

Tuberculosis Pathogenesis and Transmission

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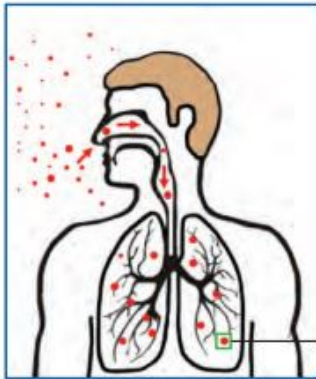
Objectives

- Identify why the paradigm shift identifying the caseating granuloma as the characteristic lesion of all TB occurred with the introduction of effective antibiotics
- Understand how using a three act model can better identify the actual pathology that is occurring in tuberculosis
- Review questions that can be addressed only by using the new paradigm
- Very briefly look at diabetes as a risk factor for progression to active disease

Looking at TB Pathogenesis With a Traditional Eye

Pathogenesis of LTBI and TB Disease

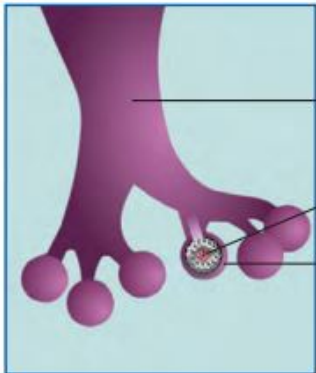
1.



**Area of
detail for
boxes 2, 4,
and 5**

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

2.



Bronchiole

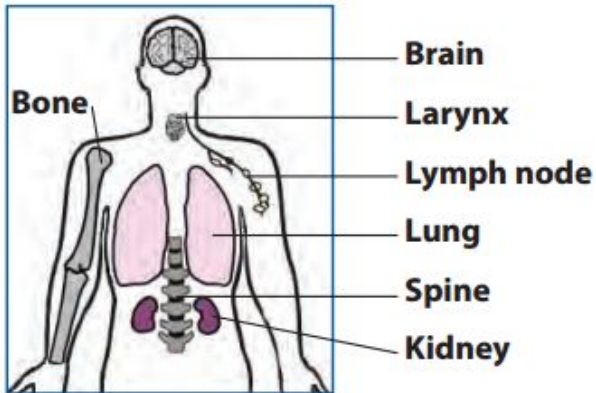
Tubercle bacilli

Alveoli

Tubercle bacilli multiply in the alveoli.

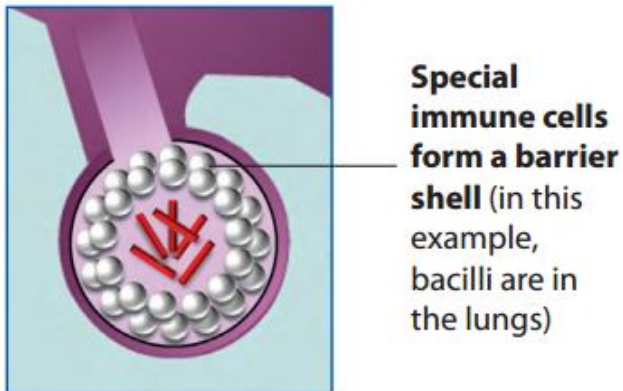
Looking at TB Pathogenesis With a Traditional Eye

3.



A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

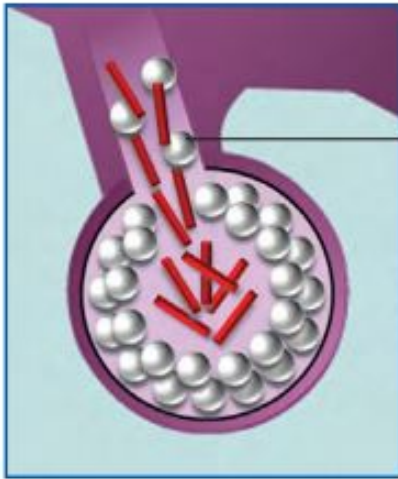
4.



Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (**LTBI**).

Looking at TB Pathogenesis With a Traditional Eye

5.



**Shell breaks
down and
tubercle
bacilli escape
and multiply**

If the immune system **cannot** keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (**TB disease**). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone (see diagram in box 3).

