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ANIMAL HOSTS IN EXPERIMENTAL LYMPHATIC FILARIASIS RESEARCH

by

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Introduction

Lymphatic filariasis is a menace in much of the hot and humid tropical world. The disease in humans is caused by the filarial nematodes *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi* and *B. timori* (brugian filariasis). The massive lymphoedemas which may follow the onset of chronic disease cause disfiguring or even crippling conditions and the accompanying socio-economic repercussions. It is estimated that 90.2 million people are afflicted by lymphatic filariasis world-wide who show microfilaraemia and/or the clinical disease; of these, 81.6 million are accountable to bancroftian filariasis and 8.6 million to brugian filariasis. In addition, 905 million people living in lymphatic filariasis endemic areas, where active transmission of the disease is known to occur, remain potentially exposed to the risk of infection (107).

Besides the three known causative agents of human lymphatic filariasis, a number of other species of *Brugia* and *Wuchereria*, which dwell in the lymphatic vascular system of a variety of animal hosts, are known to occur. Thus, *B. pahangi* occurs in dogs and cats in Malaysia (13), *W.* (=*B.*) *patei* in cats and dogs in Pate Island, Kenya (14), *B. buckleyi* in hares in Sri Lanka (36), *B. ceylonensis* in dogs in Sri Lanka (60), *B. guyanensis* in coati-mundi in Guyana (71), *B. beaveri* in racoon in Louisiana (8), *B. tupaiae* in tree shrew in Malaysia (72), *W. kalimantani* in leaf-monkeys in Indonesia (75) and *B. lepori* in rabbits in Louisiana, USA (37). An unnamed *Brugia* sp. found in cat in California (12) has been added to the list. Though relatively rare, cases of zoonotic brugian filariasis, mostly as non-patent infections in humans are reported in the New World (73).

The various aspects of host-parasite relationships including the mechanism of pathogenesis of lymphatic filariasis in humans can be adequately studied on those animal models susceptible to lymphatic dwelling filariae and the findings extrapolated. It would, therefore, be ideal if the species of lymphatic dwelling filariae could be successfully maintained and propagated in a convenient laboratory host. Although many of the above mentioned filariid nematode species occurring in the lymphatics of animals may appear of academic interest only, few of these have evolved as most popular parasite models in lymphatic filariasis research. In the following account the various animal definitive hosts which have been evaluated for their susceptibility to

lymphatic dwelling filariae are treated and their potential in lymphatic filariasis research as models is examined.

Laboratory rodents

Jird (Meriones unguiculatus)

The jirds, *M. unguiculatus*, were successfully infected with the third-stage infective larvae (L3) of *B. pahangi* and subperiodic *B. malayi* subcutaneously (sc) by Ash and Riley (9, 10). Their findings are summarised in Table 1. Up to six weeks post-infection with *B. malayi* in the hind limb, most of the parasites were present in the lymphatics distal to the popliteal gland and from seven weeks onwards most of these were present in the heart-lungs and some in the testes (43). The patent infections of these parasites were established in a larger proportion of the male jirds than in the females as shown in Table 2 (6, 7, 44).

TABLE 1

Development of third stage larvae of *Brugia pahangi* and *B. malayi* in jirds following subcutaneous inoculation (9, 10).

Brugia spp.	Third moult	Fourth moult	Prepatent period	Proportion of the exposed animals developing patent infection	Localization of adult worms
B. pahangi	6-9 DPI	18-24 DPI	67 DPI	76 %	Heart-lungs, testes
B. malayi	7-8 DPI	29-35 DPI	93 DPI	68 %	Testes, heart-lungs

DPI: Days post-infection.

TABLE 2

Relative susceptibility of male and female jirds to *Brugia pahangi* and *B. malayi* infections (6, 7, 44)

Brugia spp.	Sex of jird host	Prepatent period	Proportion of the exposed jirds developing patent infection	Proportion of the inoculated larvae reaching adult stage
B. pahangi	Male	67-76 DPI	82 %	More adult worms were present in the male jirds than in females
	Female	87-94 DPI	12 %	
B. malayi	Male	129 DPI (mean)	96 %	17 %
	Female	117 DPI (mean)	43 %	8 %

DPI: Days post-infection.

