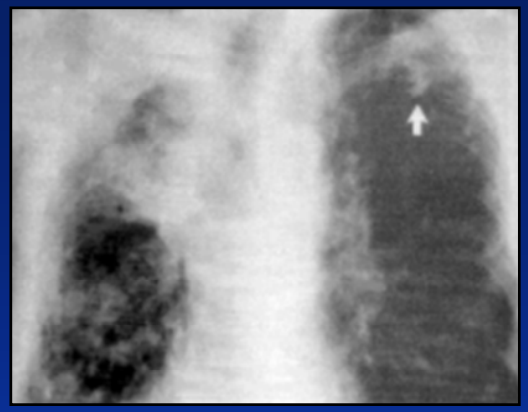


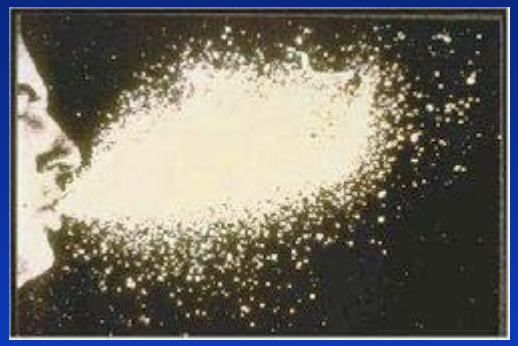
11th Annual Conference
North American Region
INTERNATION UNION AGAINST TUBERCULOSIS AND LUNG DISEASE

What are the Gamma-Interferon Release Assays Teaching us About Latent TB Infection?

David Lewinsohn, MD, PhD
Pulmonary & Critical Care Medicine

Portland VA Medical Center
Oregon Health & Sciences University

Natural History of TB



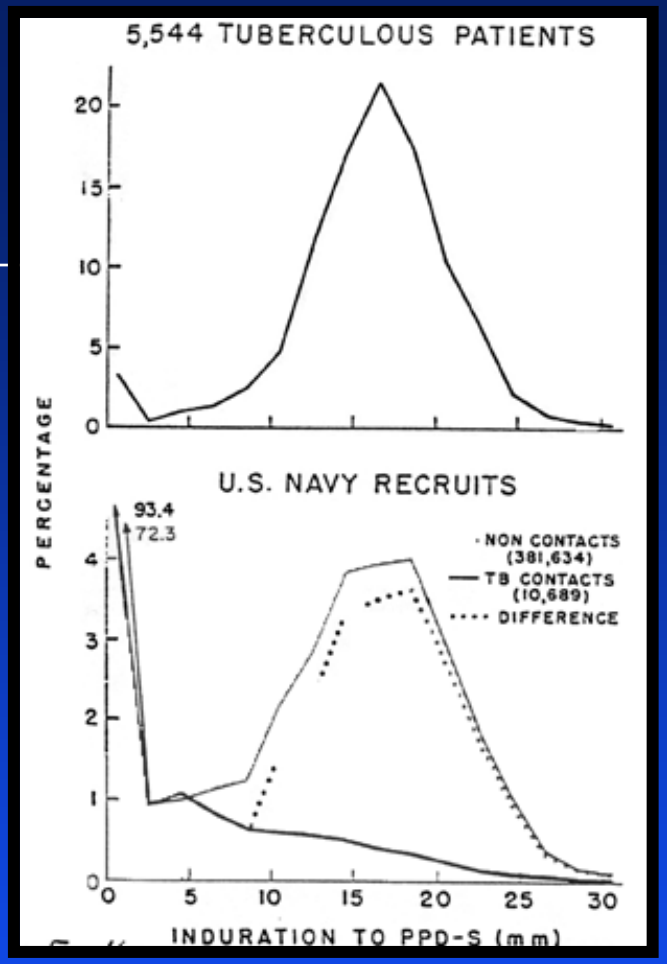
Possible Outcomes

- Active Tuberculosis
- Latent Tuberculosis
- Clearance(?)

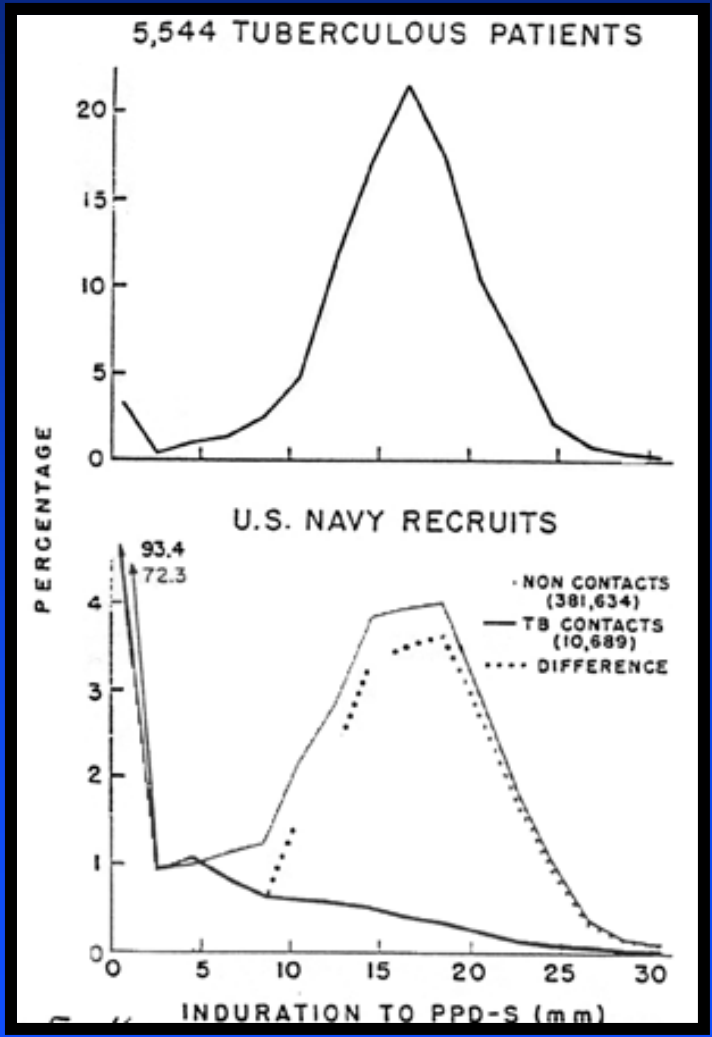
"Sputum induction is putting a patient and Ann Elarth together in a well-ventilated room."