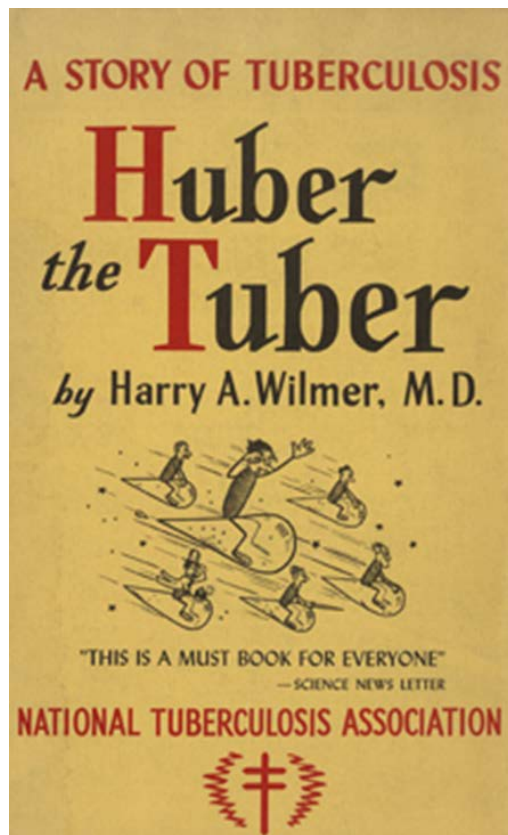
Unanswered Questions For Traditional Paradigm of Pathogenesis of Tuberculosis

- What protects most adults from disease following infection?
- Why are immunocompetent young adults especially susceptible to disease and death?
- Why does recovery from disease fail to produce immunity, but actually produces increased susceptibility to recurrent disease?
- 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?

Then and Now

What Was Old Is New Again

1942



2016

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 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 in to bronchi.

To claim reward, send reprint to Robert.L.Hunter@uth.tmc.edu

Robert L. Hunter, Tuberculosis as a three-act play: A new paradigm for the pathogenesis of pulmonary tuberculosis, *Tuberculosis*, Volume 97, March 2016, Pages 8-17, ISSN 1472-9792, <http://dx.doi.org/10.1016/j.tube.2015.11.010>. (<http://www.sciencedirect.com/science/article/pii/S1472979215301402>)

What Were They Thinking?

(and how did they get off track?)

- Antibiotics has reduced the number of cases seen by pathologists of post primary tuberculosis
- Pre-antibiotic era investigators consistently described post primary TB as an exudative reaction
 - A tuberculous lipid pneumonia of foamy alveolar macrophages
 - Undergoes caseation necrosis and fragmentation to produce cavities
- Granulomas in post primary disease arise only in response to old caseous pneumonia and produce fibrosis, NOT cavities
- Concept that cavities arise from caseating granulomas arose from *M.bovis* studies
 - *M.bovis* does not produce post primary tuberculosis in any species
 - Produces an aggressive primary TB that can develop small cavities by erosion of caseating granulomas



Once Infected, It's All About the Balance

- Protection in TB has traditionally meant containment, not eradication of *Mtb*
- Once host immunity is affected, the balance is tipped in *Mtb*'s favor and LTBI progresses to active TB
- The difference between LTBI and active TB is paralleled by different tissue reactions
- Progression from LTBI to active TB (and sometimes back to LTBI) has to be viewed as a continuum and not as a defined step
- Each granuloma represents a disease entity in itself

Stefan H.E. Kaufmann, Introduction, *Seminars in Immunology*,
Volume 26, Issue 6, Pages 429-430