Jirds have also been infected with success with *B. pahangi* L3 by intraperitoneal route (ip), by oral route by instilling the larvae in the mouth

and by intra-ocular route by depositing the larvae on the eye corneal surface. The establishment rate of adult worms was twice as high by ip route as by sc route; the majority of the adults in the former case were found free in the peritoneal cavity with a few in the lymphatics of the peritoneum and the spermatic cords. Also, the microfilariae in the former case accumulated mainly in the peritoneal cavity (2, 33, 64). The jirds exposed by oral route showed patent infections and the majority of the adult worms were localised in the heart-lungs and the thoracic cavity (53, 54). Following oral and sc infection in the groin, the larval recovery rates 10-11 days post-infection were 13.9 % and 23.1 % respectively; in the case of oral infection the larvae were localised in the anterior carcass, namely, heart-lung and thorax whereas in case of sc infection these were found in the posterior carcass, namely, the abdominal viscera and testes (92, 93). The jirds showed patent infections also following intra-ocular infection; an appreciable number of the adult worms were present in the heart and the pulmonary artery and a proportion in various lymphatics and the peritoneal cavity (1).

The course of development of *B. pahangi* or *B. malayi* in the jirds following the bite of infected mosquito is closely parallel to the one induced by sc inoculation of infective L3 (2). About 3.4 % of the larvae carried by the mosquitoes reached maturity in the jirds (109).

A dog- and a jird-strain of *B. pahangi* did not vary in their infectivity to the jirds although the jird-strain produced twice as high microfilaraemia as the dog-strain (101). Immature specimens of *B. pahangi* from infected jirds were transplanted into naive recipient jirds and these matured to microfilaria producing stage. The microfilariae of *B. pahangi* of feline origin transfused intravenously (iv) into naive jirds survived in their peripheral blood until seven days of the transfer (15, 111). Superimposed infections of *B. pahangi* conferred some degree of acquired immunity in jirds (33, 62) although some evidence to the contrary is also available (61).

The infective larvae of subperiodic Samoan strain of *W. bancrofti* inoculated sc in the jirds did not develop beyond the fourth larval stage; these were localised in the testes and the associated tissues (11). Similarly, the infective L3 of periodic Liberian strain of *W. bancrofti* inoculated ip or into the orbital sinus of jirds developed only up to the fourth larval stage and were localised in the heart-lungs. The microfilariae of this nematode transfused iv in the naive jirds could survive in their peripheral blood for upto nine days (110, 111).

Multimammate rat (Mastomys natalensis)

Following sc infection, the developing stages and the adults of *B. pahangi* were recovered from the heart-lungs, testes and lymph glands and 31.5 % of the exposed mastomys developed microfilaraemia (3, 5). This host could also be infected with success by subperiodic *B. malayi* by sc route; the mean prepatent period was 136 days, 81 % of the exposed animals became microfilaraemic and the adult worms were localised in the lungs (37 %), testes (29 %) and lymphatics (34 %) (76). The males of mastomys were more susceptible to *B. pahangi* (5) or to *B. malayi* (70) than the females.

Sänger et al. (81) studied the development of *B. pahangi* and *B. malayi* in mastomys in exhaustive detail. Their observations are summarised in Table 3. The mastomys model was used for experimental studies on *B. pahangi* by the present authors; an infection inoculum of 150 freshly harvested infective L3 were used for sc injection in the groin region of young animals and this produced unfailing patent infections in all the exposed animals 78 to 91 days later (26, 100).

TABLE 3
Susceptibility of multimammate rats to *Brugia pahangi* and *B. malayi* infections (81)

Brugia spp.	Site of subcutaneous inoculation	Prepatent period	Proportion of animals showing patent infection	Adult worm recovery rate	Percent of adult worms localised in heart-lungs
B. pahangi	Neck region	73 DPI	100 %	33.1 %	78.5 %
	Groin region	85 DPI	100 %	22.4 %	35.7 %
B. malayi	Neck region	107 DPI	95.5 %	21.1 %	84.4 %
	Groin region	116 DPI	66.7 %	11.1 %	61.7 %

DPI: Days post-infection.

