Tuberculosis, Morphology and Physiology

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Tuberculosis

- Communicable chronic granulomatous disease caused by *Mycobacterium tuberculosis*
- Usually involves the lungs but may affect any organ or tissue in the body
- Typically results in caseating granulomas

Routes of infection

- Respiratory tract
  - Most cases are acquired by direct person to person transmission of ***airborne*** droplets with organisms from an ***active case*** to a susceptible host
- Intestinal tract
- Skin by inoculation
- Congenital by transplacental spread

Microorganism

- **M. tuberculosis hominis**
  - Transmitted by inhalation of infective droplets,
  - Coughed or sneezed into the air from patients with active “open” Pulmonary TB
  - “airborne” or by exposure to contaminated secretions
- **M. bovis**
  - Transmitted by milk from diseased cows causing intestinal & oropharyngeal TB
  - Rare disease for human
- **M. avium-intracellulare**
  - Very low virulence
  - Rarely cause disease in normal hosts
  - Cause disseminated infection in 10-30% of AIDS patients

Predisposing Factors

Number of factors predispose to the development of TB

- ***Access of organism***: close contact with open cases of disease, e.g. increased in crowded & unhygienic working and living conditions

- ***Susceptibility of individual***: the old, very young, black & Asian populations have and increased susceptibility

Predisposing Factors

- ***Nutrition***: a disease of the undernourished & under privileged “poor”
- ***Occupation***: increased incidence of TB in some types of pneumoconiosis (silicosis & in health workers)
- ***Other Diseases***:
  - pre-existing chronic lung disease,
  - chronic renal failure,
  - Hodgkin diseases,
  - diabetes mellitus,
  - alcoholism,
  - corticosteroid,
  - immunosuppressive cytotoxic drug therapy
  - Immunodeficiencies including (HIV/AIDS)

Characters of the Organisms

- ***Aerobic***, ***acid-fast bacilli***
- Has ***no known exotoxins, endotoxins***
- Has waxy coat "high contents of complex lipids" that causes them to retain the red dye when treated with acid in ***acid-fast stain*** & resist de-colorization

Pathogenesis

- ***Macrophages*** are the primary cells infected by *M. tuberculosis*.

- ***Early*** in infection, tuberculosis bacilli replicate essentially unchecked, while

- ***Later*** in infection, the **T-helper response** stimulates **macrophages** to contain the proliferation of the bacteria.

Pathogenesis

- *M. tuberculosis* ***enters*** macrophages by ***endocytosis*** mediated by several macrophage receptors:
  - ***Macrophages mannose receptors***
  - ***Complement receptors***
- Once **inside** the macrophage, *M. tuberculosis* ***replicates within the phagosome*** by ***blocking fusion*** of the phagosome & lysosome

Pathogenesis

- The earliest stage of ***primary tuberculosis (<3 weeks)*** in the nonsensitized individual is characterized by unchecked proliferation of bacteria in the pulmonary alveolar macrophages & airspaces, with resulting ***bacteremia*** & seeding of multiple sites

- Despite the bacteremia, most patients at this stage are ***asymptomatic*** or have a mild flulike illness

Pathogenesis

- The ***genetic make-up*** of the host may influence the course of the disease
- In some people with ***polymorphisms in the NRAMP1 gene***, the disease may progress from this point without development of an effective immune response “decreased microbicidal function”
- ***NRAMP1 protein*** is a ***transmembrane protein*** found in endosomes and lysosomes & may have role in ***generation of anti-microbial oxygen radicals***
- ***About 3 weeks*** after infection, ***a T$_H$1 response*** against *M. tuberculosis* is mounted that activates macrophages to become ***bactericidal***

Pathogenesis

- ***<u>T_H0 cells are stimulated by</u>*** mycobacterial antigens drained to the lymph node, which are presented with class II major histocompatibility proteins by antigen presenting cells “macrophages”
- Differentiation of T_H1 cells depends on the presence of ***<u>IL-12</u>***, which is ***<u>produced by antigen presenting cells</u>*** that have encountered the mycobacteria
- Mature T_H1 cells, both in lymph nodes and in the lung, produce ***<u>IFN-γ</u>***

Pathogenesis

- ***IFN-γ*** is the critical mediator which ***activates macrophages to become competent*** to contain the M. tuberculosis infection

- IFN-γ ***stimulates formation of the phagolysosomes*** in infected macrophages, exposing the bacteria to an inhospitable acidic environment

- IFN-γ ***also stimulates inducible nitric oxide synthase (iNOS),*** which ***produces nitric oxide (NO)***

