

EDITORIAL

The mouse footpad model

PHILIP DRAPER

38 Boreham Holt, Elstree, Borehamwood, Herts WD6 3QG, UK

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It may be hard, now that *Mycobacterium leprae* is just another entry in the large catalogue of pathogens whose DNA sequence is known and leprosy is just another treatable bacterial disease, to understand the excitement generated by the mouse footpad model when it was introduced. It is, after all, not obviously exciting: 10,000 bacilli are injected into the hind footpad of a normal mouse. This is the lowest dose that allows any organisms to be found when the footpad is homogenized and the suspension is stained and examined with a microscope. After a wait of several months, during which the mouse remains healthy and its footpad is macroscopically normal, about 1 million bacteria can be found in the footpad. There is no spread of infection to other parts of the animal, and no further increase in bacterial numbers occurs throughout its life.

One needs to understand the situation at the time. The association of *M. leprae* with the disease leprosy had been discovered by Armauer Hansen in the nineteenth century, but it had never been possible rigorously to show that the bacterium caused the disease. The organism could not be cultivated in any laboratory medium, and no reproducible animal model was known. Metabolically *M. leprae* seemed almost inert, though experiments were hard to perform and interpret because the only available bacteria were obtained from human biopsies and were heavily contaminated by host tissue. Though the disease was treatable it was not curable, and there was no method, apart from laborious and doubtfully ethical human trials, to investigate any potential new drug. Study of the immunology and pathology of leprosy was frustrated by being limited to studies on people; since diagnosis of leprosy was only possible long after the original infection had occurred, the development of the infection was opaque. A number of people—scientists and clinicians—had realized that hugely increased knowledge obtained in other fields should be applied to leprosy research, to try to control this continuing global problem, but exactly how this could be done was not clear.

The discovery of the mouse footpad model by Charles Shepard was characteristic of that remarkable man. Many attempts had been made to infect a variety of animals without success, always using large inocula. Shepard had the experimental skill and the patience to use minimal inocula and observe the results, and to be certain that the model was reproducible. Also characteristic was that he realized that he would be unable to exploit all the possible applications of his model, so he encouraged collaborators. A remarkable group of people assembled and, in an informal manner, shared the field. In particular, Shepard concentrated on the bacteriology of the infection, Dick Hilson and Lou Levy on its use in

developing and comparing anti-leprosy drugs, and Dick Rees and Graham Weddell on the immunology and pathology of the infection. (Many others were involved; those named may be regarded as ‘team leaders’.) There was also a major effort to train people in many parts of the world in the use of the technique, and especially in the rather difficult and demanding process of counting *M. leprae* in suspensions with a microscope.

The effect of all this on the understanding and treatment of leprosy was spectacular, and the model retains a place even nowadays. The realization that immunologically suppressed animals are more susceptible to infection with *M. leprae*, and the subsequent discovery of the armadillo model have made the mouse footpad model less important as a potential source of bacilli, but it would still be the method of choice for testing a potential new anti-leprosy drug, or for the routine measurement of viability of a suspension of bacilli. The model did not immediately convince everyone; some maintained that the mouse infection was quite unlike the human infection, but this position became untenable as the details of the footpad infection were studied. Some held that human leprosy was caused by some quite different pathogen, or even by a combination of pathogens, a theory which could only finally be disproved when it became possible to apply molecular biological techniques to *M. leprae*. (It may be noted that Shepard was also among the first to try to apply molecular biology to the leprosy bacillus.) However, the theory had already become scarcely believable, given the practical results obtained with the mouse footpad model.

A few mysteries remain. There was a systematic discrepancy between the counts and, especially, the assessment of morphology (which was known to be correlated with viability) obtained in Shepard’s and Rees’ laboratories. A complex series of collaborative experiments was planned and initiated to resolve the matter, but completion and analysis was prevented by the death of Shepard. By studying *M. leprae* from different sources, and subculturing them through numerous generations of mice, Shepard found reproducible strain differences, displayed as time taken to reach a ‘plateau’ of growth in the footpad and the exact numerical level of the plateau when it was reached. Unfortunately these strains were lost before it was possible to discover, by molecular biological techniques devised later on, what genetic differences were involved. It is probably also true that the explanation of the limitation, by site and by numbers, of the growth of *M. leprae* in normal mice is not fully understood, though it clearly involves cellular immunity.

Nonetheless, it is hard to underestimate the impact that the mouse footpad model made on the disease, and it is entirely appropriate that this issue of *Leprosy Review* should contain an extensive review of the model.