In the mastomys exposed to infective larvae of periodic *W. bancrofti* by inoculation into the orbital sinus, the parasite developed only upto fourth larval stage by 175 days of infection and were localised in the heart-lungs (110).

Golden hamster (Mesocricetus auratus)

The golden hamster has been infected with success with *B. pahangi* or *B. malayi* by several authors since the early sixties (9, 10, 39, 63, 90, 108) although a smaller proportion of exposed animals show successful infection than jirds or mastomys. Neither the age nor sex of the host influence the susceptibility to *B. pahangi* (90). The worm establishment rate of *B. pahangi* in male hamsters was 14 %, the prepatent period was 89 days and the worms were localised in the lymphatics of the testes, epididymis and the spermatic cords besides the other lymphatics and heart-lungs (69). The lymphatic pathology due to *B. pahangi* in hamsters is of more severe intensity than in jirds (67).

The PD4 inbred hamsters showed a higher susceptibility to *B. pahangi* than the outbreds; the adult worm recovery rate was 16.9 % in the former and 3.9 % in the latter (68). Similarly, the MHA and PD4 inbreds appeared more susceptible to subperiodic *B. malayi* than the CB, LSH or LHC inbred strains though even in the more susceptible strains, the worm establishment rate was low (2.5 to 6.5 %) and not all the exposed animals showed patent infections. The worms were localised in the heart-lungs (18). In another study, using *B. pahangi* and based on its prepatent period (69 days), worm establishment rate (36 %) and localization in the host (heart-lungs, testes), it was claimed that the male hamster of GN strain is a good alternative to the jird model (85). However, despite that the worm establishment rates and the prepatent periods in the jird and PD4 hamster were identical, the microfilaraemia in the jird was significantly higher than in the PD4 hamster (17).

Rat (Rattus norvegicus)

In a small proportion of intact or splenectomised white rats exposed to *B. pahangi* or subperiodic *B. malayi* infective L3, the filariids matured to adult stage and showed microfilaraemia of extremely low grade (3, 5, 39). A detailed study showed that about 55% of the white rats exposed to *B. pahangi* became microfilaraemic, the prepatent period ranged from 55 to 105 days and the adult worms were mainly present in the heart-lungs (55). The susceptible rats were selectively bred with a view to further enhance the susceptibility of the offsprings to *B. pahangi*. When compared with the parent stock, the offsprings showed somewhat increased susceptibility (90, 91).

Few laboratory rat strains, namely, the Lewis, Fisher-344 and Brown Norway were shown most susceptible to *B. pahangi,* WF and AC1 strains were moderately susceptible and the Buffalo strain was resistant. About 65% of the exposed Lewis rats showed microfilaraemia (49, 52). Also, the athymic rats, PVG-rnu/rnu, were more susceptible to *B. pahangi* than their normal counterparts, PVG (RTI); all the 30 athymic rats exposed to the infection showed adult parasites and/or microfilaraemia, only 20 of the 34 normal rats similarly exposed did so (25).

Mouse (Mus musculus)

Among the mice exposed to *B. pahangi* by ip route, a higher proportion showed microfilaraemia and produced higher adult worm burden than those exposed by sc route (51, 95, 96). It was shown that certain inbred stains of mice were more susceptible to this infection than the outbreds; among the inbreds the BALB/c mice were more susceptible than the other inbred strains such as C57BL/10, C3H/He, 101, and CBA/Ca. Sixteen weeks following ip exposure with the infective L3 of *B. pahangi*, the BALB/c mice showed the adult worm recovery rate of 7.5% and the microfilariae were present in the peritoneal cavity (59, 96).

