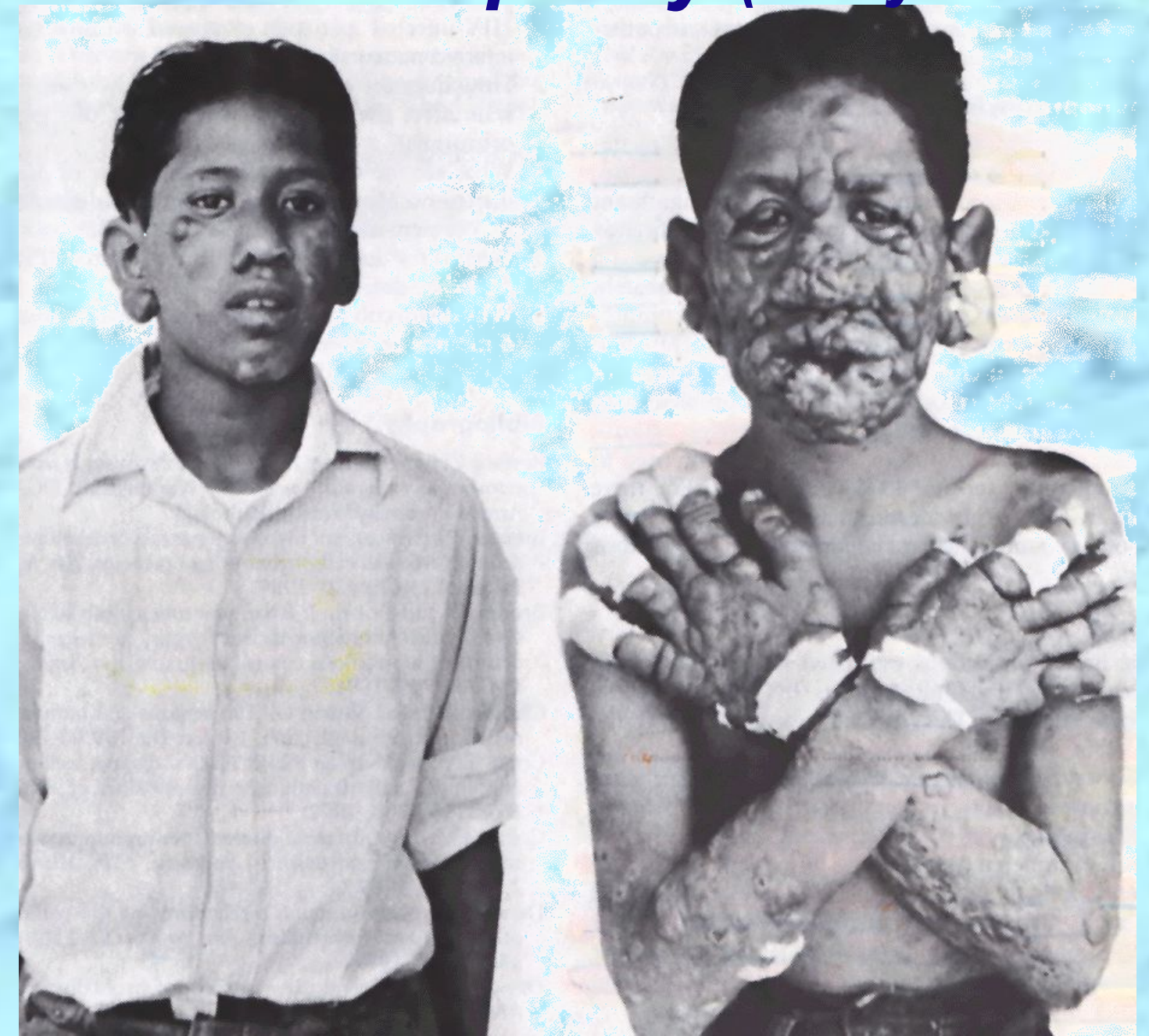
Disease is controlled through the prompt recognition and treatment of infected people.

