

The enigma of extra-pulmonary tuberculosis

EXTRA-PULMONARY TUBERCULOSIS embodies more than anything else the protean manifestations tuberculosis can assume, and it continues to guard some of its enigmas.

In this issue of the *Journal*, Mor and colleagues report on their experience with extra-pulmonary tuberculosis in Israel.¹ Among other observations, they highlight the female preponderance, a finding consistent with others. Women with tuberculosis appear to be at increased risk of virtually any form of extra-pulmonary tuberculosis, barring pleural tuberculosis, compared to men, even after adjustment for various potential confounders.^{2,3} With some exceptions, children with tuberculosis are more prone to developing extra-pulmonary disease manifestations than adults. Arvid Wallgren meticulously recorded the sequence of events following primary infection in his seminal work more than 60 years ago.⁴

The relation between time elapsed since infection and extra-pulmonary site manifestation is untested. One therefore shouldn't really lump together all non-pulmonary manifestations of tuberculosis as if they were a single entity. It is apparent that quite different underlying factors play a role between, say, progression to meningeal or genitourinary tuberculosis, respectively, or indeed neither of these. The former is linked to dissemination, notably among the very young, while the latter is more likely to be found at the opposite end of the age spectrum. The varying proportions of patients who develop tuberculosis as a result of recent infection versus endogenous reactivation disease can thus explain some of the observed age differences.⁵ Age is nevertheless likely secondary to time elapsed since infection, and is in itself modified by the risk of infection in a community.

It has also been noted that extra-pulmonary tuberculosis differs in relative frequency not only by race/ethnicity and provenance, but indeed within groups, such as among different nationalities of European descent who immigrated to Canada, most conspicuously shown in that particular case for genitourinary tuberculosis.⁶ Such differences might also be explained to some extent by the varied underlying experiences in the current and accumulated force of transmission.

But how can one reconcile sex differences within the same group of persons? There is likely a difference between the sexes in the average time elapsed since acquisition of infection. Tuberculin skin test surveys

show that among children there is usually hardly any sex difference in the age-specific prevalence of infection with *Mycobacterium tuberculosis*. Such differences start to emerge beyond puberty, when males commonly become the higher infection prevalence group than their female age peers. Thus, a group of young, latently infected men will include a higher proportion of individuals with recent infection compared with a group of infected women of the same age. Should we therefore expect more extra-pulmonary tuberculosis among these men than among the women? Observation shows quite the contrary. This would seem to make a strong argument that factors other than recency of infection are additional modifiers of the risk of progression to extra-pulmonary tuberculosis.

Extra-pulmonary manifestations will continue to hold their fascination for researchers as many epidemiologic questions remain and await more satisfying answers than we can currently come up with.

HANS L. RIEDER
*International Union Against
Tuberculosis and Lung Disease
Paris, France
Institute of Social and Preventive Medicine
University of Zurich
Zurich, Switzerland
e-mail: TBRieder@tbrieder.org*

Conflict of interest: none declared.

References

- 1 Mor Z, Pinsker G, Cedar N, Lidji M, Grotto I. Epidemiology of extra-pulmonary tuberculosis in Israel, 1999–2010. *Int J Tuberc Lung Dis* 2013; 17: 229–233.
- 2 Rieder H L, Snider D E Jr, Cauthen G M. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis* 1990; 141: 347–351.
- 3 Forssbohm M, Zwahlen M, Loddenkemper R, Rieder H L. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. *Eur Respir J* 2008; 31: 99–105.
- 4 Wallgren A. The time-table of tuberculosis. *Tubercle* 1948; 29: 245–251.
- 5 Rubilar M, Sime P J, Moudgil H, Chilvers E R, Leitch A G. Time to extend 'the timetable of tuberculosis'? [Editorial] *Respir Med* 1994; 88: 481–482.
- 6 Enarson D A, Ashley M J, Grzybowski S, Ostapkowicz E, Dorken E. Non-respiratory tuberculosis in Canada. *Am J Epidemiol* 1980; 112: 341–351.