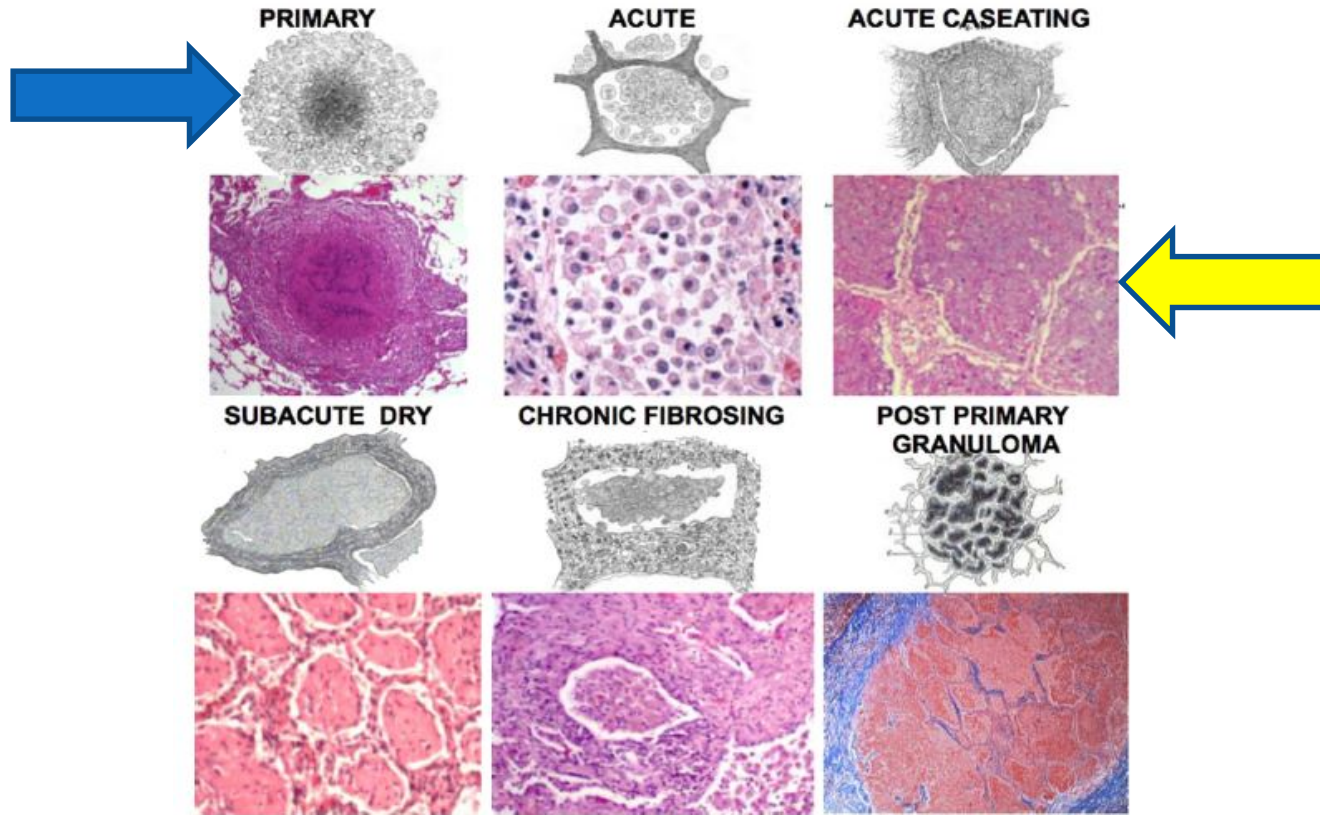
<http://dx.doi.org/10.1016/j.smim.2014.09.007>

For MTB, Success Is Found Through Elusiveness

- MTB is most successful when it infects a child, then hides for decades before forming a cavity in the lung of a person with sufficient immunity to prevent infection in every other part of the body.
- This person may live for decades expelling infectious organisms into the community without ever becoming seriously ill.
- In several studies, half of the people who expectorate virulent MTB from cavitory tuberculosis have no symptoms of disease and deny that they even have a cough.
- Post primary tuberculosis is a very effective adaptation of MTB to the longevity and life styles of its host, namely people.

