Editorial

Immunotherapy: a new strategy for tuberculosis control?

It is an undisputed fact that modern short-course chemotherapy can cure over 95% of patients with tuberculosis, providing that the bacilli are susceptible to the drugs and that the patient complies fully with the prescribed course of treatment (1). Indeed, more research has been put into developing optimum drug regimens for tuberculosis than for any other infectious disease.

Why, therefore, did the World Health Organization (WHO) in 1993, two decades after the introduction of modern short-course chemotherapy, take the unprecedented step of declaring tuberculosis a "global emergency"? The statistics are, by now, depressingly familiar: one-third of the world's population infected, 10 million new cases of active tuberculosis and three million deaths annually, and a predicted 30-40 million needless deaths by the year 2004 unless we completely revise our control strategies (2). To this tragic scenario, the impact of the HIV pandemic may be added. Indeed, so serious is this impact that any data on prevalence are outdated by the time they are published. As if all this is not bad enough, a combination of poor drug supply, sub-optimal formulations, faulty prescribing, interrupted drug supplies, poor compliance and many other factors has led to the widespread emergence of drug and multi-drug resistance.

The obvious conclusion is that tuberculosis control measures which are irrefutable on paper have, with a few exceptions, proved singularly unsuccessful in practice (3). Unfortunately, the few 'showcase' successes have received undue emphasis in the literature. Also, despite the thoroughly researched statement of the WHO that, in terms of years of good quality human life saved, treatment of tuberculosis is among the most cost-effective of all therapeutic interventions, the extent of global financial aid allocated to control of this disease is derisory (2). One of the problems is the extraordinary stigma attached to tuberculosis. As early as 1908, Leonard Williams complained of the backsliding and complacency of the medical profession (4), and the subsequent introduction of anti-tuberculosis drugs and BCG were more effective in eradicating interest in this disease than in eradicating the disease itself (5).

The human race needs to make an unequivocal decision very soon. Do we want to conquer tuberculosis or would we prefer the disease to continue needlessly destroying the health of millions and depriving many of their lives? Assuming that we have enough humanity to select the former option, we need to ask some very fundamental questions concerning our approach to the control of the disease.

The three major control strategies that have been intensively researched since the discovery of the tubercle bacillus by Koch in 1882 are chemotherapy, vaccination and immunotherapy. The great benefits of chemotherapy cannot be doubted but, as outlined above, its deployment has been faced with serious difficulties, and its future usefulness is threatened by multi-drug resistance. Few pharmaceutical companies have the incentive to search for new anti-tuberculosis drugs; those agents emerging in recent years, such as quinolones and macrolides, were developed for other purposes. Even if a powerful new agent was to be found, it would soon lead to yet another form of drug resistance unless the entire strategy of drug use and control is radically revised. Vaccination with BCG has certainly saved the lives of many children who would otherwise have developed serious forms of primary disease such as tuberculous meningitis. By contrast, the impact of vaccination on the infectious (post-primary) forms of tuberculosis has been minimal and BCG has therefore contributed little to the overall conquest of the disease.

Large sums of money are being invested in 'molecular biology' with the hope of characterizing protective epitopes and producing novel, recombinant, vaccines. Clearly, it is to be hoped that this intensive and costly work will lead to
much more effective vaccines capable of preventing post-primary as well as primary disease, rather than a mere re-invention of the wheel. It should be noted, however, that even if such a vaccine is produced, its evaluation in the human population will be fraught with very serious problems and will take considerable time.

In view of the difficulties and drawbacks of the conventional measures, we need to seriously consider novel ones. In this issue of *Respiratory Medicine*, results of clinical trials of an innovative form of tuberculosis control, namely immunotherapy with a heat-killed suspension of *Mycobacterium vaccae*, are presented in two papers (6,7). The concept of immunotherapy has not been universally accepted and the approach taken over the last decade by Stanford *et al.* has not been free from criticism, sometimes quite hostile. Thus, a recapitulation of the history of this immunotherapeutic approach, the difficulties encountered in its clinical evaluation and the support of the concept from recent advances in immunology is indicated.

Despite the fact that tuberculosis is such a prevalent and widespread disease, the human immune response is usually very good. Only 5% of persons infected by the tubercle bacillus develop clinically evident primary disease within 3 yr of infection, and only a further 5% develop post-primary disease due to endogenous reactivation or exogenous re-infection years or decades later. Thus, in the absence of an obvious immunosuppressive disorder such as HIV infection, the tubercle bacillus is non-pathogenic in 90% of those infected. This begs the obvious question as to the nature of the difference between this protected majority and the minority of persons who develop the disease. For decades it has been suspected that immune responses leading to protective immunity on the one hand and to tissue-destroying hypersensitivity and progression of disease on the other are qualitatively different (8). In 1975, Lefford postulated that the two opposing responses might be due to different T-lymphocyte populations, or to a single population at different stages of maturation (9). Recently, this postulate has been confirmed by the finding that 1-helper cells mature into two functional types, Th1 and Th2, and that the cytokines produced by one type inhibit the other maturation pathway (1). As a result, an immune response tends to become ‘locked in’ to one or other pattern of response (11). In many cases, an infection elicits (fortunately!) a protective response, but if for some reason the host is locked in to an inappropriate response, the response itself contributes to tissue damage and progression of disease. There is now ample evidence that a Th1 response is required for protection against tuberculosis, whereas a Th2 (or mixed Th1 and Th2) response leads to tissue damage resulting, for example, in extensive pulmonary cavitation (12-14). Once the disease process of tuberculosis is established, endocrine changes due, at least in part, to the effect of cytokines on the adrenal gland, further enhance Th2 maturation and progression of the disease (15). Accordingly, recent immunological findings indicate that a therapeutic measure able to switch from a Th2 to a Th1 response would be of great benefit in tuberculosis. In this context, heat-killed *M. vaccae* has been shown to be a powerful Th1 adjuvant (12).