REVIEW

Lepromatous vs. Tuberculoid Leprosy

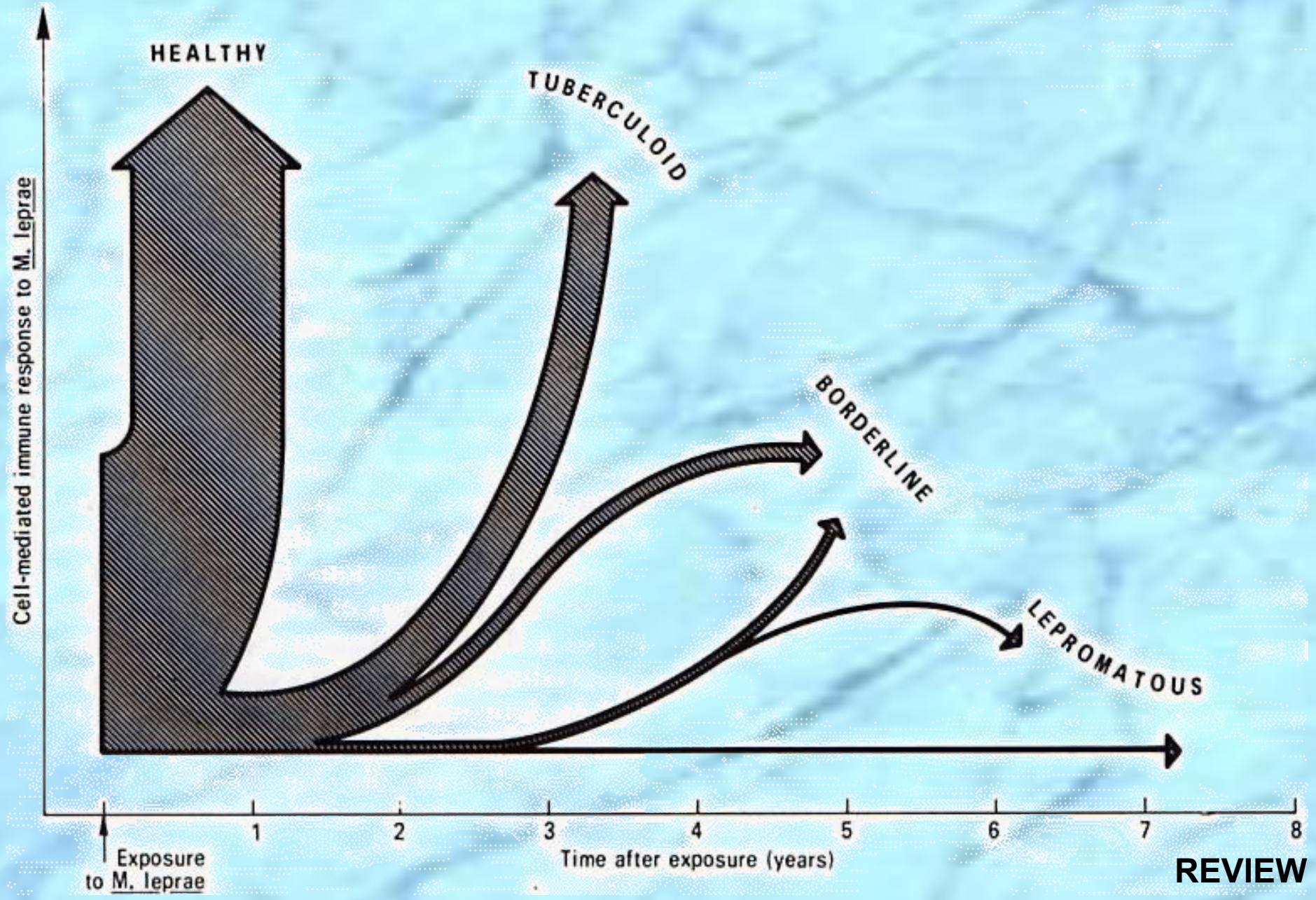
REVIEW

Lepromatous Leprosy (Early/Late Stages)



