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## Fitness advantages in multiple blood-feeding: the *Aedes aegypti* example

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### Abstract

Only a few of the over three thousand species of mosquitoes in the world have evolved a close association with human settlements (i.e. domestic habits) and a subsequent heavy reliance on humans as their primary blood source. These include the most important vectors of human parasitic diseases, i.e., malaria, dengue and filariasis. Representatives of all three major mosquito genera have made this transition from wild to domestic environments, so this association seems to have evolved independently on several occasions due to similar environmental circumstances. Mosquito feeding preferences are not well understood in terms of either neurobehaviour or genetics but would appear, superficially at least, to be a good target for genetic transformation, i.e., turning human-feeding species into species that seldom feed on humans or transmit their diseases. Understanding how domestic species arose and the current fitness advantages for maintaining those behavioural traits is critical for assessing the potential for manipulating and reversing this process. *Aedes aegypti*, perhaps the most domesticated of all mosquito species, is used as the prime example in exploring these issues.

**Keywords:** *Aedes aegypti*; mosquito, blood-feeding behaviour, fitness

### Introduction

Blood-feeding facilitates mosquito transmission of infectious agents so it is logical to consider how blood-feeding behaviour might be manipulated to reduce or avoid transmission (Dye and Hasibeder 1991; Edman 1991; Edman and Spielman 1986; Gillett 1985; Hasibender and Dye 1988). Although specific genes regulating feeding behaviour have not yet been identified, they surely exist. Might these genes be good targets for genetic manipulation? To answer this and other related questions, perhaps the key issue to consider is just how robust is this trait? Although some mosquito species show remarkable host specificity, few of the world's 3000+ mosquito species feed primarily on humans. The few species that do, have attracted the bulk of interest in blood-feeding behaviour because of their great importance as vectors of human disease (see Table 1). How and why did human-feeding preference evolve among these species but not others? Can this behaviour be manipulated or reversed? These are the questions I will address in this article.

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Table 1. Mosquitoes reported to prefer to blood-feed on human hosts.

SPECIES	DISEASES VECTORED
<i>Aedes aegypti aegypti</i>	Dengue and Yellow Fever
<i>Anopheles gambiae sensu stricto</i>	Malaria and Wucherarian filariasis (in Africa)
<i>Anopheles funestus</i>	Malaria (in Africa)
Some other tropical <i>Anopheles</i>	Malaria (in Africa, Asia and South America)
<i>Culex pipiens quinquefasciatus</i>	Wucherarian Filariasis

## Background

Few attempts have been made to understand the underlying genetic basis of mosquito feeding preferences (Gillies 1964). However, human blood and body emanations associated with skin, sweat and breath have been fractionated and tested for over 50 years in an effort to identify and replicate the critical cues and search processes responsible for human-feeding preferences (Braks, Anderson and Knols 1999; Costantini et al. 2001; Dekker and Takken 1998; Dekker, Takken and Braks 2001; Dekker et al. 2002; Duchemin et al. 2001; Gibson and Torr 1999; Healy and Copland 2000; Healy et al. 2002; Knols et al. 1997; Mboera et al. 1997; Mboera, Takken and Sambu 2000; Pates et al. 2001a; 2001b; Sousa et al. 2001). Although complex and unresolved, such information could be exceedingly useful in developing trap-out or diversionary strategies for reducing human-biting. It could also assist in identifying genetic targets for possible manipulation of feeding behaviour using transgenic technology (Aultman, Beaty and Walker 2001). The diversity and number of host-derived cues shown to have a possible role in feeding choice are too complex for a brief, meaningful summary here. Moreover, many of the hosts utilized as blood sources by mosquitoes occur in aggregations (e.g., humans, bovines, dogs), so mosquitoes also can choose to feed on the most suitable or defenceless individuals in these species groups (Kelly 2001). Recent DNA-based studies document the non-random nature of feeding on aggregated hosts (Prior and Torr 2002; De Benedictis et al. 2003). Certain host cues employed by mosquitoes may not just signal the presence of the blood source but also its nutritional quality, and there is evidence that host choice may be reinforced through limited learning on the part of mosquitoes (McCall and Eaton 2001).

