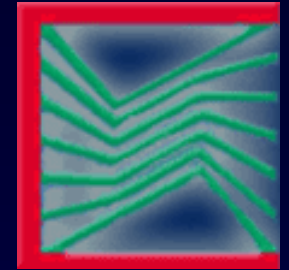




Università di Perugia

Facoltà di

Medicina e Chirurgia

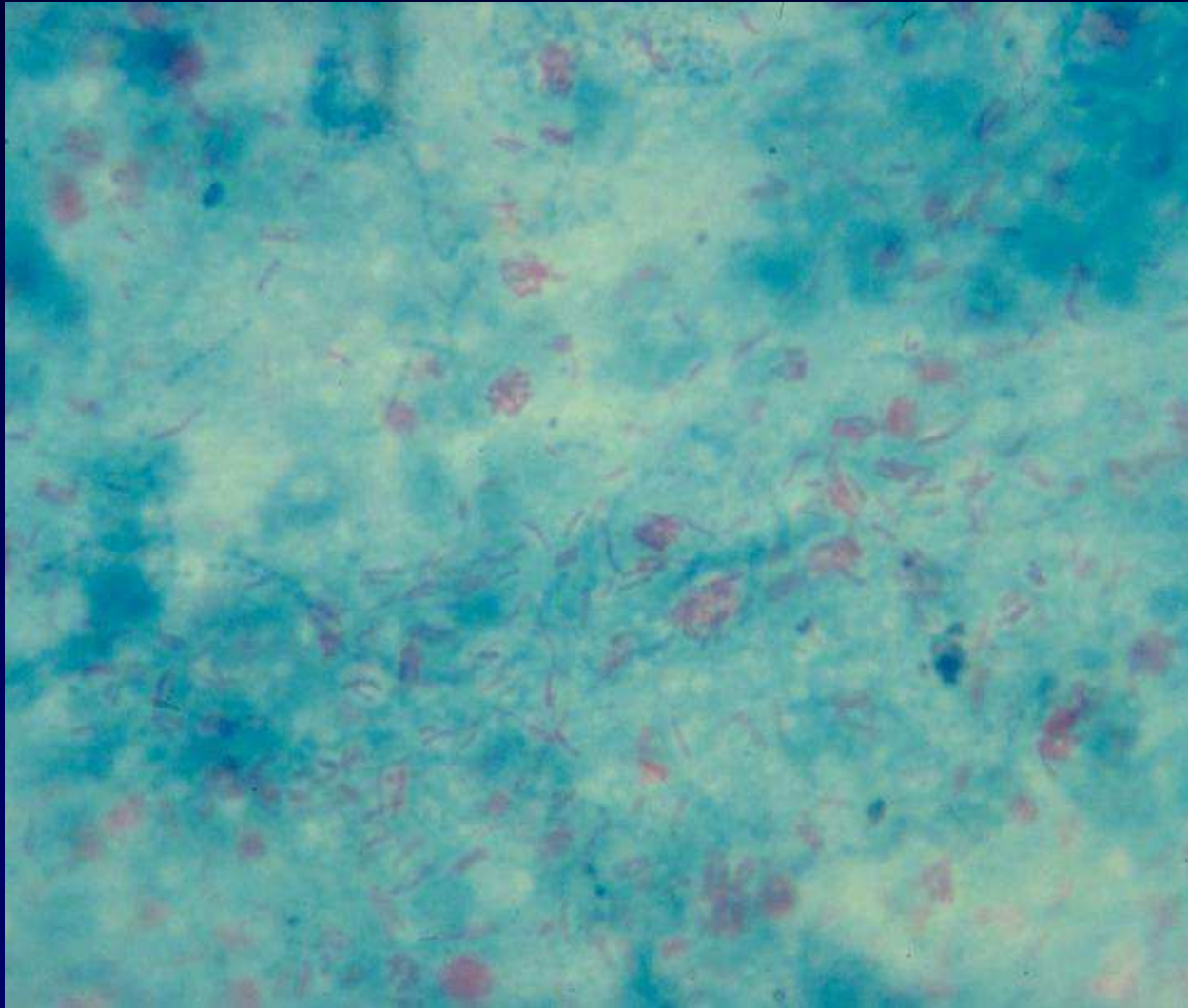


Cattedra di Malattie dell'Apparato Respiratorio

LA TUBERCOLOSI POLMONARE

Lucio Casali

Bacillo di Koch

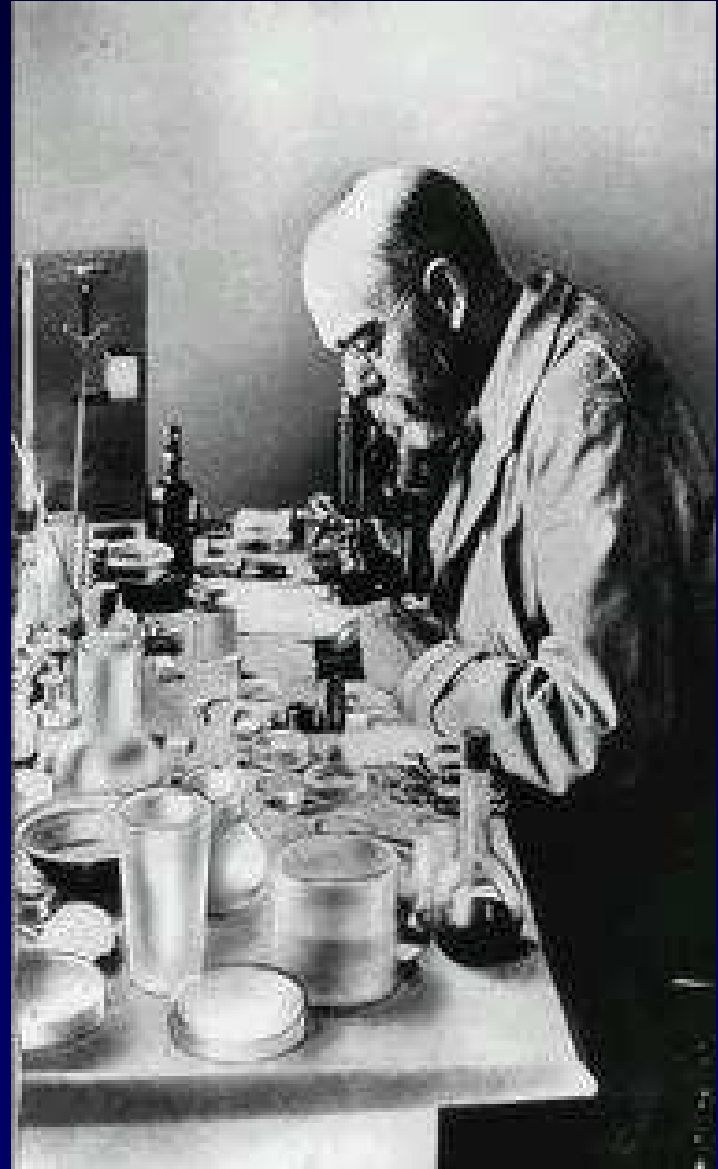


Mycobacterium Tuberculosis
Complex

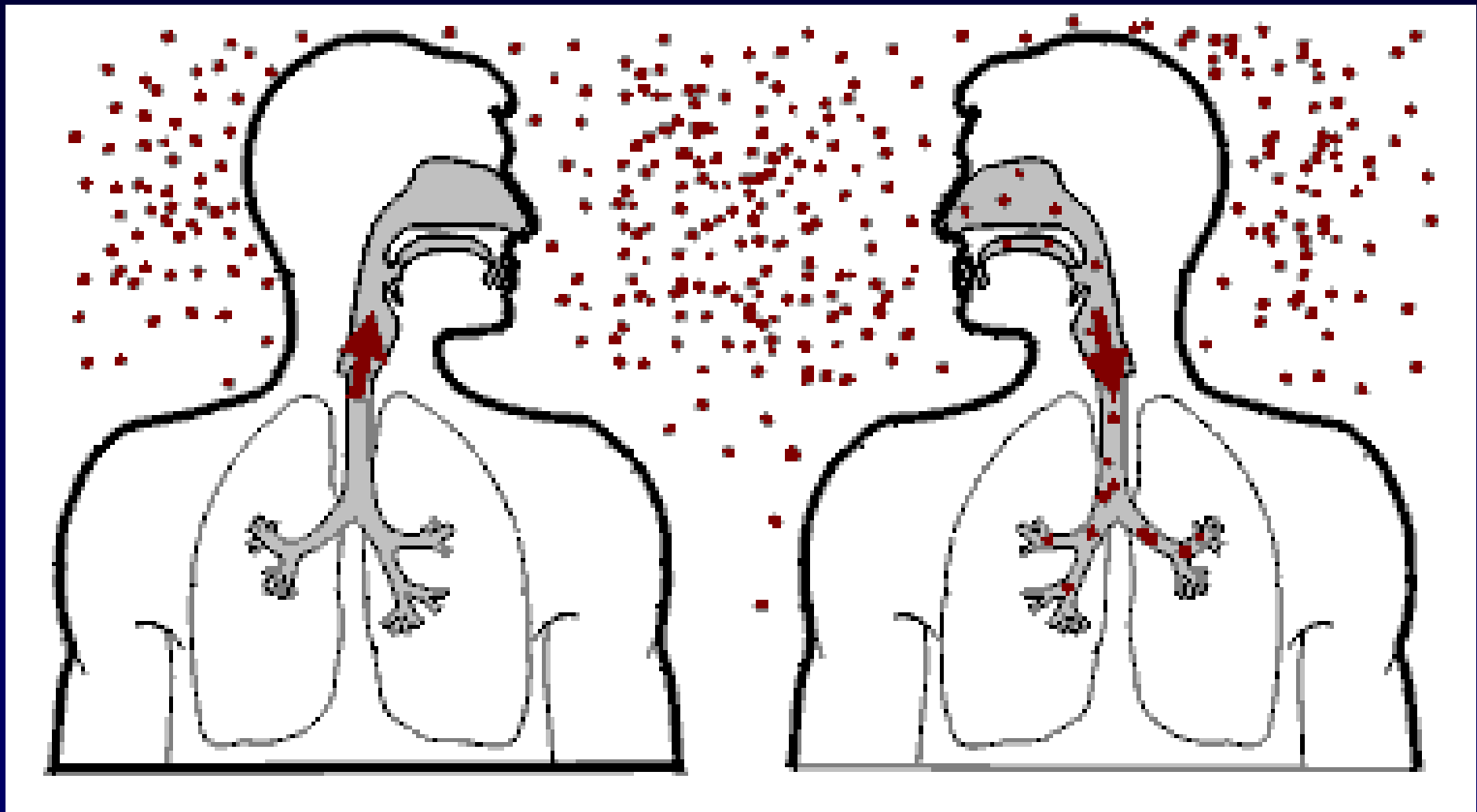
- M. Tuberculosis
- M. Bovis
- M. Microti
- M. Africanum
- M. Pinnipedii
- M. Caprae

Robert Koch 1882

... I bacilli sono
solitamente inspirati
con l'aria...



TB: trasmissione dell'infezione



Le particelle infettanti

Goccioline di Pflügge → Sospensione nell'aria → Evaporazione

e riduzione a dimensioni di 1-5 μ con
bacilli vivi e vitali



Possibilità di essere inalati fino a livello alveolare

Risk of Infection Given Exposure: Largely Exogenous Factors

$$\frac{\text{Particles}}{\text{Volume}} \times \text{Exposure time}$$

Particles: Production of infectious droplet nuclei
Volume: Volume of air and ventilation
Exposure time: Time of inhaling air with droplet nuclei



3000 – 5000 droplet nuclei (< 5 μ m) / cough

Probabilità di acquisire l'infezione TB in funzione dei rapporti con la fonte bacillare

Contatti stretti (familiari, compagni di camera, amici, colleghi di lavoro). **21-23 %** C.D.C. 2000

Elemento importante: condivisione stabile di uno spazio confinato per molte ore al giorno

Contatti regolari: condivisione regolare dello stesso spazio chiuso

Contatti saltuari: amici, colleghi o familiari che abbiano contatti non ravvicinati. **12 %** Enarson D., 2000

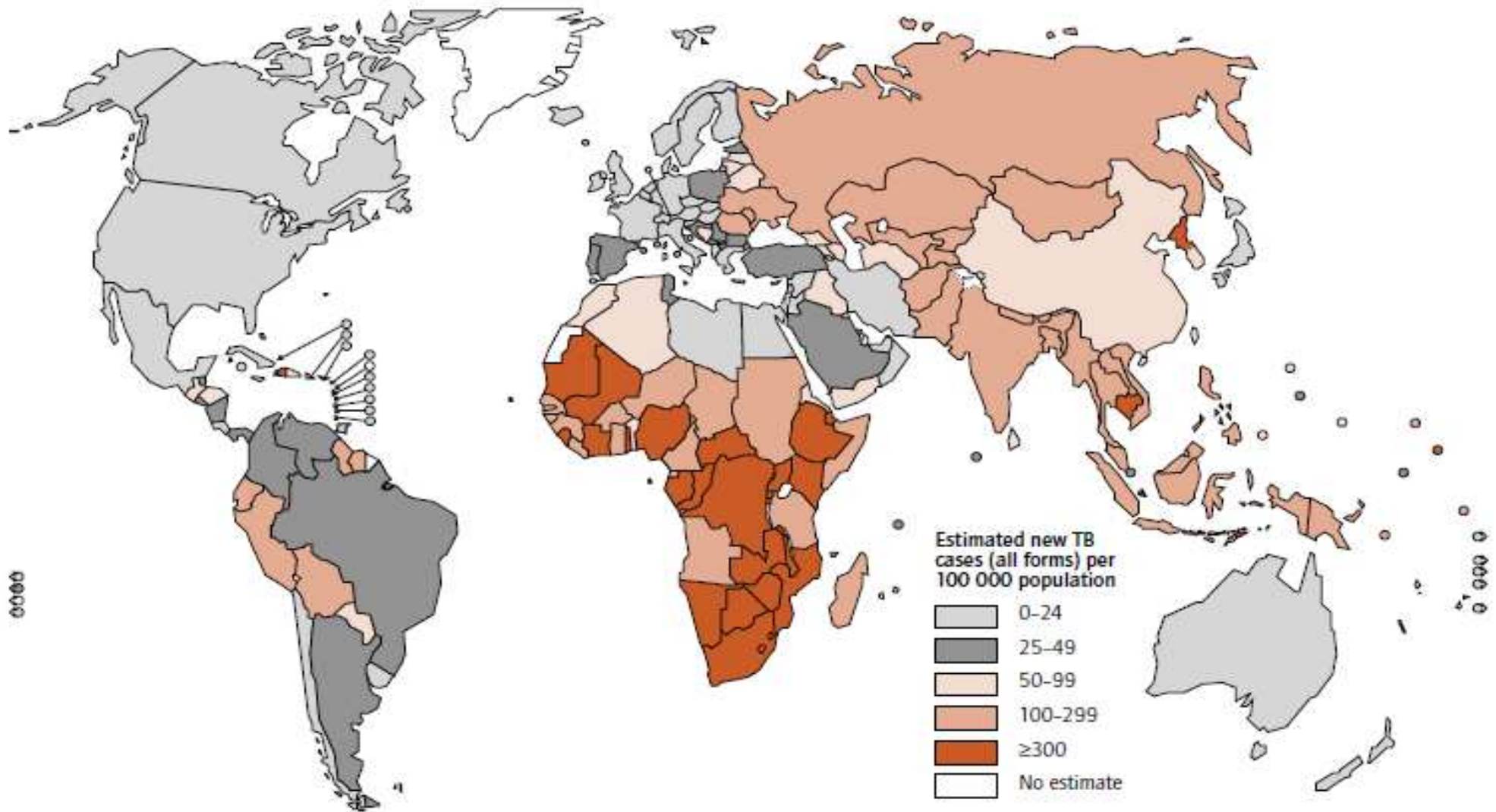
Ciclo di trasmissione poco efficace !!!

È pericoloso il contagio ?

- ❖ Ogni paziente contagioso infetta 7-10 contatti
- ❖ Il 40-50 % dei contatti stretti si infetta
- ❖ Nei contagiati il 5-10 % si ammala di TB
 - 3-5 % malati nei primi 2 anni
 - 2-5 % cumulativo per il resto della vita
- ❖ Nei malati:
 - Probabilità di guarigione = 80 %
 - Probabilità di morte = 1 %

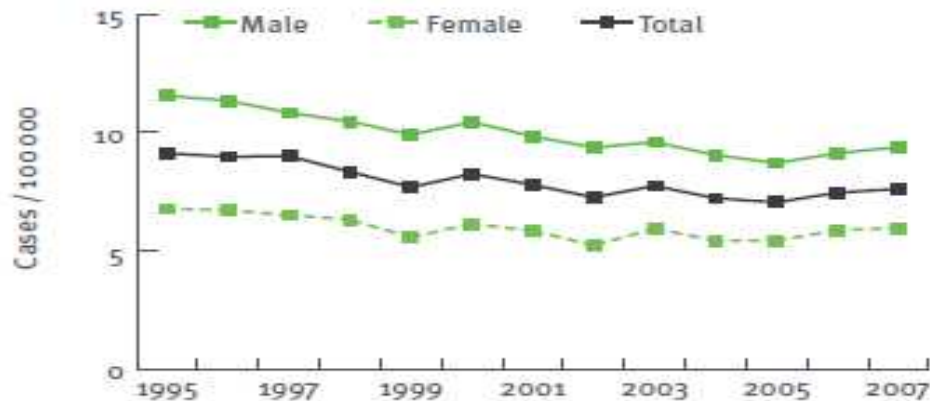
■ **FIGURE 1.2**

Estimated TB incidence rates, by country, 2007

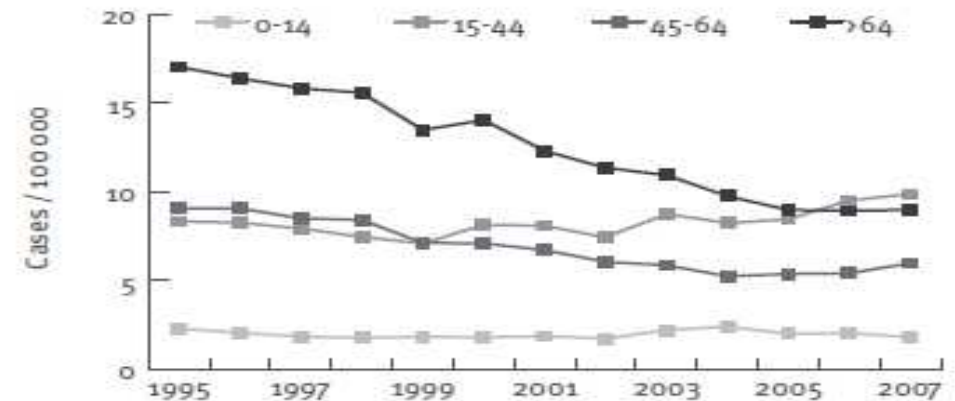


Tuberculosis surveillance in Europe

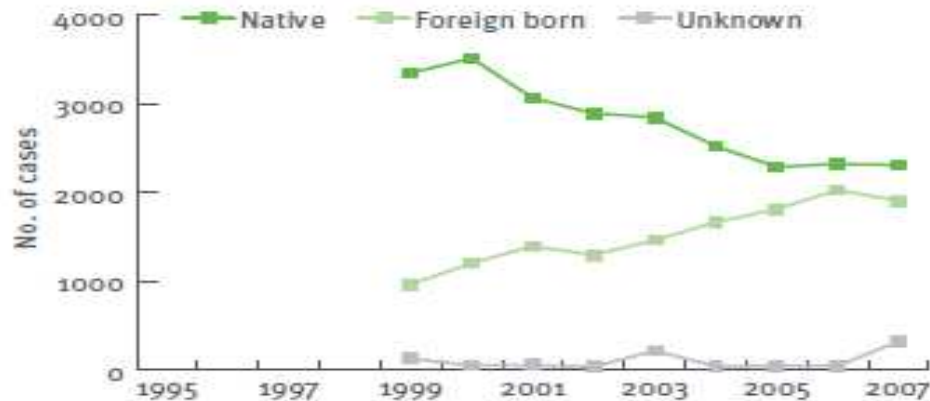
Tuberculosis notification rates by sex, 1995–2007



