WHY DO MOSQUITOES "CHOOSE" TO BITE SOME PEOPLE MORE THAN OTHERS?

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Biological Chemistry Department, Centre For Sustainable Pest and Disease Management, Rothamsted Research, Harpenden, Hertfordshire, AL5 2JQ helps to explain why some individuals are bitten more by mosquitoes than others

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Introduction

There is much anecdotal evidence that mosquitoes bite some people more than others. In recent years, scientists have proven scientifically that this phenomenon does actually exist and that it is likely to be mediated by differences in body odours. However, investigations have merely scratched the surface in their attempts to explain the chemical basis for differential attraction - until now. It might be logical to assume that if you are bitten less by mosquitoes, your body produces less in the way of attractants. But, recent evidence may have turned this theory on its head, suggesting that being 'unattractive' to mosquitoes is caused by an 'in-built defence system' of naturally produced compounds that interfere with the way they find their human hosts.

Mosquito sense of smell (olfaction)

Mosquitoes, like many biting insects, require a blood meal in order to produce eggs. The most dominant sense used during this process is olfaction which allows the mosquito to 'sniff out' chemicals that signify a suitable human host. Carbon dioxide (CO_2) is thought to 'activate' the mosquito to fly and also attract it towards the host. This compound is released in breath and body odour and is known to work along side certain other chemicals, such as lactic acid, 1-octen-3-ol and ammonia (see Logan & Birkett 2007 for review), as part of a "suite" of host-related olfactory signals. Although there is some suggestion that CO_2 and lactic acid might be involved in differential attraction (Acree *et al.,* 1968; Brady *et al.,* 1997; Steib *et al.,* 2001; Bernier *et al.,* 2002), no study has quantified these compounds accurately in body odour profiles and related them directly to mosquito behaviour. And since these compounds are likely to be bi-products of primary metabolism it is unlikely that they play a role in differential attraction.

Recent work at Rothamsted Research and Aberdeen University investigated the differential attractiveness of volunteers to the Yellow Fever mosquito, *Aedes aegypti*, by testing odour from their hands in a large windtunnel (Logan *et al*., 2008). The volunteers were then placed inside an aluminiumised plastic bag and their body odour was extracted (Figure 1). The extracts were analysed using coupled gas chromatography-electroantennography, a technique which uses the mosquito's antenna as a detector to identify only the relevant compounds in human body odour mixture. The study revealed that several compounds, but in particular 3 aldehydes (octanal, nonanal and decanal) and two ketones (geranylacetone and 6-methyl-5-hepten-2-one), were present in higher quantities in individual volunteers that were 'unattractive' to mosquitoes than individuals who were 'attractive'. These natural human-derived chemicals significantly reduce mosquito flight activity, demonstrating that they play a role in differential attraction. How these compounds 'interfere' with mosquito behaviour is not yet fully understood and further work is underway to determine the mechanism, however, for ease of reading, they are referred to as repellents here.

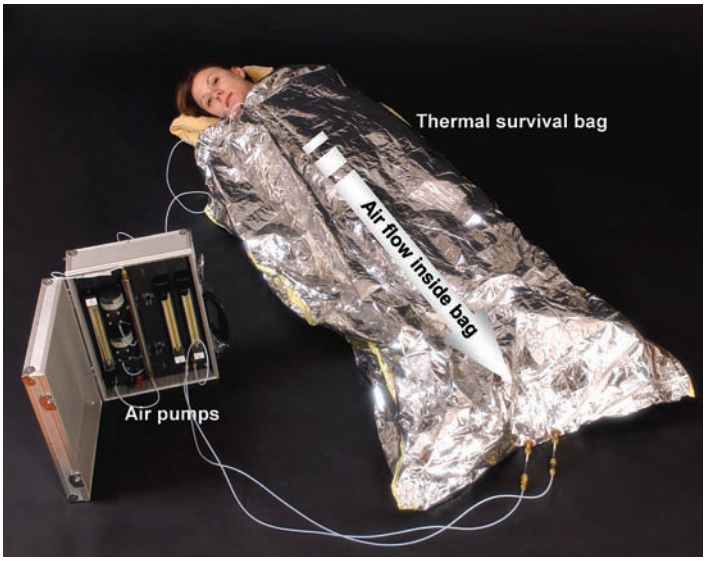

Figure 1. **'Air entrainment' set-up using a Lifesystems™ thermal bag (2.4 m x 09 m) to collect volatile odours from human volunteers.**

But why are some people bitten more than others?

Some reports say that mosquitoes may respond differentially to people of different ages, gender, reproductive status and size. It is known that odours produced by individual human beings may convey such information, so mosquitoes might detect olfactory signals associated with the above factors (Halpin, 1986; Penn & Potts, 1998). However, in the Logan *et al*., (2008) study, there was no significant association

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Table 1. Volunteer information obtained from a non-compulsory pre-experiment questionnaire.Volunteer information is divided into two groups according to level of attractiveness to mosquitoes in laboratory experiments (Logan *et al* 2008).