Understanding the circumstances in which human-feeding preference evolved is fundamental to any sustainable attempt to modify this behaviour. There must have been intense selection pressure for mosquitoes to acquire strategies to locate, discriminate and successfully obtain blood from hosts that maximized their fitness (Daniel and Kingsolver 1983; Ribeiro 1985; 2000). Such pressures vary among the habitat of different mosquito species. Feeding behaviour and host choice largely may have been driven by the density-dependent defensiveness of the vertebrate hosts available to a mosquito in its particular home range (Kelly 2001). Home range is generally defined by the distribution of requisite larval habitats. Stable host populations and ecological overlap between hosts and mosquitoes that bite them are prerequisites for a mosquito species to evolve highly specialized feeding preferences. One of the most sustainable environments in which mosquito feeding behaviour has been shaped (since the advent of agrarian societies) is the domestic environment, but only a few species (but in three different genera) have exploited the fact that humans provide suitable aquatic development sites for larvae, and suitable resting places and reliable blood sources for adults (Coluzzi et al. 2002). Domestication first required larval adaptation to aquatic

sites linked with human activity (Edman 1985), but these species often share other biological characteristics as well (see Table 2).

Table 2. Biologic traits commonly found among domestic mosquitoes

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1. Immatures often develop in man-made water in or near human dwellings
2. Endophagic (females feed indoors, usually at night when hosts are asleep)
3. Endophilic (adult mosquitoes rest inside houses)
4. Mating may occur indoors (male <i>Ae. aegypti</i> also are attracted to and mate near humans).

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Populations of certain forest mosquitoes became increasingly domesticated, as forests with their natural breeding sites and hosts were gradually destroyed and replaced by emerging agrarian societies (see Table 3). These species presumably acquired a fitness advantage when feeding on human blood, which in turn favoured sensitivity to cues that signalled human hosts. This is a process that is still being played out and is now intimately related to expanding human populations, agricultural mechanization (eliminating beasts of burden), diseases restricting livestock and increases in mosquito-borne infections like malaria and dengue (Coluzzi et al. 2002).

Table 3. Characteristics of environments in which human-feeding evolved.

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• Destruction of forests and natural mosquito breeding sites
• Permanent human dwellings providing forest-like environments (cool, shady, humid)
• Human storage of water during the dry season
• Permanent water storage in and around homes
• Domestic and companion animals that attract mosquitoes to villages
• Wild animals attracted to stored food in villages which also attract mosquitoes
• Mosquito species that feed on defensive hosts (e.g. rodents and wild primates)
• Less sugar sources and more blood sources, leading to a greater reliance on blood
• Expanding human populations making them the dominant mammal
• Domestic animals become unavailable/unreliable during drought and disease outbreaks.

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*Aedes aegypti*, the principle vector of dengue and urban yellow fever, is a prime example of a highly evolved domestic species and is perhaps the most suitable target for developing new strategies for disease prevention that exploit the critical and dynamic nature of blood-feeding behaviour (see Figure 1). My colleagues and I have investigated the feeding characteristics of this mosquito in dengue endemic areas in Puerto Rico and Thailand (Scott et al. 2000a; 2000b). Some of our results are summarized below to illustrate this species' extreme domesticity and the fitness advantages of its unique synanthropic life style.