Charlie Nolan

TST: TB Controllers' Comfort Food



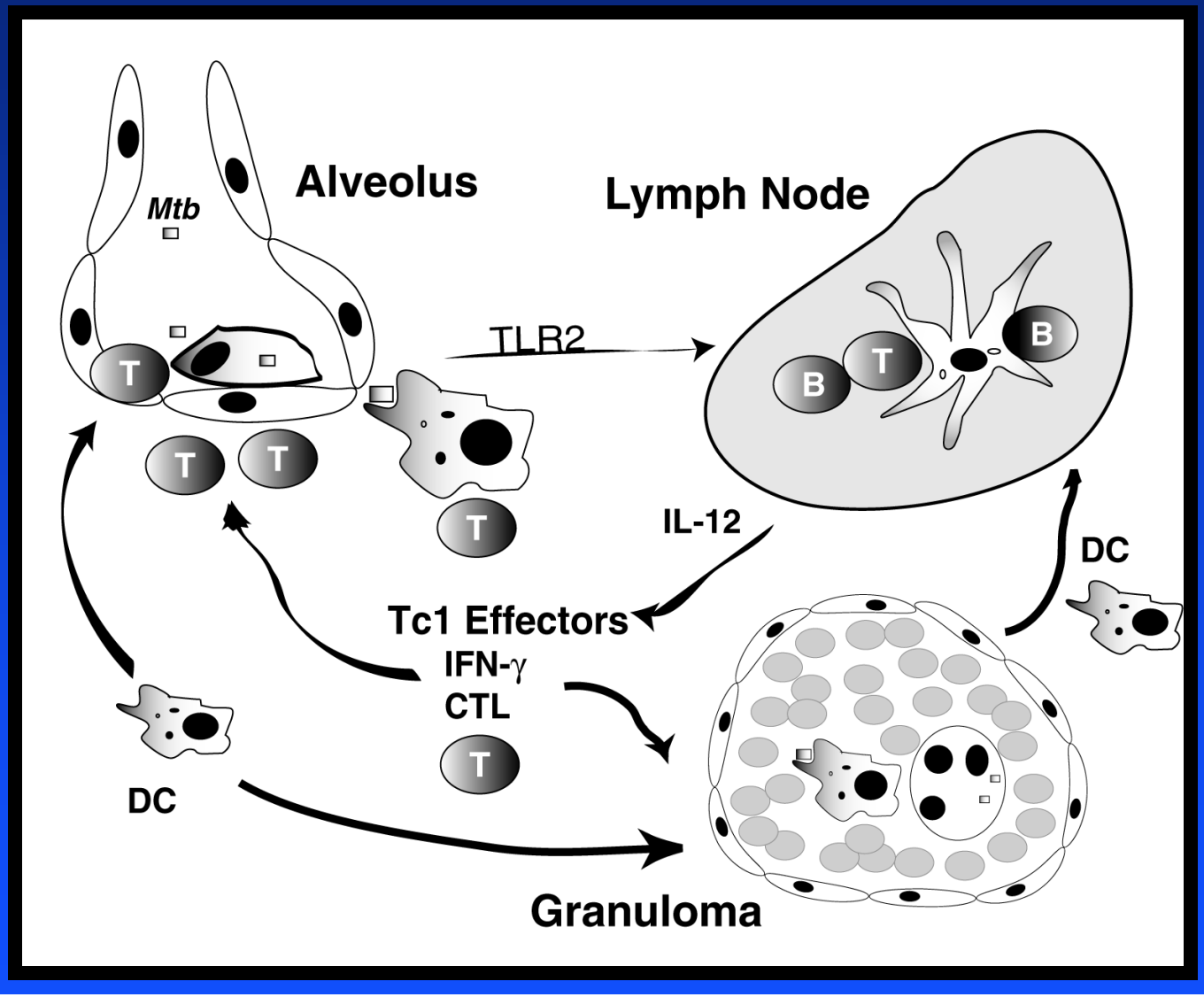
The Natural History of Tuberculosis: Current Status



TST

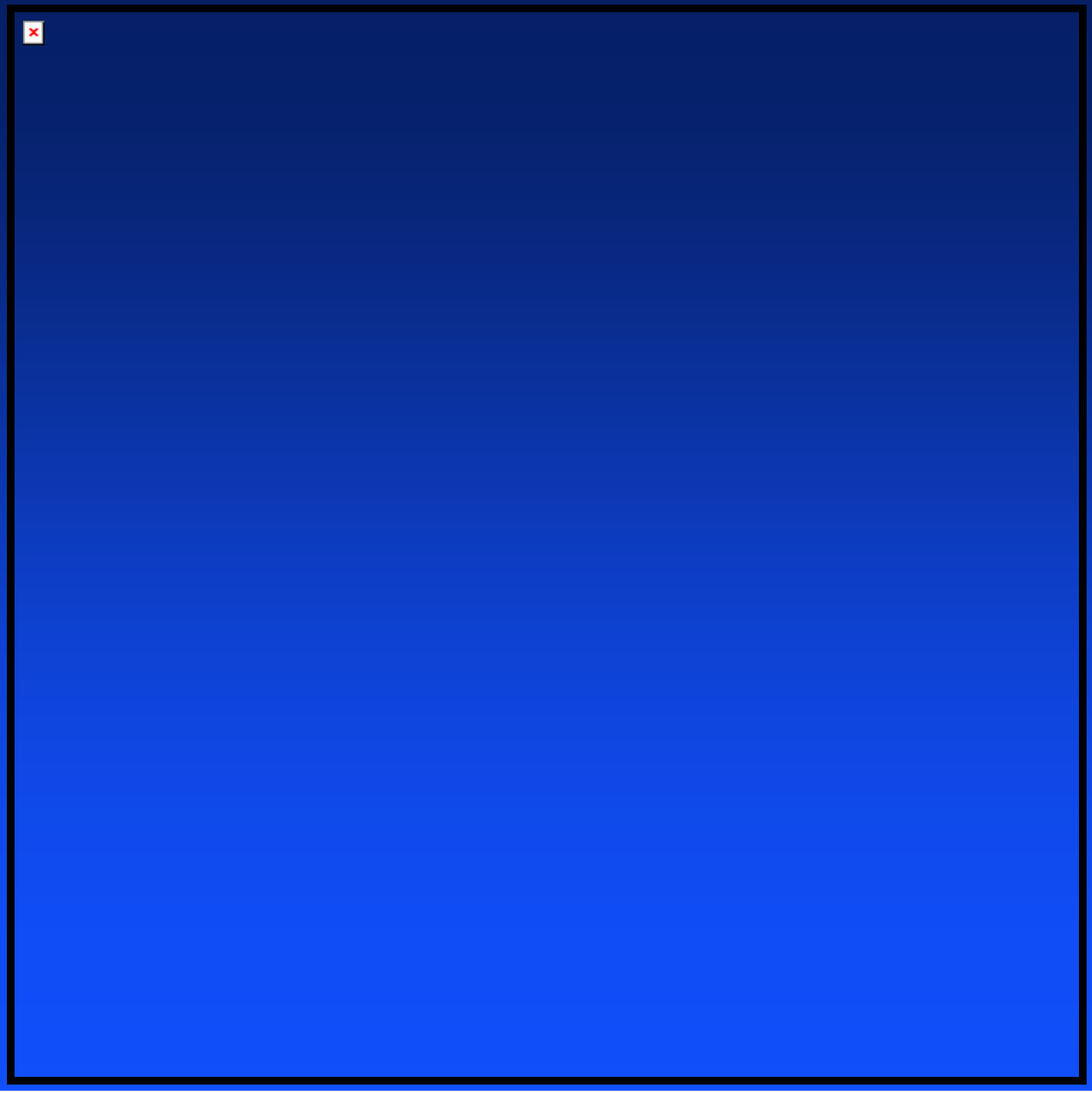
- Yes or No
  - i.e. size of TST does not reflect:
    - Time from infection
    - Active vs Latent Disease
    - Risk of progression
    - Response to Rx
- Associated with Exposure to Mtb
- Conversion associated with risk of disease

