Pseudomonas pseudomallei: danger in the paddy fields

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'Whitmore's disease', 'moriah injector's septicaemia', 'the great mimicker' and 'Vietnamese time-bomb' are some of the more colourful names which have been given to melioidosis since it was first described in Burma by Whitmore & Krishnaswami (1912). Pseudomonas pseudomallei has caused outbreaks of infection amongst animals in such diverse settings as a Hong Kong dolphinarium and zoos in Paris (Galimand & Dodin, 1982). It received considerable attention as a cause of illness amongst French and American soldiers in Vietnam (Howe et al., 1971), and at one stage was considered as a potential agent for bacteriological warfare (Levi, 1960). Until relatively recently, however, melioidosis was usually regarded as a rare and esoteric tropical disease, found only in south-east Asia and northern Australia. The provision of modern microbiological facilities in rural areas of Thailand has unearthed large numbers of both mild and life-threatening P. pseudomallei infections (ChaoWagul et al., 1989; Leelarasamee & Bovornkitti, 1989), suggesting that melioidosis may be greatly under-diagnosed where laboratory facilities are less well developed. In addition to south-east Asia, sporadic cases have been diagnosed in the Indian subcontinent, central Africa and central and south America (Leelarasamee & Bovornkitti, 1989). The factors which influence the local incidence of clinical melioidosis are poorly understood, and the true worldwide distribution and incidence of the disease are therefore unknown.

Melioidosis is a strikingly seasonal disease, with approximately 80% of cases in north-east Thailand presenting during the rainy season from June to November (ChaoWagul et al., 1989; Dance et al., 1989a). These infections are presumably recently acquired, since P. pseudomallei is an environmental saprophyte, and is most easily isolated from soil and water during the rainy season (Leelarasamee & Bovornkitti, 1989). In Thailand, most patients are rice-farmers, who are thought to contract infection through cuts and abrasions sustained whilst working in flooded rice-paddy (ChaoWagul et al., 1989; Leelarasamee & Bovornkitti, 1989). Experimental animals can be infected by inhalation and ingestion of P. pseudomallei, but the importance of these routes in naturally acquired infection is uncertain. Iatrogenic infections are occasionally reported (Jenkins et al., 1990), but human-human transmission has been reported only once (McCormick et al., 1975), which questions the value of the barrier nursing and chemoprophylaxis of contacts that are sometimes recommended (Sheppard et al., 1990). Infection is seen in all age groups, whilst males outnumber females 3:2.

Relatively little is known about the pathogenesis of P. pseudomallei infection. Although melioidosis may affect apparently healthy individuals, the disease behaves predominantly as an opportunistic infection in man. 70% of patients with septicaemic melioidosis in Thailand have underlying diseases; most commonly diabetes mellitus or chronic renal failure (ChaoWagul et al., 1989; Leelarasamee & Bovornkitti, 1989). A wide range of immunopathology is associated with both these conditions, and the precise deficits which render an individual susceptible to melioidosis are unknown. It is likely that cell-mediated immunity plays an important role in control of P. pseudomallei infection, so the spread of the acquired immune deficiency syndrome in endemic areas may unmask many further cases of melioidosis. P. pseudomallei possesses several possible virulence factors, although the importance of each in the pathogenesis of natural melioidosis is obscure. These include endotoxin, a heat-labile exotoxin, and several potentially tissue-damaging digestive enzymes (Leelarasamee & Bovornkitti, 1989). There is increasing evidence that intracellular survival of P. pseudomallei plays an important role in the disease, particularly in the long latent periods and relapses after treatment which gave rise to the term 'time-bomb disease' (Prusksachartvuthi et al., 1990).

