9 The Immunology and Pathogenesis of Tuberculosis

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9.1 Introduction

Tuberculosis is a global emergency, currently aggravated by HIV, the break-down of health care systems and increases in drug resistance (Espinal et al. 2001). There are now more cases of tuberculosis than ever before in the history of mankind. The current failure to control tuberculosis is attributable to several factors that must be taken into consideration in any account of the immunology of the disease. These factors are:
1. The inadequacy of the current vaccine, Bacillus Calmette-Guerin. The protection given varies from zero to about 80% (Fine 1995).

2. Inadequate understanding of the biology of the organism itself. Mycobacterium tuberculosis can remain viable within the tissues without causing symptoms for the life of the individual (Wayne 1994) and, at least in countries with low or moderate tuberculosis endemicity, many cases of tuberculosis result from reactivation of latent infection (van Rie et al. 1999).

3. The best available chemotherapy must be continued for at least 6 months. This treatment regimen is not a realistic proposition in most developing countries, or even in the inner cities of rich ones, because the patients feel well after a few weeks and stop taking the drugs. WHO now admits that directly observed therapy short-course (DOTS), in which the patient is supervised while taking every dose of therapy, helps but does not solve the problem (Butler 2000).

4. Our inadequate understanding of the mechanism of protective immunity, which hampers efforts to design better vaccines, and the extraordinary problem of knowing how to select and test the best vaccine candidates.

5. Inadequate understanding of how to implement immunotherapy. Immunological manipulations that correct the patients’ failing immune responses may be the only way to shorten treatment regimens.

9.1.1 Latent Tuberculosis and Its Relationship to Persisters After Chemotherapy

There are two interrelated reasons for the requirement for 6-month regimens. The first is obvious and often discussed. The chemotherapy kills the vast majority of the bacteria within a few days, but there are subpopulations of “persisters” (Grange 1992). It is not clear whether these organisms are in true stationary phase (Siegele and Kolter 1992) or merely replicating extremely slowly. Nor is it clear whether these persisters, defined as organisms that survive chemotherapy, are the same as “latent” or “dormant” bacilli that remain in the tissues of the approximately 90% of individuals who show no clinical disease after infection. These bacteria are evidently controlled by the immune response, but not killed by it. Most research has addressed dormant rather than persister bacilli, though they are likely to be similar populations. It was assumed that latent bacilli are in old lesions or sites of fibrosis or calcification, where oxygen availability may be low. However, in a forgotten paper published in 1927, Opie and Aronson reported that 80% of tuberculous lesions were already sterile (as determined by culture in guinea-pigs) 5 years after the primary infection, whereas live bacilli could be found in macroscopically normal lung tissue (Opie and Aronson 1927).

A major recent advance is the detection, by in situ polymerase chain reaction of DNA, of M. tuberculosis in lung tissue from victims of accidental death with no history or post mortem signs of tuberculosis (Hernández-Pando et al. 2000a). When such samples were taken from countries with endemic tuberculosis (Ethiopia and Mexico), 30–40% of samples were positive. In contrast, no DNA of M. tuberculosis was found in samples from Norway, where transmission within the community ceased several decades ago. In the positive Ethiopian and Mexican samples, the DNA was seen in histopathologically normal tissue and was not confined to macrophages. Cell types containing M. tuberculosis DNA included type II pneumocytes, endothelial cells and fibroblasts (Hernández-Pando et al. 2000a). These observations raise the possibility that by entering cells that are not “professional antigen-presenting cells”, M. tuberculosis is able to escape detection and perhaps subvert the immune response.

9.1.2 Protection Versus Immunopathology

The second reason for the need for prolonged treatment is usually overlooked. Most tuberculosis patients have a necrotising pattern of response to M. tuberculosis, analogous to the phenomenon first noted by Koch in guinea-pigs (Koch 1891). There is overwhelming evidence that the Koch phenomenon is not a correlate of optimal protective immunity to tuberculosis. Indeed, pre-immunisation of animals so that they have a Koch phenomenon before they are challenged with virulent M. tuberculosis results in a clear and reproducible increase in susceptibility to the disease, compared to unimmunised controls (Wilson et al. 1940). This and other aspects of the Koch phenomenon are discussed in detail later. Its relevance at this point is that this inappropriate pattern of response may not correct itself rapidly during treatment. Therefore, if chemotherapy is stopped at 3 months, relapse rates are high even when the chemotherapy was an optimal rifampicin-containing one that achieved sputum negativity well before