### Host-feeding patterns

In both Thai and Puerto-Rican communities, blood-engorged *Ae. aegypti* were collected inside and outside houses weekly for two years. Blood-meal sources were identified by

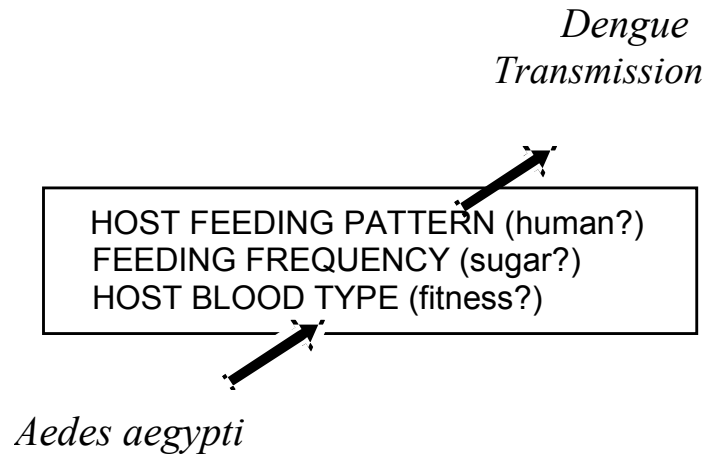


Figure 1. Blood feeding dynamics

ELISA. Regardless of the community, time of year or place of collection, about 97 percent of blood meals were from human hosts (Scott et al. 1993; Scott et al. 2000a). This was true despite the fact that many other hosts (e.g. dogs, cats, pigs, cattle, water buffalo, chickens, ducks, caged pet birds etc.) were available for mosquitoes to bite at both domestic study environments. However, most mosquitoes (~80%) were collected resting indoors and most blood-feeding appears to take place indoors as well.

We also examined the sugar-feeding behaviour of *Ae. aegypti* and unexpectedly discovered that females seldom fed on plant nectar in domestic environments (Figure 2, Van Handel et al. 1994; Edman et al. 1992). Mosquitoes from Florida were collected in a rural tyre dump away from any human dwellings, demonstrating that the lack of sugar-feeding was facultative and associated with the presence of humans in domestic environments. This led us to question what impact a lack of carbohydrate-feeding might have on the frequency of blood-feeding and the way blood-meal nutrients are utilized. Males also fed less on sugar in domestic environments and this may reflect their reduced flight demand for securing mates.

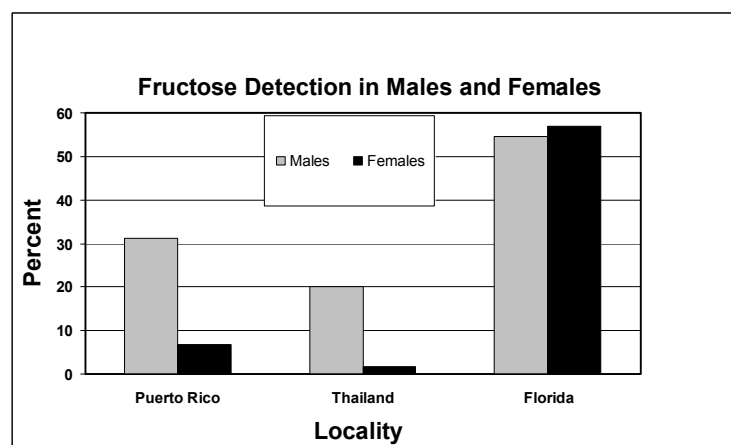


Figure 2. *Ae aegypti* sugar-feeding rates in two domestic and one non-domestic (Florida) environment.

## Blood-feeding frequency

Feeding frequency was first assessed by histological methods (Scott et al. 1993) and later by DNA fingerprinting (Chow Shaffer et al. 2000; De Benedictis et al. 2003). One-third to three-quarters of all wild-caught females contained blood and only 2-4 days were required for females to become gravid (Scott et al. 2000a). In general, the engorgement rate was higher indoors than outdoors, during the hot versus cool season and in Puerto Rico versus Thailand. Histological examination revealed that nearly one-half of all engorged females in Thailand contained more than one blood meal and about one-third of all meals in Puerto Rico were multiple. From these data we estimated that *Ae. aegypti* females take blood every 0.76 days in Thailand and every 0.63 days in Puerto Rico or 2-3 times per gonotrophic cycle rather than once, as was commonly assumed. DNA fingerprinting of the blood in engorged mosquitoes indicated a lower level of multiple feeding on different people in Puerto Rico (18%) but multiple meals taken from the same person are not revealed by this analysis. Because host selection was not random (e.g., 3 people accounted for 56%, of all blood meals in the Puerto Rican sample) significant multiple feeding on the same host might be expected.