The Cellular Immune System Contains Mtb



Unusual Features of Mtb

- Intracellular pathogen
- Long periods of persistence (?antigenic)
- Possible immune evasion
- Ongoing exposure to mycobacteria (Mtb and Environmental)



Questions to be Addressed

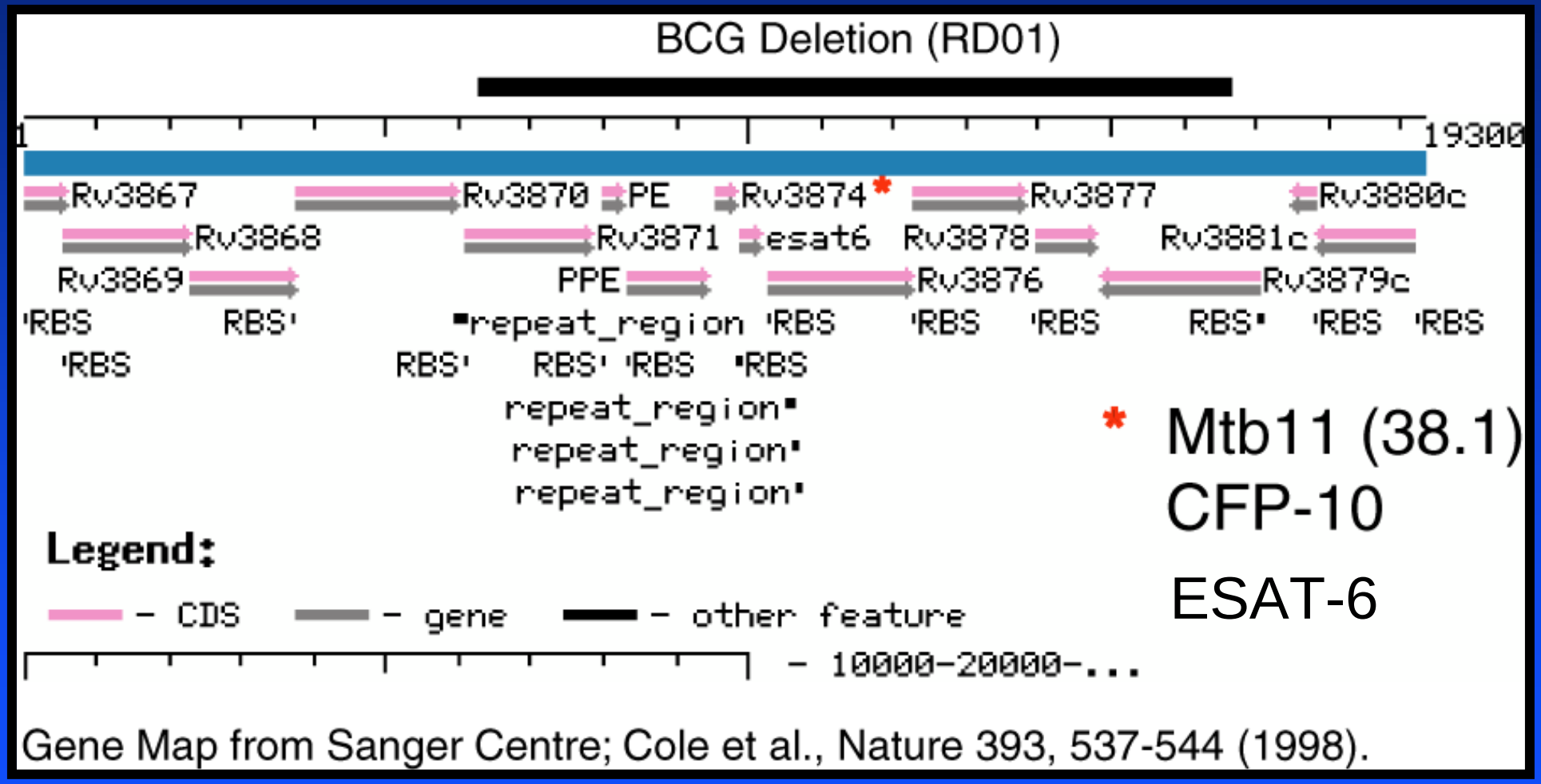
- Can we distinguish recent from remote infection?
- Is there evidence for transient exposure and/or infection?
- Can we assess response to therapy?
- Can we discern the transition from latent to active TB?

Out of the Comfort Zone – Laboratory Based Diagnosis of Latent TB

IFN vs DTH

	TST	IFN
Cell Types	CD4 CD8 Basophils DC and Macrophages	CD4 (CD8)
Cytokines	IL-4, IFN-γ TNF-α, IL-10, IL-12, G-CSF,	IFN-γ
Associated with Protective Immunity	No	Yes
Timing	2-5 Days	Short Term
Homing Phenotype	Skin	Polymorphic

Antigens Absent from BCG



Gene Map from Sanger Centre; Cole et al., Nature 393, 537-544 (1998).

Diagnosis of Latent Disease

The holy grail – increased specificity and sensitivity

- Specificity – Antigen
- Sensitivity
  - – 2nd Generation QFT
    - Limit of detection 0.05 IU/mL vs. 1.5 IU/mL for QFT-TB
  - – ELISPOT
    - Limit of detection 1/25,000 effector cells

Summary of RD1-based IGRAs

- Sensitivity for active TB is excellent.
- Specificity is much improved over TST.
- Both are more closely associated with exposure to Mtb than TST.

Redefining the natural history of latent TB

- Can we distinguish recent from remote infection?

