Epidemiol. Infect. (2005), **133** (Suppl. 1), S9–S10. © 2005 Cambridge University Press
doi:10.1017/S095026880500422X

2. A glanders-like disease in Rangoon

Whitmore A. J Hyg 1913; **13**: 1–34

AN APPRECIATION BY DAVID DANCE

Public Health Laboratory, Plymouth, UK
(david.dance@HPA.org.uk)

'The opportunities of a pathologist at a large Eastern Hospital are many; but his time for research work is short, and his conveniences are few.' So begins this landmark paper written by Alfred Whitmore and published in the journal in 1913 [1]. He goes on to demonstrate just how well that short time can be used by someone with the energy, intelligence and scientific rigour in order to make the most of those opportunities. I first read this paper 15 years ago and have re-read it many times since, usually reflecting on how remarkably little our knowledge of melioidosis has advanced since 1913. I notice something new each time I read it and, most importantly of all, each time it is an absolute pleasure to read. How many modern scientific papers leave one feeling the same way?

Whitmore had trained in medicine in Cambridge and London. Not long after qualifying, he joined the Indian Medical Service, and was sent out to Burma to establish a new laboratory in Rangoon General Hospital. Within two years he and his assistant, C. S. Krishnaswami, had stumbled across what they astutely recognized as a new disease. Soon after the establishment of the laboratory, Whitmore had reported to the Rangoon authorities a number of cases of human glanders which, in those days before widespread motor transport, was an important scourge of horses but a rare cause of infection in man. In the ensuing search for more cases, Whitmore and his colleagues detected the first case of this new disease during post-mortem examination of a 40-year-old Burman morphia addict, who had died after a 10-day febrile illness. He was found to have numerous abscesses at the site of his injections and cheesy consolidation of the lungs, from which smears suggested the possibility of glanders. This suspicion was questioned when no apparent link to horses could be identified. Whitmore's attempts to grow the organism were immediately successful and initially suggestive of a particularly luxuriant growth of the non-motile *Bacillus mallei* (the causative agent of glanders), until animal inoculation experiments revealed a motile organism. Here serendipity (or perhaps this was just Whitmore's modesty in failing to acknowledge his intrinsically enquiring mind) intervened. Rather than accepting this finding as indicative of contamination with bowel flora, the workers went on to show that the non-motile organism they had first observed had lost its motility after a few days cultivation, but regained it on subculture. Thus, Whitmore knew he was dealing with a new disease.

Whitmore's paper goes on to describe 38 cases of the disease seen over an 18-month period, in all but one of whom the diagnosis was made post mortem. He describes graphically the patho-anatomical features of each case, and recounts his bacteriological and animal experiments in meticulous detail. The organism was isolated from all 38 cases, proved highly virulent and lethal for guinea-pigs, and pure cultures of the organism were obtained from the experimental animals at post mortem, thereby elegantly fulfilling Koch's postulates. He was even able to initiate fatal infection in guinea-pigs by contaminating their feed and drink. Whitmore proposed the name *Bacillus pseudomallei* for this organism, and although it has undergone many taxonomic changes since his day, the specific epithet proposed by Whitmore has been retained in its current name, *Burkholderia pseudomallei*. Its close relationship to the causative agent of glanders has also been confirmed by modern molecular techniques. Indeed, strict taxonomists might

regard them as one and the same species. It is perhaps a shame that the epithet 'whitmori' has not immortalized Whitmore's contribution, although French workers still refer to the 'Baccille de Whitmore'. The name for the disease, melioidosis, incidentally, was not coined by Whitmore but by Stanton and Fletcher some 8 years later [2].

Whitmore recognized the disease as a septicaemic process which usually, but not invariably, affected the lung, and not infrequently led to lesions elsewhere, particularly in the liver, kidney and spleen, cultures of the latter frequently yielding his new bacillus. As far as the route of infection was concerned, Whitmore yet again proved very perceptive. Although 31 of his 38 cases bore marks of morphia injections, giving rise to the later nickname 'morphia injectors' septicaemia' [3], Whitmore did not jump to the obvious conclusion that the infection had been introduced by contaminated injections, but analysed the facts more thoroughly. He recognized that the wastrels and vagabonds of society 'were over-represented amongst the subjects on whom he was permitted to conduct autopsies'. He also noticed that, in most of the cases, there was no evidence of localized infection with his bacillus at the site of injections, and concluded that the reason for the association was that the 'morphia habit is so disastrous to the well-being of its victims.' We now know that *B. pseudomallei* usually behaves as an opportunistic pathogen, more often associated with underlying diseases such as diabetes mellitus these days, and so yet again Whitmore's acute powers of observation led him unerringly to the right conclusion. We also know that some cases of melioidosis are, in fact, acquired by inoculation, usually when directly contaminated by the soil or muddy water that constitute the natural habitat of this environmental saprophyte. This only accounts for 5–25% of cases, however, and we still have no idea how the remainder are acquired, so it may yet prove that Whitmore was correct to suggest that some are acquired from contaminated food and drink.

The paper in the *Journal of Hygiene* was not the first published description of melioidosis, but was perhaps more widely accessible than Whitmore's publication the previous year in the *Indian Medical Gazette* [4], and more comprehensive than his brief description of the disease at a meeting of the British Medical Association, published in the *British Medical Journal* in 1912 [5]. The remarkable achievement of this work was to recognize the new disease and to carry out all the work necessary to prove its aetiology, with strict attention to the scientific method, in conditions of limited resources, and in almost total isolation. There are lessons for all of us in this.

After this discovery early in his career in Rangoon, Whitmore remained there until 1924, becoming deeply involved in the establishment of the Burma Medical School. Latterly, he returned to the Department of Pathology in Cambridge, where he was noted for his stimulating teaching of several generations of undergraduates and his meticulous research. He died in 1946.

Although he was still deeply engaged in research into coronary thrombosis at the time of his death, he never again quite matched the discovery earlier in his career, but then again, which of us now will ever describe an entirely new disease almost single-handedly. In 1998, Professor Nick White, who has led a research programme on melioidosis in Thailand since 1986, arranged for the Wellcome Trust, who have supported this research programme, to sponsor a plaque commemorating Whitmore's discovery to be hung in Whitmore's old laboratory in Rangoon General Hospital.

Coincidentally, as I was in the process of preparing this appreciation, a colleague who had just retired and was throwing out her files, sent me her copy of Whitmore's paper. She described it as 'written at a time when no-one worried about the length of a scientific paper'. Perhaps that is because they knew how to write one!

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