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COWDRIA RUMINANTIUM INFECTION IN THE MOUSE: A REVIEW

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ABSTRACT

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The current knowledge of the pathogenicity, clinical signs and mortality of artificial infections by syringe inoculation of *Cowdria ruminantium* in laboratory and wild strains of mice is reviewed. It is concluded that a wide spectrum of pathogenicity for mice exists in stocks of the organism.

INTRODUCTION

The disease heartwater, so called because of the effusions into the pericardial sac of domestic ruminants, has been known since 1838 (Neitz, 1947) and was shown to be due to a rickettsia *(Rickettsia ruminantium)* by Cowdry (1925). The name *Cowdria ruminantium* was later suggested by Moshkovski in 1947 (Philip, 1974).

No such disease has ever been recognized to exist in mice as a result of natural infection. The search by scientists for a suitable laboratory model for the study of *C. ruminantium* has led to the isolation of various stocks of the organism which can subsist or thrive in the mouse.

THE DISEASE IN LABORATORY MICE

Pathogenicity and mortality

In accordance with the suggestion by Wassink, Franssen, Uilenberg & Perie (1987), following the recommendations made by WHO (Anon., 1978) in regard to the terminology of trypanosome populations and by Irvin, Dobbelaere, Mwamachi, Minami, Spooner & Ocama (1983) for populations of *Theileria*, the term 'stock' is used to describe the various isolated uncloned and not strictly defined populations of *C. ruminantium*.

The disease in laboratory mice is complicated by 3 important factors: the existence of a variable degree of pathogenicity between different stocks of *C. ruminantium*, a variation in susceptibility of strains of laboratory mice to some stocks of the organism, and a variable pathogenicity of some stocks according to the route of infection.

The first isolation of a stock of *C. ruminantium* which was highly pathogenic to laboratory mice was that of Du Plessis & Kümm (1971) since designated the Kümm stock. Three other stocks were also shown to be highly pathogenic: the Kwanyanga stock (MacKenzie & Van Rooyen, 1981), the Nonile stock (MacKenzie & McHardy, 1984) and the Welgevonden stock (Du Plessis 1985).

There also exist stocks of the organism which, although producing no clinical signs of disease in mice, can nevertheless be passaged successfully in laboratory mice and still maintain pathogenicity for sheep and cattle. The K2 Malagasy stock was passaged by Ramisse (Uilenberg, 1983) 100 times in mice treated with corticosteroids. Haig (1952), using five different isolates including the Mara and Ball 3 stocks, was able to maintain the organism in laboratory mice for 90 days and still retain pathogenicity for sheep. Successive passages were not accomplished in the mice though 9 alternating passages between sheep and mice were achieved. Similar observations were made by Ramisse & Uilenberg (1971) with a Malagasy stock. Working with the Zeerust stock berg (1983) was able to achieve one passage in mice though no clinical signs of disease were noted in the mice.

The Umm Banein, São Tomé and Nigerian D225 stocks were not pathogenic to mice and could not be passaged (Uilenberg, 1983). Similar findings were reported for the Gardel and Moribabougou stocks by Logan, Endris, Birnie & Mebus (1985) and for 15 stocks isolated from infected animals on Guadeloupe in the Caribbean by Barré & Camus (1983). The variable pathogenicity of the various stocks is summarised in Table 1.

These findings have supported the contention that there is a whole spectrum of pathogenicity to mice of stocks of *C. ruminantium* (MacKenzie & Van Rooyen, 1981; Uilenberg, 1983; Du Plessis, 1985).

A variation in susceptibility to the Kwanyanga stock of *C. ruminantium* by strains of laboratory mice was demonstrated by McHardy & MacKenzie (1984). It was shown that the Kwanyanga stock was most virulent in Balb/c mice and least virulent in CD-1 mice. Intermediate virulence was noted in CBA/CA, C3H/HE, C57/BL6 and DBA/2 mice. However the Kümm stock was equally virulent in all six mouse strains (Table 2).