## Host blood type

Older literature suggests that human blood is deficient in the essential amino acid isoleucine and that this deficiency led to the reduced fecundity among all species of human-fed mosquitoes that were tested. We questioned why *Ae. aegypti*, or any other species, would selectively feed on a host whose blood yields a reproductive disadvantage (Harrington, Edman and Scott 2001). Results from our subsequent experiments in which *Ae. aegypti* were artificially fed human blood or human blood supplemented with isoleucine (=high ILE blood) indicated that low-isoleucine blood did not reduce fecundity when females were offered blood daily in the absence of sugar. Surprisingly, mosquitoes fed low-isoleucine (normal) human blood accumulated significantly more nutritional reserves, especially lipids, than those fed the same blood supplemented with isoleucine (Figure 3, Harrington, Edman and Scott 2001)

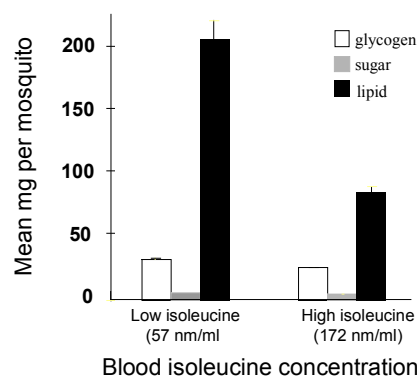


Figure 3. Nutritional reserves in *Ae. aegypti* fed normal and isoleucine-supplemented human blood through an artificial membrane.

Mosquitoes fed artificially through membranes generally take smaller blood meals, so this comparison was repeated using live hosts with naturally high (rodent) or low (human) isoleucine levels in their blood. Once again fecundity was not reduced but lipid and glycogen reserves were enhanced when females repeatedly ingested low-isoleucine

human blood (Harrington, Edman and Scott 2001). Another difference that we observed, which is undoubtedly related to the differences in nutrient reserves, was that human-fed mosquitoes survived significantly longer than those in the rodent-fed group (Figure 4, Harrington, Edman and Scott 2001).

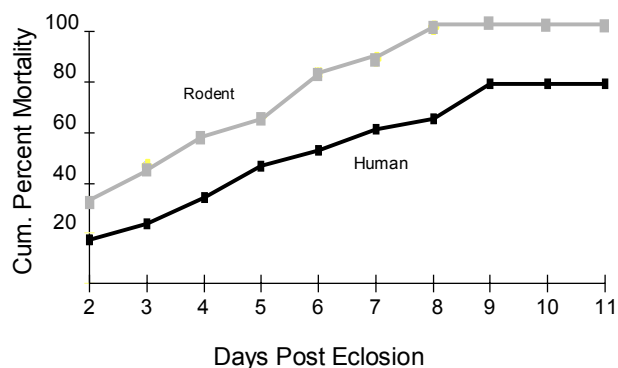


Figure 4. Accumulated daily mortality among human-fed and rodent-fed *Ae. aegypti*.

To confirm that multiple blood-feeding in a single gonotrophic cycle and lack of sugar-feeding caused the difference between our results and those in the literature that found low isoleucine to limit egg production, we repeated this experiment with uniform-sized mosquitoes that were sugar-fed and only allowed a single blood meal before fecundity was assessed. Results from this experiment, although this protocol was at odds with what we have observed in nature (i.e., little sugar-feeding and multiple blood-feeding during each gonotrophic cycle), indicated that human blood did result in few eggs when the unnatural scenario reported in the older literature was maintained (Table 4, from Harrington, Edman and Scott 2001). While not fully understood, this suggests that there is metabolic variation in the way human blood is processed compared with other types of blood (Naksathit, Edman and Scott 1999b; 1999a). Suboptimal levels of an essential amino acid may limit egg production in the short term, but it also may trigger diversion of blood resources into the lipid pool of stored reserves (Ryan and van der Horst 2000). The long-term result is that females that take only human blood accumulate more nutritional reserves so they live longer. However, they still lay a maximum number of eggs because when offered unlimited access to human hosts they feed so frequently that egg production is not inhibited by insufficient isoleucine.

