A New Paradigm for the Pathogenesis of Pulmonary Tuberculosis

Bronchogenic tuberculosis

The ‘missing link’ between primary and post-primary disease

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M. tuberculosis (MTB) an Obligate Human Parasite.

- MTB is a human pathogen because it can survive in humans and complete its life cycle, not because it is especially virulent for humans.
- The life cycle of MTB is to infect a person, remain dormant for decades and then induce a cavity that produces massive numbers of MTB to infect a new generation of people.
- Much is known about early tuberculosis and how it is localized and resolved.
- Very little is known on how MTB drives the late stage leading to transmission.

The Current Paradigm

Granulomas are the characteristic lesion of all tuberculosis.

First Signs of Problems

- Mice are considered to be a poor model of tuberculosis because they don’t make caseating granulomas.
- We found that mice could produce a spectrum of caseating granulomas simply by adjusting the protocol of injection of organisms and cord factor (Hunter et al 2006).
- This initiated a decade long investigation of the pathology and pathogenesis of human pulmonary tuberculosis.
- Surprisingly, we did not find any support for the current paradigm.

WANTED

Manuscript supporting the prevailing paradigm of tuberculosis by any author
DEAD or ALIVE
$1,000 REWARD

For decades, most TB research has developed the paradigm that granulomas are the characteristic lesion of both primary and post-primary (adult type pulmonary) TB. We have not found any original papers that support this paradigm.

Consequently, a reward of $1,000 is offered to the first person to produce a paper written by an investigator who personally studied the pathology of developing human post-primary pulmonary TB that supports the paradigm that granulomas are the characteristic lesion of both primary and post-primary TB and that cavities arise by erosion of granulomas into bronchi.

To claim reward, send reprint to Robert.L.Hunter@uth.tmc.edu.
Origin of the Current Paradigm.
• This paradigm dates from studies with M. bovis in rabbits in the late 20th century.

Availability of human lung tissue with untreated tuberculosis plummeted with the introduction of antibiotics and decline in autopsies in the 1950s.

Rabbits infected with M bovis were the only model that produced cavities and fibrocaseous disease.

In the absence of human tissues for study, this has become the nearly universally accepted paradigm.

A 10 year Odyssey to Understand Pulmonary Tuberculosis in Humans
• Tissues for study have not been readily available since the 1950s.
• The literature in the pre-antibodies era, proved exceedingly difficult to find and read because the nomenclature had changed, there were very few images and many distractors.
• We began a search for microscope slides of untreated human pulmonary tuberculosis.
  – The first cases came from medical examiners autopsies of people who died outside of healthcare system.
  – We traveled to India twice and Russia three times seeking slides and blocks.
  – We learned of the historic collections of Johns Hopkins Hospital.
• Finally, the pathology human tuberculosis has become quite clear.

Literature from the Pre-antibiotic era.
Studies published from the 1820s through the 1960 reported that human pulmonary TB has not just one, but two characteristic lesions:

1. The caseating granuloma (nodular tuberculosis or productive reaction).
2. Tuberculous pneumonia (infiltration or exudative reaction).

Asymptomatic bronchogenic spread of pneumonia initiates post-primary tuberculosis.

Granuloma Pneumonia
Literature from the Pre-antibiotic era.
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Granuloma

Pneumonia

How Good is the Data
"It has been found by all who have studied early human pulmonary lesions that they represent areas of caseous pneumonia rather than nodular tubercles." [Rich, 1951]

Supporting publications with more than 1,000 cases each:
- Lazzaric 1821
- Virchow 1863
- Powell 1876
- Cornil and Ranvier, 1880
- Hamilton 1883
- Hektoen 1901
- Döder 1921
- Levine 1949
- Canetti 1950
- Rich 1951
- Medlar 1955
- Pagel 1960

CT Signs of Developing Post-Primary Tuberculosis
"The tree-in-bud sign is the method of choice to reveal early bronchogenic spread, with 2 to 4 mm centrilobular nodules and sharply margined linear branching opacities around terminal and respiratory bronchioles" [Sukora, 2015]

CAT Scans of Early Post-Primary Tuberculosis
Tree in Bud Sign – Obstructive Lobular Pneumonia

Early Stage of Post-Primary TB
Bronchogenic Spread

Tree-in-Bud sign of Bronchogenic Spread of Tuberculosis

Bronchial Obstruction

Post Obstructive Lobular Pneumonia
Formation of Cavities

"Cavities form by dissolution of the center of the caseous pneumonic mass"

Stages of Tuberculosis in Humans

- No Immunity
- Induction of CMI
- Effective Systemic Immunity

<table>
<thead>
<tr>
<th>Disseminated</th>
<th>Primary</th>
<th>Post-Primary Bronchogenic</th>
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<td>Obstructive Resolving (95%)</td>
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<td>Pneumonia</td>
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<td>Caseous Pneumonia</td>
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Key Findings Supporting a New Paradigm of Post-Primary TB

1) Bronchogenic spread of obstructive lobular pneumonia is the early lesion of pulmonary TB.
2) Bronchial obstruction produces post-obstructive lipid pneumonia that has a propensity to cavitate.