The clinical spectrum of P. pseudomallei infections is extremely wide, and it is perhaps something of a historical accident that these various clinical pictures are grouped together under the name melioidosis, whereas there is no equivalent name for P. aeruginosa infections, for example. There is also much overlap between sub-types of the disease, with the result that no entirely satisfactory classification has been devised. The usual outcome of contact between man and environmental P. pseudomallei appears to be asymptomatic seroconversion, or perhaps trivial infections which are not brought to medical attention (ChaoWagul et al., 1989; Leelarasamee & Bovornkitti, 1989). In some studies, serological evidence of past infection has been present in as many as 47% of normal individuals (Khupulsup & Petchclai, 1986), and in rural rice-farming communities the prevalence may be still higher. At the other end of the spectrum, approximately 60% of melioidosis cases seen in Ubon Ratchatani had positive blood cultures (White & Dance, 1988). Most of these patients presented with the picture of Gram-negative septicaemia, with evidence of multi-system failure and widespread metastatic infection, particularly in the lungs, liver and spleen (ChaoWagul et al., 1989). The remaining 40% had localized infections, most commonly a cavitating pneumonia often confused
with tuberculosis. Skin and soft-tissue infections, liver or splenic abscesses, supplicative parotitis in children and lymphadenitis are other common manifestations (DANCE et al., 1989a; LEELARASAMEE & BOVRONKITT, 1989).

The clinical diagnosis of melioidosis is fraught with difficulty because of the broad spectrum and non-specific nature of clinical manifestations. Within an endemic area, the diagnosis should be considered in all patients with community-acquired septicaemia, particularly in the presence of multi-nodular pneumonia and hyperglycaemia or uraemia. The identification of Gram-negative rods in pus, sputum or urine may also help, although the classical 'safety-pin' bipolarity is not always seen. _P. pseudomallei_ is easy to grow and identify (DANCE et al., 1989c), although the use of selective media will increase the yield from sites with a normal flora (WUTHIEKANUN et al., 1990). The indirect haemagglutination test is most widely used for serodiagnosis of melioidosis, but lacks specificity in populations regularly exposed to the organism in the environment (CHAOWAGUL et al., 1989). Tests for the detection of specific immunoglobulin M antibodies to _P. pseudomallei_ show greater specificity for the detection of active disease, and enzyme-linked immunosorbent assays for this purpose have recently been described (ASHDOWN et al., 1989; KUNAKORN et al., 1990). What is urgently needed is a rapid test to assist with therapeutic decisions in life-threatening infections, for example to detect _P. pseudomallei_ antigens or nucleic acids directly in clinical specimens. Such assays are under development, but await validation in clinical use (WONGRATANACHEEWIN et al., 1990).

Resuscitation, intensive care and surgical drainage of abscesses are all of paramount importance in the management of patients with melioidosis. Antibiotic therapy has, until recently, been based on anecdotal regimens which have not been assessed prospectively. _P. pseudomallei_ is intrinsically resistant to many antimicrobials, including the aminoglycosides and early β-lactams, and is thus totally unresponsive to the early β-lactams, and is thus totally unresponsive to the empirical regimens used to treat community-acquired septicaemia in many tropical regions (DANCE et al., 1989b). The third generation cephalosporin ceftazidime has been shown to halve the mortality of acute, severe melioidosis, and is now the treatment of choice (WHITE et al., 1989), although several other agents possess promising _in vitro_ activity and warrant further assessment. Many problems remain, however. The cost of ceftazidime and other new β-lactams may be prohibitive as _P. pseudomallei_ is intrinsically resistant to many antimicrobials, including the aminoglycosides and early β-lactams, and is thus totally unresponsive to the empirical regimens used to treat community-acquired septicaemia in many tropical regions (DANCE et al., 1989b). The optimum duration of treatment, and appropriate oral agents for 'maintenance' therapy and treatment of mild infections, remain to be defined. Chloramphenicol, tetracyclines, co-trimoxazole and amoxicillin/clavulanic acid are all currently used for this purpose, but in north-east Thailand relapse of infection has been seen in up to 30% of survivors of severe melioidosis, despite treatment for at least 2 months (and longer in patients with persisting abscesses or osteomyelitis: W. Chaowagul _et al._, unpublished data). The emergence of resistance in _P. pseudomallei_ during treatment has been a further problem with both 'conventional' agents and the newer drugs alike (DANCE et al., 1989b).

The past decade has seen a great resurgence of interest in 'Whitmore's disease', accelerated by the recognition of its importance as a public health problem in north-east Thailand. Whether this is an isolated quirk produced by a combination of ecological, sociological and medical phenomena, or a reflection of the true prevalence of the disease elsewhere, remains to be determined. Many other fascinating questions are posed by melioidosis and _P. pseudomallei_, and with the armamentarium of techniques at our disposal in the 1990s, many answers should be rapidly forthcoming.

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References


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