OLFACTION IN MOSQUITO–HOST INTERACTIONS
The Ciba Foundation is an international scientific and educational charity (Registered Charity No. 313574). It was established in 1947 by the Swiss chemical and pharmaceutical company of CIBA Limited—now Ciba-Geigy Limited. The Foundation operates independently in London under English trust law.

The Ciba Foundation exists to promote international cooperation in biological, medical and chemical research. It organizes about eight international multidisciplinary symposia each year on topics that seem ready for discussion by a small group of research workers. The papers and discussions are published in the Ciba Foundation symposium series. The Foundation also holds many shorter meetings (not published), organized by the Foundation itself or by outside scientific organizations. The staff always welcome suggestions for future meetings.

The Foundation's house at 41 Portland Place, London W1N 4BN, provides facilities for meetings of all kinds. Its Media Resource Service supplies information to journalists on all scientific and technological topics. The library, open five days a week to any graduate in science or medicine, also provides information on scientific meetings throughout the world and answers general enquiries on biomedical and chemical subjects. Scientists from any part of the world may stay in the house during working visits to London.
## Contents

**Symposium on Olfaction in mosquito–host interactions, held in collaboration with the World Health Organization at the Ciba Foundation, London, 31 Oct–2 Nov 1995**

*This symposium is based on a proposal made by John Hildebrand*

*Editors: Gregory R. Bock (Organizer) and Gail Cardew*

<table>
<thead>
<tr>
<th>J. G. Hildebrand</th>
<th>Chairman's introduction</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. F. Curtis</td>
<td>Introduction I: an overview of mosquito biology, behaviour and importance</td>
<td>3</td>
</tr>
<tr>
<td>M. J. Lehane</td>
<td>Vector insects and their control</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>16</td>
</tr>
<tr>
<td>G. Gibson</td>
<td>Genetics, ecology and behaviour of anophelines</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>37</td>
</tr>
<tr>
<td><strong>General discussion I</strong></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>E. E. Davis</td>
<td>Introduction II: olfactory control of mosquito behaviour</td>
<td>48</td>
</tr>
<tr>
<td>R. T. Cardé</td>
<td>Odour plumes and odour-mediated flight in insects</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>66</td>
</tr>
<tr>
<td>A. Cork</td>
<td>Olfactory basis of host location by mosquitoes and other haematophagous Diptera</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>84</td>
</tr>
<tr>
<td>R. de Jong and B. G. J. Knols</td>
<td>Selection of biting sites by mosquitoes</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>100</td>
</tr>
<tr>
<td><strong>General discussion II</strong></td>
<td></td>
<td>104</td>
</tr>
<tr>
<td>J. A. Pickett and C. M. Woodcock</td>
<td>The role of mosquito olfaction in oviposition site location and in the avoidance of unsuitable hosts</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>119</td>
</tr>
</tbody>
</table>
C. Costantini  Introduction III: odours for host-finding mosquitoes  124

M. Geier, H. Sass and J. Boeckh  A search for components in human body odour that attract females of Aedes aegypti  132
  Discussion  144

H. Mustaparta  Introduction IV: coding mechanisms in insect olfaction  149

R. A. Steinbrecht  Structure and function of insect olfactory sensilla  158
  Discussion  174

General discussion III  178

S. Anton  Central olfactory pathways in mosquitoes and other insects  184
  Discussion  192

M. F. Bowen  Sensory aspects of host location in mosquitoes  197
  Discussion  208

M. J. Klowden  Endogenous factors regulating mosquito host-seeking behaviour  212
  Discussion  223

General discussion IV  226

A. J. Grant and R. J. O’Connell  Electrophysiological responses from receptor neurons in mosquito maxillary palp sensilla  233
  Discussion  248

B. Pappenberger, M. Geier and J. Boeckh  Responses of antennal olfactory receptors in the yellow fever mosquito Aedes aegypti to human body odours  254
  Discussion  263

G. Ziegelberger  The multiple role of the pheromone-binding protein in olfactory transduction  267
  Discussion  275

General discussion V  281

D. S. Hekmat-Scafe and J. R. Carlson  Genetic and molecular studies of olfaction in Drosophila  285
  Discussion  296
Contents

W. Takken  Synthesis and future challenges: the response of mosquitoes to host odours 302
  Discussion  312

Index of contributors  321

Subject index  323
Participants

S. Anton  Department of Ecology, Ecology Building, Feromonggruppen, Lund University, S223 62 Lund, Sweden

J. Boeckh  Universität Regensburg, Institut für Zoologie, Lehrstuhl Boeckh, Universitätsstrasse 31, D-93040 Regensburg, Germany