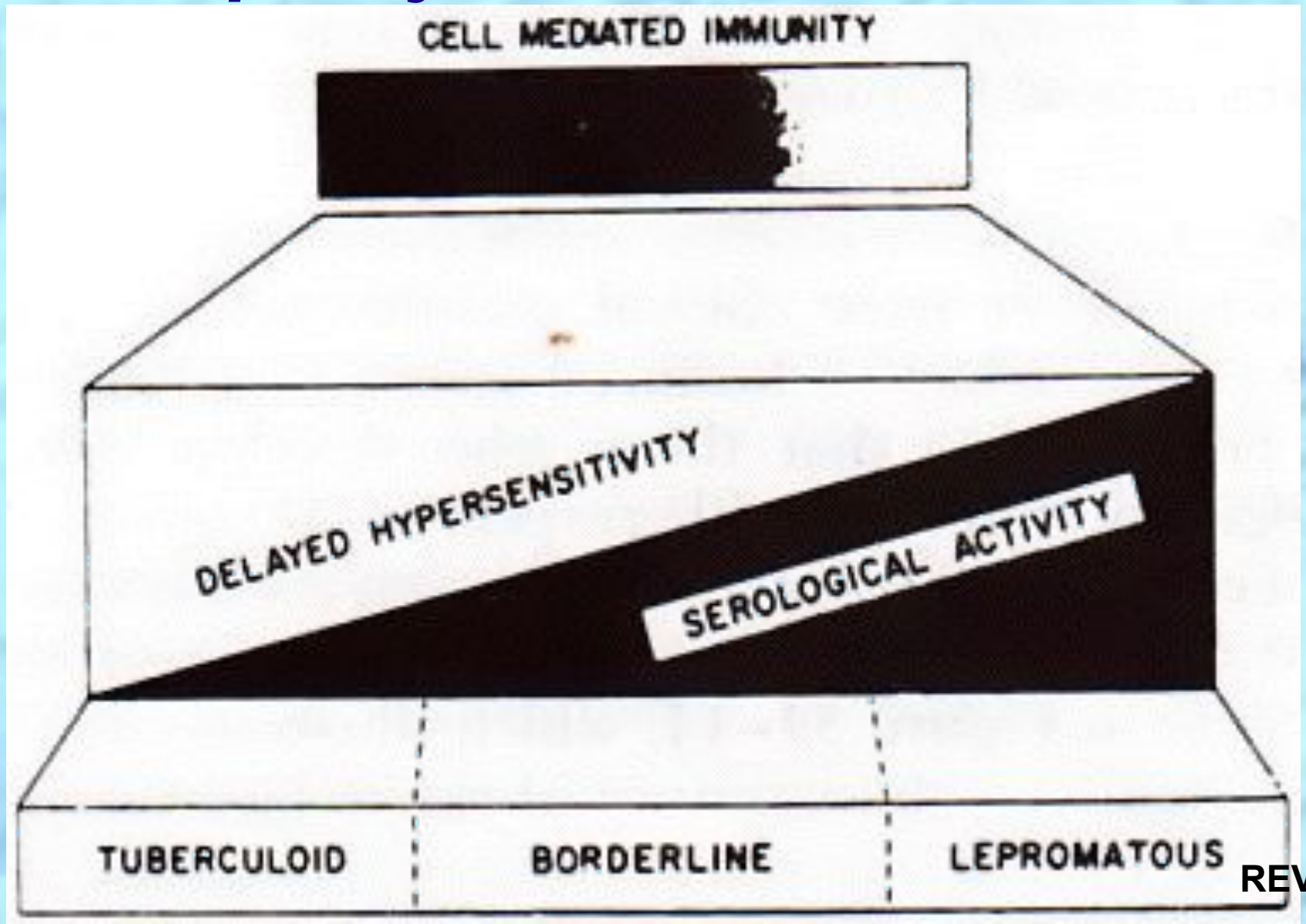
REVIEW

Clinical Progression of Leprosy



REVIEW

Effect of Cell-Mediated Immunity on Leprosy Clinical Outcome



REVIEW

Review of Mycobacterium avium-intracellulaire Complex (M. avium)

Mycobacterium avium-intracellulaire Infections

Physiology and Structure

Weakly gram-positive, strongly acid-fast aerobic bacilli.
Lipid-rich cell wall.

Virulence

Capable of intracellular growth.
Disease primarily from host response to infection.

Epidemiology

Worldwide distribution, but disease is seen most commonly in countries where tuberculosis is less common.

Acquired primarily through ingestion of contaminated water or food; inhalation of infectious aerosols is believed to play a minor role in transmission.

Patients at greatest risk for disease are those who are immunocompromised (particularly patients with AIDS) and those with long-standing pulmonary disease.

REVIEW

Mycobacterium avium-intracellulaire Infections

Diseases

Asymptomatic colonization.