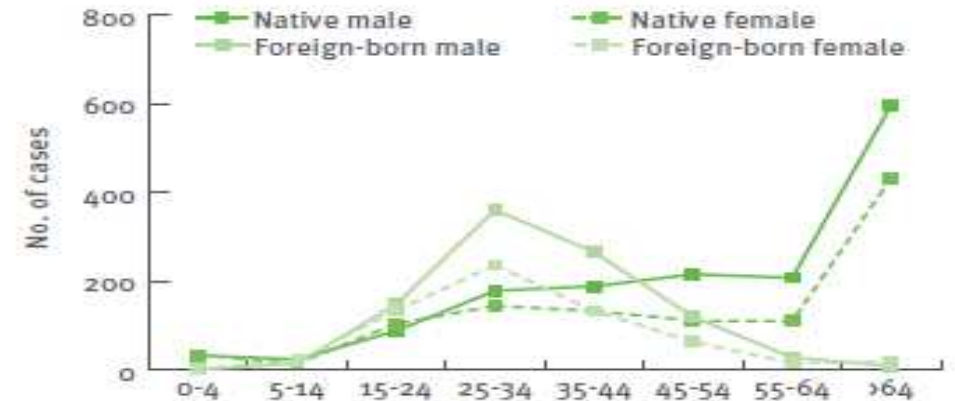
Tuberculosis notification rates by age group, 1995–2007



Tuberculosis cases by geographical origin, 1995–2007

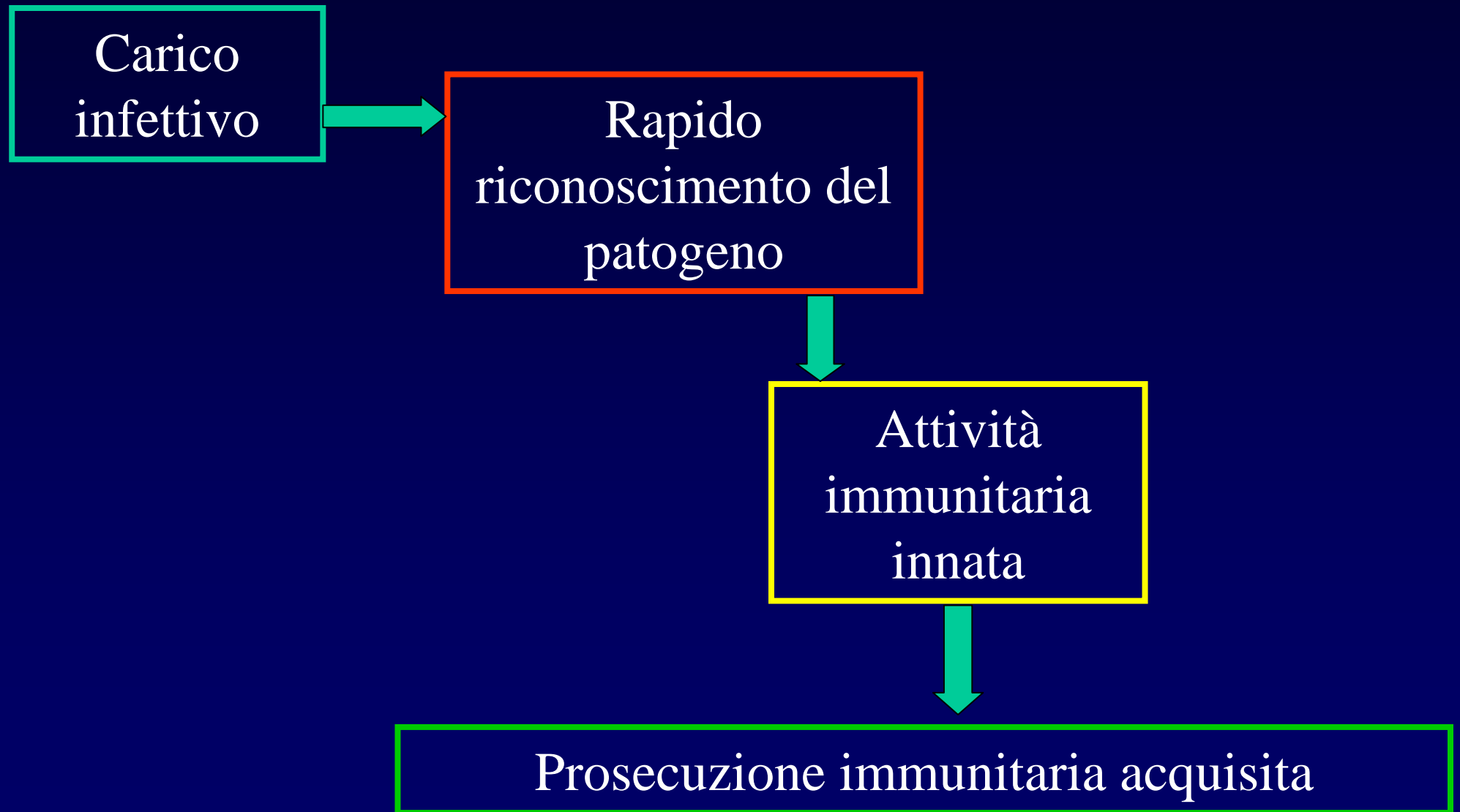


Tuberculosis cases by origin, age group and sex, 2007



SITUAZIONE ITALIANA

Schema generale della risposta immune



Host Innate Immune Response to *Mycobacterium tuberculosis*

KAMLESH BHATT¹ and PADMINI SALGAME^{1,2}

Journal of Clinical Immunology (© 2007)

DOI: 10.1007/s10875-007-9084-0

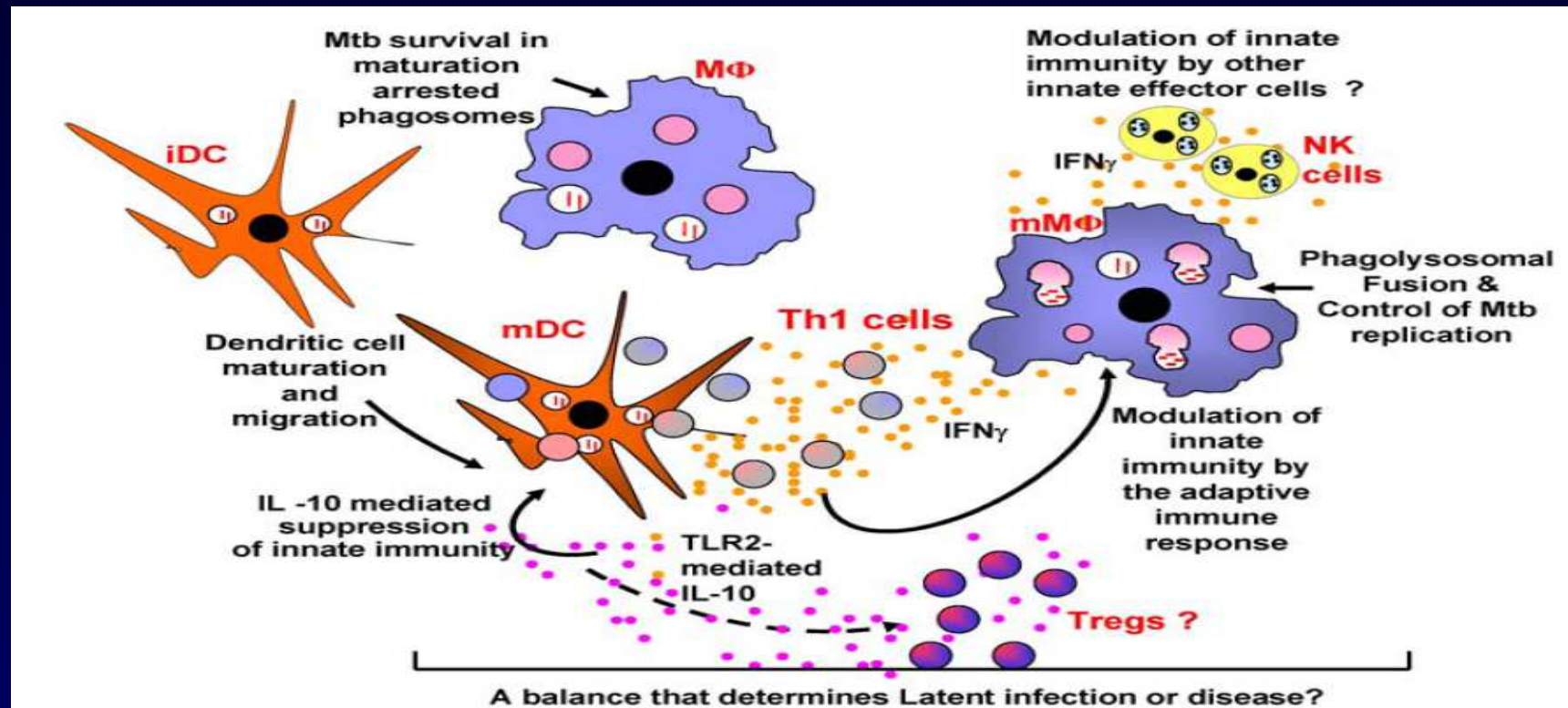
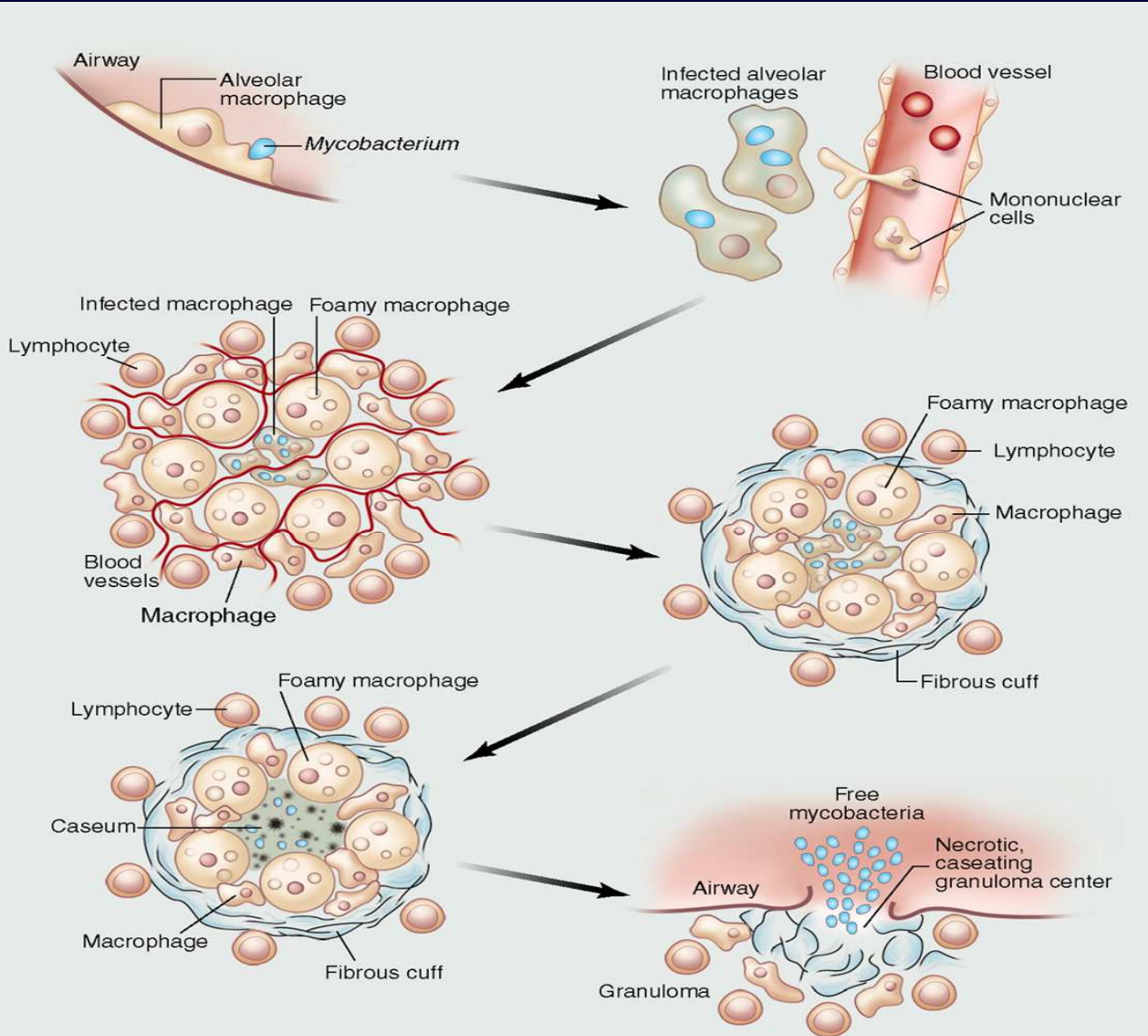


Fig. 2. A paradigm for how the innate immune response to Mtb regulates the adaptive immune response. Initially, Mtb survives and replicates inside macrophages since it can prevent fusion of its phagosome with the lysosomal compartment. Concomitantly, dendritic cells capture Mtb, undergo maturation, and migrate to the draining lymph nodes. Adaptive response is initiated in the draining lymph nodes wherein naïve antigen-specific T cells are primed by dendritic cells to Th1 and cytotoxic effector cell types. Mycobactericidal function of macrophages is dependent on IFN γ , initially produced by innate immune cells such as NK cells and later on provided by effector T cells. The secreted IFN γ promotes phagolysosomal fusion and enhances Mtb killing. TLR2-mediated innate IL-10 is released during the induction of innate immune response and subsequent Th1 induction. The role of the innate IL-10 is to control the magnitude of the Th1 response by either down modulating antigen-presentation function or by inducing T regulatory cells. The TLR2/IL-10 axis, on the one hand, is important for allowing Mtb to achieve the latent state and, on the other hand, may also cause excessive immunosuppression leading to disease. The *unbroken lines* indicate that experimental evidence is available and *dashed lines* indicate that it is speculative and is an area for future investigation.

Tuberculosis: What We Don't Know Can, and Does, Hurt Us

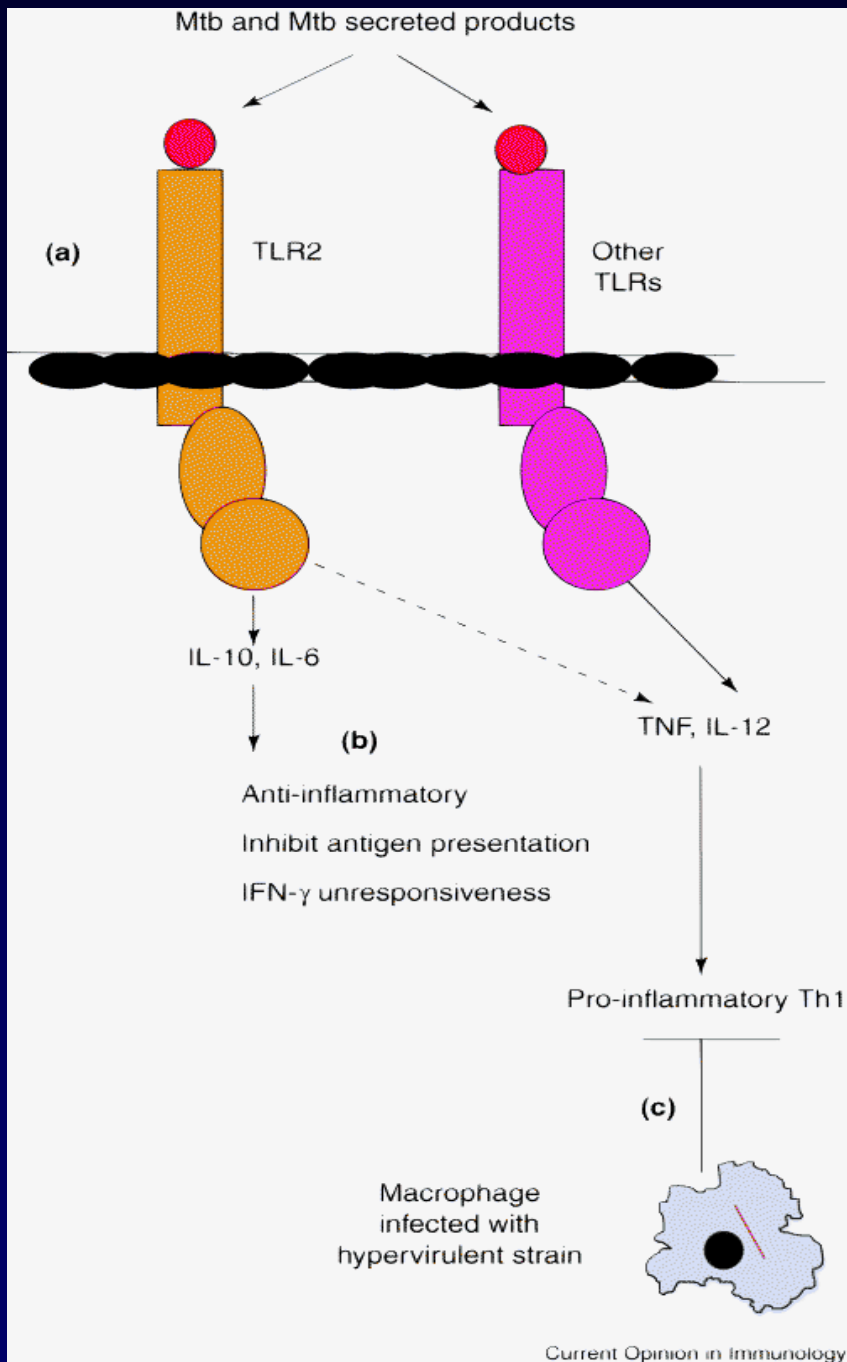
David G. Russell,^{1*} Clifton E. Barry 3rd,² JoAnne L. Flynn³



The life cycle of *M. tuberculosis*.

