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Full Length Article

Reactivation or reinfection in adult tuberculosis: Is that the question? ☆

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ABSTRACT

Looking at the chapter on "natural history" in any tuberculosis (TB) reference book, there is a kind of certainty regarding TB in adults. That is the concept of "post-primary" TB described as the reactivation of dormant bacilli hidden in an old lesion developed during infancy due to a type of local immunosuppression. Intriguingly, this concept involves at least two major uncertainties: how can dormant bacilli remain for such a long period, almost a lifetime, in an old lesion, taking into account granuloma dynamism; and what sort of local immunosuppression is the one that facilitates reactivation? The controversy between reactivation and exogenous reinfection as the cause of active TB started very soon in TB research. Interestingly, this "balance" was disturbed in the 1960s when the "Unitary Concept" became very successful in supporting the reactivation dogma. The "Unitary Concept" was mainly based on the data of tuberculin surveillance during the pre-antibiotic era as well as the data obtained from experimental modelling in animals. At the same time, the "Three-risks model" appeared to explain the relationship between the risk of infection and TB incidence, granting reinfection a key role in adult TB together with primary infection. This role was reinforced by the studies of recurrence based on molecular epidemiology, and a better knowledge of the immune response, granuloma dynamics, and lung physiology. Now it is a matter of taking it into account when designing new prophylactic and therapeutic strategies and also reflecting it in text books to better illustrate to our students.

Introduction—"The Unitary Concept

Reviewing the origin of the dogma of reactivation of an old lesion as the main source of tuberculosis (TB) in adults, it appears that this theory was written to convince the scientific community about the rarity of exogenous reinfection in TB.

The author of this theory, William Stead, introduced the topic citing the publications written by several authors around the 1920s supporting the role of exogenous reinfection, putting it on a par at least with the exacerbation of dormant foci [1]. In particular, the author cited several German specialists (i.e., Assmann, Redeker, and Braeuning) that sup-

☆ "... per això, malgrat la boira, cal caminar." (...therefore, in spite of the fog, you need to walk.) Lluis Llach (1974).

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ported exogenous reinfection as a key factor to developing adult TB (also called as chronic pulmonary TB). They named this concept "The New Theory" and soon after, several American doctors (i.e., Opie, Pinner, Myers, Longe, Medlar, and Terplan) supported it, to the point it was included in the Diagnostic Standards and Classification of the National Tuberculosis Association [2]. The "New Theory" was based on the experience of the wide use of roentgenograms, which started during the First World War to identify TB among the soldiers [3], and was thereafter used mainly for the control of therapeutic pneumothorax. With this technology, they found the "early infiltrates" not detectable by physical examination. These minimal lesions were detected in heavily exposed young adults (nurses or medical students) as they were assumed to have been previously infected in childhood, and the German doctors concluded that those early infiltrates in the upper lobes were the consequence of exogenous reinfection.

However, several Scandinavian specialists posed a strong argument against "The New Theory". According to the tuberculin skin test (TST) surveys among nursing and medical students between 1920 and 1930, there were a considerable number of patients who underwent TST. They then supported the concept that the majority of TB cases in adults, considered to be caused by reinfection, were actually cases of progression of recent primary infections [4].

Does TB incidence depend only on tuberculin status?

Stead considered that the main argument to determine the role of reinfection in adult TB incidence was to compare the incidence of TB between heavily infected persons (close contacts), considering their TST status, and non-exposed persons (control group) in order to relativize the factor of reinfection. He used data from the pre-antibiotic era [5–7]. Interestingly, he found that previous TST-positive (+) persons had a significantly lower incidence of TB in both groups than TST-negative (–) persons. In particular, the ratio between close contacts and controls in TST+ was approximately 2×, whereas that in TST− was approximately 5× (Table 1). Surprisingly, the author considered the higher TB incidence in close contacts of the TST+ group irrelevant, arguing that the contact group was mainly integrated by nursing and medical students. According to Stead, this group developed more TB because they were subjected to "longer working hours and greater bodily fatigue" than the TST+ control group. Therefore, he considered this higher ratio of re-exposure (exogenous reinfection) irrelevant to the TB incidence in TST+ persons and concluded that the most important risk in TST+ persons was reactivation.

Table 1 – Incidence (rate/1000 person-years) of Tuberculosis in Different TST groups [5–7].

	Close contact	Control
TST+	7.6*	4.3*
TST–	49.4**	10.8**

Note. TST = tuberculin skin test.
* $p < .05$.
** $p < .01$.

What is the upper lobe scenario about?

This idea concludes that TB in adults is mainly the consequence of an old lesion in the apex, induced after the hematogenous dissemination that takes place following primary infection. This is in contrast to primary lesions, which usually occur in the middle or lower lobes. Stead used the presence of lesions in the upper lobes in 20% of autopsies of patients with successfully controlled primary lesions [1] as an argument to support this; the other argument was that such lesions tend to have more active bacilli and to be more prone to reactivation than the primary lesions. Following the criteria of the Scandinavian authors [4], the author also favored the possibility that typical adult lesions could occur after a primary infection in the upper lobe, as has recently been demonstrated using molecular epidemiology tools [8].

In this regard, it is important to bear in mind that the upper lobes represent 20% of the lung volume [9,10], so the presence of such lesions is exactly what should be expected.

Stead also supported the concept that the most common site for metastatic implantations is the pulmonary apex because the very high oxygen tension provides a favorable milieu for the bacilli. High oxygen pressure is precisely a consequence of low blood perfusion. Therefore, lesion localization should be less important at this site. It has been clearly demonstrated that TB lesions progress more in the upper lobes [11,12]. The fact is that, in the upper lobes, there is a small breathing amplitude which favors an increased local bacilli–alveolar macrophages ratio leading to an excessive inflammatory response; this in turn favors the recruitment of neutrophils and the induction of exudative lesions. These lesions are the ones that are able to grow quicker and avoid encapsulation by the interlobar septae. Thus, active disease can be induced [13] by local dissemination of new daughter lesions that will finally coalesce, also aided by exogenous reinfection [14]. Equally, the higher tension borne by these septae, as a consequence of the force of gravity, makes these structures less reactive against the presence of local lesions. An interesting and very "graphic" observation was described in miliary TB cases where the lung nodules are larger in the upper lobes than in the lower [15–17].

Lymphatic and hematogenous dissemination as a source of pulmonary and extrapulmonary lesions

After a primary infection, there is a delay in the immune response, and thus, the bacillary bulk that reaches the draining lymph nodes is higher than that in the presence of a previous immune response. In addition, the lymph node is not homogenous at all; in fact, there is a proximal site where macrophages are infected and a real infection is developed, and there is a distal site where dendritic cells are affected, generating the specific lymphocytes. Fortunately, these lymphocytes do not go directly to the infected site of the lymph node; they reach the cava vein, the right heart, and the lung again where they are attracted to the infected sites and