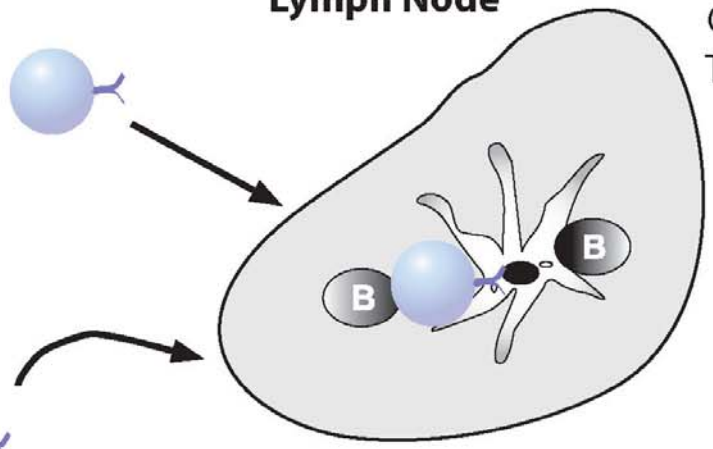
Naive T Cell

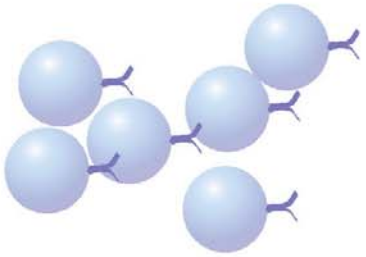
Secondary LN Homing
No Effector Function
CD62L
CD45RA
CCR7

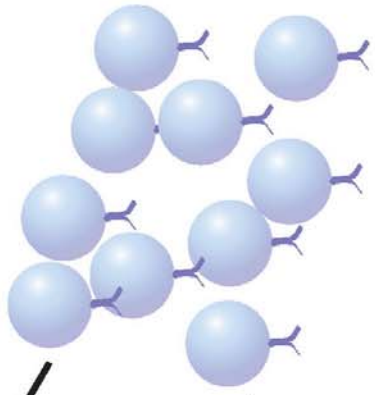
Memory Effector Cell (TEM)

Peripheral
Homing phenotype
Rapid Effector Function
CD45RO
Tc1 or Tc2
Cytokines
Cytolytic

Lymph Node

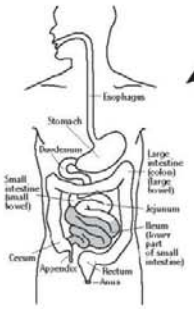




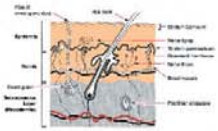


Overnigt Assay

gut



skin



lung

Central Memory (TCM)

Secondary LN Homing
Retains Tissue Selectivity
Rapid proliferation to antigen
CD62L
CD45RO/RA
CCR7

5 Day Assay

Pai et al., JAMA 2005, 293:2786

- Cross Sectional Study 726 HCW
- Comparison of QFT / TST
- 84% Overall Agreement

Table 3. Agreement Between TST and IFN-γ Assay Results (n = 719)

Results*	TST Cutpoint, mm ≥5	≥10	≥15
Positive TST/positive IFN-γ assay	259	226	148
Negative TST/negative IFN-γ assay	254	359	412
Positive TST/negative IFN-γ assay	177	72	19
Negative TST/positive IFN-γ assay	29	62	140
Agreement, %	71.4	81.4	77.9
κ (95% CI)	0.45 (0.39-0.51)	0.61 (0.56-0.67)	0.51 (0.44-0.57)

Abbreviations: CI, confidence interval; IFN-γ, interferon γ; TST, tuberculin skin test.
*IFN-γ assay cutpoint was at least 0.35 IU/mL.

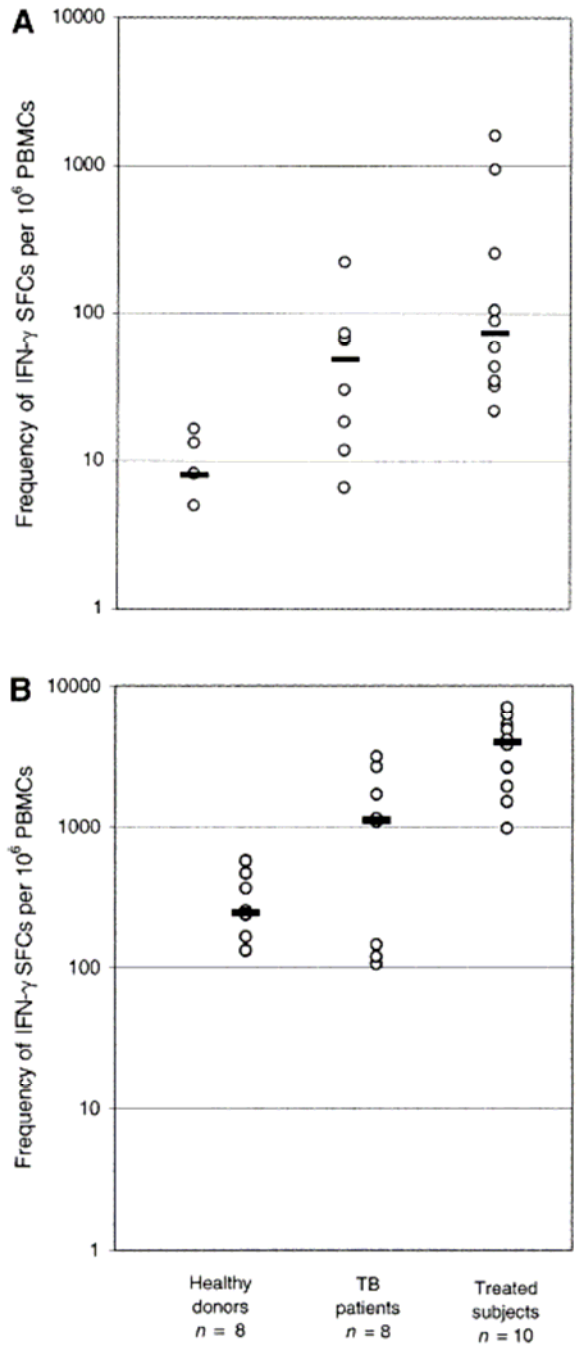
Arend et al.,
Am J Respir Crit Care Med. 2006 Dec 14

- Investigation of contacts of smear positive grocery store employee
- Sample of 316 contacts
- IGRA's associated with exposure to active case
- TST associated with age
- For TST > 15 mm, sensitivity of
  - QFT-GIT 42%
  - T-SPOT.TB 51%