Table 4. Effect of sugar-feeding with high- and low-isoleucine blood on egg production

Treatment	N	Mean <sup>1</sup> # Eggs / mg Blood Ingested ± SE (mean rank)
Human blood alone	36	13.6 ± 1.5 (29.2) <sup>a</sup>
Human blood w/ sugar	36	32.4 ± 1.9 (80.6) <sup>b</sup>
Rodent blood alone	27	19.8 ± 1.8 (44.3) <sup>a</sup>
Rodent blood w/ sugar	37	47.7 ± 2.2 (112.6) <sup>c</sup>

<sup>1</sup>Mean ranks followed by the same letter are not significantly different from each other ( $P < 0.001$ , Kruskal-Wallis test)

## Fitness

We then conducted a life-table experiment with four cohorts: (1) human blood, (2) human blood plus sugar, (3) rodent blood, and (4) rodent blood plus sugar, in order to compare the fitness effects associated with these dietary strategies (Figure 5, from Harrington, Edman and Scott 2001). These and other results (Costero et al. 1998; Morrison et al. 1999) clearly demonstrate that *Ae. aegypti* feeds preferentially and frequently on human blood and seldom imbibes plant sugar, because there is a reproductive and survival advantage associated with this feeding strategy. Frequent human-host contact associated with this feeding strategy does not increase host-induced mosquito mortality even among day-biting *Ae. aegypti*, presumably because their approach is so stealthy and their bites are so benign (Day, Edman and Scott 1994). However, their multiple feeding strategy does increase the fitness of dengue virus (Scott et al. 1997). There is evidence that the domesticated mosquito vectors of malaria (Beier 1996; Takken, Klowden and Chambers 1998) and filariasis (O'Guinn et al. unpublished data) may have evolved similar feeding strategies for similar reasons. This needs much further investigation.

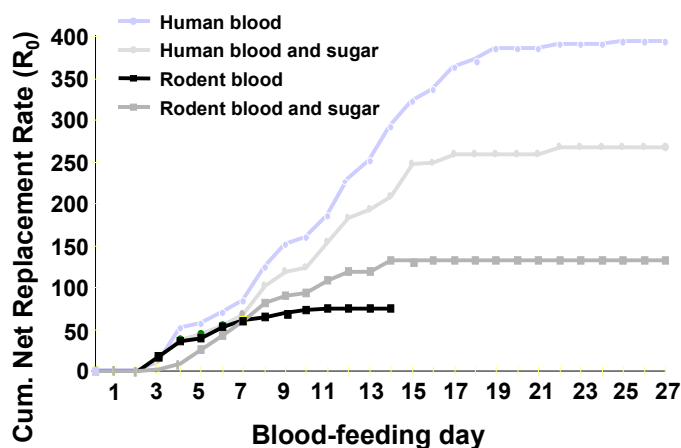


Figure 5. Life-table analysis of female *Ae. aegypti* fed four different diets.

## Impact of blood-feeding behaviour on maintenance of dengue-virus transmission

Field data for *Ae. aegypti*'s feeding behaviour can be used to demonstrate the relative impact of different feeding dynamics on vectorial capacity and the maintenance (basic reproductive rate) of dengue virus (Dye and Hasibeder 1991). In the example that follows, it is assumed that (1) 30% of the human population is susceptible (=non-immune) to dengue infection, (2) the dengue viremic period in humans averages 4 days, (3) the vector abundance in relation to humans is two bites per person per day, (4) the daily survival rate of the vector is 90%, and (5) the mean extrinsic incubation period for dengue virus is 10 days. All of these estimates are within the range of field observations that we or other investigators have made in dengue endemic areas. To demonstrate the relative impact of blood-feeding behaviour versus vector competence (the principal trait considered for genetic transformation), these components of the formula for the reproductive rate of arboviruses (Reisen 1989) are manipulated in Table 5. Two different human-feeding percentages (50 and 95%) and two feeding frequencies are