As was the case with the athymic rats, the congenitally nude mice, C3H/HeN(nu/nu), were highly susceptible to *B. pahangi* when compared with the phenotypically normal litter-mates. In the nude mice the infection became patent 50 days after infection and the average adult worm recovery rate was 15%. The T-cell deprived (thymectomized and treated with antithymocytic serum) CBA mice were more susceptible than the normal CBA mice. Also, the neonate Swiss mice were more susceptible to *B. pahangi* than the eight-week old Swiss mice. These evidences support that the susceptibility of mice to *B. pahangi* infection is cell mediated (50, 51, 95, 96, 103).

In none of the athymic C3H/HeN (nu/nu) mice exposed to the infective L3 of Haitian *W. bancorfti* by sc or ip routes were the worms present at necropsy 11 to 75 days post-exposure (102).

Cotton-rat (Sigmodon hispidus)

A small proportion of the cotton-rats exposed to the L3 of *B. malayi* or *B. pahangi* developed patent infections with low grade microfilaraemia; the

prepatent period in the respective infections ranged from 92 tot 98 days and from 83 to 95 days (39, 78). Since the microfilaraemia in the peripheral blood was of extremely low grade, it was considered that the cotton-rat may not constitute a suitable laboratory host (5).

Guinea-pig (Cavia porcellus)

In the guinea-pigs exposed to *B. pahangi* or subperiodic *B. malayi* infections, neither microfilariae were ever detected in the peripheral blood nor any developing or adult worms were present in their tissues (39, 42). The procedures of splenectomy, irradiations or treatment with 6-mercaptopurine of the host were ineffective in breaking down their natural resistance to these infections (4).

Rabbit

The rabbits, *Oryctolagus cuniculus*, were refractory to *B. pahangi* or subperiodic *B. malayi* infections (27, 39).

Cat, dog and ferret

Cat

Experimental transmission of *B. malayi* from humans to cat was successfully achieved in the late fifties through the inoculation of L3 recovered from the mosquitoes, *Mansonia uniformis.* Such a transmission was also possible through the bite of infected mosquitoes previously fed on a human carrier host. The prepatent period ranged from 80 to 96 days and the microfilariae and adults found in cats were indistinguishable from those found in man (40, 104). Later, it was possible to passage the infection from cat to cat (41). The inoculated L3 reached the regional lymph glands and vessels within 16 hours and the site of their recovery from the host was, in general, related to the site of inoculation. The third larval moult occurred nine to 10 days and the last moult occurred 35 to 40 days post-inoculation; about 13 per cent of the inoculated larvae could be recovered as adults (38). In a series of experiments (45, 46, 47, 48), the migratory pattern, the sequential rate of worm recovery as also the rate of worm recovery in male and female cats and in young and old cats following inoculation of L3 of subperiodic *B. malayi* was studied in detail.

B. pahangi infection in cats had a shorter prepatent period (64-81 days) than the subperiodic *B. malayi* infection (80-107 days); the former infection also showed a higher microfilarial peak count and the microfilaraemia persisted for longer period of time than the latter (105). About 86 per cent of the cats exposed to *B. pahangi* became microfilaraemic (90). Studies on the evolution of microfilaraemia, migration, distribution and recovery rate patterns of *B. pahangi* in the domestic cat following a primary inoculation with the L3 were carried out in considerable detail (31, 94).

The cats receiving up to 20 superimposed challenge inoculations of *B. pahangi* showed three types of responses in the level of microfilaraemia; (i) in most of such cats the level of microfilaraemia either increased considerably or (ii) in a minority of the cats this level did not tend to alter for at least eight months or (iii) the level of microfilaraemia increased initially but then levelled off to a stable level and maintained for at least eight months. While those with the responses (ii) and (iii) showed a sudden decline in the level of microfilaraemia and became amicrofilaraemic over a period of time, this was not the case with the cats showing response (i). The cats which became amicrofilaraemic also showed most advanced pathology. The adult worm burden in cats receiving superimposed infections was very high since it increased proportionately up to 15 challenge inoculations, but after 20 challenges there was no further increase in the worm establishment (29, 30, 32).