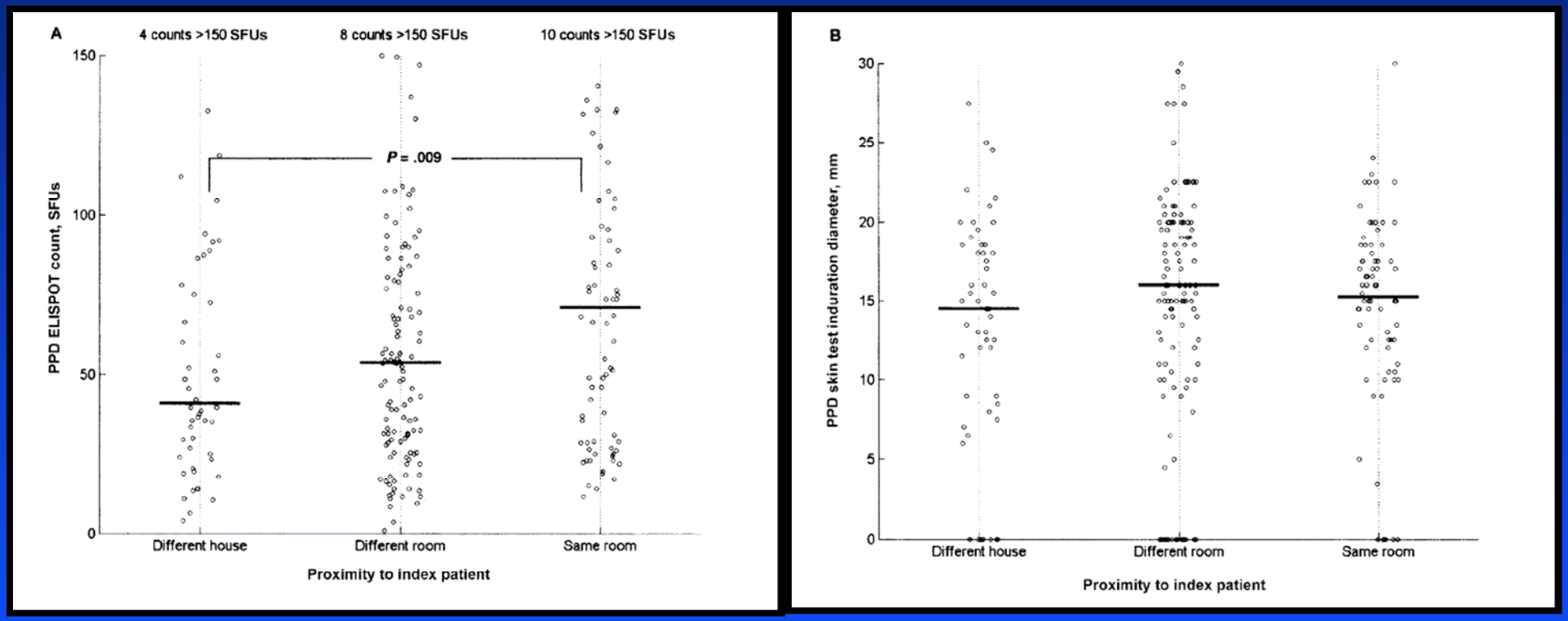
Overnight

Ferrand et al., INT J TUBERC LUNG DIS 9(9):1034–1039 © 2005

6 Day Assay



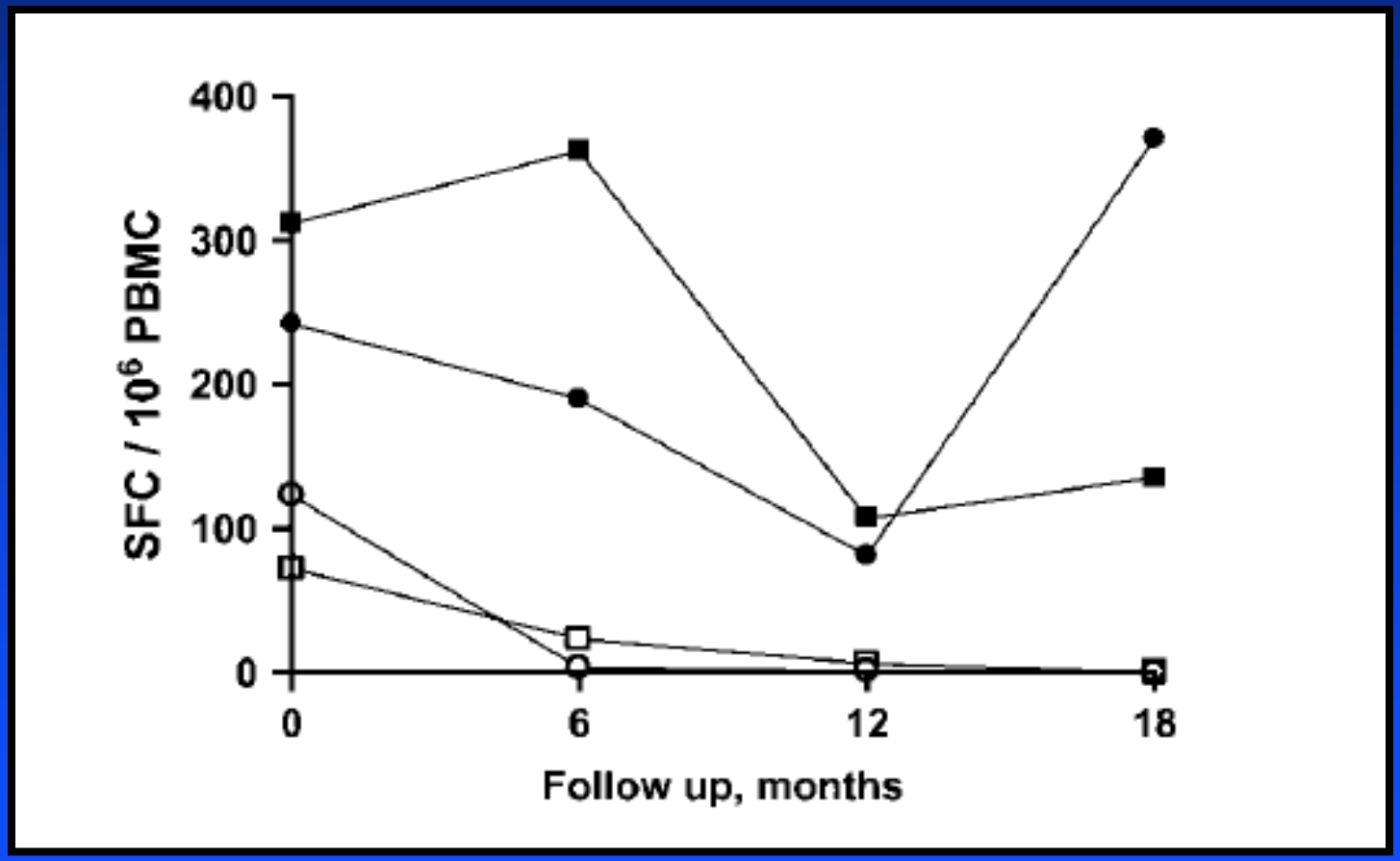
Hill et al., Clinical Infectious Diseases 2005; 40:273–8