Post-Obstructive Lipid Pneumonia

Foamy alveolar macrophages with apoptosis and interstitial lymphocytic inflammation.

Cavity produced by chemotherapy of post-obstructive pneumonia caused by cancer.

Cavity formed in one week following initiation of chemotherapy.
Cavity produced by chemotherapy of post-obstructive pneumonia caused by cancer.

Key Findings Supporting a New Paradigm of Post-Primary TB

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1) Apical localization facilitates obstructive lobular pneumonia.

Apical Distribution of TB vs. 4dCT Lung Movement

Lowest movement, ventilation, blood flow, and lymph drainage in the apices facilitates obstructive lobular pneumonia.

Key Findings Supporting a New Paradigm of Post-Primary TB

1) Bronchogenic spread of obstructive lobular pneumonia is the early lesion of pulmonary TB.

1) Bronchial obstruction produces post-obstructive lipid pneumonia that has a propensity to cavitate.

1) Apical localization facilitates obstructive lobular pneumonia.

1) Alveolar cells in developing tuberculosis asymptptomatically produce and store large amounts of secreted mycobacterial antigens.

Key Feature of Developing Post-Primary TB

MTB Antigen Accumulation in Alveolar Macrophages

A. Immunocompetent person with developing post-primary TB
B. Higher power of same section. AFB stain was negative
C. AFB in a patient with HIV and disseminated TB
D. IHC stain for MTB of SAME section

Key to Understanding Post-Primary TB

Very few MTB produce and store secreted antigens and host lipids in alveolar macrophages asymptptomatically for months behind an obstructed bronchus. They spread as bronchogenic tuberculosis.
Key Findings Supporting a New Paradigm of Post-Primary TB

1) Obstructive lobular pneumonia is the early lesion of pulmonary TB.
2) After many months, the lesion suddenly undergoes caseous necrosis. The necrotic lung is coughed out to produce cavities or remains to become fibrocaseous disease.

New Paradigm - Tuberculosis as a Three Act Play

ACT 1: War of Attrition
- Immunity: None → Strong
- Granulomas form, contain MTB, as CMI develops
- Lymphatic/Hematogenous spread
- Bronchial spread (tree-in-bud)

ACT 2: The Sneak Attack
- Effective Systemic Immunity
- Resolution (95%)
- MTB antigens and host lipids accumulate in obstructive lobular pneumonia
- MTB antigens in cell
- Earliest lesion: Obstructive Lobular pneumonia
- Caseating Pneumonia (5%)
- Sudden onset
- MTB Pellicle
- Caseating Granulomas
- Primary (Granuloma)
- Post-Primary (Pneumonia)

ACT 3: The Fallout
- No spread
- MTB antigens and host lipids accumulate in obstructive lobular pneumonia
- MTB Pellicle
- Homogeneous caseum with peripheral lipid
- Ghosts of alveolar structures surrounded by granuloma
- Found in all organs
- Found only in lung

Untreated Human Tuberculosis with Early Cavitation
Necrosis of tuberculous pneumonia occurs rapidly to produce cavities.

Pathology of Pulmonary Tuberculosis
Caseating granulomas are characteristic only of primary tuberculosis. Post-primary (secondary) tuberculosis is an endogenous lipid pneumonia that characteristically develops in people with sufficient immunity to heal caseating granulomas.
Obstructive Bronchiolar Pneumonia
Plausible Answers to Long Standing Questions

• What mediates resistance of most humans?
• Why are immunocompetent young adults especially susceptible to disease and death?
• How can multiple stages of TB exist in a single lung?
• Why does recovery from disease fail to produce immunity?
• Why have vaccines that prevent disseminated TB in children, failed to protect adults from pulmonary TB?
• Why does post-primary TB localize in the upper lobes of the lungs?

Obstructive Bronchiolar Pneumonia
Plausible Answers to Long Standing Questions

- This lesion spontaneously resolve because of failure of obstruction, accumulation sufficient antigens or other.
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Obstructive Bronchiolar Pneumonia
Plausible Answers to Long Standing Questions

- Obstruction of lobules starts the clock for storage of mycobacterial antigens and host lipids. That drives all the rest.
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• Why have vaccines that prevent disseminated TB in children, failed to protect adults from pulmonary TB?
• Why does post-primary TB localize in the upper lobes of the lungs?

Obstructive Bronchiolar Pneumonia
Plausible Answers to Long Standing Questions

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- Why have vaccines that prevent disseminated TB in children, failed to protect adults from pulmonary TB?
- Why does post-primary TB localize in the upper lobes of the lungs?
  - The apices have the least ventilation, perfusion, lymph flow and movement. This facilitates obstructive lobular pneumonia.

Animal Models

- No animal develops TB like humans. However,
  - Several animals can develop parts of the human disease
- Must try to reproduce the conditions in animals that exist in people at different stages of disease.
  - DO NOT only reproduce the route of infection.
- Measure pathologic effects, not just CFUs.

“A central problem in tuberculosis research is to explain why immunity to infection does not enable mice, guinea pigs, rabbits, or susceptible humans to resolve lung infection and thereby stop the development of disease.” (North 2004)

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