Pathology of Human TB

R.L. Hunter / Tuberculosis 97 (2016) 8–17

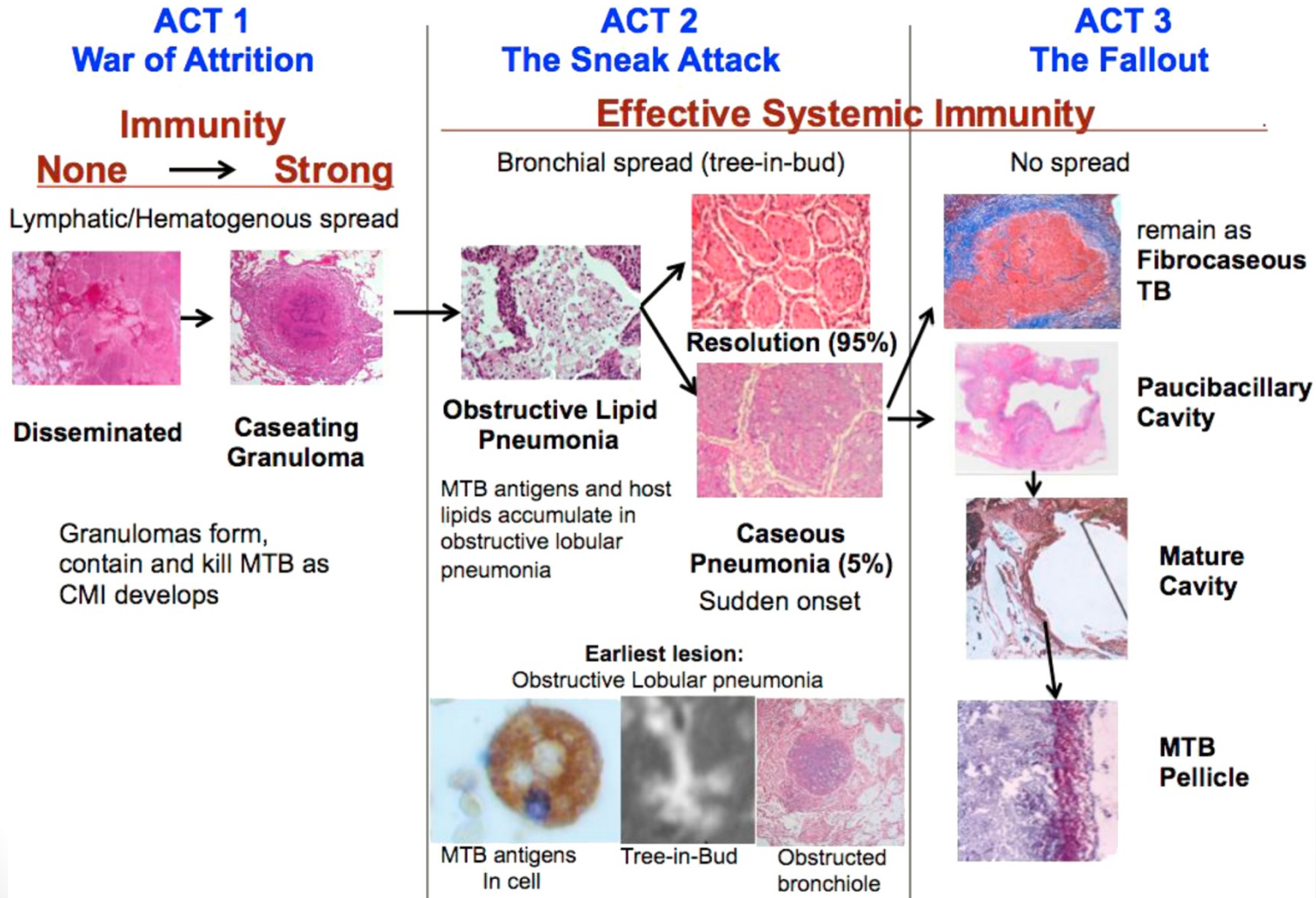


Hunter 2016

“Old” Paradigm Thinking

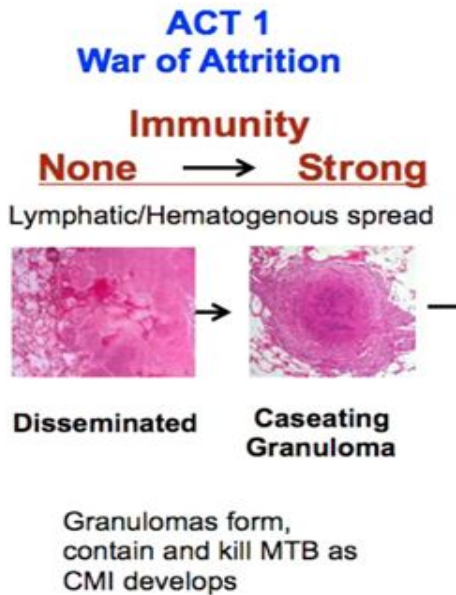
The current paradigm of the pathogenesis of TB considers TB to be a one act play in which the caseating granuloma modulated by cell mediated immunity (CMI) is the characteristic lesion of all TB. While this is an appropriate model for M. bovis and primary TB, it fails to recognize the existence of obstructive lobular pneumonia that initiates and drives all of post-primary TB.