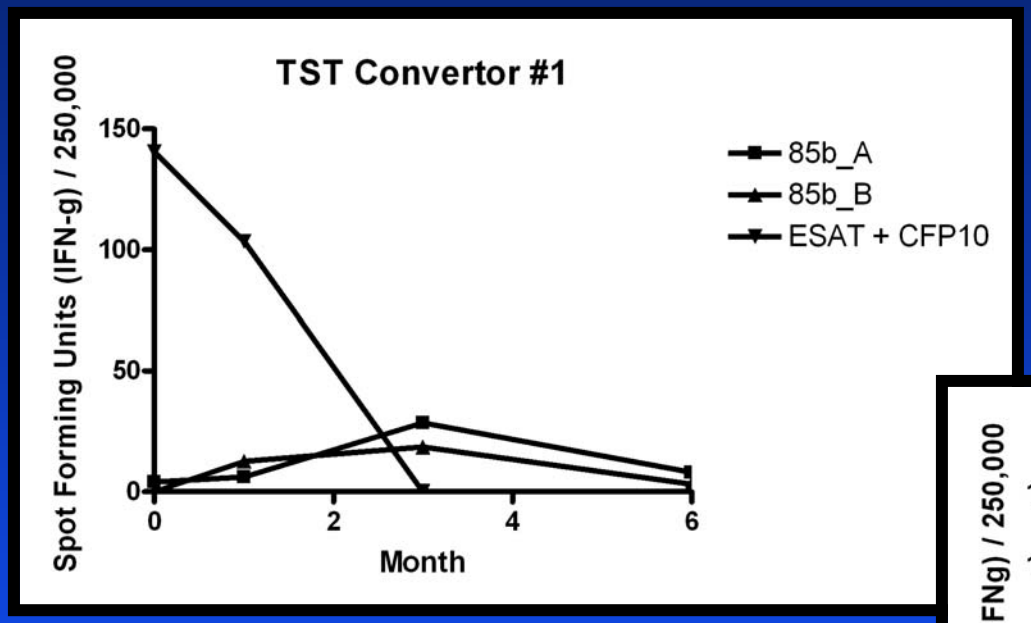
Redefining the natural history of latent TB

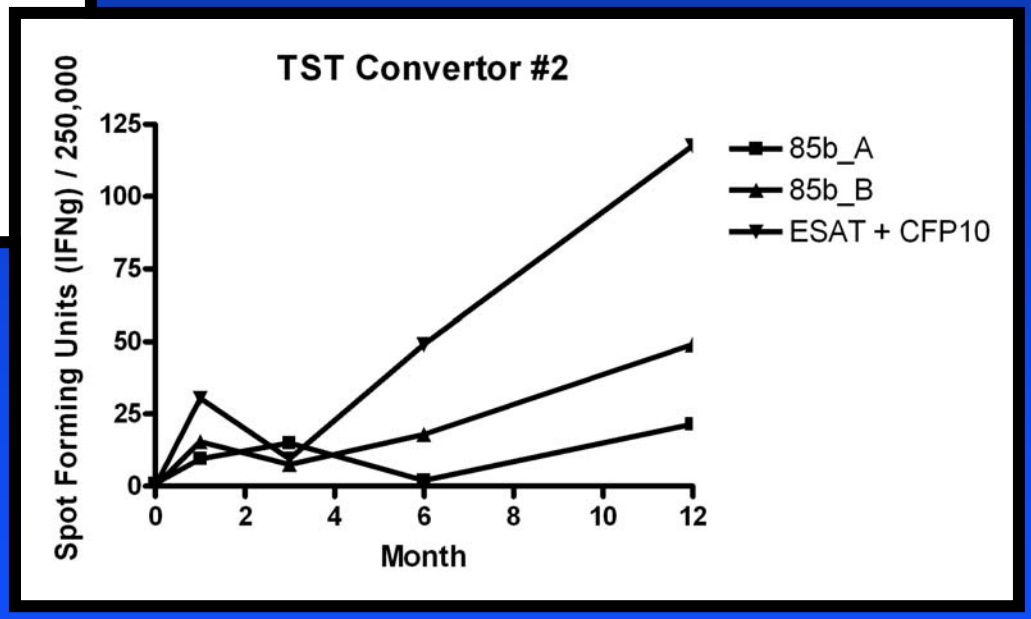
- Is there evidence for transient exposure and/or infection?