TABLE 1 Pathogenicity of stocks of *C. ruminantium* to mice

Pathogenic stocks	
Kümm stock	(Du Plessis & Kümm, 1971)
Kwanyanga stock	(MacKenzie & Van Rooyen, 1981)
Nonile stock	(MacKenzie & McHardy, 1984)
Welgevonden stock	(Du Plessis, 1985)
Infective but non-pathogenic stocks	
Mara stock	(Haig, 1952)
Ball 3 stock	(Haig, 1952)
K2 Malagasy stock	(Ramisse, 1970)
Malagasy stock	(Ramisse & Uilenberg, 1981)
Zeerust stock	(Uilenberg, 1983)
Non-infective stocks	
Umm Banein stock	(Uilenberg, 1983)
São Tomé stock	(Uilenberg, 1983)
Nigerian D225 stock	(Uilenberg, 1983)
Guadeloupe stocks	(Barré & Camus, 1983)
Gardel stock	(Logan *et al.*, 1985)
Moribabougou stock	(Logan *et al.*, 1985)

TABLE 2 The variation of susceptibility of strains of laboratory mice to the Kwanyanga and Kümm stocks of *C. ruminantium*

Mouse strain	Kwanyanga stock		Kümm stock	
	Mortality/10	Days to death	Mortality/10	Days to death
Balb/C	10	9,0 ± 0,0	10	9,7 ± 0,5
CBA/CA	10	9,7 ± 0,48	10	9,6 ± 0,5
C3H/HE	10	10,4 ± 0,52	10	10,0 ± 0,0
C57/BL6	10	10,7 ± 0,67	10	10,1 ± 0,32
DBA/2	10	12,0 ± 1,25	10	9,6 ± 0,5
CD1	7	12,1 ± 2,48	10	9,2 ± 0,42

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TABLE 3 Pathogenicity of three stocks of *C. ruminantium* to a single strain of laboratory mice: Variation according to route of infection

Stock	Route of infection[1]	Mortality %
Kümm	i.p.	>90
	i.v.	>90
Kwanyanga	i.p.	11
	i.v.	97
Nonile	i.p.	30
	i.v.	98

[1] i.p. intraperitoneal
i.v. intravenous

Andreasen (1974), working with the Malagasy K2 stock, compared pathogenicity and infectivity in homozygous congenitally athymic (nude) mice, heterozygous nude mice and homozygous normal mice. After 8 passages the blood from the homozygous normal mice was no longer infective to sheep but blood from the two nude mice strains retained its infectivity for sheep. Mortality attributed to *C. ruminantium* infection was only evident in the homozygotic nude mice.

The route of administration also appears to affect pathogenicity for mice in a variable manner among the murinotropic stocks of the organism.

The Kümm stock is highly pathogenic to mice when injected by either the intraperitoneal or intravenous route causing a high mortality rate in 10–14 days (Du Plessis & Kümm, 1971). Both the Kwanyanga and Nonile stocks are highly pathogenic when the intravenous route of infection is used resulting in 97 % mortality after 6–22 days, and 98 % mortality after a period of 5–22 days (Table 3). The mortality of the mice was reduced to 11 % and 30 % when infected by intraperitoneal inoculation (MacKenzie & Van Rooyen, 1981; MacKenzie & McHardy, 1984; Uilenberg, 1983). In a separate series of investigations using the Kwanyanga stock, Swiss mice infected intravenously with homogenised liver from moribund mice in Snyder's medium, had a mortality rate of between 60 and 100 %, but when the same inoculum was administered intraperitoneally a mortality rate of 10 to 30 % resulted (Logan *et al.*, 1985).

The K2 Malagasy stock was seen to behave in a similar manner to the Kwanyanga and Nonile stocks (Ramisse & Uilenberg, 1971). The Welgevonden stock was initially pathogenic to laboratory mice infected intraperitoneally with either infected liver or spleen homogenates but at the fifth passage a marked decrease in infectivity occurred (Du Plessis, 1985).

Clinical signs

The clinical signs of the disease in laboratory mice have been described for the Kwanyanga, Nonile and Welgevonden stocks. All the reports refer to infections in outbred Swiss Albino mice.

Visual signs of disease in the mice infected with the Kwanyanga stock were usually evident within 24 h prior to death and were observed as an increase in respiratory rate, piloerection and lethargy. Signs of encephalitis in the form of incoordination were occasionally seen in moribund mice (MacKenzie & Van Rooyen, 1981).

Prozesky & Du Plessis (1985) reported an incubation period of 10–14 days with tachypnoea, lethargy, anorexia and ruffled coats in mice infected with the Welgevonden stock.

A constant feature of the disease is the hypothermia which is evident within 12–72 h prior to death. The mice are cold to the touch and monitoring of rectal temperatures has shown that in mice infected with the Kwanyanga stock, the body temperature falls by as much as 10 °C prior to death.