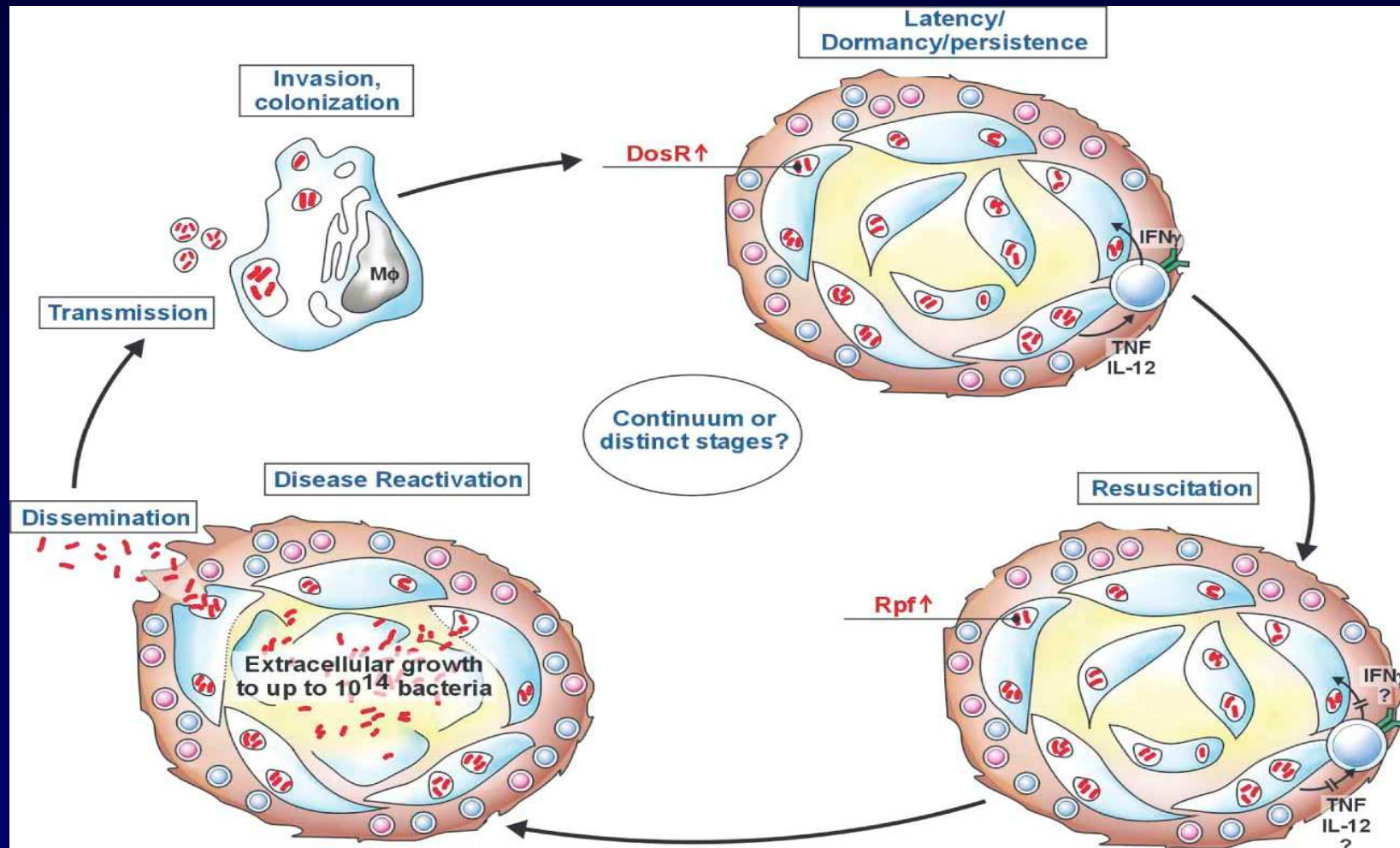
The infection is initiated when *Mtb* bacilli, present in exhaled droplets or nuclei, are inhaled and phagocytosed by resident alveolar macrophages. The resulting proinflammatory response triggers the infected cells to invade the subtending epithelium. This response also leads to the recruitment of monocytes from the circulation, as well as extensive neovascularization of the infection site. The macrophages in the granulomas differentiate to form epithelioid cells, multinucleate giant cells, and foam cells filled with lipid droplets.

The granuloma can become further stratified by the formation of a fibrous cuff of extracellular matrix material that is laid down outside the macrophage layer. Lymphocytes appear to be restricted primarily to this peripheral area. Many of the granulomas persist in this balanced state, but progression toward disease is characterized by the loss of vascularization, increased necrosis, and the accumulation of caseum in the granuloma center. Ultimately, infectious bacilli are released into the airways when the granuloma cavitates and collapses into the lungs.

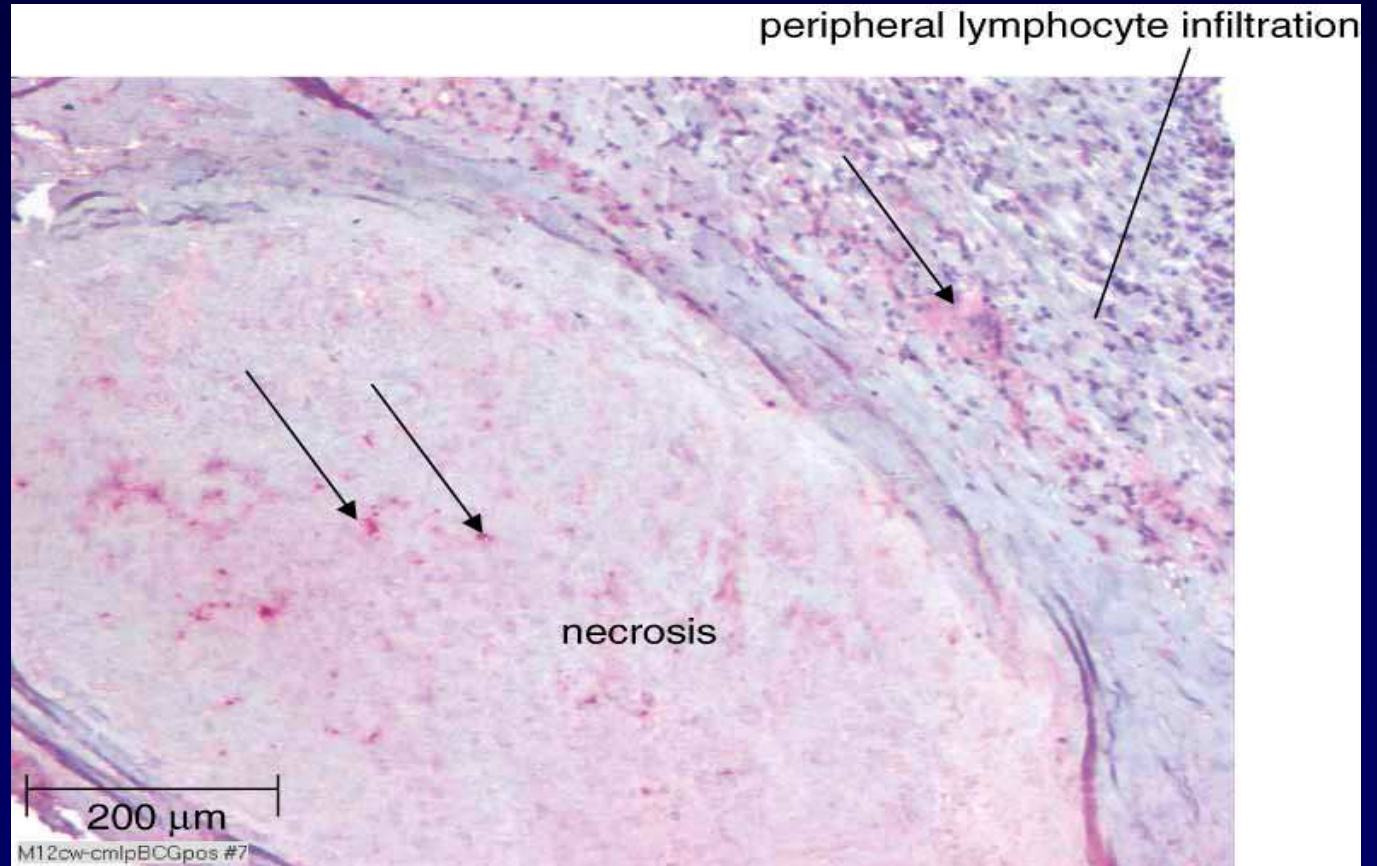
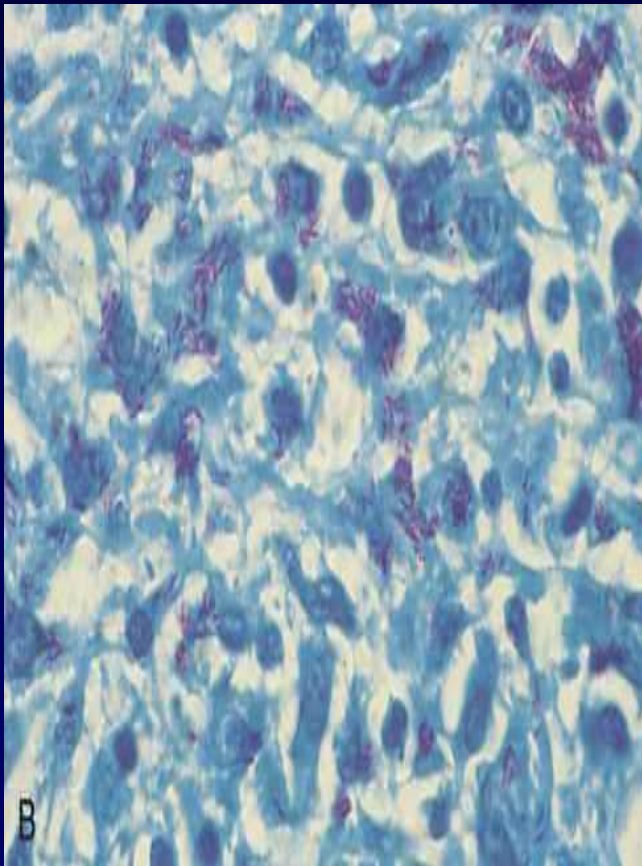


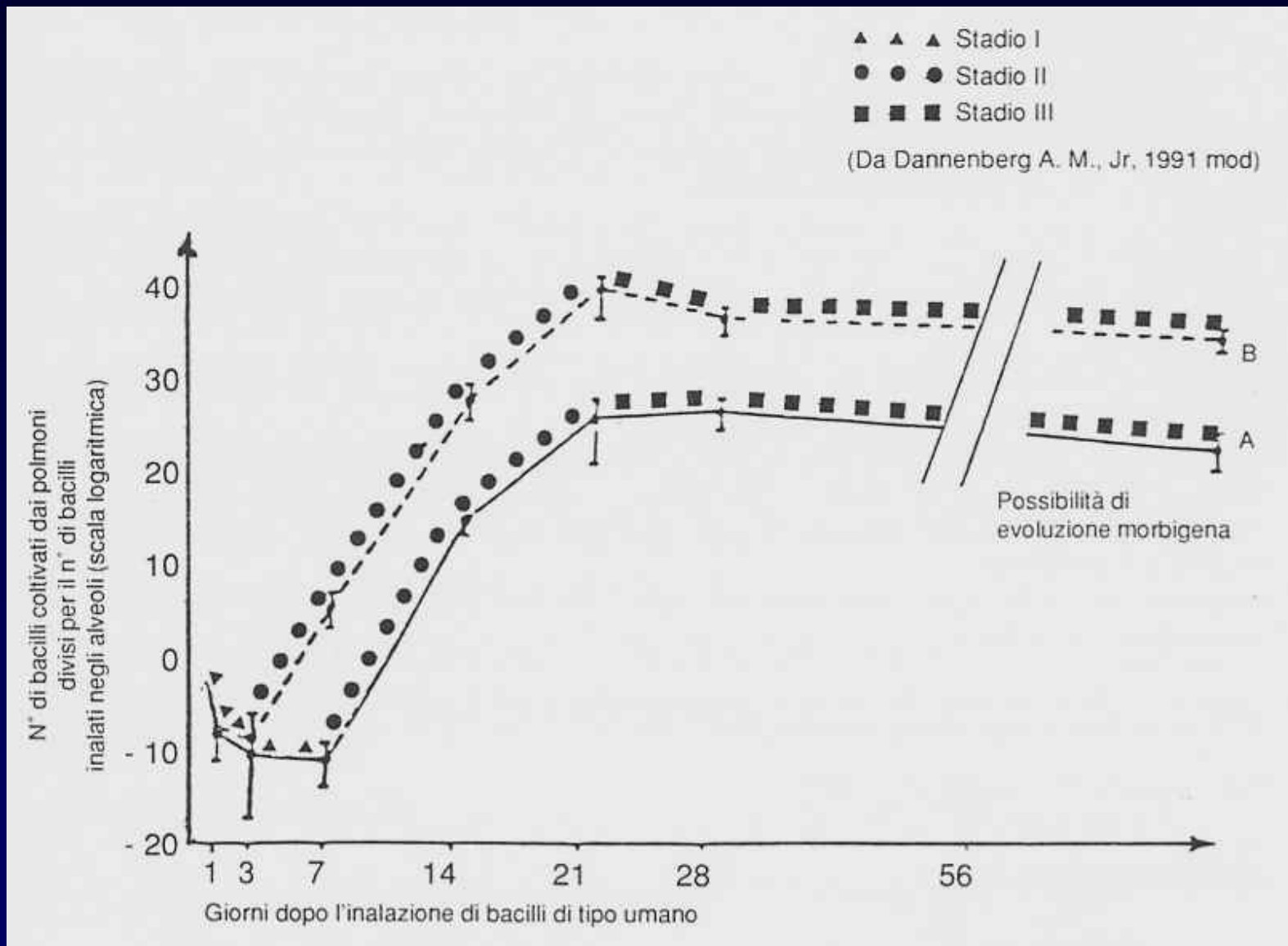
TLR-mediated pro- and anti-inflammatory cytokine production. The figure depicts (a) TLR-mediated Mtb recognition by host cells, (b) TLR2-mediated anti-inflammatory response, inhibition of antigen presentation, and IFN- γ unresponsiveness to Mtb and its secreted products, (c) inhibition of pro-inflammatory cytokine production by a hypervirulent strain.

Ipotesi di trasformazione del Granuloma da una condizione di equilibrio



Distribuzione del materiale micobatterico all'interno del Granuloma

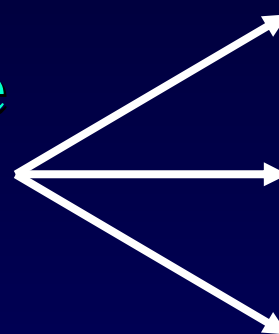




Variazione del numero di bacilli tubercolari nei polmoni di conigli naturalmente resistenti (A) e naturalmente suscettibili (B) a intervalli differenti dopo aerosol dosato. Sulle curve di crescita sono stati individuati i corrispondenti stadi della tubercolosi

Diagnosi di infezione tubercolare

**Intradermoreazione
tubercolinica
secondo Mantoux**

- 
- Persona non malata (es. esposta)
 - Determinare l'indice tubercolinico in un gruppo di soggetti
 - Esame di un caso sospetto



tenere il becco di flauto rivolto verso l'alto



tendere la cute e inserire sotto la superficie epidermica l'ago



iniettare la soluzione



(idem)



(idem)

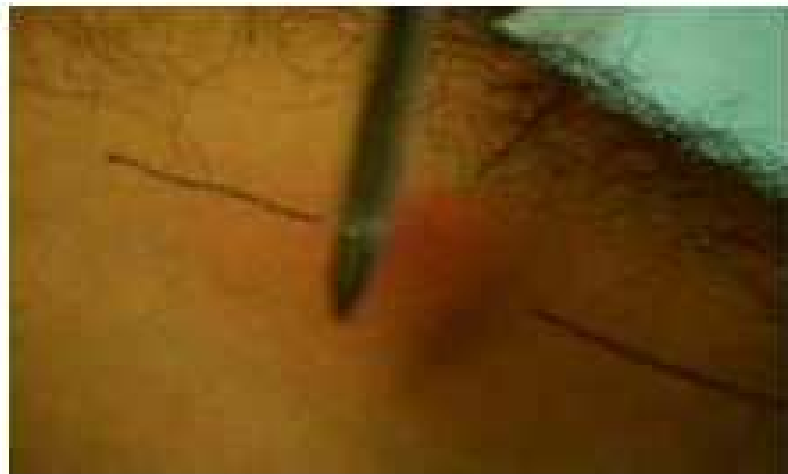


estrarre l'ago e tamponare leggermente

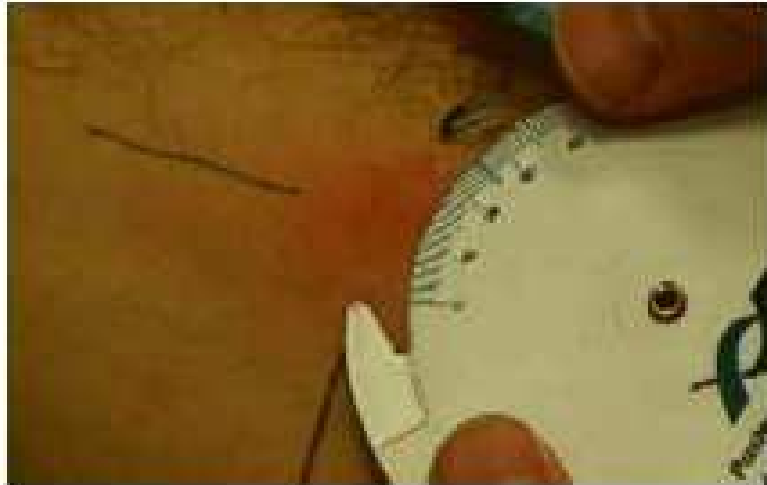


La presenza di un moderato e pallido sollevamento cutaneo (a buccia di arancia) dalle dimensioni comprese tra i 6-10 mm di diametro conferma la corretta esecuzione dell'introduzione della soluzione nel derma.

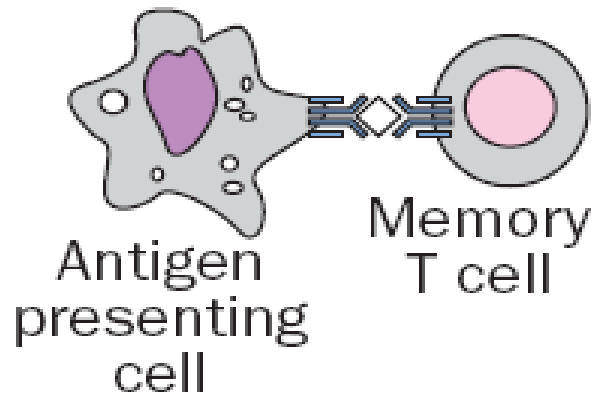
Talora, in caso di sottocutaneo molto lasso, il pomfo può risultare meno evidente.