The Three Distinct Stages Hypothesized



Act I

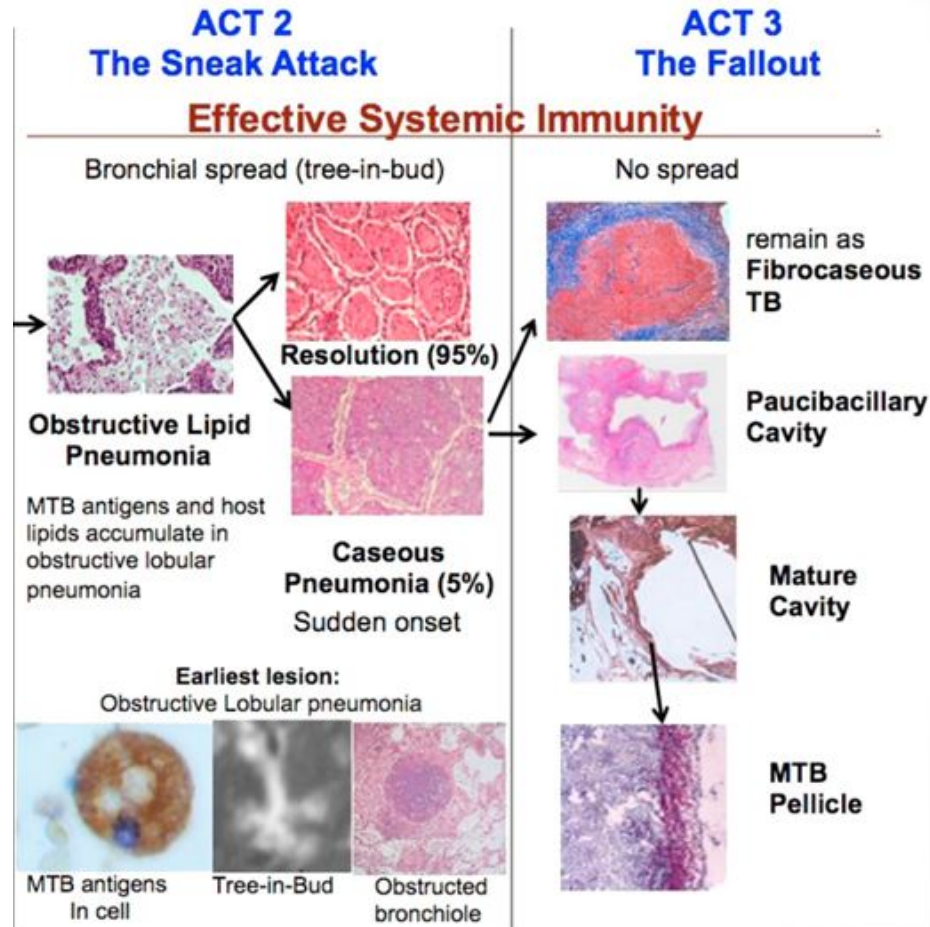
The War of Attrition



- MTB try to multiply while the host attempts to contain them within granulomas
- With no or little immunity, there is greater lymphatic or hematogenous spread
- Control is through cell mediated immunity

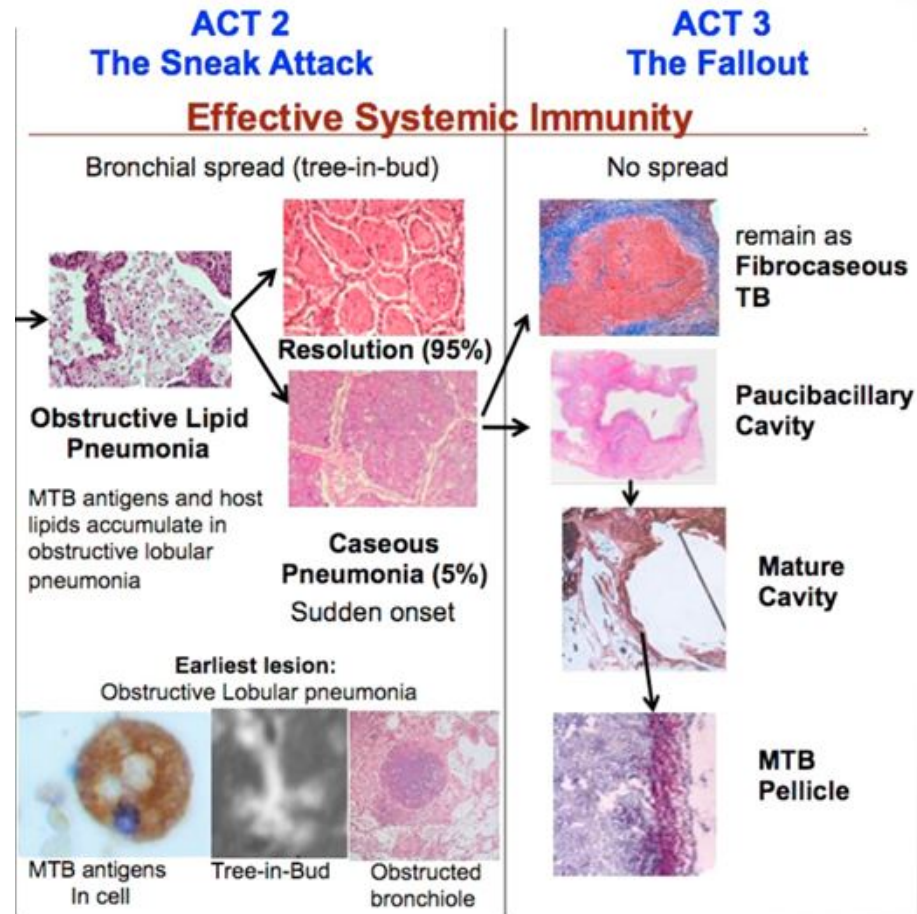
Act II-The Sneak Attack

- Act II Post-primary bronchogenic TB begins asymptotically in the apices of the lung, at some distance from the site initial infection
- It is part of latent TB since there are no clinical symptoms
- Few numbers of MTB in modified alveolar macrophages drive accumulation of host lipids and mycobacterial antigens in an isolated section of lung in preparation for a sudden necrotizing reaction sufficient to produce a cavity