Volunteer number	Age group	Sex	Height (cm)	Weight (kg)	BMI	Smoker	When you are on your own how often do you get bitten?	When with others how often do you get bitten?
Y01	21-30	M	188.9	82	22.7	no	Frequently	Always
X04	21-30	F	170	57.8	20	no	Always	Always
X07	21-30	F	158	58	22.7	no	Always	Always
X08	41+	F	166	57.2	22.3	no	Frequently	Frequently
X05	21-30	F	161	45	17.6	no	Frequently	Rarely
X09	31-40	F	157	48.8	19.1	no	Rarely	Rarely
Mean			168.2	57.258	20.1			
X06	31-40	F	165	43.6	15.1	yes	Always	Always
Y04	21-30	M	183	81	25	no	Rarely	Never
Y07	31-40	M	165	54	19	no	Rarely	Never
Y05	41+	M	173	70	24.2	no	Rarely	Never
Mean			169.5	63.45	21.8			

between the responses of mosquitoes and volunteer characteristics (Table 1). This could have been a by-product of the failure to detect significant differences in a small sample size and, therefore, a larger study is needed to determine whether the above factors have any association with attractiveness to mosquitoes.

The production of natural repellents by vertebrates could be a natural defence against biting insects which could lead to an overall increase in fitness of the host by reduced risk of contracting vector-borne diseases. But fitness might also be increased by reduced distress and suffering from insect bites themselves which can be energy-depleting (Kelly, 2001). For example, cattle and sheep that are heavily attacked by biting insects have a reduced milk yield, a reduced weight gain, a decreased feeding efficiency, a lower fecundity and are more prone to disease. This can lead to substantial economic losses in many countries (Byford *et al.,* 1992). Human hosts may be affected by bites in a similar sort of way. For example, the forestry industry in Scotland reportedly loses 40 % of working hours due to the bites of the Scottish biting midge, *Culicoides impunctatus* (Hendry & Godwin, 1988).

From the perspective of the insect, could it be that unattractive individuals signify a blood-meal that would be too difficult to access? Vertebrate hosts are commonly found in groups, for example, domestic animals in fields and pens, birds in roosts, game animals in herds and human beings in dwellings. Therefore, if some hosts provide a better reward than others, biting insects should be able to select those hosts and avoid others (Kelly, 2001). The avoidance of inappropriate hosts may benefit insects as there can be intense selection pressure to feed on the most accessible blood meals (Kelly, 2001). As feeding success can be partially determined by host defensive behaviour, mosquitoes might prefer to feed preferentially on least defensive hosts (Charlwood *et al.,* 1995). This would suggest that the most defensive hosts produce more natural repellents. However, demonstrating that mosquitoes avoid defensive hosts has never been done and would be difficult to assess using human subjects.

Mosquitoes might also want to avoid people that are injured, diseased or malnourished. Although such individuals might be less host-defensive, they may provide a poorer quality blood meal than healthy individuals (Kelly, 2001) and there is some evidence that mosquito fitness can be affected by blood-feeding on different individuals (personal observation). There are numerous reports that certain chemicals are associated with physiological conditions. For example, isoprene, acetone and methanethiol, identified from exhaled breath, blood and urine are associated with cancer (Miekisch *et al.,* 2001; Phillips *et al.,* 2003). Volatile compounds have also been reported for other diseases including heart disease, schizophrenia, rheumatoid arthritis, pneumonia and inflammatory bowel disease. The key question is: do these 'marker chemicals' for diseases have any effect on the host location process of a mosquito? Interestingly, 6-methyl-5-hepten-2-one is thought to be produced by stressed cattle that are under attack by cattle flies and, when applied to individual cows as a slow-release formulation, it reduces fly loads significantly (Birkett *et al.,* 2004). Therefore, 6-methyl-5-hepten-2-one and other natural repellent chemicals could be associated with 'stress' in human beings. We also know that mosquito behaviour can be influenced by alterations in human odours caused by disease. For example, children infected with the malarial parasite (*Plasmodium falciparum*), at the stage where it is transmissible to mosquitoes, attract more *Anopheles gambiae* mosquitoes than uninfected children, or those infected with the asexual (non-infective) stage (Lacroix *et al.,* 2005). This suggests that body odour changes when a person is infected with the malaria parasite. The volatile chemicals associated with malaria have not yet been identified and we do not know whether mosquitoes respond differently to

human beings that are 'stressed' due to other factors. However, modern techniques could now provide an efficient way in which to perform such investigations. The identification of volatile compounds associated with health disorders could even lead to the development of novel non-invasive diagnostic techniques.