- ***NO*** generates reactive ***nitrogen intermediates*** and other ***free radicals*** capable of ***oxidative destruction*** of several mycobacterial constituents, from cell wall to DNA

Pathogenesis

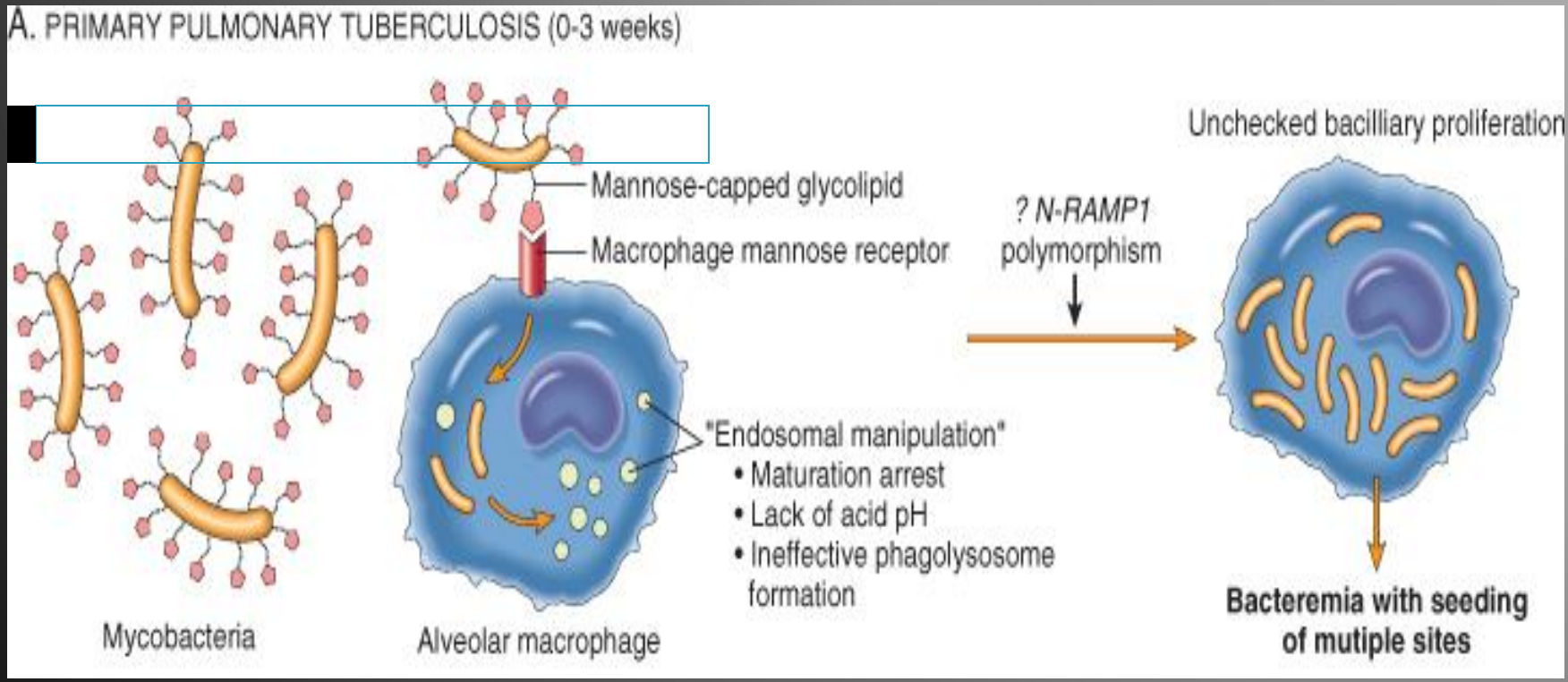
- In addition to stimulating macrophages to kill mycobacteria, the ***T_H1 response*** orchestrates the ***formation of granulomas & caseous necrosis***
- ***Activated macrophages***, stimulated by IFN-γ, produce ***TNF***, which ***recruits monocytes***
- These monocytes ***differentiate into the "epithelioid histiocytes"*** that characterize the granulomatous response
- ***CD4+ T_H1 cells*** ***also facilitates development of CD8+ T cells,*** which can kill the TB-infected macrophages
- ***Defects*** in any of steps of ***T_H1 response*** result in poorly formed granulomas, absence of resistance, & disease progression