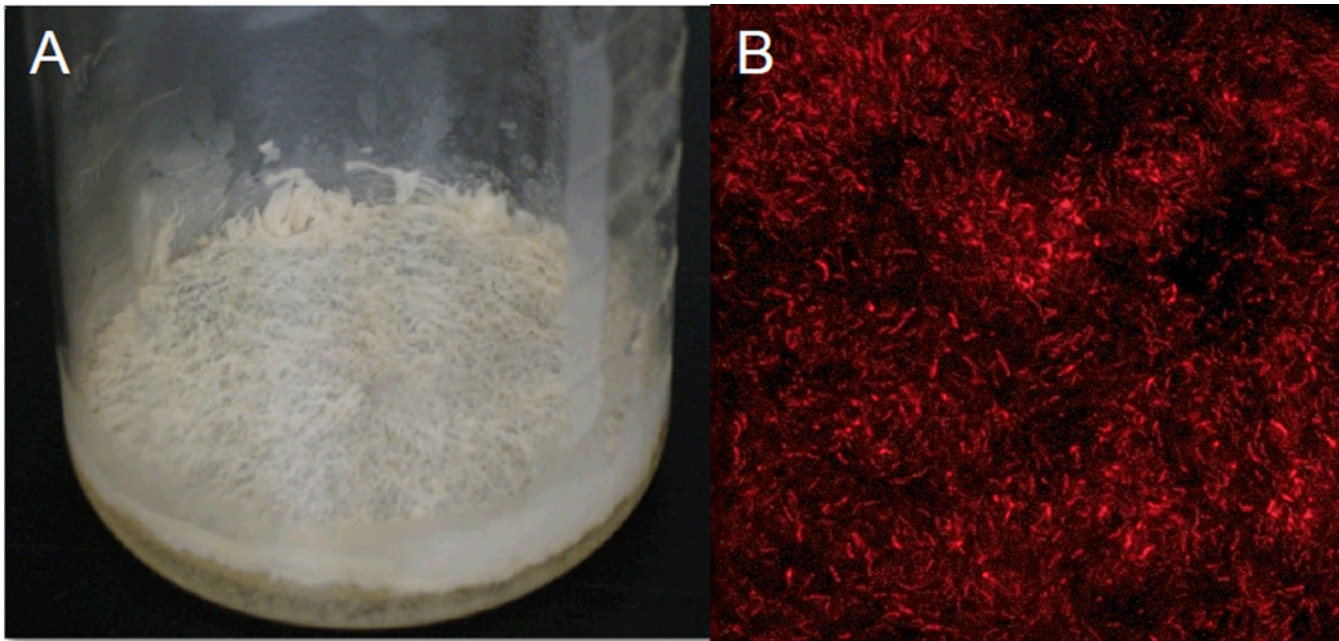
Act III-The Fallout

- The stage encompasses the further evolution of necrotic caseous pneumonia
- It is either coughed out to form a cavity or becomes surrounded by epithelioid cells and fibrosis
- This produces granulomatous inflammation and most clinical disease
- Cavities form when caseous pneumonia softens, fragments and is coughed out of the body leaving a hole.
- Pneumonia that is not coughed out remains to induce inflammation. It dries to become fibrocaseous TB