Genetic association

It is unknown whether the production of repellent chemicals has evolved from selective pressures or is a by-product of metabolic processes (Rebollar-Téllez, 2005). If it has evolved as a natural defence trait in some human beings, one might expect there to be genetic evidence for this. Kirk *et al.,* (2000) performed a survey on adolescent twins and demonstrated that there was indeed a strong genetic influence on frequency of being bitten by mosquitoes of children between the age of 12 and 14. Other studies have demonstrated that odours of twins are similar and thus may indicate the importance of genetic make up on body odour (Roberts *et al*., 2005). These odour cues of genetic similarity could be used in mate selection (Wedekind & Furi 1997) or kin recognition (and therefore inbreeding avoidance; Weisfeld *et al.,* 2003) and are thought to be heavily influenced by major histocompatibility complex (MHC) genes (Pen & Potts, 1999). Odours that are associated with MHC genes are produced from MHC derived peptides or their metabolites, microflora on the skin, or are produced by the metabolism of peptides by the microflora (Leinders-Zufall *et al.,* 2004; Penn & Fischer, 2004). Since olfactory signals for mosquitoes are believed to be produced in a similar way, it is not too outrageous to suggest that there could be a direct correlation with MHC genes although this is far from proven. But if there is a genetic component to the production of olfactory cues used by mosquitoes, one would expect that human populations, particularly those in areas with high selection pressure such as Africa, would produce repellent chemicals through natural selection. Although there is no evidence for this currently, in some places, 80% of malaria cases are prevalent in only 20% of the population which suggests that this may have happened (Smith *et al.,* 2005). However, disease prevalence may also be related to immunity and it is, therefore, difficult to separate this from attractiveness to mosquitoes.

Conclusions

Much evidence now exists for the differential attraction of mosquitoes and other blood-feeding insects to their hosts but there is little scientific evidence to describe why this phenomenon occurs. It is hypothesised that there is a link between certain human characteristics (including physiological 'stress' or illness) and level of attractiveness, and indeed there is much anecdotal evidence to support this (Table 2). However, to determine this accurately, larger studies involving many individuals chosen randomly from the human population are required. The methods used in the Logan *et al* (2008) study could form a template on which to base such investigations.

It was recently demonstrated that natural repellent chemicals are associated with differential attraction of mosquitoes to human beings (Logan *et al*., 2008), but to understand why, we must also figure out how the chemicals are produced. It is possible that the chemicals are produced by skin cells, bacteria on the skin, or both. Revealing the biosynthetic pathway will give a better understanding of how the body provides natural resistance to biting insects and could aid the development of targeted control for individuals that are most susceptible to insect attack. It could even lead to a new control technology by way of induced production of these chemicals in human beings using drugs. If the production of olfactory stimuli used during the host location process by biting insects is genetically determined this could

Table 2. Anecdotal comments, provided in letters and e-mails from the public, about their experiences with differential attraction of mosquitoes.

Anecdotal topic	No. of times mentioned	Comments
Age/sex	5	• Lady gets badly bitten by mosquitoes on holiday and husband, doing the same activities, rarely gets bitten. Their daughter (age 12) rarely gets bitten but her son (age 7) does • Man got bitten lots when younger, but after age 50 rarely gets bitten • Man gets bitten more than his wife
Health		
– diabetes	2	• Lady bitten when diagnosed as having diabetes. After treatment with insulin she rarely gets bitten
– cold/general health	2	• Bitten less when fit and have low body mass index • Not bitten and never gets a cold
– cancer/tumours	2	• Arm that had tumour on does not get bitten but other arm does • Rarely bitten when diagnosed with cancer. After treatment for cancer this person always gets bitten
– blood pressure	1	• Lady and female friends get bitten more when taking medication for high blood pressure
– Chronic fatigue syndrome	2	• Lady and daughter rarely bitten when suffering from ME. After ME treatment, they get bitten more often and associate this with a sour smell
Blood type	1	• O+ blood = always bitten; O- blood = never bitten
Reproductive status	3	• Not bitten during pregnancy • Lady bitten before hysterectomy but afterwards and with oestrogen medication, not bitten any more
Food	12	• Bitten less if consume: garlic, alcohol, yeast tablets, marmite, Vitamin B12, Vitamin B3

lead to breeding programs for livestock to select for unattractive individuals. However, for now, the genetic basis of differential attraction is undefined and requires further investigation.

The key to effective mosquito control is to understand the pest, its host and the interaction between the two. This is clearly a complex process but several studies have already identified natural chemicals that can alter mosquito behaviour (such as the attractants and repellents described above) and these can be exploited in monitoring and control strategies. However, better technologies are still needed. More than one million people die from malaria and five hundred million people become severely ill each year. Recent UN estimates report that this is likely to soar to almost one billion in the years to come due to climate change. It is, therefore, crucial that we understand more about the interaction between mosquitoes and their hosts.

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