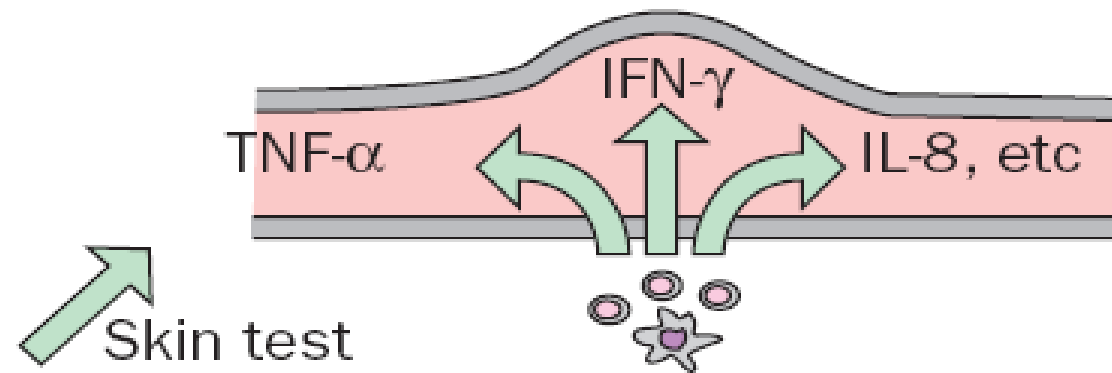
▪ Misurazione



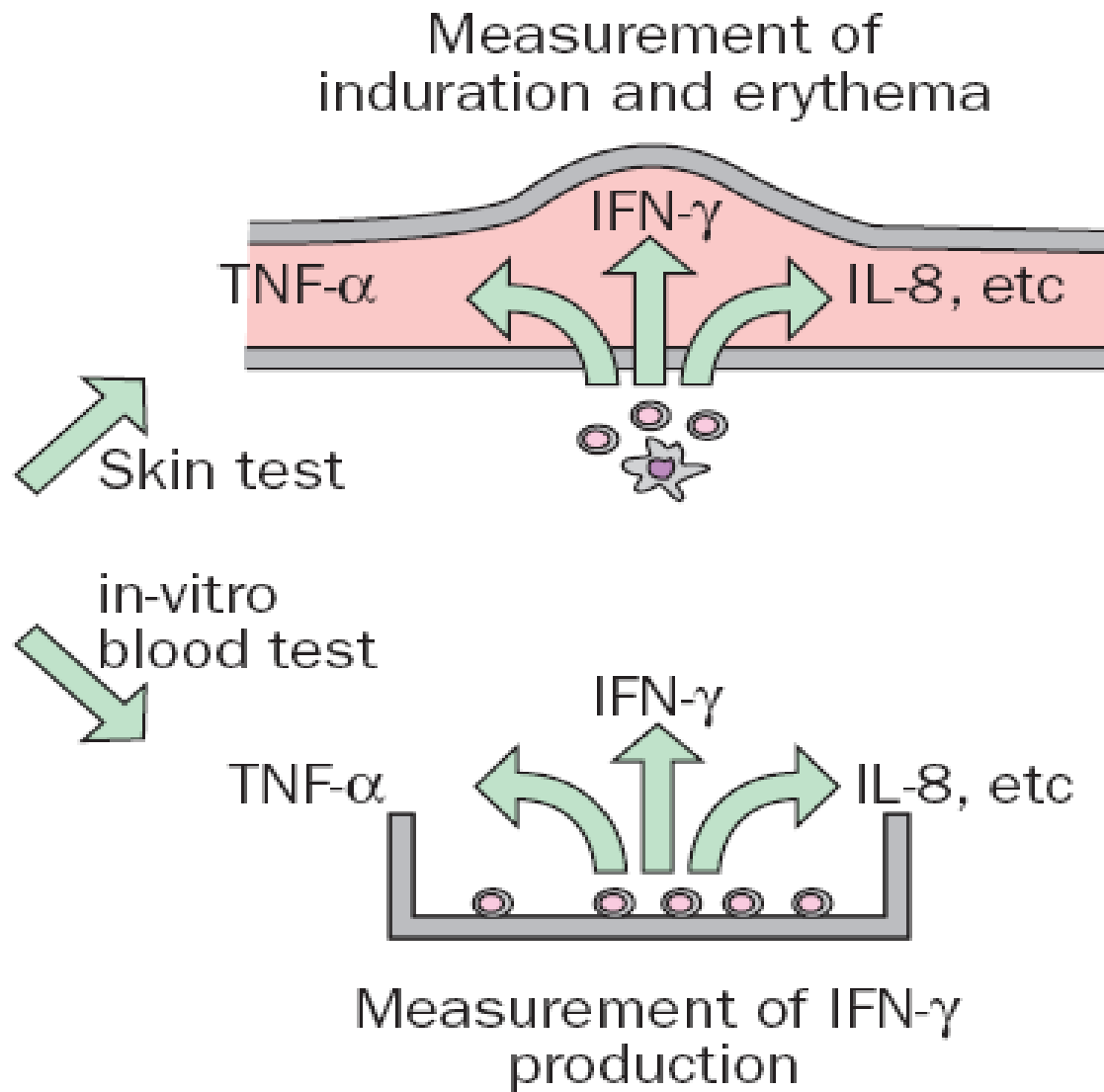
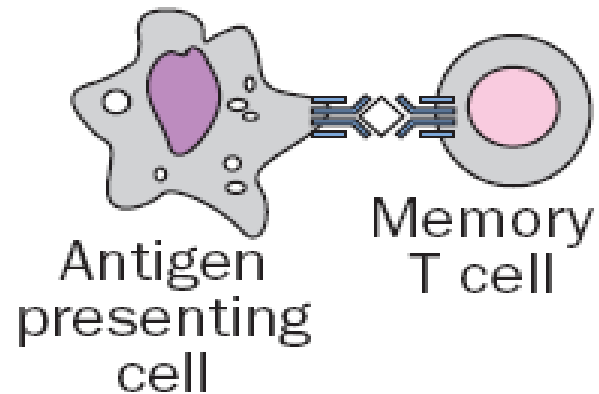
Presentation of mycobacterial antigens

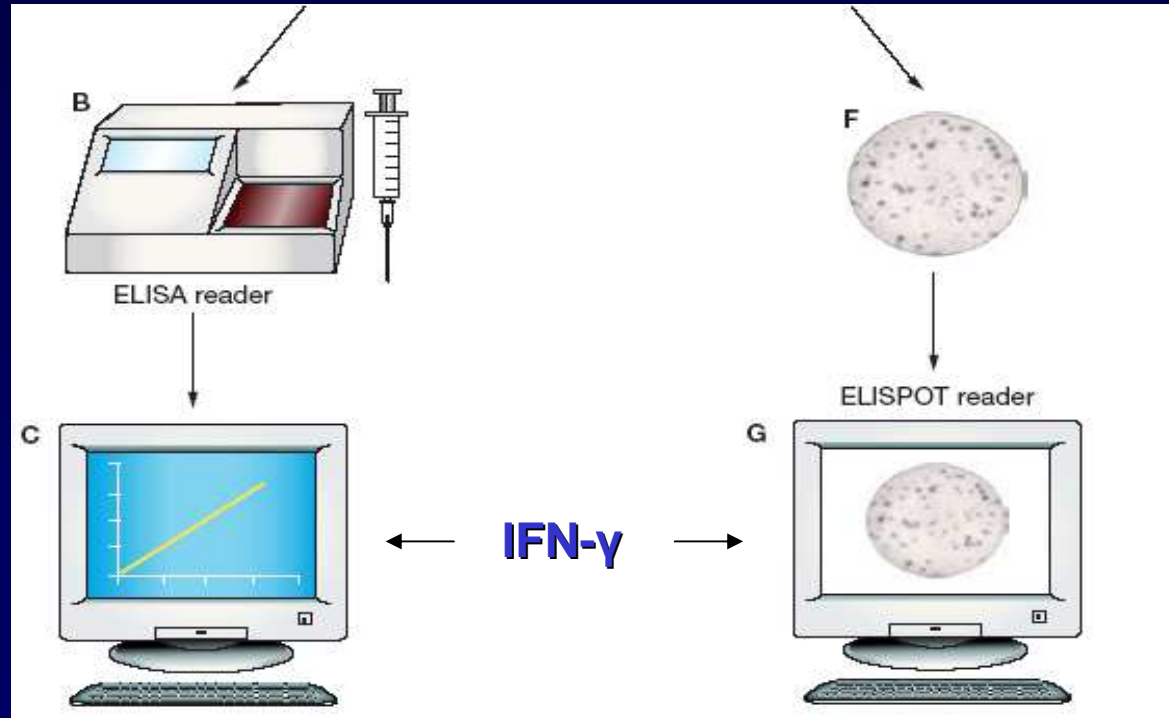
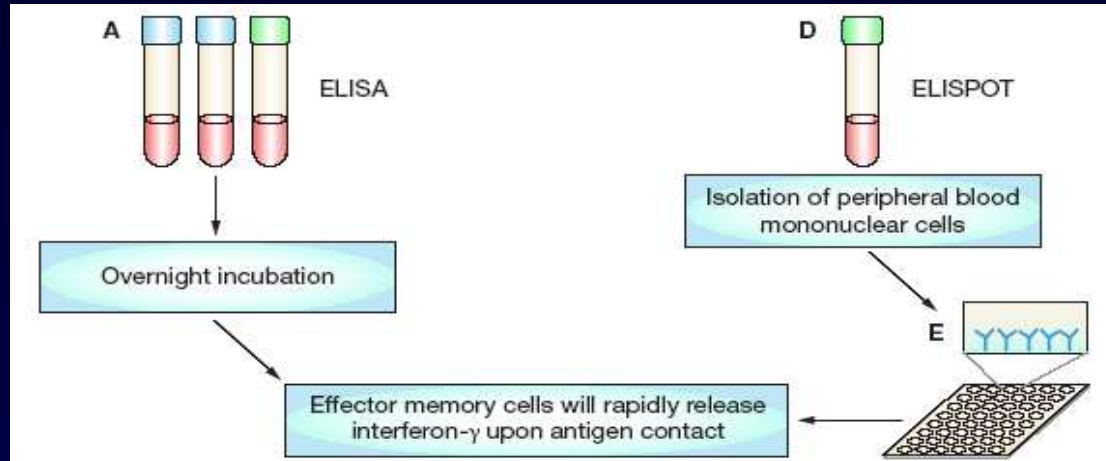


Measurement of induration and erythema



Presentation of mycobacterial antigens





- QTF-TB (PPD)
- QFT-TB Gold (ESAT-6, CFP10)
- QFT-TB Gold in tube (ESAT-6, CFP10, Tb7.7)
- Home-made QFT (RD1, PPD etc.)

- T-SPOT.TB (ESAT-6, CFP10)
- Home-made ELISPOT (RD1, PPD etc.)



HIV -	<i>Sintomi e segni clinici</i>	HIV +
Febbricola serotina+		Febbricola serotina++
Sudorazioni notturne +		Sudorazioni notturne++
Calo ponderale+		Calo ponderale++
Astenia anoressia+		Astenia anoressia++
Tosse+		Tosse+
Espettorazione+		Espettorazione+
Emoftoe+		Emoftoe-
Dolore toracico-		Dolore toracico+
Linfoadenopatie -		Linfoadenopatie++
Interessamento del SNC-		Interessamento del SNC+
Disseminazione ematogena-		Disseminazione ematogena+
Insufficienza respiratoria-		Insufficienza respiratoria+
Shock--		Shock++

Elementi di sospetto per tubercolosi

Segni e sintomi d'organo: tosse produttiva (> di 3 settimane); dolore toracico; emottisi

Segni e sintomi sistemici: febbre, brividi, sudorazioni notturne, inappetenza, calo ponderale, affaticabilità

Dati anamnestici: storia di esposizione a fonti morbigene, pregressi trattamenti per TB, rischi di ordine demografico, censo, appartenenza a gruppi a rischio, valutare i sintomi a carico di organi e apparati al di fuori del polmone