Chronic localized pulmonary disease.

Disseminated disease, particularly in patients with AIDS.

Diagnosis

Microscopy and culture are sensitive and specific.

Treatment, Prevention, and Control

Infections treated for prolonged period with clarithromycin or azithromycin combined with ethambutol and rifabutin.

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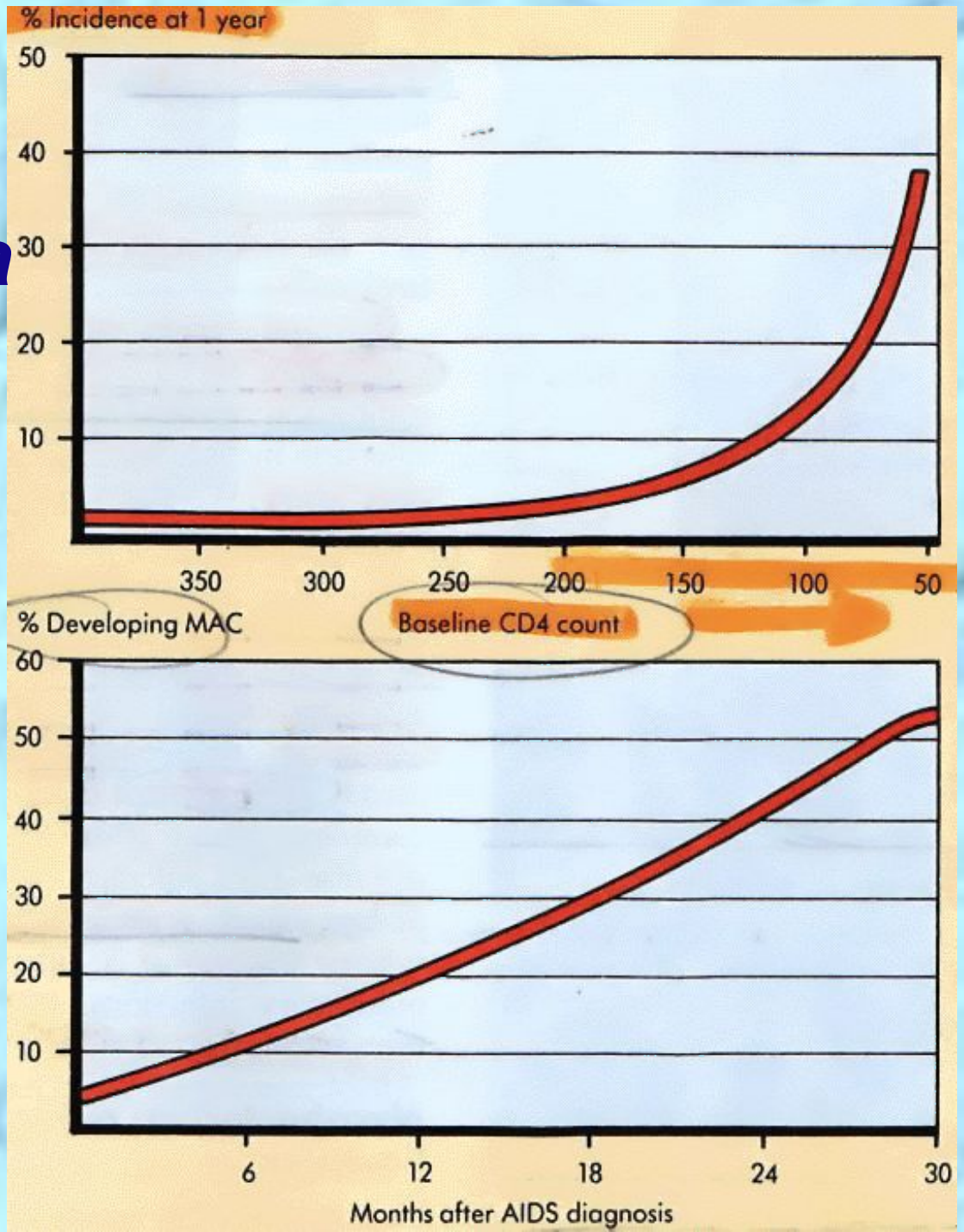
REVIEW

M. avium-intracellulare Complex (MAC) Progression vs. CD4 Count in AIDS Patients



REVIEW