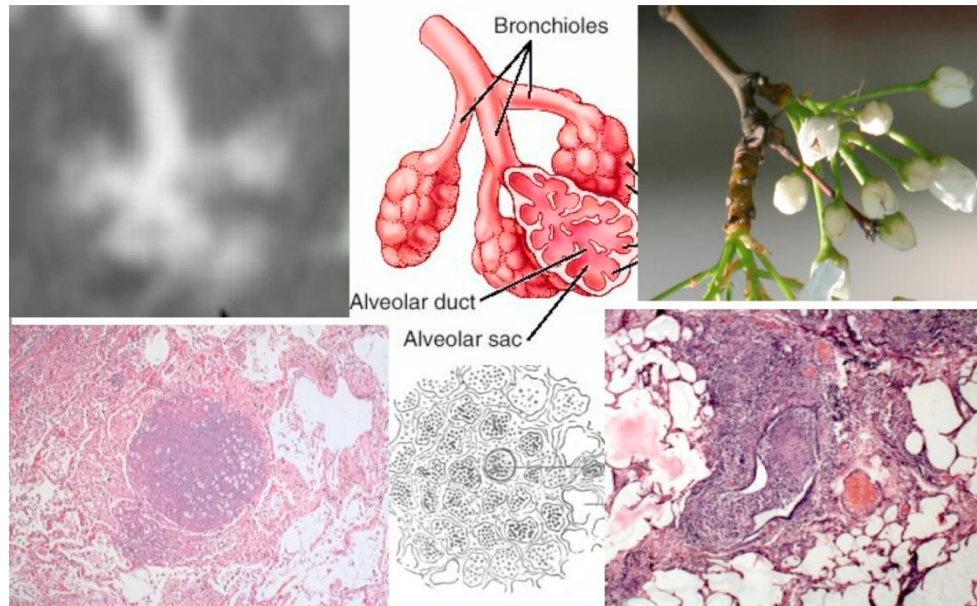


What's a Pellicle?

"*In vitro* pellicle, or biofilm mode of growth, where bacteria grow to produce a thick aggregate at the air-liquid interface and exhibit increased phenotypic resistance to antibiotics"



Why does post-primary TB localize in the upper lobes of the lungs?



Hunter 2016

What protects most adults from disease following infection?

Everyone's posting photos with the caption

#tb

Hashtag throwback

Usually used when someone wants to post an old photo on Instagram and expects reactions such as "awe so cute" or "that was so great"

Hashtag throwback

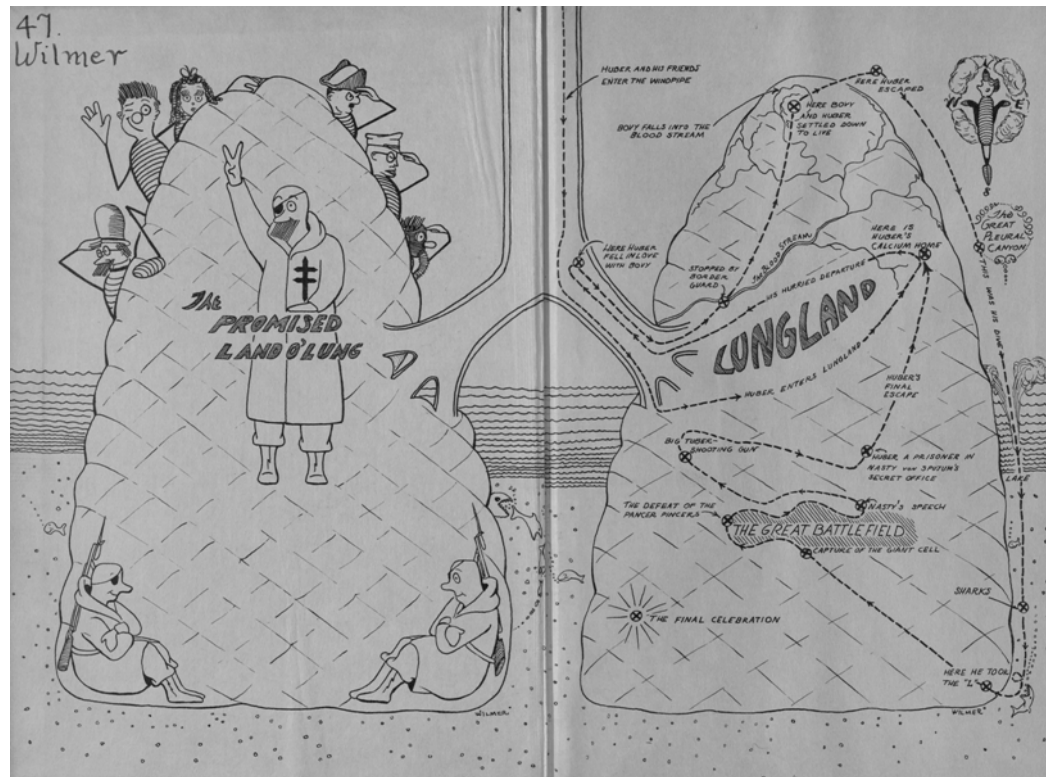
Usually used when someone wants to post an old photo on Instagram and expects reactions such as "awe so cute" or "that was so great"

And I'm all like, "Do people know what that is?"