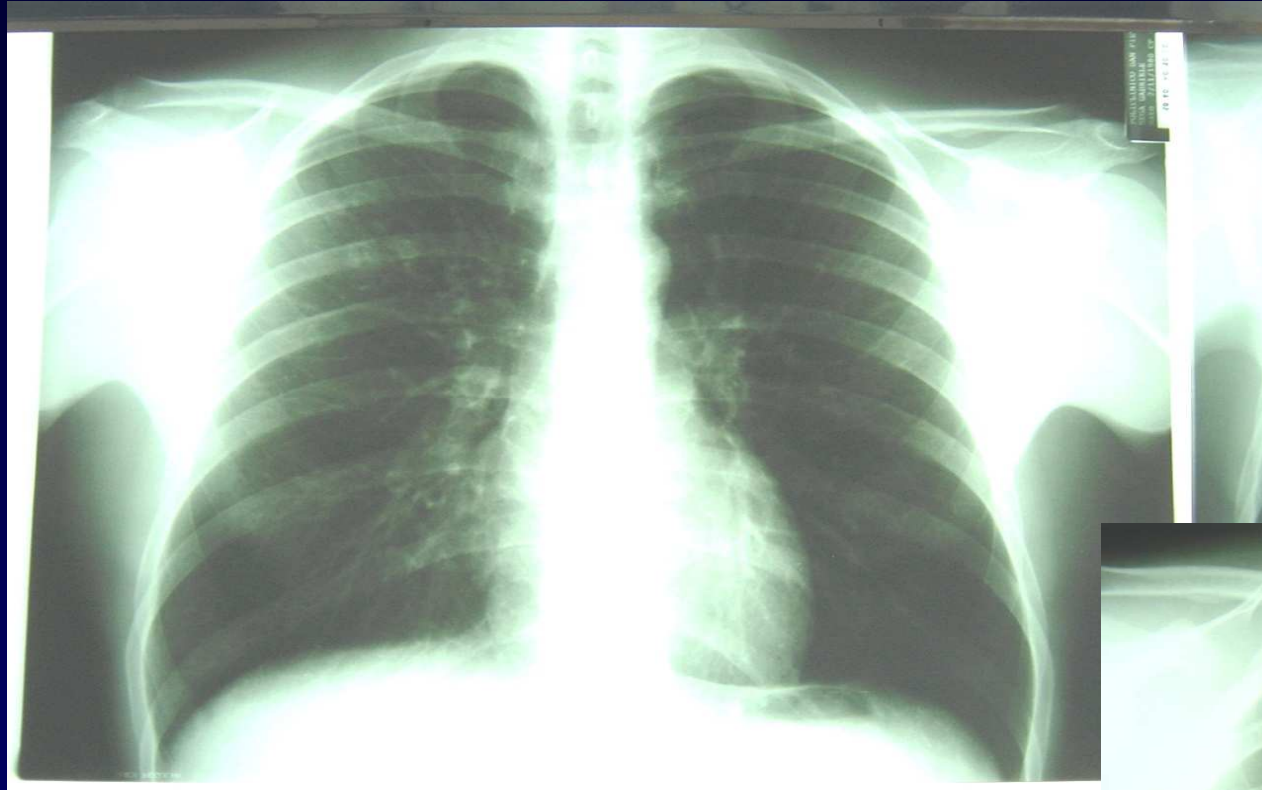
Esame obiettivo: spesso aspecifico

Conoscenza epidemiologica

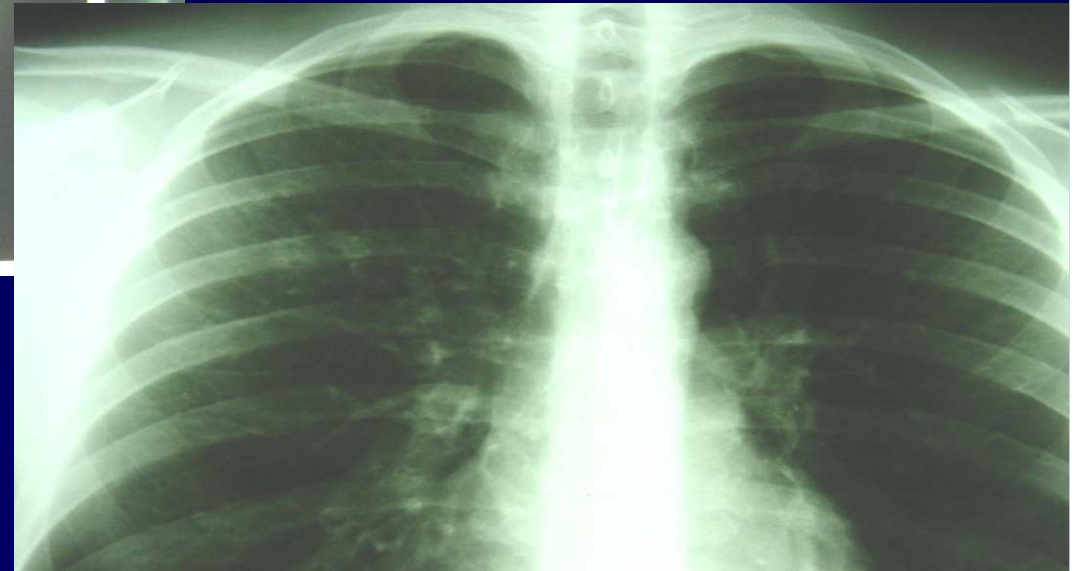
I gruppi a rischio

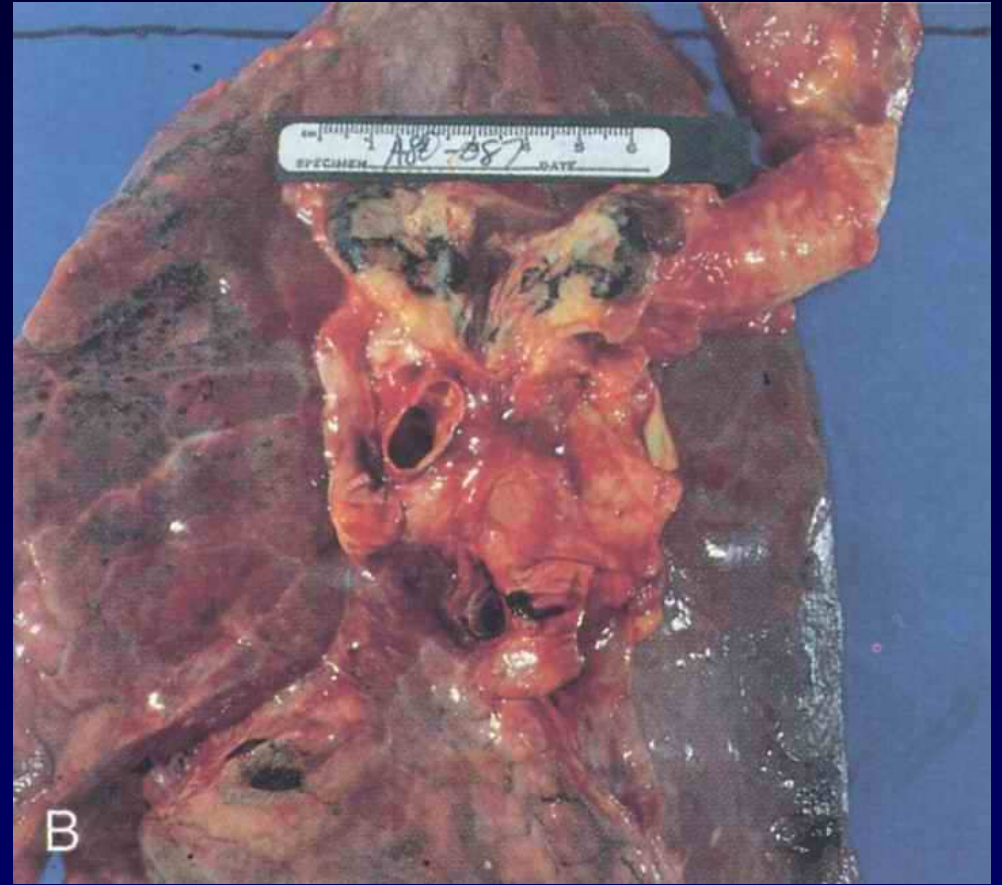
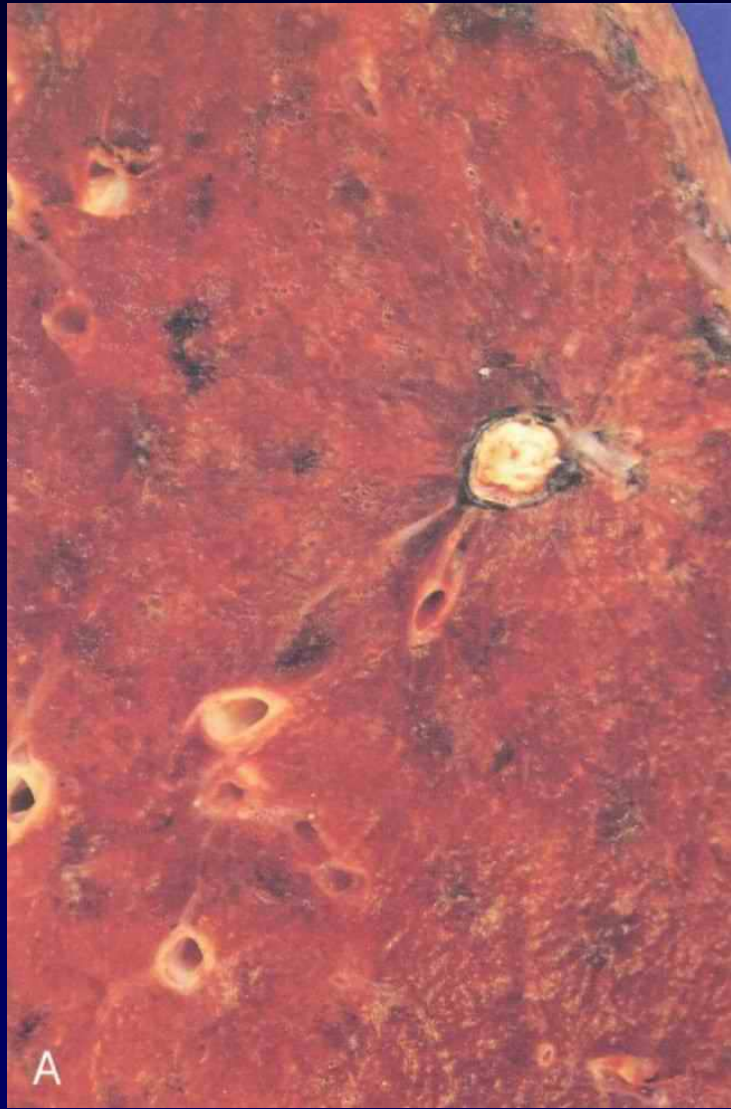
Nel nostro paese, la malattia è concentrata nei cosiddetti gruppi a rischio:

- Casi contatto
- Immigrati
- HIV+
- Personale sanitario
- Case di accoglienza e di riposo
- Comunità di poveri, rifugiati, baraccati...etc.
- Immunodepressi per:
 - Età (anziani, neonati)
 - Patologia (leucemie, tumori, diabete, anoressia etc.)
 - Terapie (chemioterapia,f. biologici,steroidi,etc.)

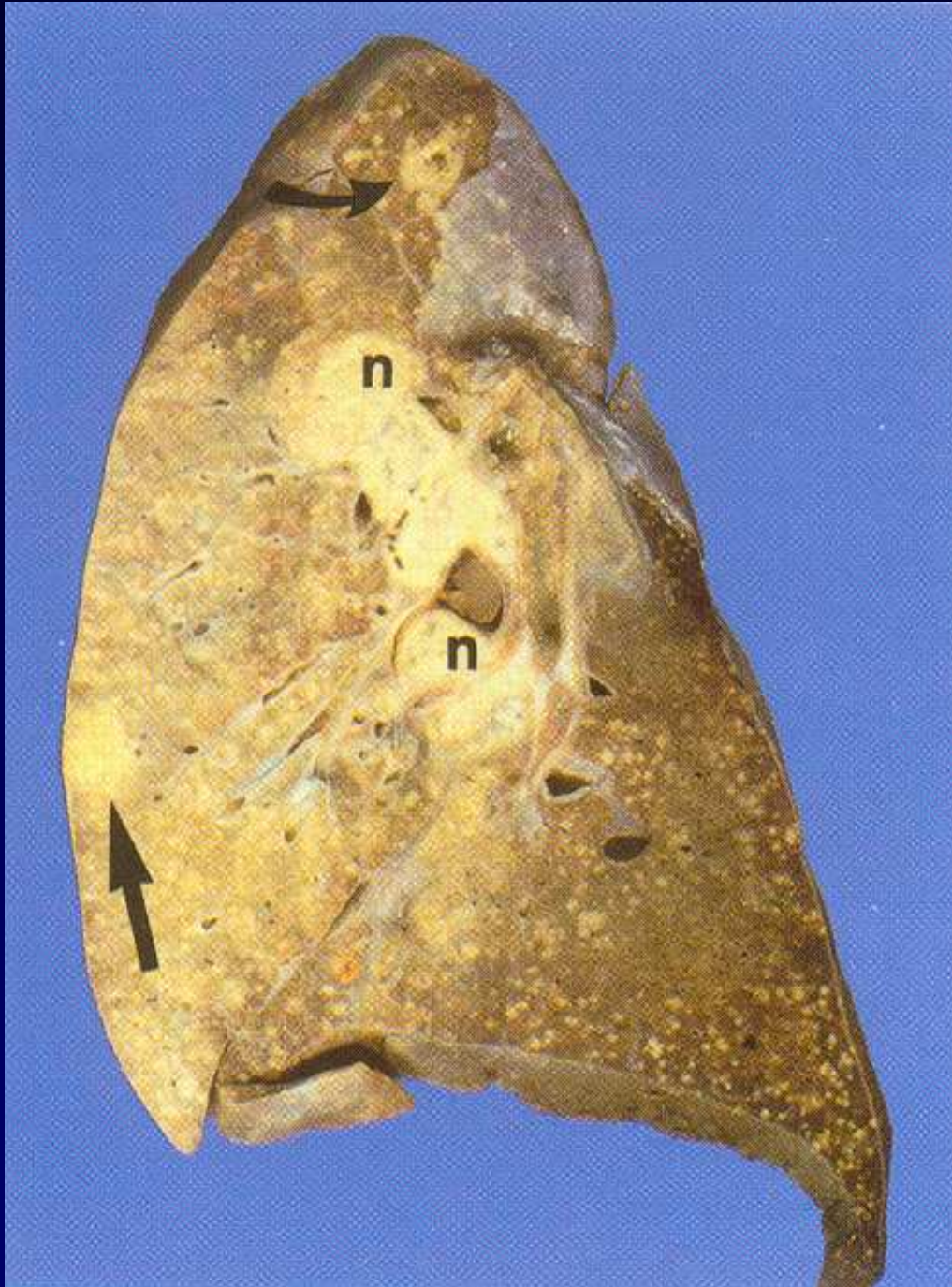


TB
primaria

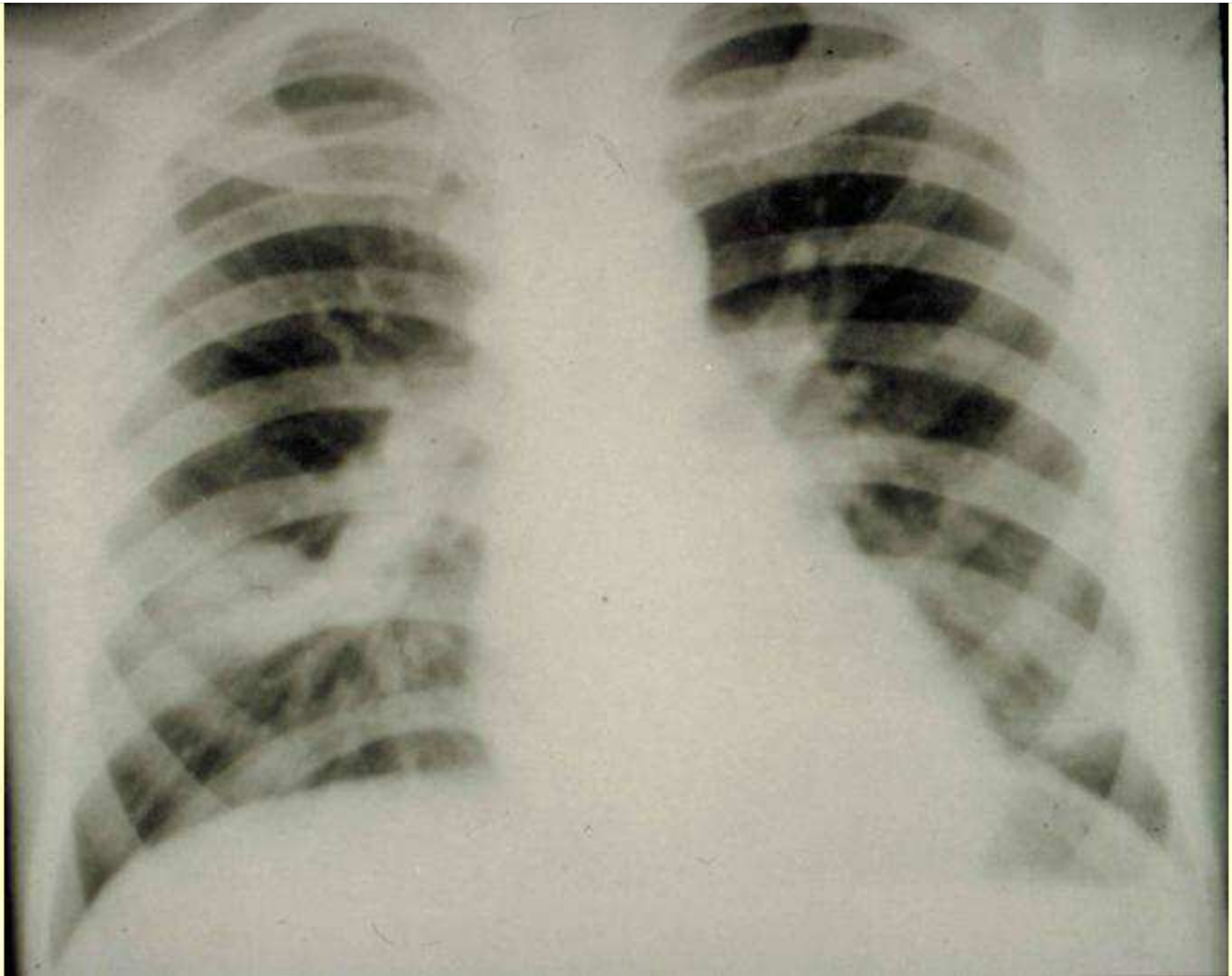


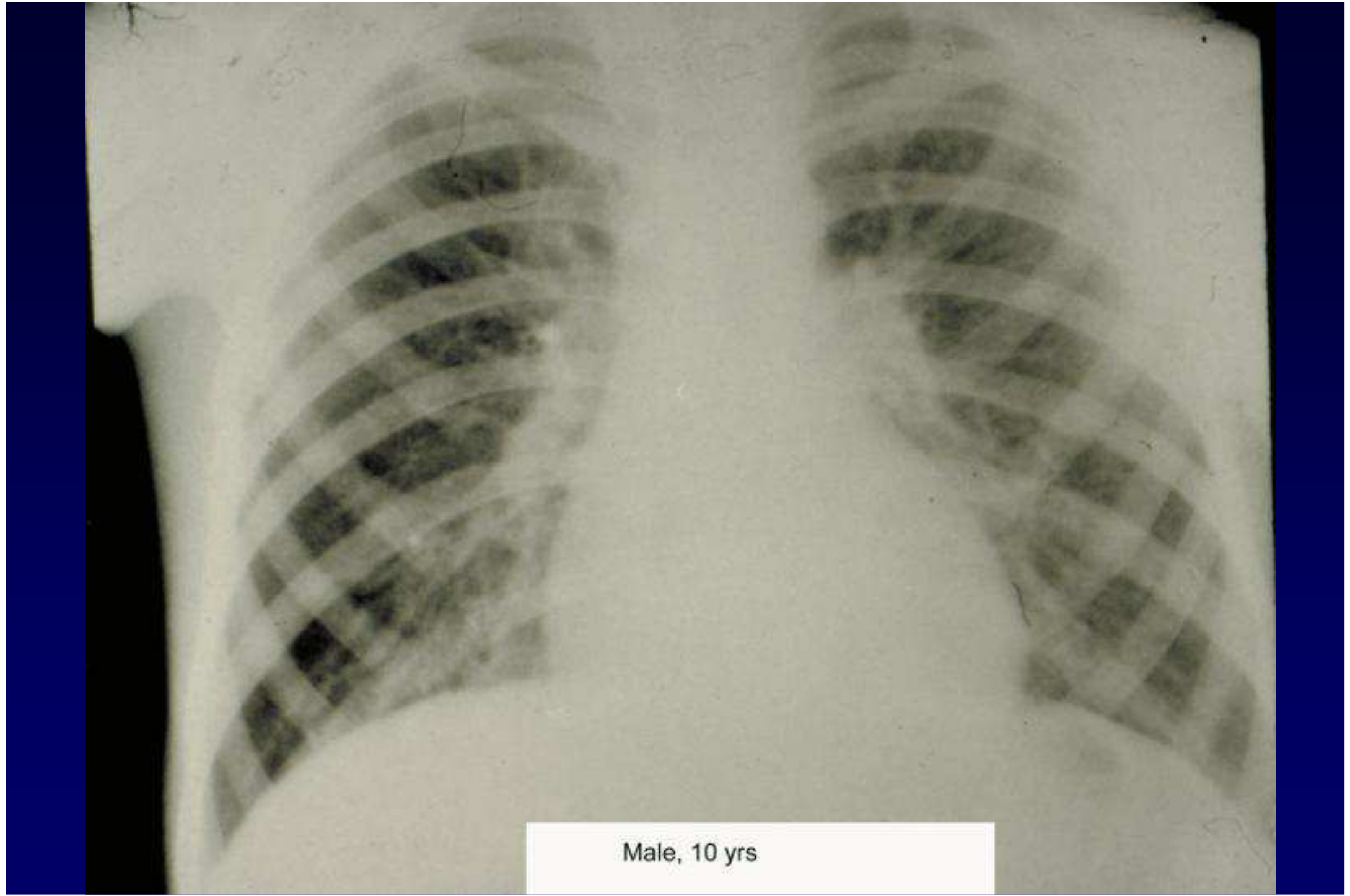


- A. Primary site of TB infection (Ghon focus) in the lung periphery, exhibiting caseous necrosis**
- B. Caseous necrosis in regional hilar lymph nodes**

