Commentary: Reconciling historical epidemiological, bacteriological and immunological observations in tuberculosis

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Kristian Andvord had the remarkable insight that looking at cohort experience was by far more informative than a solely cross-sectional view of tuberculosis mortality data. A comprehensive paper by Andvord makes his thinking accessible for the English readership in this issue of the journal.

What Andvord unravelled is schematically shown in Figure 1a. A common presentation of tuberculosis surveillance data is reporting them as age-specific morbidity or mortality in a given calendar year. Any change in successive years becomes thereby apparent in sequential reports. Nevertheless, this approach hides whether early life experience may predict mortality later in life. That this is the case was unravelled by Andvord. Furthermore, as Wade Hampton Frost in the US extending on Andvord’s approach subsequently demonstrated, the cross-sectional view conceals the fact that, where tuberculosis is in decline, the commonly observed high tuberculosis rates among the elderly is just a residual of an even higher mortality that each generation had experienced when it was younger.

To explain the role of childhood experience on tuberculosis among adults, the ‘once infected, always infected’ hypothesis has been espoused. As tuberculosis has seemingly no finite incubation period, disease onset among adults could be satisfactorily explained by reactivation of an infection acquired earlier in life. Molecular epidemiology proves that recent infection can play a major role in low-incidence countries, and re-infection disease may contribute substantially to morbidity in high-incidence settings.

In the same decade Andvord and Frost furthered our epidemiological insight, Georges Canetti demonstrated that a large proportion of persons with clear evidence of prior acquisition of Mycobacterium tuberculosis had in fact eliminated all living tubercle bacilli from their old lesions. Although the annual risk of becoming infected with M. tuberculosis had been in the order of 10% among the children who were adults by the time they came under Canetti’s observation, in a large proportion it was not the primary, but a super-imposed re-infection that led to the disease (Figure 1b). Yet, Andvord’s epidemiological
observations leave no doubt that the childhood experience leaves its imprint on adults. How then can these two observations be reconciled?

While tremendous progress has been made in our understanding of the cellular immune responses, the phenomenon reported by Robert Koch in 1890 already points to an explanation: a first infection with *M. tuberculosis* primes the individual to react violently with tissue necrosis to a subsequent challenge with *M. tuberculosis* antigens (a filtrate of killed bacilli in his experiments) (Figure 1c). In extension, this suggests indeed that becoming infected as a child determines the mortality from tuberculosis later in life, not through a reactivation of that first infection, but by an immunological response elicited by a re-infection. In this regard, the *M. microti*/BCG trial among adolescents initiated by the British Medical Research Council (BMRC) between 1950 and 1952 is highly educational. Dissemination and replication of BCG is a pre-condition for the vaccine to induce the immunological response required for protection. Yet, the normal course subsequent to immunological priming is that *M. bovis* BCG is virtually always entirely eliminated from the body. That this elimination occurs as well, albeit to a lesser extent, with the more virulent *M. tuberculosis* was established by Canetti and confirmed by molecular studies. What is remarkable in the BMRC study is that protection against tuberculosis from infection with *M. tuberculosis* acquired subsequent to vaccination did not slowly dwindle over time, but persisted for about a dozen years at a high, virtually unchanged level, only to then precipitously vanishing entirely within just a few years (Figure 1d). This indicates that the immunological memory for *M. tuberculosis* antigens is sufficiently long to prime a response to a re-infection occurring in young adults who had been infected the first time as children but had meanwhile eliminated the then infecting strain.

The cohort-age contour approach has consistently shown that within each generation tuberculosis and tuberculosis mortality peak among young adults. Data availability has limited these studies to settings where tuberculosis has been long in decline and thus the risk of becoming infected at a very early age was always larger than becoming infected later in age, and if re-infection happened, the effects were devastating. The keen observations of our forebears from different disciplines can provide a comprehensive explanation for the observed dynamics in the interactions between man and *M. tuberculosis*. There remains the slightly discomforting consequence that BCG vaccination, where it fails to protect, may actually do harm, a suspicion that cannot yet be quite dismissed.

References

Commentary: Tuberculosis down the generations—a comment on ‘Continued studies of Tuberculosis as a generation illness’ by Kr F Andvord

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Accepted 29 April 2008

Introduction

It is 70 years since Andvord first looked at the way tuberculosis affects the human race within successive generations. His object was to find the incidence of disease and so the risk of disease to an individual over that person’s life time. A method of describing the incidence for different age groups for successive years provides the means to observe the way tuberculosis affects and afflicts a generation from birth, through adult life and into old age. Frost describes this analysis of the change in mortality by age as the most significant of all analyses. ‘For every change in the rate of mortality as we pass from one age to another represents a shift in the balance established between the destructive forces of the invading bacillus and the sum total of host resistance. If we could accurately interpret this record, analyzing in detail each movement upward or downward and assigning to each factor its due share in the change, then we would be well on the way of knowing the epidemiology of tuberculosis’.2