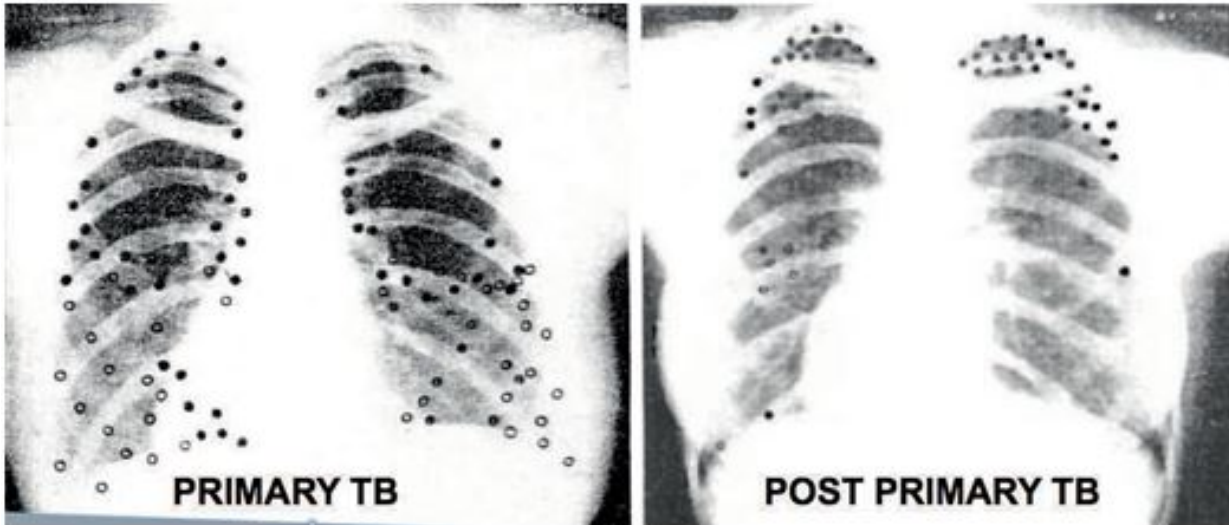
TUBERCULOSIS



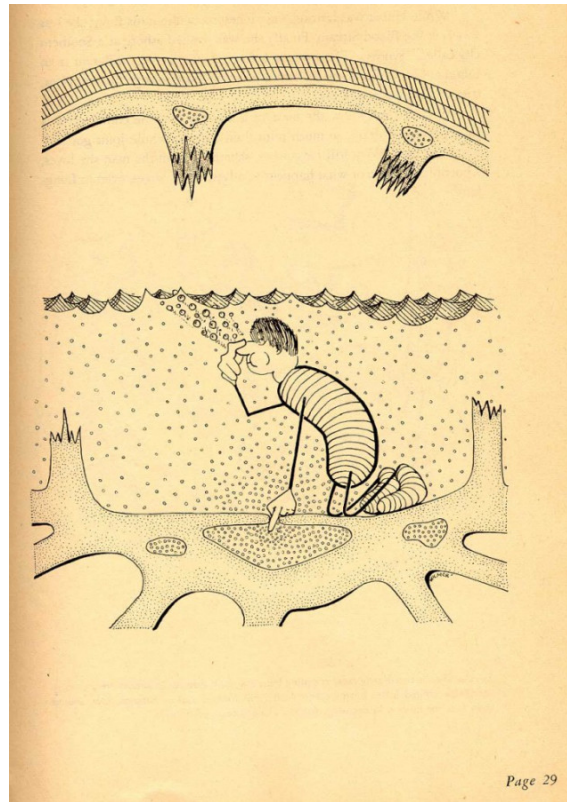
Why are immunocompetent young adults especially susceptible to disease and death?



How can multiple pulmonary lesions in a single lung act independently as if the others did not exist?





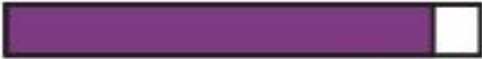
Why does recovery from post-primary TB NOT produce immunity?



Why have vaccines that prevent disseminated TB in children, failed to protect adults from pulmonary TB?



Risk of Developing TB Disease

Risk Factor	Risk of Developing TB	Description
TB infection and no risk factors	 <p>About 10% over a lifetime</p>	For people with TB infection, no risk factors , and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.
TB infection and diabetes	 <p>About 30% over a lifetime</p>	For people with TB infection and diabetes , and with no treatment, the risk is three times as high, or about 30% over a lifetime.
TB infection and HIV infection	 <p>About 7% to 10% PER YEAR</p>	For people with TB infection and untreated HIV infection and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.

<http://www.cdc.gov/tb/education/corecurr/>

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https://www.theguardian.com/science/2016/feb/23/rats-who-sniff-out-tuberculosis?CMP=share_btn_link



The long read

The rats who sniff out tuberculosis

The African giant pouched rat can be trained to sniff out tuberculosis more accurately than most lab tests. So why is the medical profession still sceptical?
by [Emma Young](#)