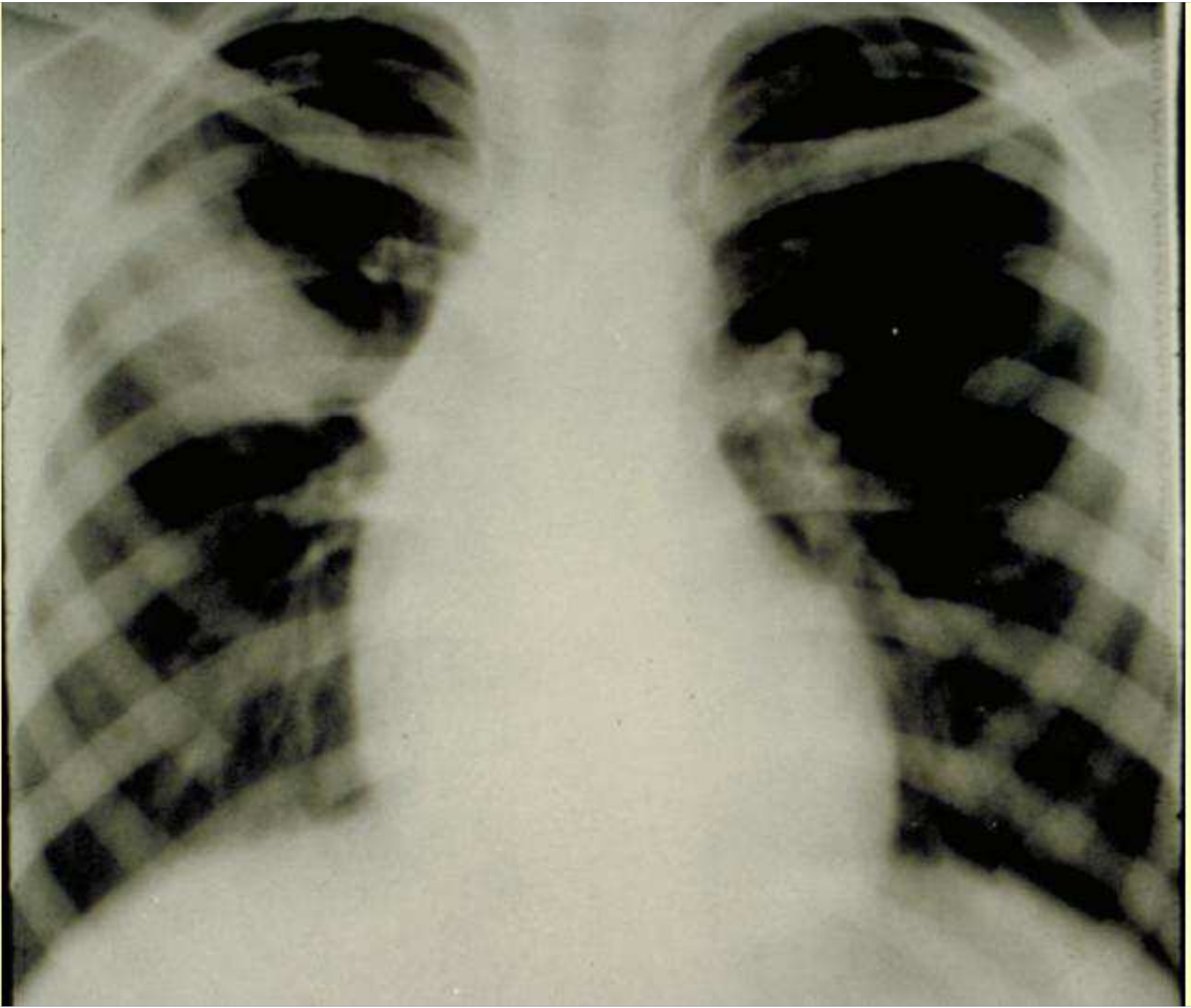


**Tuberculosis primaria
progressiva**

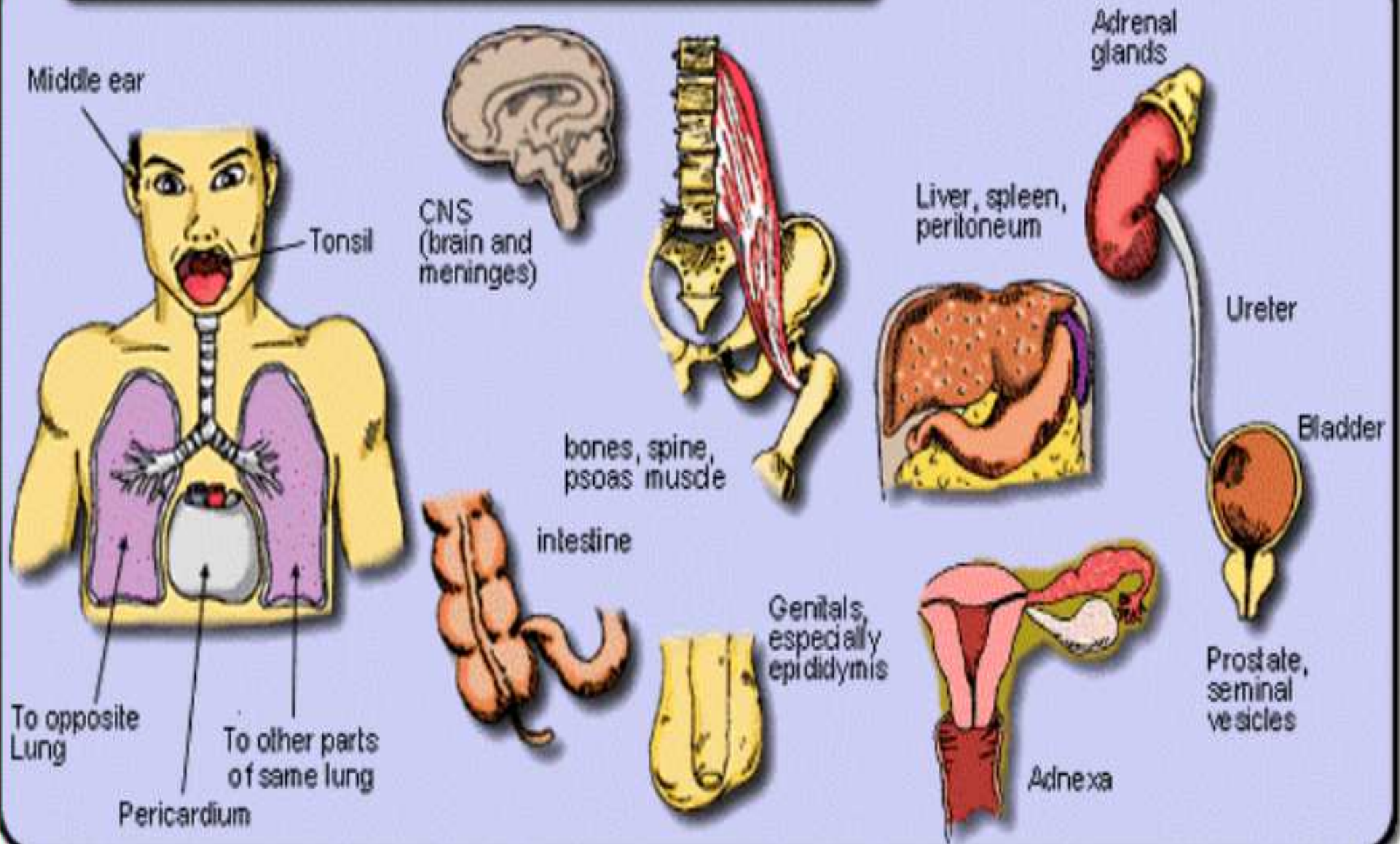


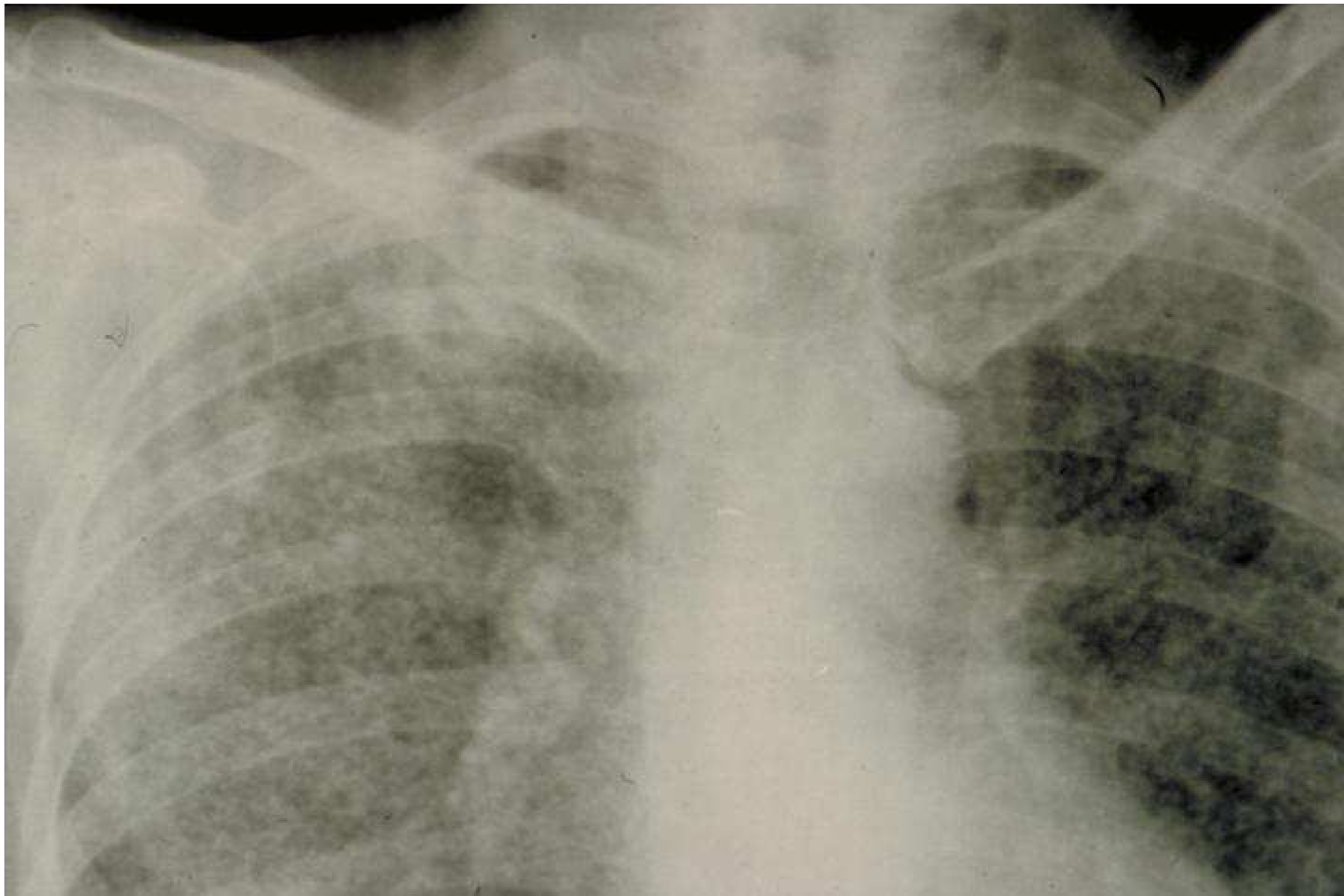


Male, 10 yrs

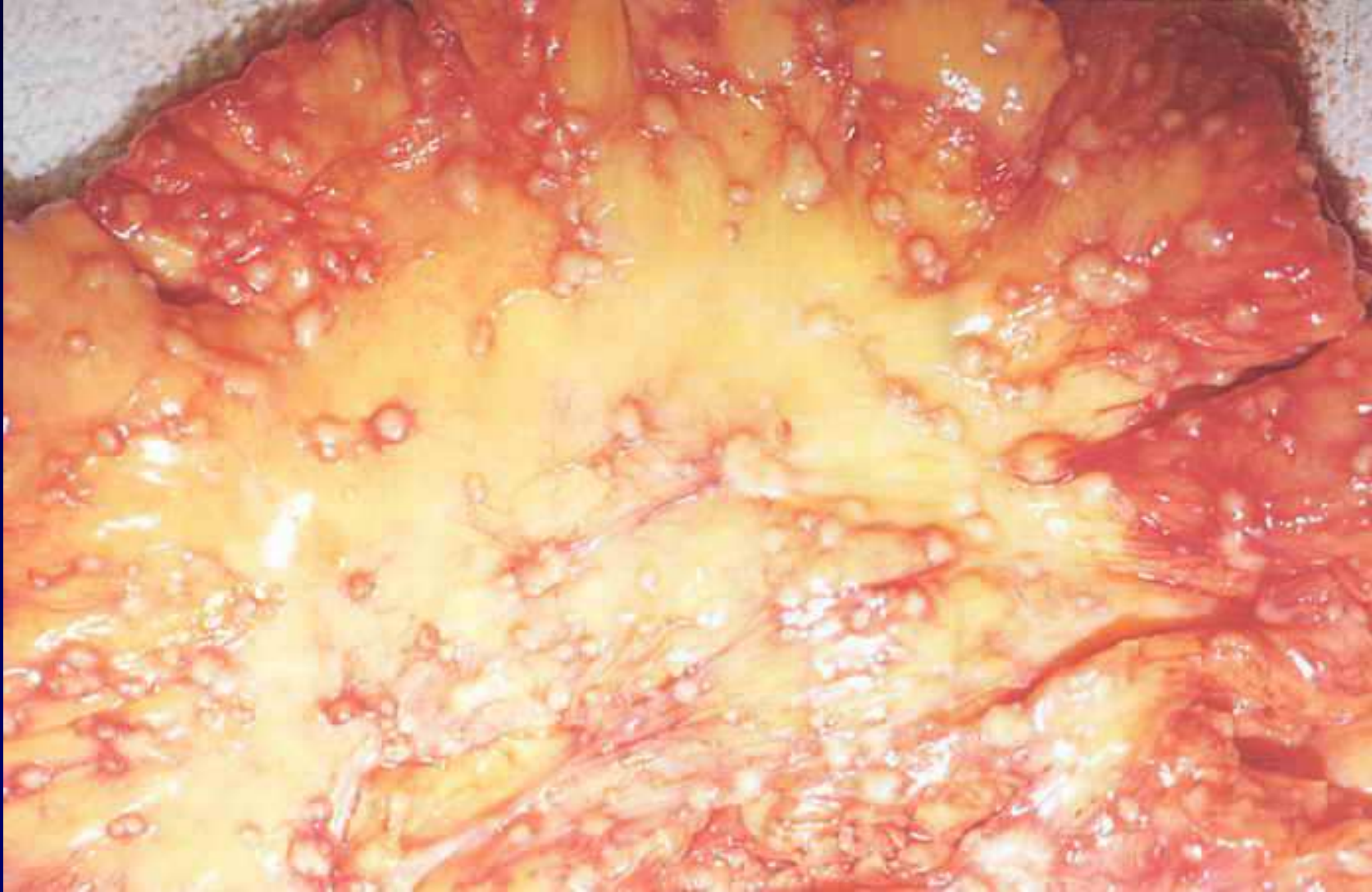


Tuberculosis Affects Many Parts of the Body





Tuberculosis miliare



TB miliare

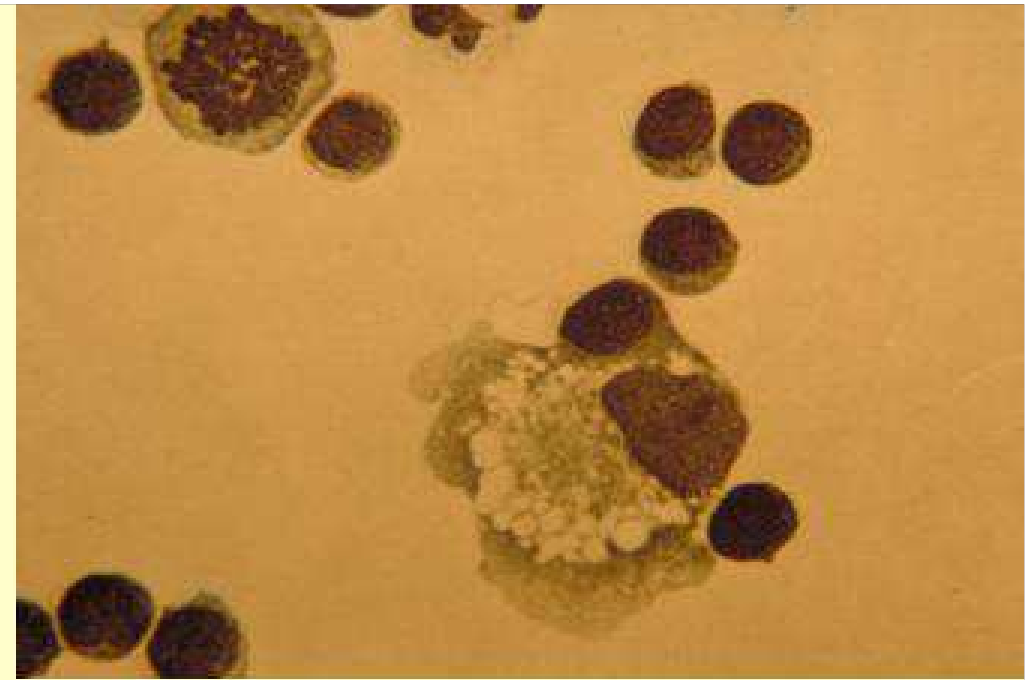
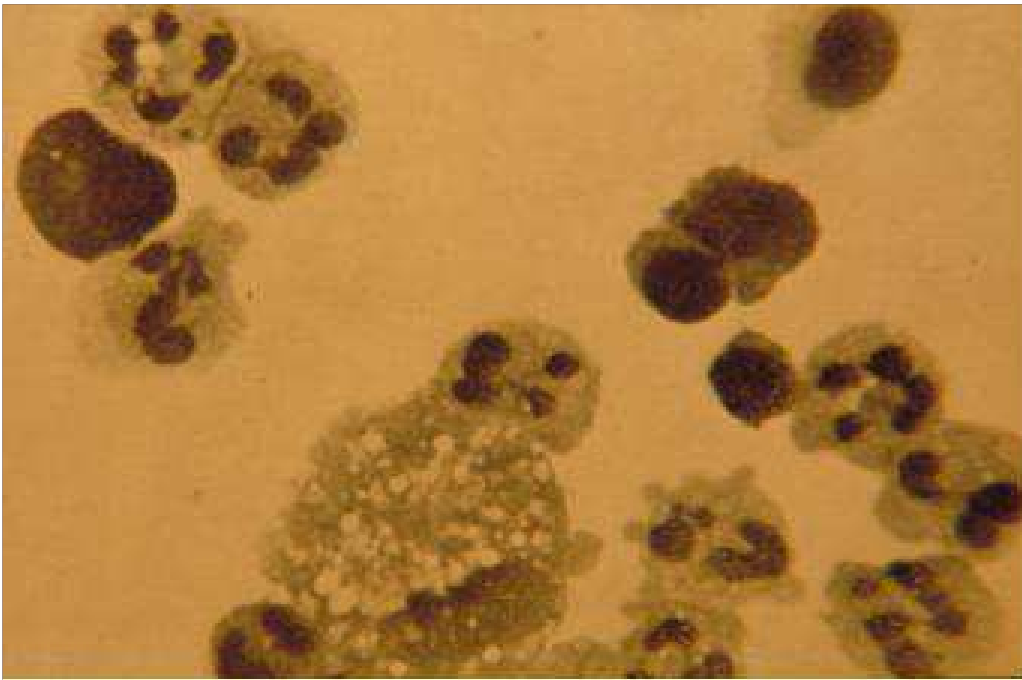
Esordio aspecifico e insidioso: febbre anche elevata, malessere, anoressia, calo ponderale: questi prodromi sono comuni sia alle forme a sviluppo criptico sia a quelle ad andamento tumultuoso

Miliari acute: abbondanza di segni e sintomi generali, scarsità di quelli respiratori. Iperensione endocranica (cefalea, vomito, deviazione oculare, scosse tonico-cloniche), epato-splenomegalia, turbe gastrointestinali, presenza di noduli coroidei

Miliari a decorso lento: colpiscono soprattutto soggetti appartenenti a minoranze etniche o soggetti autoctoni di età avanzata. Segni e sintomi di ordine generale presenti ma sfumati, rara una focalità evidente

Considerazioni: discrasie ematiche → aspirato midollare spesso BK+, epatosplenomegalia → biopsia epatica + per granulomi