Pathogenesis

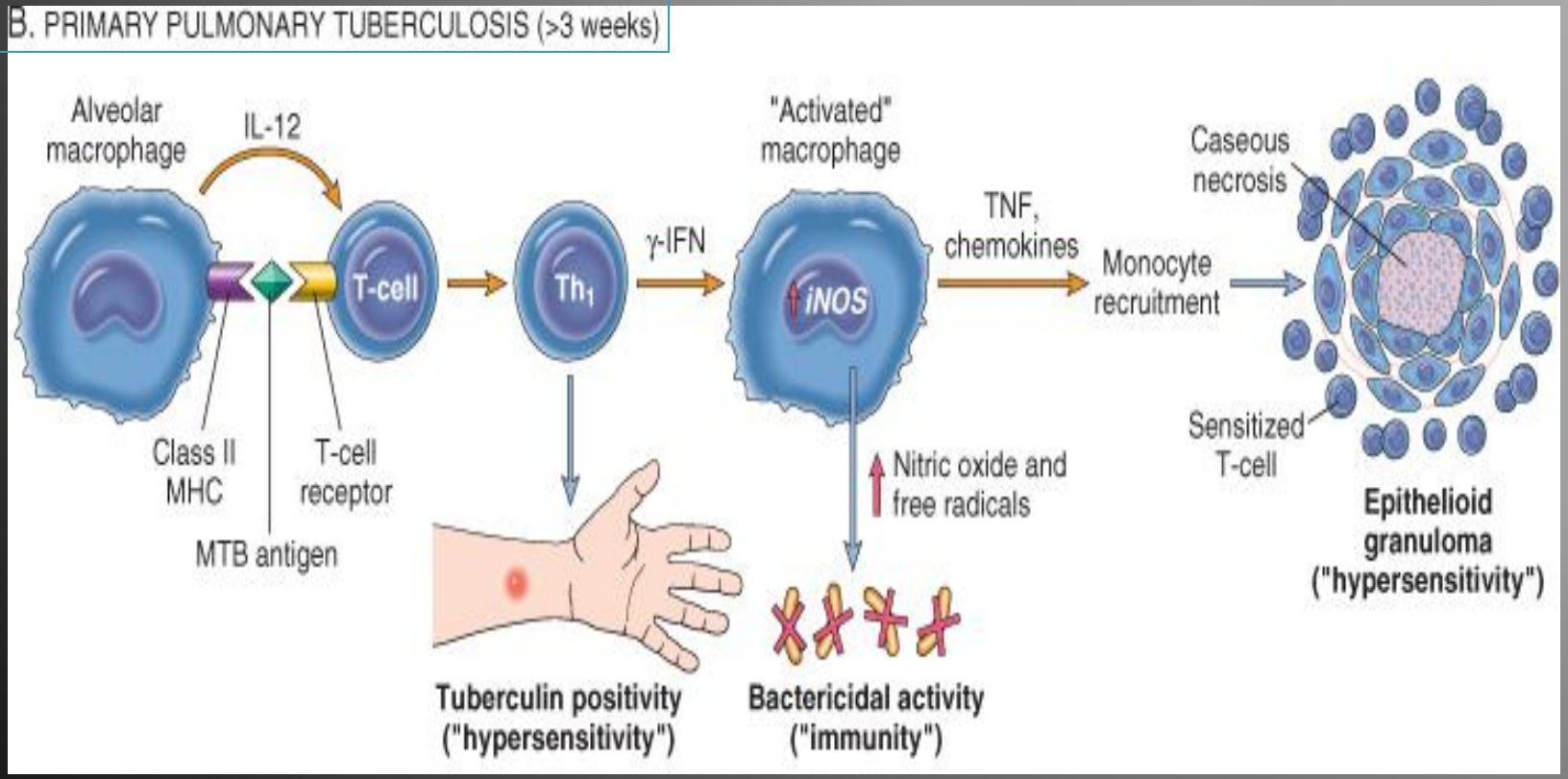
- ***In many people***, this response contains the bacteria and ***doesn't cause significant tissue destruction or illness***

- ***In some people***, the infection progresses and the ongoing immune response ***results in tissue destruction*** due to caseation and cavitation