Microfilariae of *B. pahangi* from the donor cats were transferred to normal cats. These could survive in the recipient cats for two to 136 days when transferred in whole blood, for up to 24 days when given in packed-cells concentrated by centrifugation while those transfused with the microfilariae isolated by membrane filtration disappeared from the peripheral circulation of the recipient and none were found 24 h after the transfer. In immune cats, however, the microfilariae disappeared from the circulation 18 h after the transfer (77).

In the cats exposed to *W. bancrofti* by inoculation of the L3, one to three larvae were recovered after 7 to 27 days post-inoculation and in none of the cases these moulted to the fourth larval stage (35, 79, 80).

Dog

Dogs receiving the L3 of subperiodic *B. malayi,* sc, developed patent infections 105-112 days post-infection; the microfilariae were still present in the peripheral blood 11 weeks after their first appearance and the adult worms were localised in the lymphatics (63). The dogs exposed to *B. pahangi* infection by instilling their L3 on to the eye corneal surface also produced patent infections 81-89 days post-exposure (1). As the infected dogs were shown to manifest a variety of clinical effects, such as lymphadinitis, lymphangitis, oedema of the limbs etc., which are closely parallel to the syndrome occurring in man, the pathogenesis, pathology and the dynamics of immune response in this host have been extensively studied (82, 83, 84, 86, 87, 88).

Ferret

The ferrets, *Mustela putorius furo,* usually show patent infections of subperiodic *B. malayi* during the third month of inoculation with 100 to 200 L3 (20, 98). However, the observed microfilaraemia was transient and most of these animals became amicrofilaraemic six months later; the average patent phase of the infection lasted 123 days. On necropsy five to eight months post-infection, 0.5 to 13 per cent of the inoculated larvae were recovered as adults and these were mainly localised in the lymphatic vessels.

Ferrets infected with *B. malayi* mimic pathological changes to the clinical features of human lymphatic filariasis; a transient microfilaraemia also showed a concurrent eosinophilia, the host became amicrofilaraemic over a period of time and showed lymphangitis and lymphoedema. As the ferrets appeared an appropriate model for lymphatic filariasis research, a number of workers have carried out exhaustive studies on anatomo-pathology and lymphangiography of the infected host (19, 21, 57, 58, 97, 99).

Primates

In the initial studies (41, 42), among the various species of monkeys exposed to the L3 of *B. malayi,* two of the 11 long-tailed macaque, *Macaca irus,* became microfilaraemic 81 and 93 days post-exposure and both the two exposed rhesus monkeys, *M. rhesus,* became microfilaraemic 77 and 80 days post-exposure. On the other hand, it was shown that *M. irus,* the short-tailed macaque, *M. nemestrima,* and *M. rhesus* were refractory to to *B. pahangi* infection. These were the early indications suggesting that *B. malayi* is better adapted and has a preference for monkey host than *B. pahangi* (28). Subsequently, the dusky leaf monkeys, *Presbytis obscurus,* were shown susceptible to subperiodic or periodic *B. malayi* infections; in this host microfilaraemia appeared 84 days post-exposure and a nocturnal periodicity of microfilaraemia was evident (63). *M. mulatta* were also susceptible to subperiodic *B. malayi;* those receiving double infection inoculations showed highest levels of microfilaraemia and those receiving multiple inoculations showed lowest levels (106). In as yet most successful experimental infection on a large scale (66), all the 148 silvered leaf monkeys, *P. cristata*, inoculated sc with the larvae of subperiodic *B. malayi* showed patent infections; the prepatent period was between 66 and 76 days. It is claimed that *P. cristata* is an excellent non-human primate model for the subperiodic brugian filariasis.

The callitrichid primates, because of their low susceptibility to *B. malayi* or *B. pahangi,* were considered unsuitable as laboratory models (34).