Ewer al al., Am J Respir Crit Care Med Vol 174. pp 831–839, 2006



Disparate Outcomes in Household Contacts



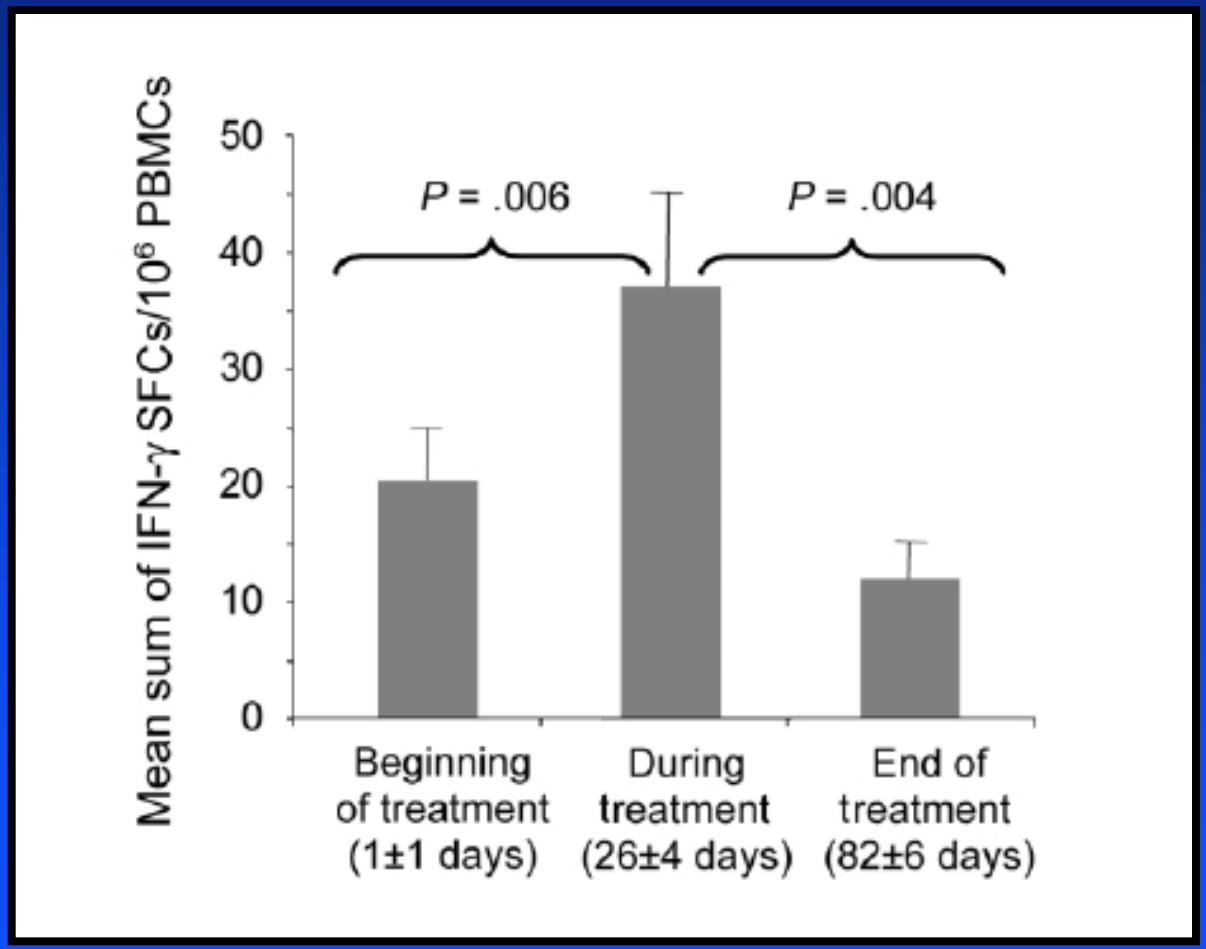


Redefining the natural history of latent TB

- Can we assess response to therapy?

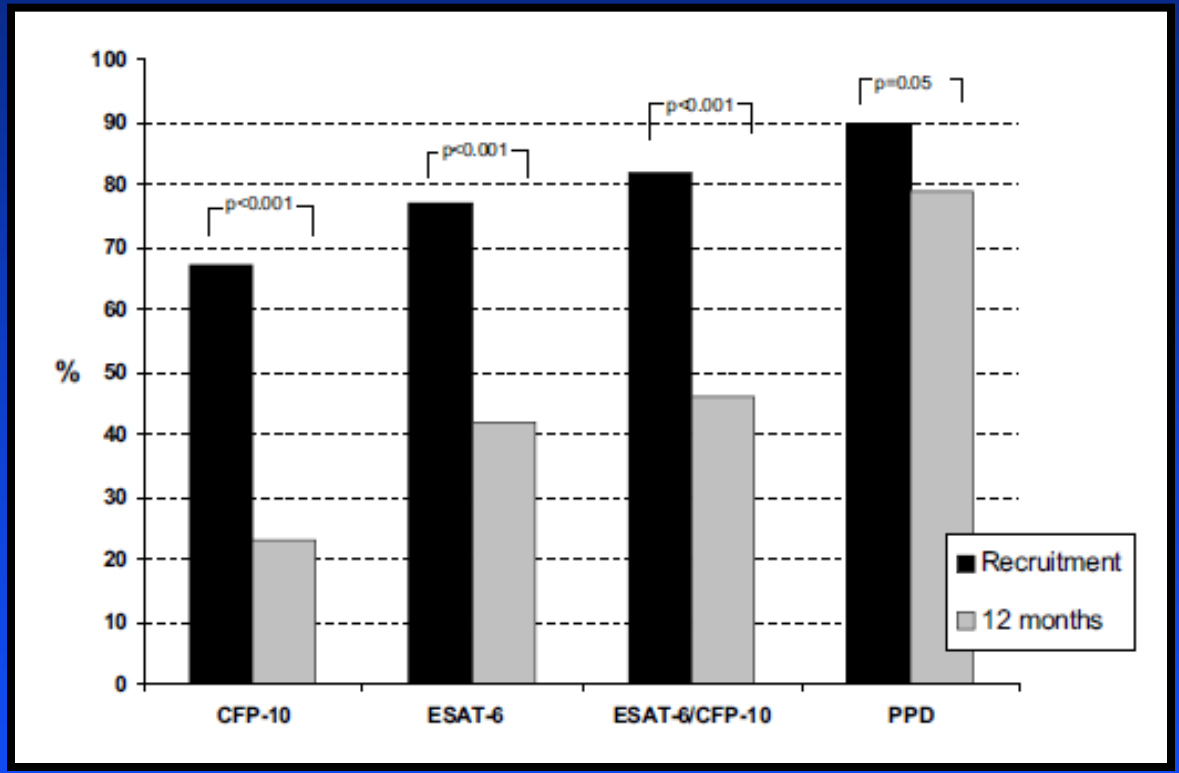
Wilkinson et al., JID 2006; 193:354–9

- Longitudinal assessment of 33 subjects treated for LTBI



Aiken et al., BMC Infectious Diseases 2006, 6:66

- ELISPOT test at diagnosis and 12 months later in 89 patients.
- 82% ESAT-6 or CFP-10 (EC) ELISPOT positive
- 55% EC ELISPOT negative at 12 months