Pathogenesis



Pathogenesis



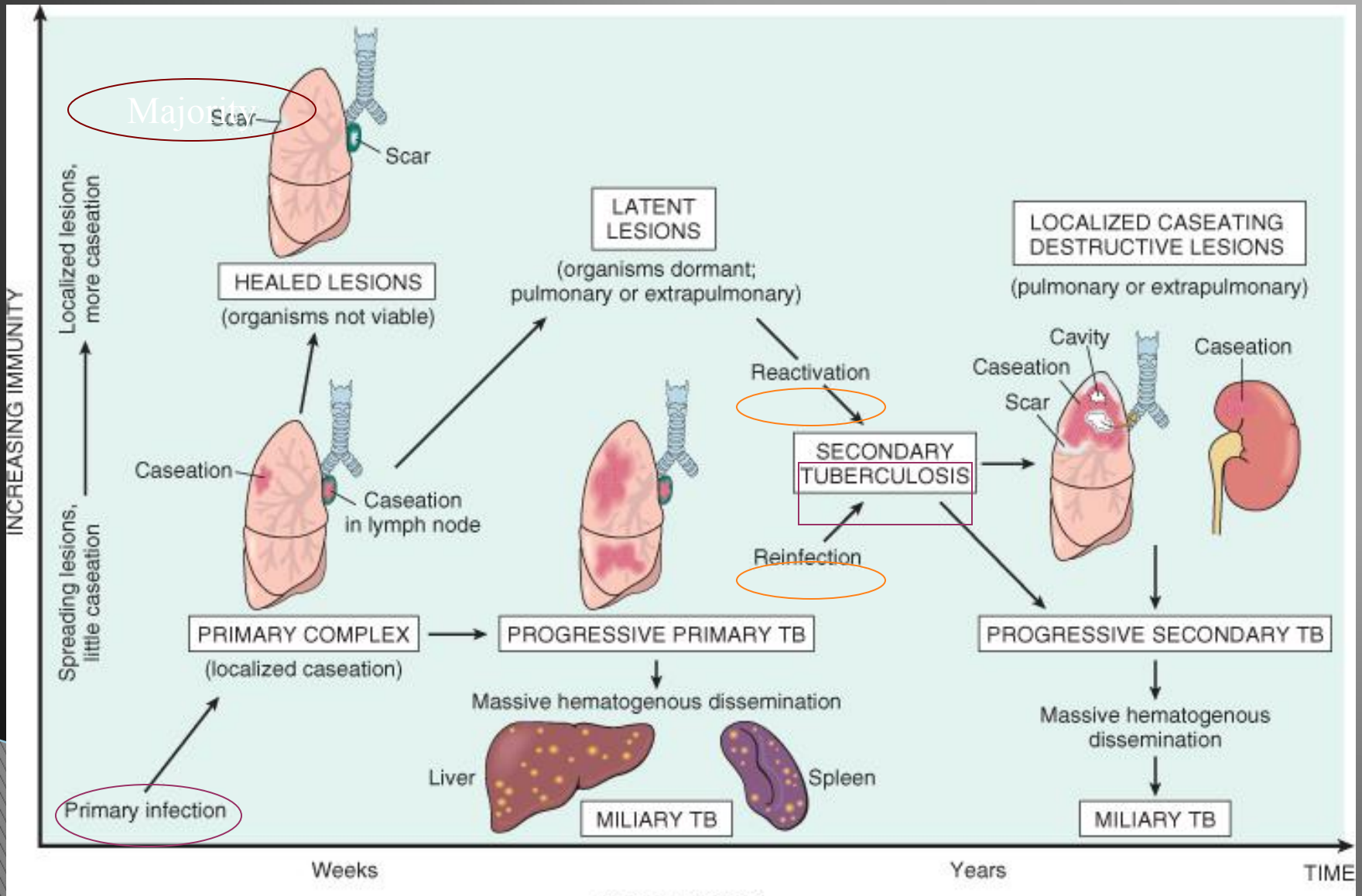
Pathogenesis Summary

- Immunity to *M. tuberculosis* is primarily mediated by **T_H1 cells**, which stimulate macrophages to kill the bacteria
- This **immune** response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction
- **Reactivation** of the infection or **re-exposure** to the bacilli in a previously sensitized host results in **rapid mobilization** of a defensive reaction but also **increased tissue necrosis**

Type IV Hypersensitivity Reaction in TB

- Can be detected by ***tuberculin "Mantoux" test***:
  - ~2-4 wks after infection, intracutaneous injection of 0.1 mL of PPD induces a visible & palpable induration "at least 5 mm in diameter" that peaks in 48-72 hrs
  - ***Positive test*** indicates cell-mediated hypersensitivity & doesn't differentiate between infection & disease
  - ***False-negative test*** may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin disease, immunosuppression & overwhelming active TB
  - ***False-positive test*** may result from infection by atypical mycobacteria

TB – Natural History & Spectrum



Thanks

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