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EDITORIAL

Annie Darwin's death, the evolution of tuberculosis and the need for systems epidemiology

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When Charles Darwin's daughter Anne Elizabeth ('Annie', Photograph 1) died at the age of 10 years on April 23, 1851 her parents were devastated. Charles Darwin was a devoted father and constantly concerned about the health of his 10 children. His concerns were also motivated by fear of the consequences of marriage between relatives: Emma Wedgewood, his wife, was also his first cousin.[1] The possible adverse effects of consanguineous marriage, which was not uncommon in England at that time, were a matter of debate. Annie's death, and self-fertilization experiments in plants, made him suspect that 'marriage between near relations is likewise injurious'.[2] In 1870, Darwin motivated his mathematician son George to study the prevalence of close-kin marriages in patients in asylums in comparison with the prevalence of the general population. The study, which is reprinted in this issue of the journal,[3] with several commentaries,[1,2,4,5] was first published in 1875 and concluded that 'the evil [of marriages between cousins] has been often much exaggerated' and that 'under favourable conditions of life, the apparent ill-effects were frequently almost nil'.[3]

Indeed, Annie died after a lingering illness, most likely of tuberculosis (TB) caused by *Mycobacterium tuberculosis*,[6] and not of the consequences of a high coefficient of inbreeding (the *F* coefficient that features in one commentary[2]). Of note, although

Photograph 1 Daguerreotype photograph of Anne Elizabeth ('Annie') Darwin 1849. Annie Darwin died in 1851, probably of tuberculosis. © English Heritage Photo Library. Reproduced with permission

Darwin may have been aware of the studies by his contemporaries, Pasteur and Koch, he did not consider the role of microbes and infectious diseases in his work.[7] *M. tuberculosis* would, however, surely have

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been of interest. This obligate human pathogen has co-evolved with humans for millennia[8] and has been extremely successful: today one-third of the world's population is estimated to be infected and 1.7 million people die from TB each year, more than anytime during previous human history.[9,10] Co-infection with HIV is an important risk factor for TB, increasing the lifetime risk of progression from infection to active disease from 5% per lifetime to 5% per year,[11] which is a particular problem in sub-Saharan Africa. Moreover, the emergence of bacterial strains resistant to most current antimicrobial drugs threatens to make TB untreatable.[9] Edmonds and colleagues,[12] in this issue, document the staggeringly high incidence of TB in HIV-infected children in Kinshasa, Democratic Republic of Congo: 20.4 per 100 person-years. Anti-retroviral therapy halved the incidence of TB, but as Boulle and Eley emphasize in their commentary,[13] additional interventions are needed to control TB in this population, including efforts to improve the diagnosis of TB in children co-infected with HIV.

Darwin would of course understand: the theory of evolution which he outlined in his seminal work *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life* is also 'the modern story of TB'.[14] The recent emergence of HIV and the introduction of effective drugs represent selection pressures that *M. tuberculosis* has not experienced for most of its evolutionary history. As one consequence of the widespread (and not always well supervised) use of drugs, resistant strains have developed. Many drug resistance-conferring mutations in *M. tuberculosis* lead to a reduction in bacterial fitness, although compensatory evolution may mitigate fitness defects.[15] In HIV-infected, immune-compromised hosts even strains with high-cost resistance mutations could be propagating efficiently, which might explain why drug-resistant TB has been associated with HIV co-infection.[16,17] TB patients could thus serve as a 'breeding ground' for highly compensated drug-resistant strains, with an increased capacity to spread in the general population. To date, no study has addressed this disturbing possibility. The strain genetic background has also been shown to influence the fitness of drug-resistant *M. tuberculosis*. For example, the Beijing lineage has been associated with drug resistance,[18] suggesting that this lineage might be 'pre-adapted' to resistance. Importantly, Beijing has also been associated with HIV[19,20] and is now emerging in South Africa, probably as a consequence of the HIV epidemic.[21,22]

Genomics, the study of the genomes of organisms, is becoming increasingly important for communicable