compared with two levels (80% and 20%) of vector competence for dengue-virus transmission (Table 5). The two feeding frequencies compared in this table are once every 4 days (0.25) or once per gonotrophic cycle, and 0.75, the frequency we observed in Thailand.

Table 5. Estimated dengue-virus reproductive rate with different values for blood-feeding parameters and vector competence.

Human population		Mosquito population			Vector	Mosquito feeding		$R_0$
Non-immune	Viremia	Abundance	Survival	Extrin Incub	Compe- tence	Hum. pref.	Freq.	Dengue Repro- duction
(%)	(days)	(bite/d/ man)	(daily %)	(days)	(%)	(%)	(meals/ day)	(mainte- nance $\geq 1$ )
0.3	4	2	0.9	10	0.8	0.50	0.25	=0.8
“	“	“	“	“	“	0.95	“	=1.5
“	“	“	“	“	“	“	0.75	=4.5
“	“	“	“	“	0.2	“	“	=1.1

If 80% of the *Ae aegypti* population is competent but females only blood feed once per gonotrophic cycle and only half of their blood meals are taken from humans, the virus reproductive rate (0.8) is insufficient to maintain dengue-virus transmission. If the human feeding rate is increased to 95%, a value consistent with our data from Puerto Rico and Thailand, the virus reproductive rate increases to 1.5, a level sufficient to maintain dengue virus. If the frequency of feeding is then increased to the level we observed in Thailand (i.e. 0.75), the virus reproductive rate increased dramatically to 4.5 or several times the level required for dengue maintenance. If the vector competence of this mosquito population was reduced 4-fold to only 20%, it could still sustain dengue-virus transmission ( $R_0=1.1$ ). From this example it is clear that managing the feeding frequency and human-feeding rate could have a dramatic affect on the ability of an *Ae. aegypti* population to sustain dengue-virus transmission in endemic foci. We know that the natural *Ae. aegypti* density and vector competence for dengue virus are often quite low but the high rate and frequency of feeding on humans can more than compensate and allow this unique domestic species to maintain dengue virus in many tropical regions of the world.

## Conclusions

Understanding the chemical signals that promote human-feeding preferences can be important in developing new strategies for reducing human-feeding, e.g., mosquito removal trapping that incorporates the specific kairomone blend that attracts anthropophilic mosquitoes to humans. However, any effort to accomplish reduced feeding by engineering the mosquito genome so that vector mosquitoes prefer to feed on non-human hosts or to do so less frequently must address the reality of the environment in which human-feeding preferences have evolved, because human-feeding now provides fitness advantages to the mosquito (Wekesa et al. 1997). Thus, if the environment is not changed in some significant ways (e.g., the addition of house screens, bed nets, alternative hosts, etc.) then the transformed population will likely revert to the original, highly anthropophilic genotype unless the strength of the drive mechanism is greater than the fitness cost associated with changes in feeding behaviour.



Of course the same argument could be made for mosquitoes transformed to be less parasite-competent if there are fitness costs associated with that phenotypic change.

## Postscript

Because of the inherent risks and unknowns that will accompany any effort to modify the behaviour or physiology of human-disease vectors through genetic transformation, it seems prudent to conduct proof-of-principle experiments first, using mosquito vectors of related animal diseases, e.g., avian malaria. Islands, such as the Hawaiian island, where both the parasite (*Plasmodium relictum*) and the vector (*Culex pipiens quinquefasciatus*) were accidentally introduced in relatively recent times would be ideal settings for such experiments. Rapidly declining native bird populations also might be saved as a consequence if such a preliminary experiment were successful.

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