The story of *M. vaccae* as an immunotherapeutic agent began, however, before these fascinating immunological discoveries threw light on its mode of action. The story, in fact, stemmed from the observations that the protective efficacy of BCG varied greatly from one region of the world to another. In one area of Uganda, it is particularly effective in protecting against both tuberculosis and leprosy (16). This indicates that whatever affords protection must be common to *M. tuberculosis* and *M. leprae*, and antigenic analysis has shown that what is common to these bacilli is common to all mycobacteria. This, in turn, led to the hypothesis that the determinant of protection in the Ugandan environment would be a free-living mycobacterium which, if isolated, might be harnessed as a vaccine against leprosy. As a result of a long series of investigations, a strain of *M. vaccae* capable of inducing skin test reactivity and other correlates of protective immunity in patients with leprosy and tuberculosis was discovered (17). After extensive safety studies, it was tentatively introduced as an immunotherapeutic agent against human tuberculosis in 1987, and the results led to guarded optimism (18). This was when many problems began. The community of tuberculosis workers had by then become so ‘locked in’ to the dogma that
The cure of this disease could only be achieved by a very long course of several chemotherapeutic agents that the idea of stimulating the patient's innate defence mechanisms by a single injection appeared preposterous and outrageous. Sadly, the enormous amount of work on immunotherapy in the pre-chemotherapy era, including that by Koch, has been largely forgotten.

The only way to prove efficacy of this new form of immunotherapy was to undertake extensive, well-controlled, clinical trails but these are very costly. Requests for funding for such trials failed because there was no evidence that the new therapy would work - a veritable 'Catch 22' situation! Consequently, Stanford et al. had little choice but to conduct a series of small studies, often under very difficult conditions, in a number of developing countries with the generous support and co-operation of dedicated local workers (19). Although without exception these studies pointed to a beneficial effect, critics complained that, because the studies had not been conducted to the very rigorous so-called 'good clinical practice' requirements of clinical trials, the results were, at best, anecdotal. Fortunately, funding was eventually obtained by launching a small company on the London Stock Exchange and extensive, well-controlled and monitored clinical studies of a standard required by regulatory authorities are underway in South Africa and London. Patient intake in the former study was completed early in 1996 and results are expected by early 1997.

The requirements for such studies raise a further problem and a paradox. For ethical reasons, it is necessary to provide all patients enrolled into the trials with a supervised, WHO-approved course of therapy which, as stated above, is expected to cure well over 95% of drug-susceptible cases. Thus, though for good reasons, immunotherapy is being evaluated under conditions least likely to demonstrate a highly significant effect. One of the papers in this issue illustrates this problem: there was little difference in the cure rate between the test and control groups with drug-susceptible disease, as both responded so well to chemotherapy (6). Also, the immunotherapy was given 1 month after starting chemotherapy, which now appears not to be the optimal time, and the rapidity of clearance of bacilli from sputum in the test and control groups was not compared. Nevertheless, other indicators of recovery including resolution of pulmonary lesions point to a beneficial effect of immunotherapy. The second paper shows a greater effect of immunotherapy when given to 'difficult-to-treat' patients (7). Even greater differences between patients and controls were observed in a study in Kano, Nigeria, where drug supply was very inadequate and there was the additional complicating factor of HIV infection (20).

If all patients with tuberculosis were diagnosed accurately before they had infected other people, if they had drug-susceptible disease and if they received a full curse of directly observed therapy, short-course (DOTS), tuberculosis could be conquered (1). But we live in a real world in which tuberculosis is an ever-growing nightmare. Immunotherapy is not a miracle cure; it has never been intended to be more than an adjunct to anti-tuberculosis drugs, although it may enable short-course chemotherapeutic regimens to become even shorter. It does, however, appear to offer promise in those all too common situations in which chemotherapy alone fails due to drug resistance, lack of suitable drugs and problems of non-compliance (21). If we are to conquer tuberculosis, we need a well-funded global campaign spearheaded by the WHO which will not only deploy the available control measures to their best effect, but will incorporate innovations, such as immunotherapy, as and when they arise.

The WHO declaration of tuberculosis as a global emergency should have shaken health services and funding bodies out of complacency and backsliding, and freed them from dogmas established decades ago. If not, in the words of Louis Pasteur, the (tubercle) bacillus will have the last laugh.

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References