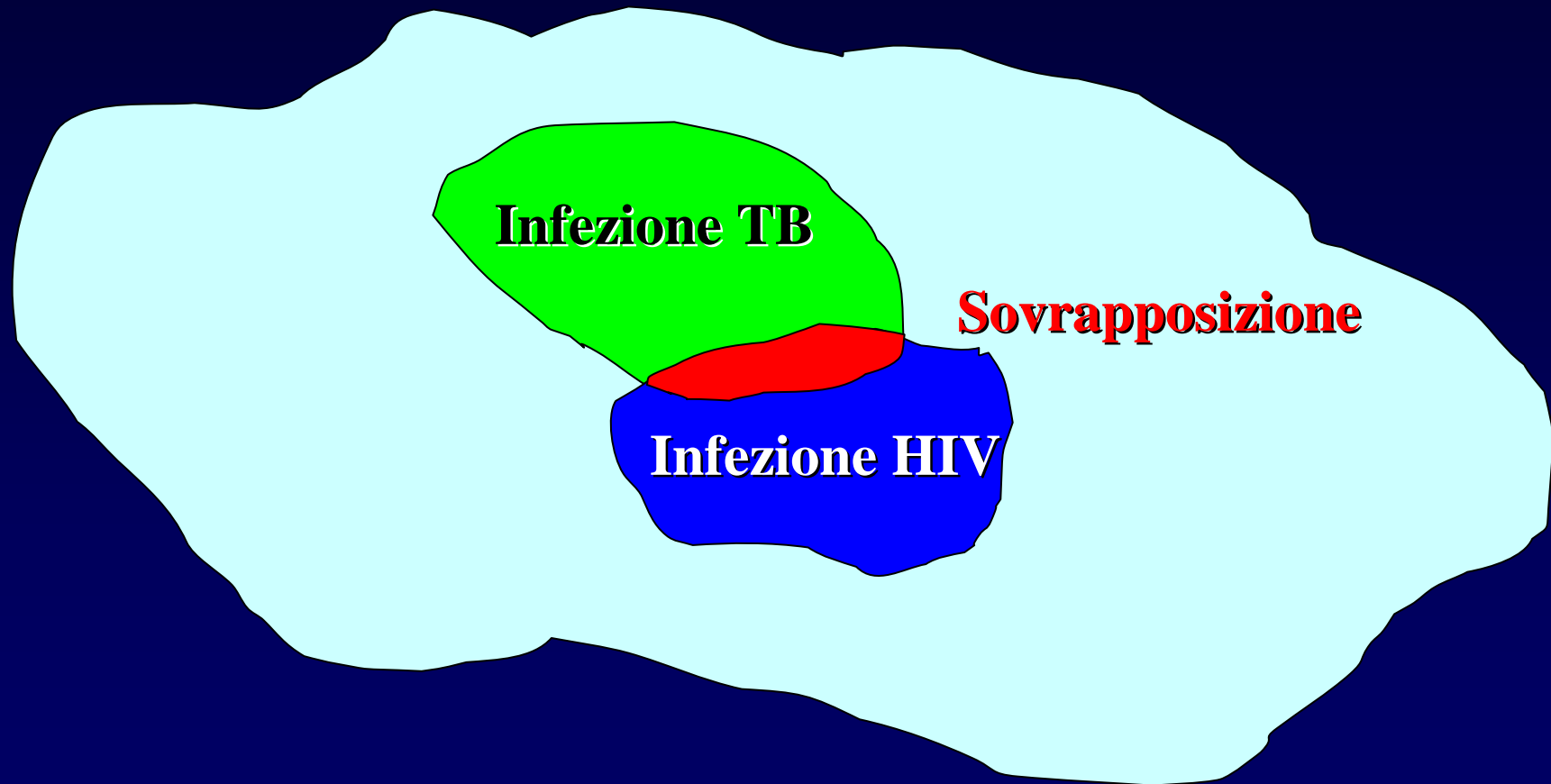
Febbre ad andamento non tipico: è possibile febbricola



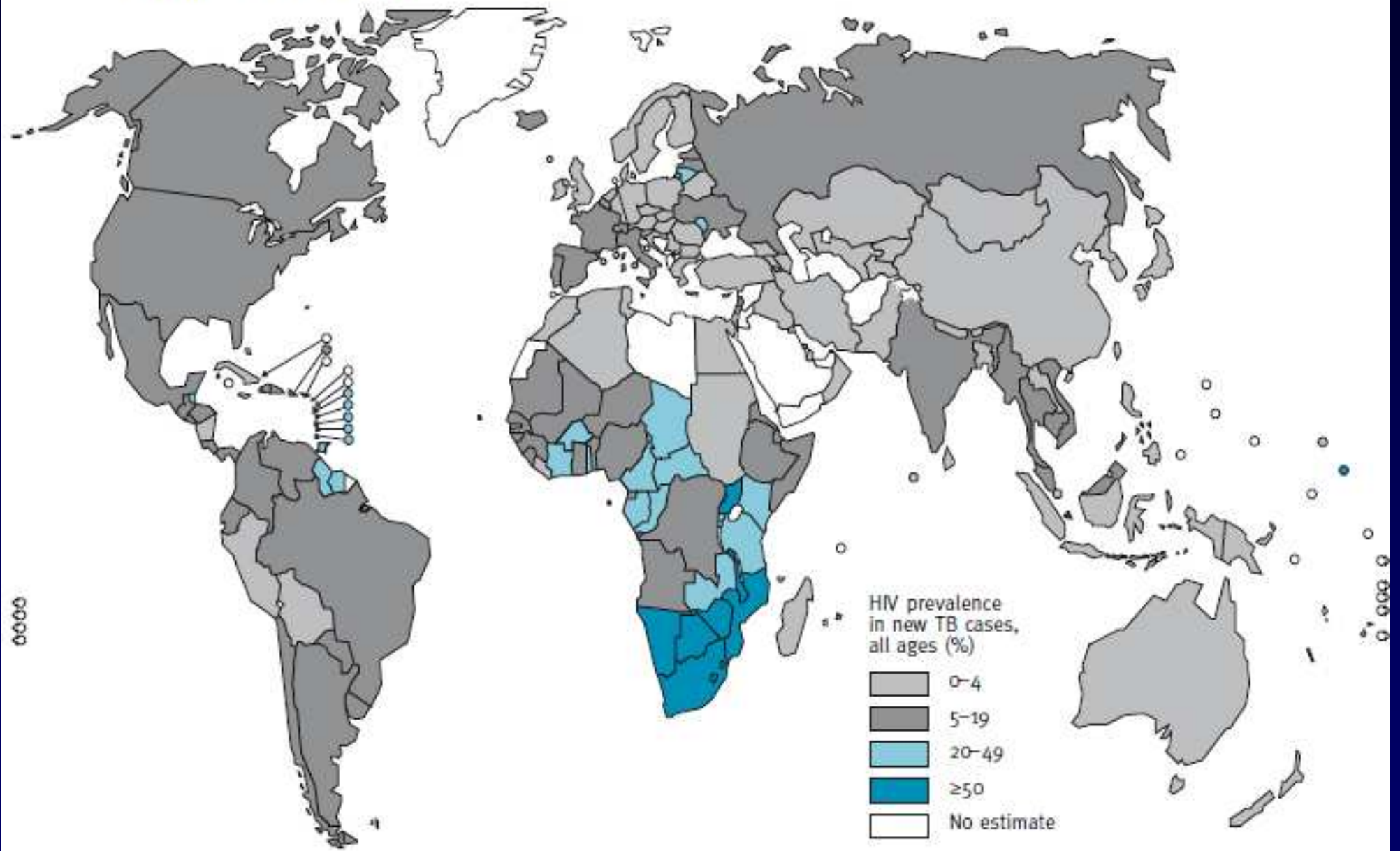
Change in cerebrospinal fluid findings in a child with tuberculous meningitis

Date	White cell count	Polynuclear (%)	Mononuclear (%)	Protein	Sugar
26 July	9	-	-	++	0
27 July	213	71	29	+++	0
30 July	509	16	84	+++	0

Impatto generale della coinfezione tra HIV e TB



Estimated HIV prevalence in new TB cases, 2009

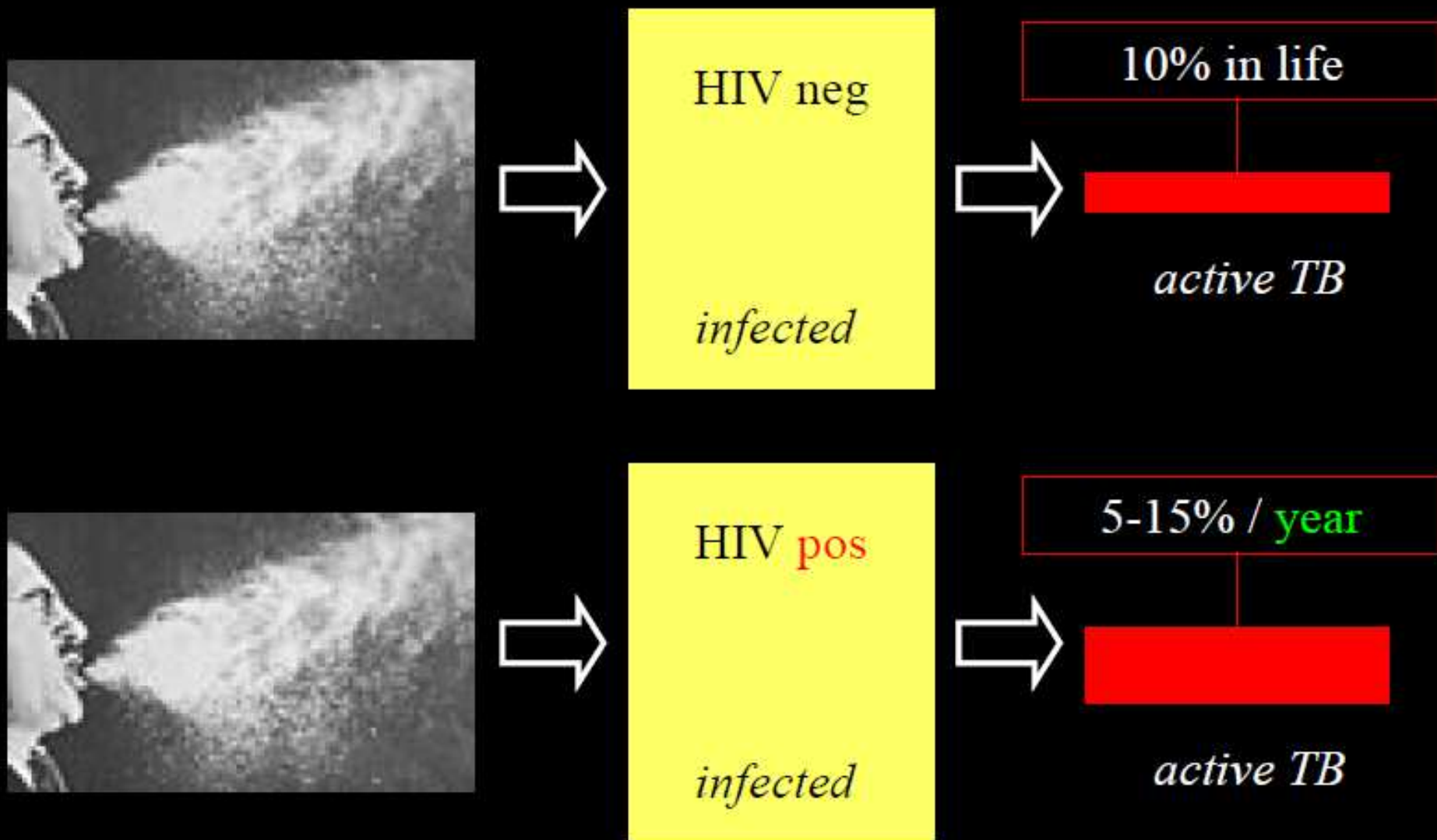


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TB in HIV-infected patients

In the presence of CD4+ T cell depletion both the risk of developing TB and the clinical picture tend to change in a proportional manner



TB/HIV + vs TB/HIV - : CLINICA

- Maggiore rapidità di progressione
- Maggiore coinvolgimento extrapolmonare
- Maggiore frequenza di quadri di tipo “primario”
- Minore frequenza di lesioni cavitarie
- Maggiore frequenza di quadri radiografici “normali”
- Maggior numero di bacilli nelle lesioni

In relazione inversa al n. dei linfociti T a fenotipo CD4+

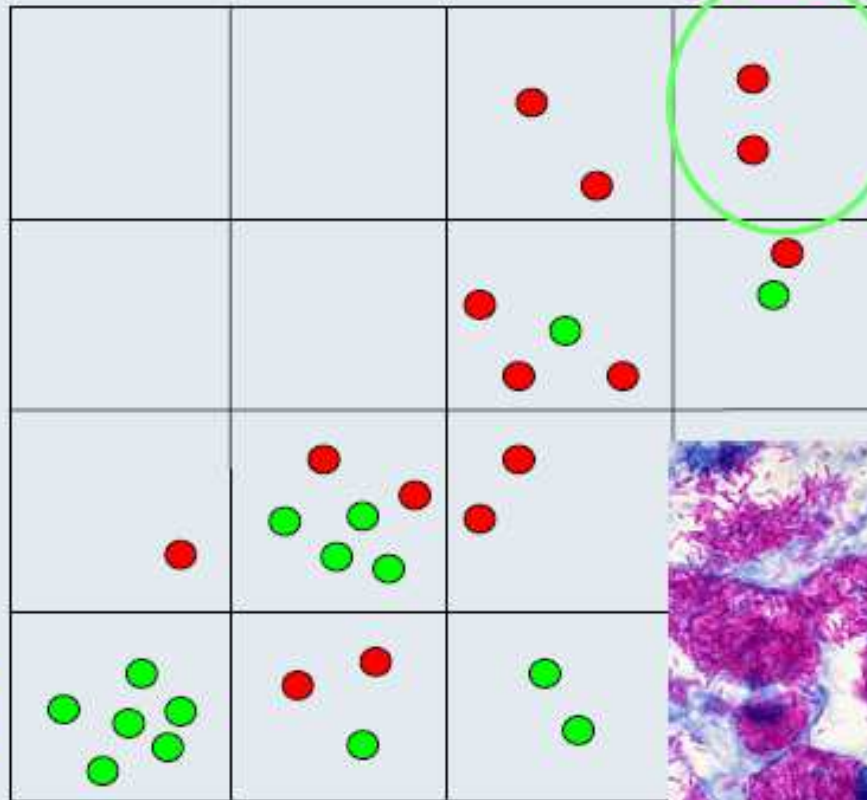
Scores for granuloma

G+

G++

G+++

G++++



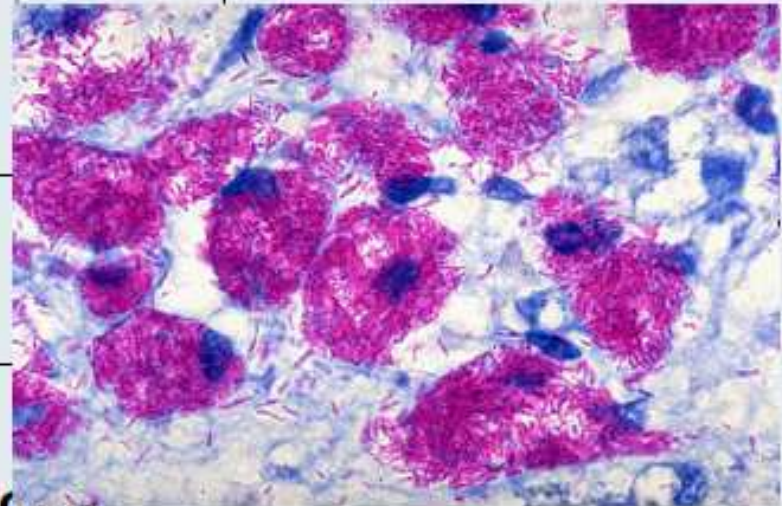
● HIV-neg
● HIV-pos

B+

B++

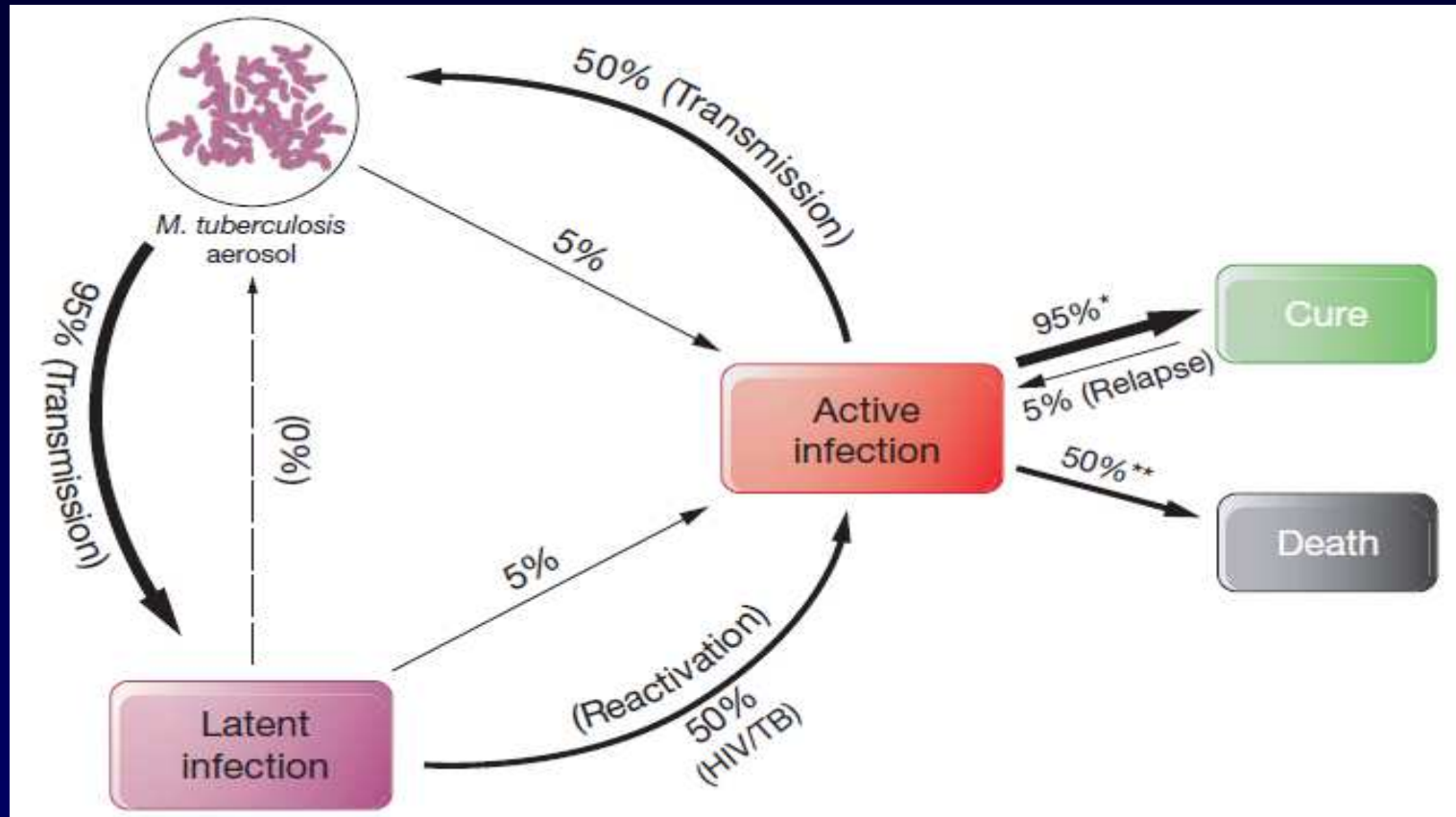
B+++

Scores for bacilli



Di Perri et al. *Tubercle and Lung Disease*, 1995

The challenge of new drug discovery for tuberculosis



Stages of *M. tuberculosis* infection. *M. tuberculosis* aerosol transmission and progression to infectious TB or non-infectious (latent) disease. A sizeable pool of latently infected people may relapse into active TB, years after their first exposure to the bacterium. Latent TB is commonly activated by immune suppression, as in the case of HIV. In cases of drug-susceptible (DS)-TB (denoted by an asterisk), 95% of patients recover upon treatment, whereas 5% relapse. If untreated (denoted by two asterisks), high mortality results.