It had been assumed that *W. bancrofti* infection is restricted to man since no natural non-human host or experimental transmission to animals to adult stage were ever reported. However, a break through was achieved when the Taiwan monkeys, *M. cyclopis,* some splenectomised and others chemically immunosuppressed, were exposed to L3 of *W. bancrofti* of Indonesian and Chinese origins (22, 23, 24). The worms recovered 8-11 days post-exposure were in the L3 stage, those recovered 14-38 days post-exposure were in L4 stage and the ones recovered 42-103 days post-exposure were young adults. A proportion of the exposed monkeys showed microfilaraemia after 8-18 months and the patent phase lasted 5-12 months. From 42 days and onwards, most worms were localised in the testes of males and in the females few worms were recovered from lymph glands and carcasses. In subsequent years the leaf monkeys were also shown susceptible to *W. bancrofti* of different origins (56, 74, 89). *P. cristata* were exposed to the L3 of this filariid originating from a human donor in Jakarta. The microfilariae appeared in the peripheral circulation 206-285 days post-exposure and the adult worms were

localised in the pericapsular region and major lymphatic vessels of the inguinal lymph gland (74). The Thai leaf monkeys of various species were exposed to the L3 of subperiodic rural Thai strain of *W. bancrofti;* in a proportion of these animals the filariid could develop to adult stage and the prepatent period ranged from 241 to 287 days (56).

W. kalimantani, a newly discovered nocturnally periodic monkey filarriid and taxonomically very closely related to *W. bancrofti,* occurs naturally in 31 per cent of leaf monkeys, *P. cristata,* in Kalimantan island, Indonesia (75). This filariid has been transmitted experimentally to *P. cristata* through sc inoculation of the L3 and show a prepatent period of 532 days (16).

Conclusions

Clearly, the last three decennia have witnessed a substancial progress in the endeavours of researchers in developing adequate animal models of lymphatic dwelling filariids. The laboratory rodents, jirds and multimammate rats, have been most successfully studied for their susceptibility to *B. pahangi* and *B. malayi* and have emerged as very widely accepted laboratory models for experimental studies. These hosts have been extensively used for the study of the developmental biology of the two filariids. Because of the ease and economy, these rodents have been exploited as models for primary screens of chemotherapeutic agents as filaricides. The host-parasite relationships in brugian filariasis including host immunomodulation in response to infection, humoral and cell mediated immune response, immunity and vaccination studies have been carried out on these rodents. These hosts are cheap sources for obtaining various developmental stages of the parasite for the study of their cuticular antigen profile.

The domestic cats are natural hosts of *B. pahangi* and *B. malayi* in Malaysia. In Indonesia, the silvered leaf monkeys and cats are the only known non-human natural hosts of subperiodic *B. malayi* infection. Conceivably, as is evident from the foregoing account, under experimental conditions also these hosts can be successfully infected with these two *Brugia* spp. Generally speaking, whereas *B. pahangi* develops more readily in the carnivores, *B. malayi* has a preference for monkey host. However, as against the laboratory rodent models, the use of cat, dog and monkey hosts as laboratory models have limitations because of the involved costs and the routine inconveniences in maintenance and handling.

An important milestone in recent years in experimental lymphatic filariasis research has been the successful establishment of *W. bancrofti* in monkeys to microfilariae producing adult stage. This filariid, hitherto considered a specific parasite of man, has been raised experimentally in Taiwan monkeys and leaf monkeys. These are rare hosts and their maintenance and breeding under laboratory conditions are difficult and costly. It would be inappropriate to assign an animal model of lymphatic filariasis which is most close to humans in presenting the gross and histological changes of the infection. Apparently, the longevity and bipedal nature of humans are unique; these features may exacerbate the onset of chronic pathogenesis of lymphstasis and lymphoedema. However, one may assume that, because of closer

phylogenetic association to man, monkey models would be useful in drawing conclusions. On the other hand, since the infected dogs and ferrets mimic the clinical manifestations seen in human lymphatic filariasis, the pathogenesis of *Brugia* spp. infections in these hosts has been exhaustively studied.

As overwhelming evidences are available that the jirds, multimammate rats, cats, dogs and ferrets constitute ideal experimental hosts of *B. pahangi* and *B. malayi* and various monkeys serve as adequate hosts for *B. malayi* and *W. bancrofti,* there is no paucity of experimental laboratory hosts for research studies on various aspects of the disease process including the therapeutic evaluation of anthelmintics. *P. cristata* infected with *B. malayi* have been used for chemotherapeutic studies (65).

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