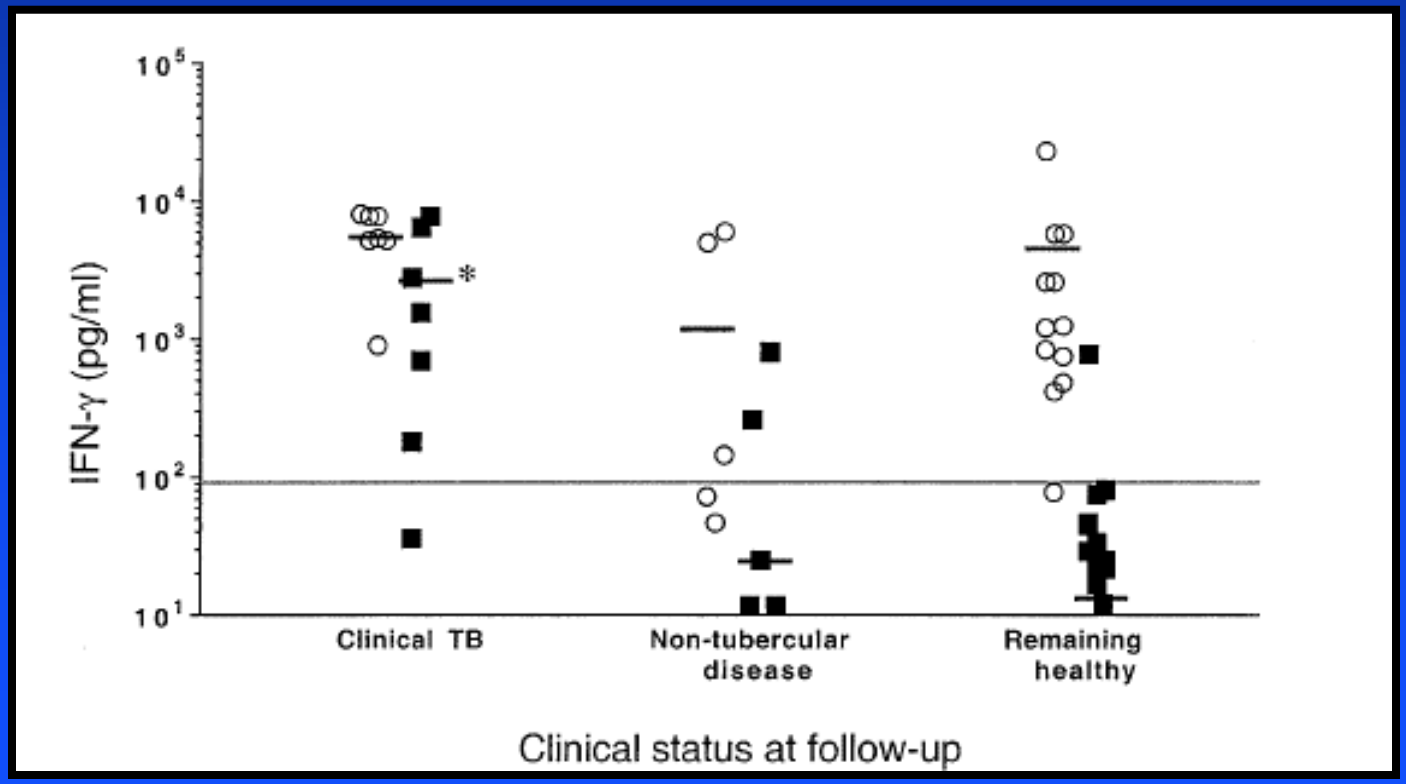


Redefining the natural history of latent TB

- Can we discern the transition from latent to active TB?

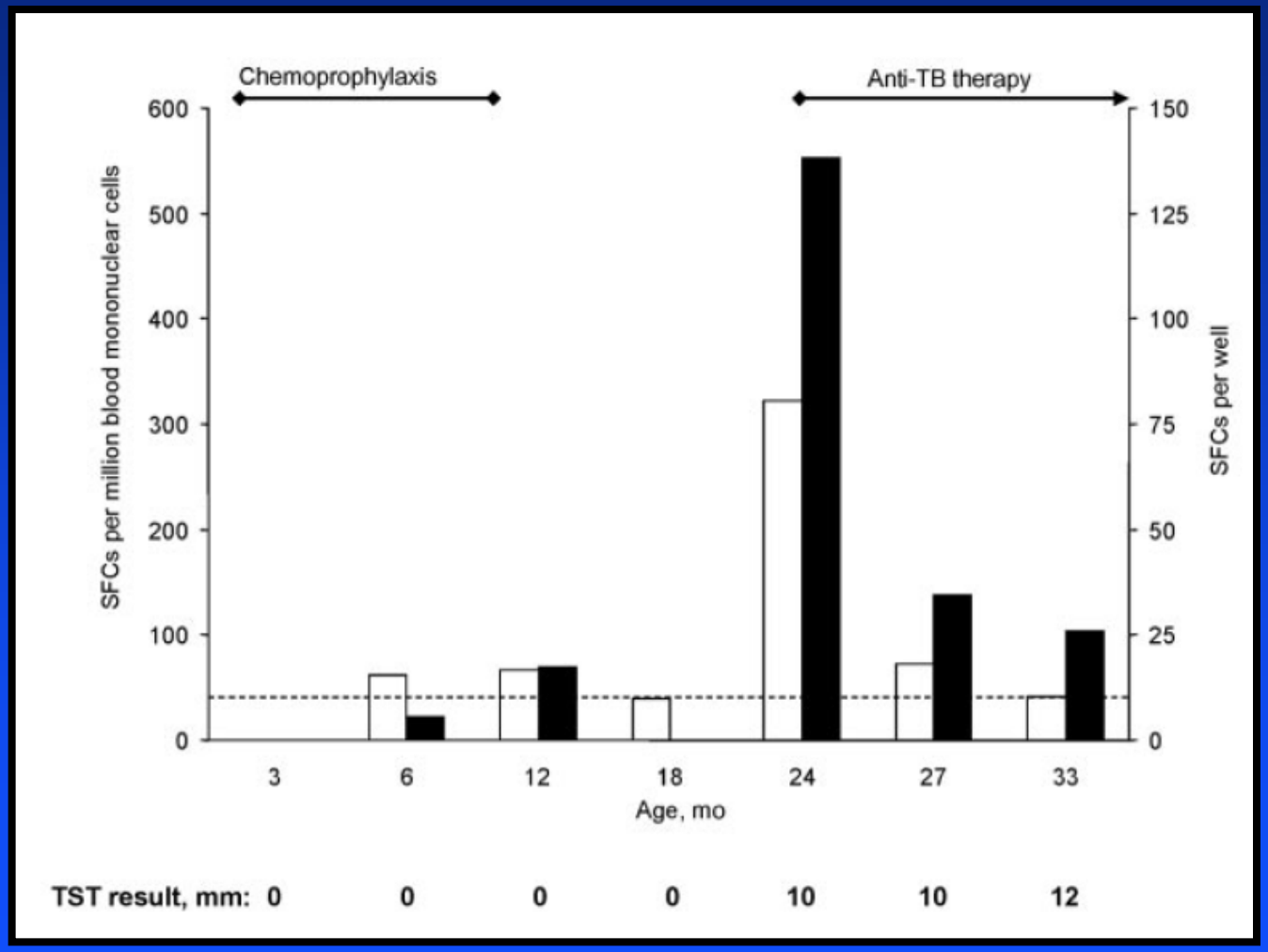
Doherty et al., JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2002, p. 704–706

- Longitudinal (2 year) evaluation of 24 household contacts, Hossana, Ethiopia
- Evaluated ESAT-6 and PPD responses by ELISA (at time of entry)



Richeldi et al., PEDIATRICS Volume 119, Number 1, January 2007

- Monitoring of TST-infant whose mother had MDR TB



The Natural History of Tuberculosis: Revisited

IFN-γ

- Associated with Exposure to Mtb
- Dichotomous
- Quantitative
  - Remote vs Recent Infection
  - Reflection Antigen Load
    - Natural variations in antigen load over time
    - Disease Treatment
    - New Exposures
    - Risk for reactivation

Food For Thought: Predictions

- In longitudinal testing, a dramatic rise in IFN-γ will indicate either recent exposure to Mtb or reactivation.
- A negative IFN-γ assay may not distinguish remote exposure from no exposure.
  - Some will be transiently exposed, and will develop TEM/TCM (like Tetanus).
  - The duration of these responses will depend on the environment.
  - Low risk for reactivation
- The IFN-γ responses will decrease with time following effective treatment.

Food for Thought: Research

- Challenges for the future
  - What constitutes a significant change in IFN?
  - How are we to interpret results that are close to the threshold?
  - Who is at risk for disease?
- Opportunities
  - Collect quantitative data
  - Be vigilant for those we missed

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