TB postprimaria

Generalmente sintomi e segni aspecifici

Decorso

- Insidioso → mesi
- Tumultuoso

Segni presenti quando coesistono lesioni importanti

Complicazioni: febbre persistente espressione di una malattia in rapida evoluzione. Può richiedere l'impiego di steroidi

Reazione pleurica: solitamente espressione di coinvolgimento di TB primaria. Possibile anche nella TB post-primaria

Empiema: per colonizzazione bacillare del liquido pleurico

Localizzazione prevalente ai lobi superiori e agli apici e segm. posteriori

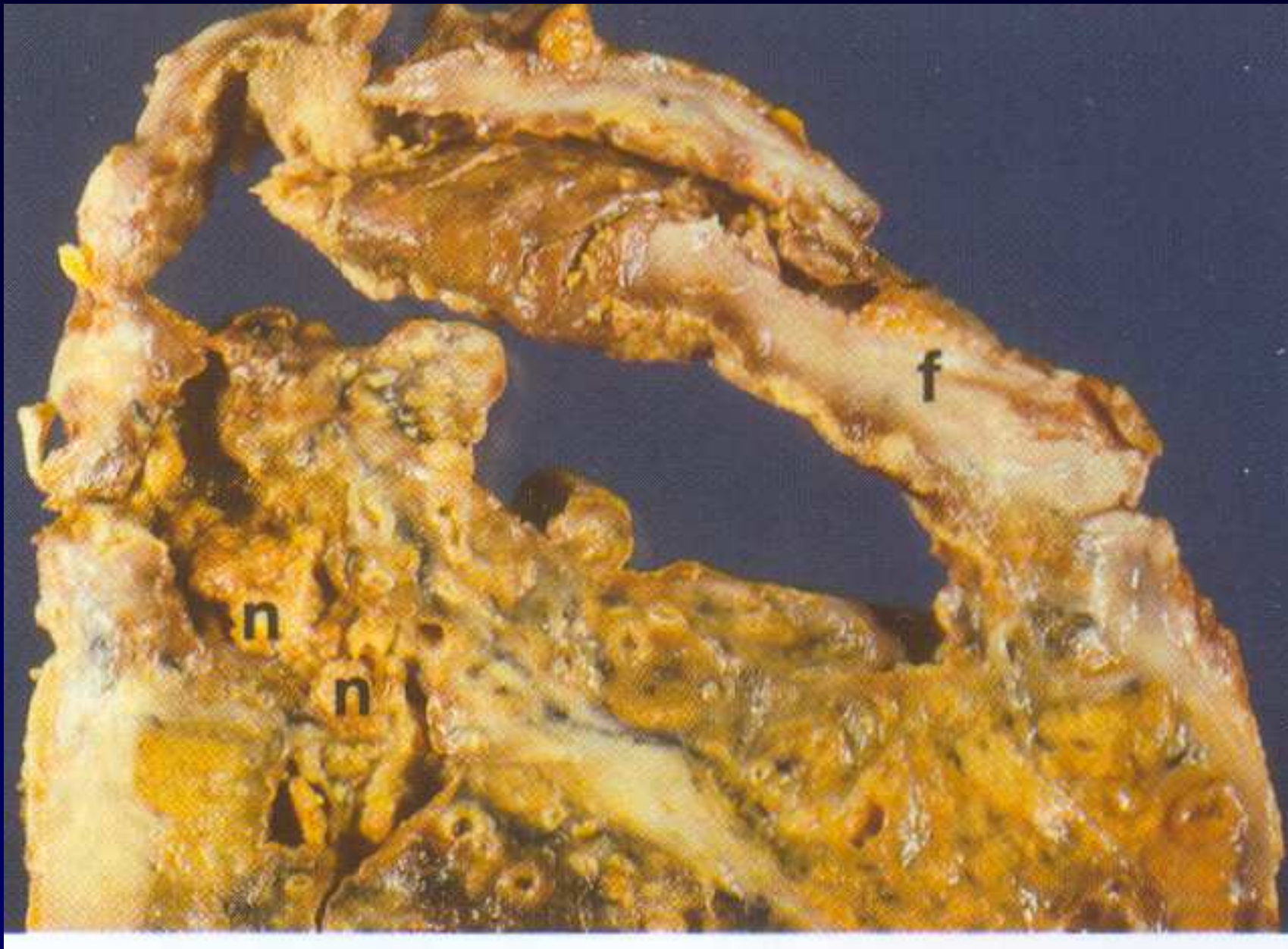
Necrosi



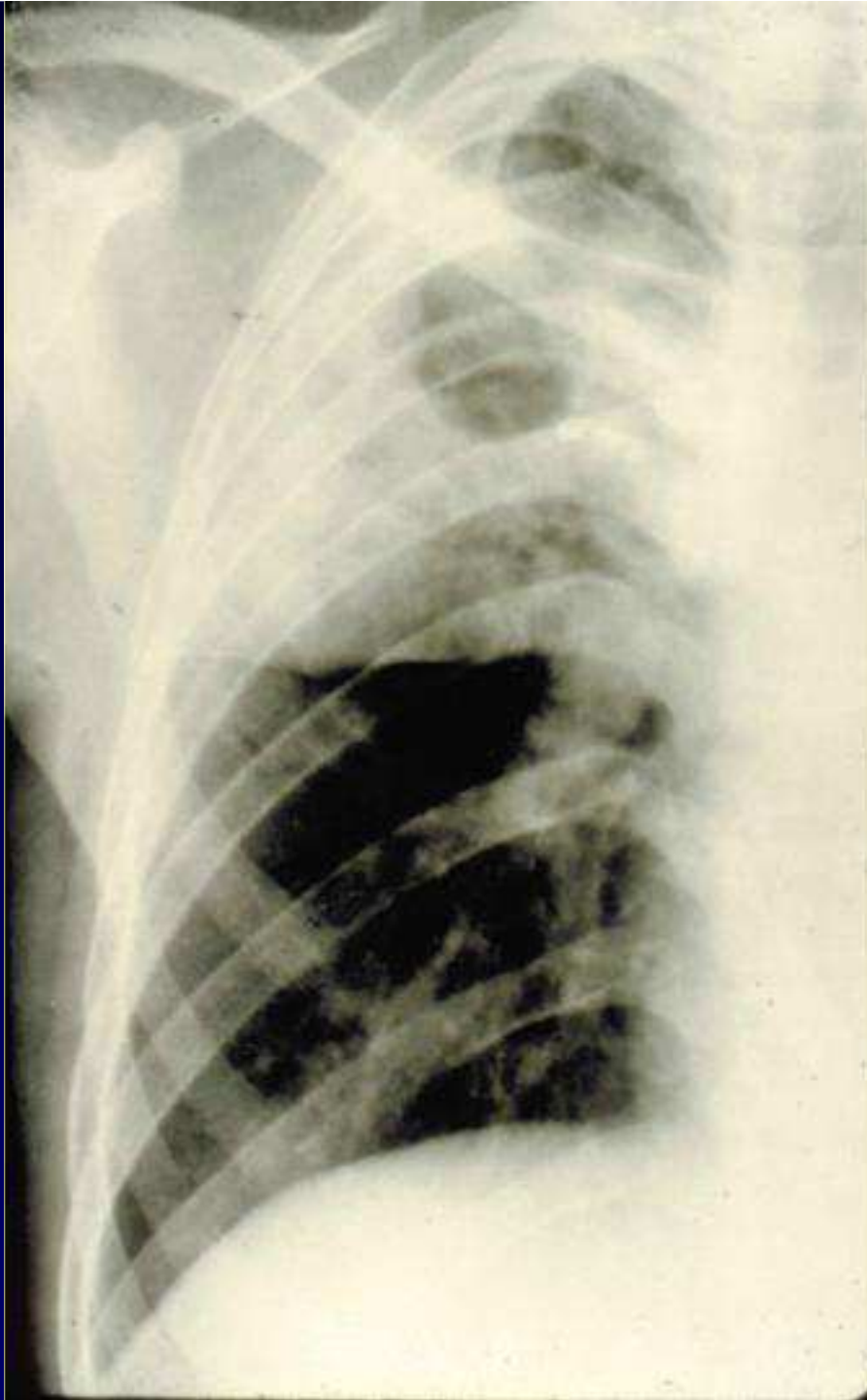
Polmonite tubercolare

Tuberculosis post-primaria

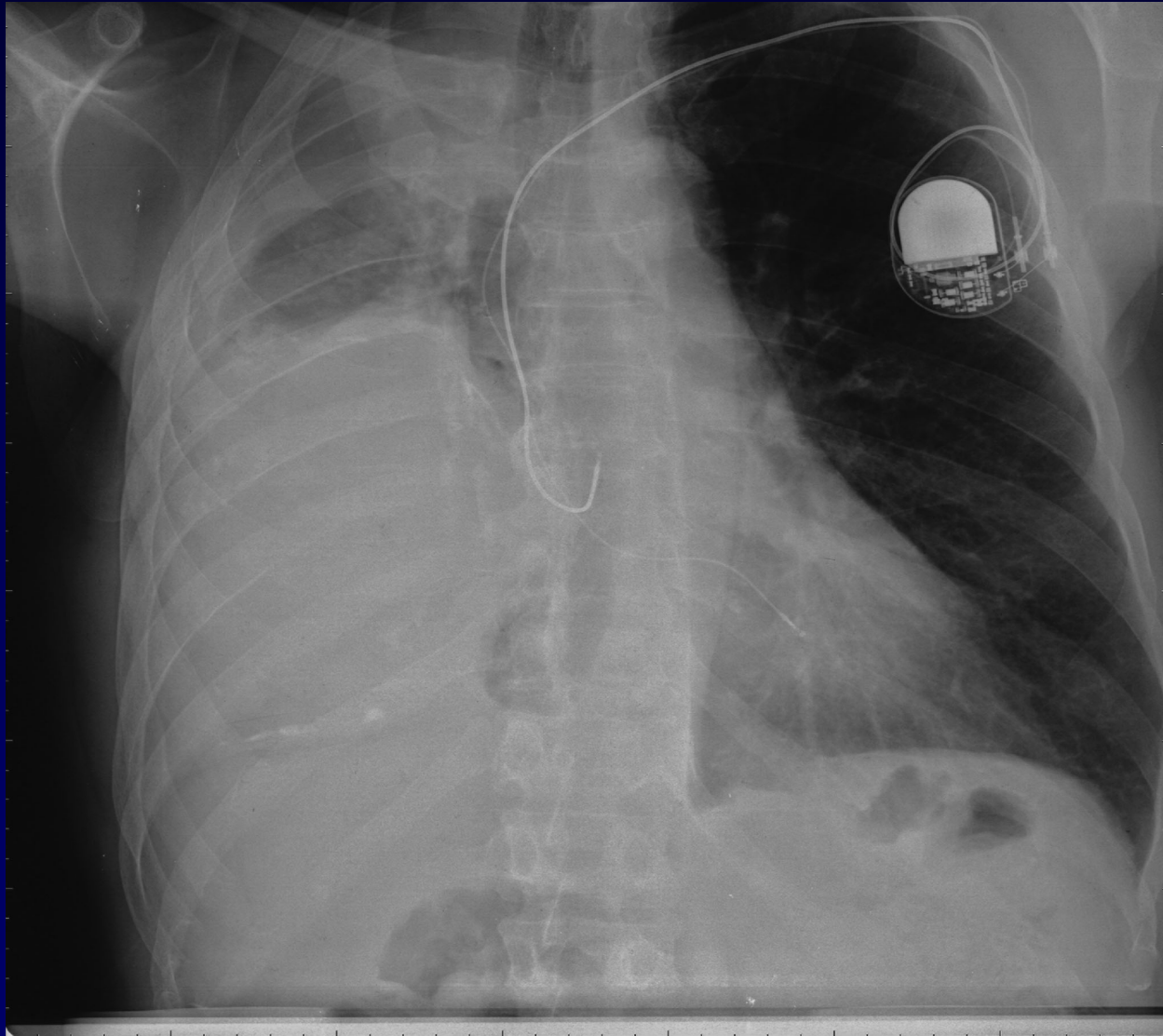




Tubercolosi - formazione cavitaria



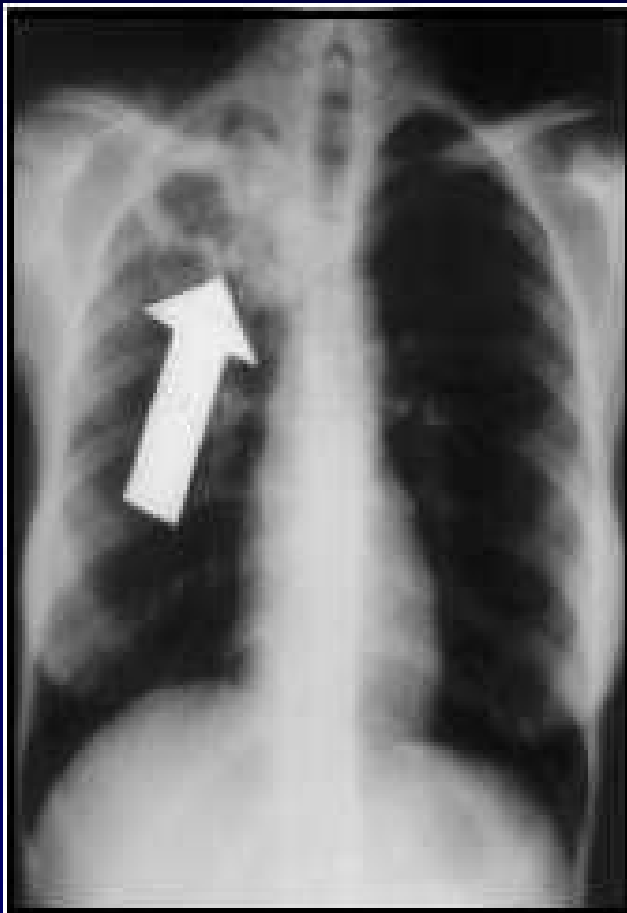
Empiema tubercolare



Procedure di diagnosi

❖ RX torace

➤ 1 ora



❖ BAAR

➤ 24 ore



❖ Coltura

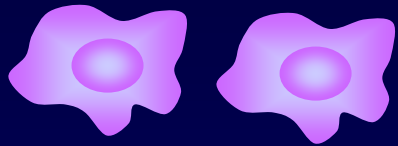
➤ Per conferma



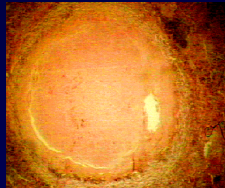
Il bersaglio batteriologico

Carica bacillare

Macrofagi (fagocitosi)
 $\cong 10^5$



Granuloma e
caseosi $\cong 10^5$



Caverna aperta

($\gg O_2 > CO_2$) $\cong 10^8-10^9$



Tassi di mutazione naturali

- INH $\cong 10^{-8}-10^{-9}$
- RMP $\cong 10^{-8}-10^{-10}$
- EMB $\cong 10^{-6}-10^{-7}$
- SM $\cong 10^{-5}-10^{-8}$
- PZ $\cong 10^{-3}$

Multiresistenza naturale: X gli esponenti dei tassi di mutazione alle singole sostanze

Acocella G., 1993

The choice of best treatment

The basic rules

Combination of antibiotics:

a) Rapid killing of mycobacteria



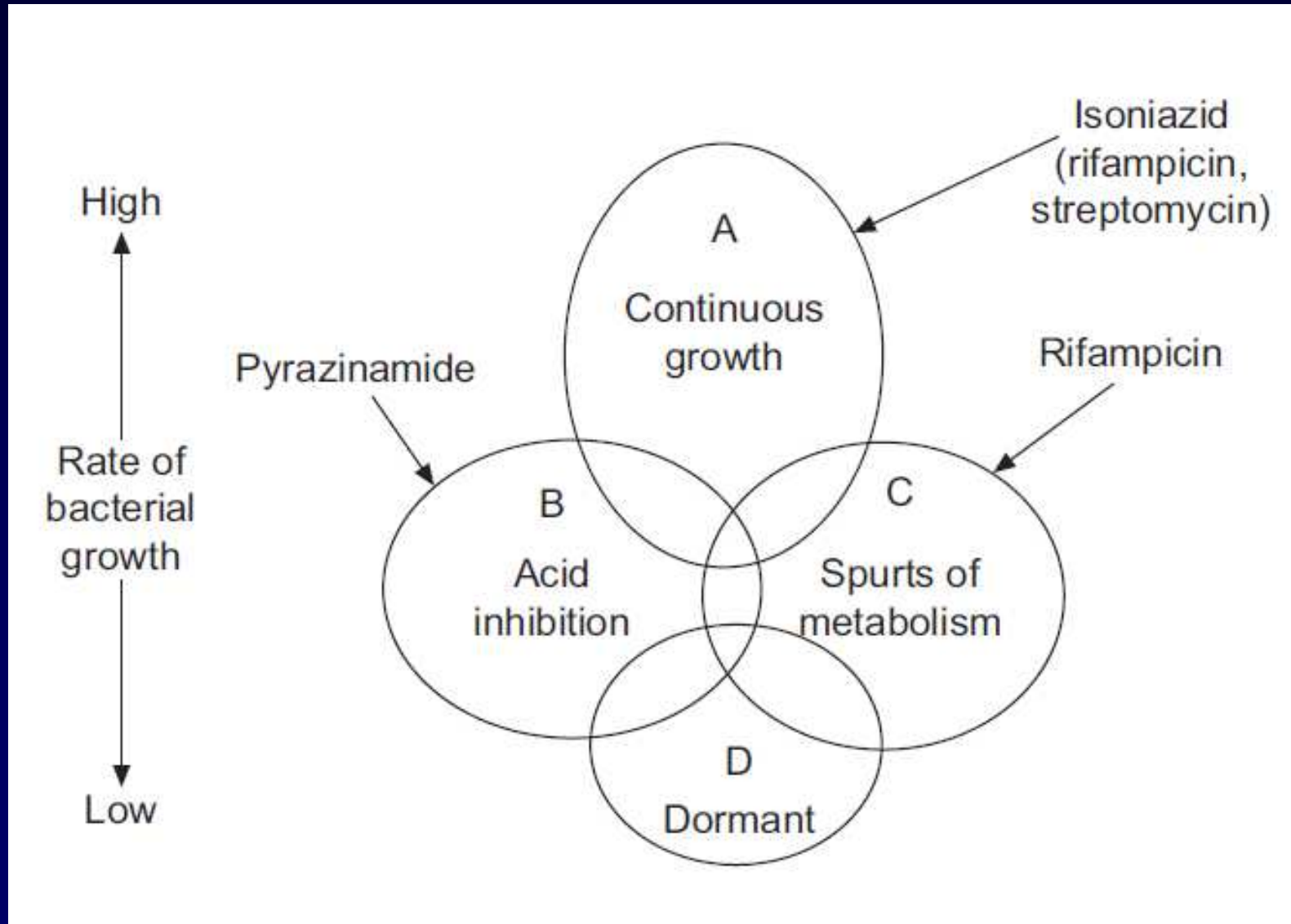
Interruption of the chain transmission

b) Sterilisation of lesions



Prevention of relapses

Sequential action of anti-TB drugs



Linee diagnostiche essenziali utili a raggiungere una diagnosi di tubercolosi