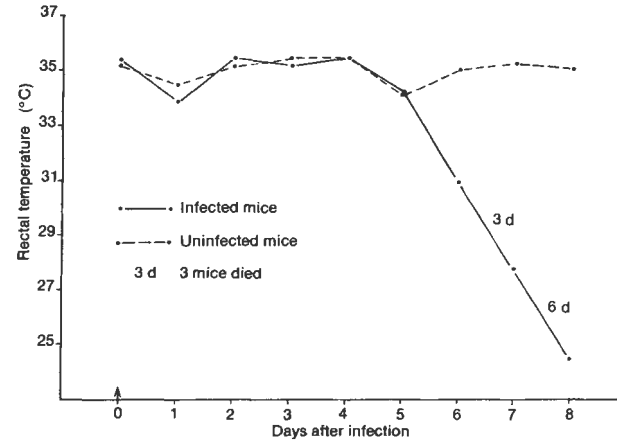

FIG. 1 The mean rectal temperatures of mice infected with the Kwanyanga stock of *C. ruminantium*

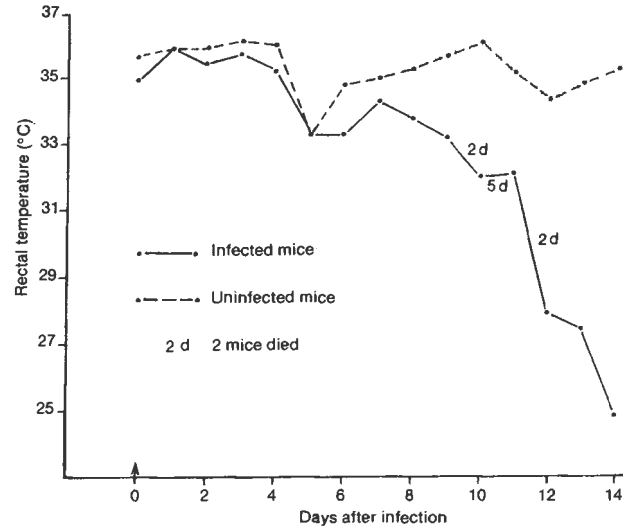

FIG. 2 The mean rectal temperatures of mice infected with the Nonile stock of *C. ruminantium*

In 10 infected mice in which the rectal temperature was monitored, an obvious drop was noted in 2 mice within 12–24 h of death, in 6 mice within 24–48 h of death and in 2 mice within 48–72 h prior to death. The mean temperature of control mice was recorded as 35,1 °C and of infected mice as 34,9 °C up to day 5 after infection. The mean temperature became progressively lower and in one surviving mouse was recorded at 24,5 °C on Day 8. A noteworthy feature was the complete absence of pyrexia in any of the mice. Similar results were obtained with the Nonile stock (MacKenzie, unpublished data, 1986). The results of this investigation are shown in Fig. 1 & 2.

Investigation of the infectivity of mouse tissues has shown that with the Kwanyanga stock, mouse tissues are infective on Day 6 after infection coinciding with the onset of hypothermia as reported above (MacKenzie & Van Rooyen, 1981).

THE DISEASE IN FERAL MICE

Pathogenicity and mortality

There has been little investigation conducted into the pathogenicity of *C. ruminantium* in wild mice. The possible survival of the organism in the striped mouse *(Rhabdomys pumilio)* was reported by Hudson & Hen-

derson (1941). In a series of experiments to elucidate the susceptibility of feral mice to the Kwanyanga stock it was shown that the multimammate mouse *[Praomys (Mastomys) coucha]* was highly susceptible to challenge by intravenous inoculation of *C. ruminantium* in tissues from infected moribund laboratory mice. Of two mice challenged, one died 7 days and the other 12 days after inoculation. Tissues from these mice proved infective to laboratory mice and subsequently to sheep, in which the organism was demonstrated microscopically. Attempts to infect the striped mouse either by inoculation or by infected nymphal ticks were unsuccessful. The nymphal ticks failed to attach to the hosts (MacKenzie & McHardy, 1984). In the latter investigations no observations were made on the clinical signs of the disease in experimentally infected wild mice.

CONCLUSIONS

Investigations have shown that a complete range of pathogenicity for laboratory mice exists in isolated stocks of *C. ruminantium*. The route of administration and choice of mouse strain may influence the infectivity and pathogenicity of isolates of the organism. Some wild rodents are susceptible to the murinotropic stocks of *C. ruminantium*. An absence of pyrexia and marked hypothermia were features of the disease in laboratory mice infected with two murinotropic stocks.

FUTURE RESEARCH

The murinotropic stocks of *C. ruminantium* provide a suitable model for laboratory investigations of the organism which can be conducted at reasonable costs. In this context the use of such models for the screening of chemotherapeutic agents is important. The pathological aspects of the disease which result in the death of the mammalian host require investigation and the mouse model may be suitable for such work.

There is a need to investigate the possible role of wild rodents in the epidemiology of the disease in endemic areas.

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