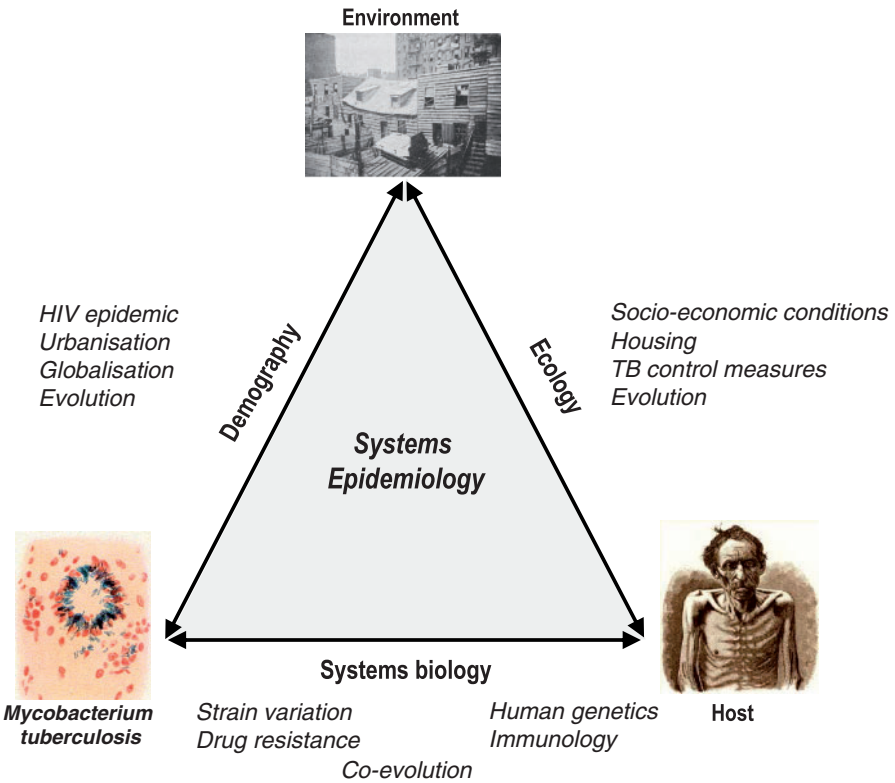

Figure 1 A 'systems epidemiology' approach to tuberculosis, which integrates demography, ecology and systems biology. Picture credits: Drawing from Koch R. Die Aetiologie der Tuberkulose. Berliner Klinische Wochenschrift, 1882; Dens of Death. Photograph from Riis JA. The Battle with the Slum. New York: MacMillan Company, 1902; Drawing of man with tuberculosis (source unknown).

disease epidemiology and control. Infectious diseases result from complex interactions between microbes, host and the environment, which are subject to evolutionary pressures and ecological changes (Figure 1). Genetic and immunological studies can answer fundamental questions about host–pathogen interaction, pathogenesis, host genetic susceptibility and the factors influencing response to treatment and prognosis.[23] Humans show remarkable variation in their response to infectious agents. For example, particular human gene polymorphisms explain some of the variation among individuals who differ in their ability to control HIV infection.[24,25] In addition to host genetic diversity, genetic variation within particular microbial species can influence the outcome of infection and disease. In *M. tuberculosis*, for example, a recent study demonstrated that the rate of progression to active TB depended on the bacterial lineage.[26] Other studies showed *M. tuberculosis* lineages to be associated with different clinical manifestations of TB.[27,28]

Both the recent changes in the human host (i.e. the emergence of HIV) and in the bacterium (i.e. the emergence of drug resistance) will influence the evolutionary trajectory of *M. tuberculosis*. We urgently need a better understanding of the genetic diversity and evolution of *M. tuberculosis* and the epidemiological and clinical consequences. How does co-infection affect the genetic population structure and evolution of *M. tuberculosis* in sub-Saharan Africa? What are the clinical and epidemiological implications of these effects? Does HIV co-infection influence the frequency and distribution of antimicrobial resistance-conferring mutations in *M. tuberculosis*? Do the clinical correlates of *M. tuberculosis* genetic diversity and the transmission dynamics of *M. tuberculosis* differ depending on HIV status and degree of HIV-induced immunodeficiency?

Improved understanding of the complex interactions between genetically diverse hosts and pathogens in changing environments will require new multidisciplinary approaches. In particular, the integration of systems biology with population sciences and ecology, in what might be described as 'systems epidemiology' is promising (Figure 1).[29] This involves combining genomic and evolutionary analyses of the host and the pathogen, with immunology, molecular and clinical epidemiology, and mathematical modelling. 'Darwinian Medicine', where evolutionary biology and biomedicine interact to enhance our understanding of both biological and evolutionary processes, is part of this concept.[30] If successful, such an integrated approach will inform the development of new diagnostics, drugs and vaccines, and guide future public health interventions. Thus, even though Charles Darwin might not have fully appreciated the significance of infectious microbes at the time, his legacy will play a crucial role in addressing challenges such as the dual epidemics of HIV and TB.

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