M. F. Bowen  SRI International, Life Sciences Division, 333 Ravenswood Avenue, Menlo Park, CA 94025–3493, USA

J. Brady  Imperial College of Science, Technology & Medicine, Department of Biology, Silwood Park, Ascot, Berkshire SL5 7PY, UK

R. T. Cardé  Department of Entomology, Fernald Hall, University of Massachusetts, Amherst, MA 01003, USA

J. R. Carlson  Department of Biology, Yale University, Kline Biology Tower, PO Box 208103, New Haven, CT 06520–8103, USA

A. Cork  Natural Resources Institute, Central Avenue, Chatham Maritime, Kent ME4 4TB, UK

C. Costantini  Imperial College of Science, Technology & Medicine, Department of Biology, Silwood Park, Ascot, Berkshire SL5 7PY, UK

C. Curtis  London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK

E. E. Davis  SRI International, Life Sciences Division, 333 Ravenswood Avenue, Menlo Park, CA 94025–3493, USA

R. De Jong  Institut de Zoologie, Université de Neuchâtel, Rue Emile-Argand 11, CH-2007 Neuchâtel, Switzerland

B. Dobrokhotov  Manager Molecular Entomology, TDR–OMS, World Health Organization, CH-1211 Geneva 27, Switzerland

R. Galun  The Hebrew University, Hadassah Medical School, PO Box 1172, 91904 Jerusalem, Israel
Participants

M. Geier  Universität Regensburg, Institut für Zoologie, Lehrstuhl Boeckh, Universitätsstrasse 31, D-93040 Regensburg, Germany

G. Gibson  Imperial College of Science, Technology & Medicine, Department of Biology, Silwood Park, Ascot, Berkshire SL5 7PY, UK

A. Grant  Worcester Foundation for Biomedical Research, 222 Maple Avenue, Shrewsbury, MA 01545, USA

P. Guerin  Institute of Zoology, University of Neuchâtel, Rue Emile-Argand 11, CH-2007 Neuchâtel, Switzerland

J. G. Hildebrand  ARL Division of Neurobiology, 611 Gould-Simpson Building, University of Arizona, Tucson, AZ 85721-0077, USA

K. E. Kaissling  Max-Planck-Institut für Verhaltensphysiologie, D-82319 Seewiesen, Germany

M. J. Klowden  Department of Entomology, University of Idaho, Moscow, ID 83844-2339, USA

B. G. J. Knols  Department of Entomology, Wageningen Agricultural University, PO Box 8031, 6700 EH Wageningen, The Netherlands

M. J. Lehane  School of Biological Sciences, University of Wales, Bangor, Gwynedd LL57 2UW, UK

H. Mustaparta  Department of Zoology, University of Trondheim-AVH, N-7055 Dragvoll, Trondheim, Norway

J. A. Pickett  Biological and Ecological Chemistry Department, IACR-Rothamsted, Harpenden, Hertfordshire AL5 2JQ, UK

R. A. Steinbrecht  Max-Planck-Institut für Verhaltensphysiologie, D-82319 Seewiesen, Germany

W. Takken  Department of Entomology, Wageningen Agricultural University, PO Box 8031, 6700 EH Wageningen, The Netherlands

G. Ziegelberger  Max-Planck-Institut für Verhaltensphysiologie, D-82319 Seewiesen, Germany
Preface

In the autumn of 1995, the Ciba Foundation organized a symposium and open meeting in London on olfaction in mosquito–host interactions. These initiatives resulted from a joint effort with the UNDP/World Bank/World Health Organization (WHO) Special programme for Research and Training in Tropical Diseases (TDR). The open meeting, moreover, was presented in cooperation with the Royal Society of Tropical Medicine and Hygiene and the Royal Entomological Society of London.

The WHO Special Programme in TDR was created in 1975 as a globally coordinated effort to bring resources of modern science to bear on the control of major tropical diseases—especially malaria, the schistosomiasis, the filariases, the trypanosomiasis, the leishmaniases and leprosy. TDR provides a mechanism for international scientific collaboration, and plays a unique role as a co-ordinator and facilitator among the growing number of national and international tropical disease research programmes.

The principal goal of this jointly sponsored symposium was to contribute to world efforts the control of mosquito-borne diseases in general, and malaria in particular by: (a) assessing the current state of knowledge about the roles and mechanisms of olfaction in host-seeking behaviour of vector mosquitoes; (b) identifying research needs and opportunities aimed at understanding and manipulating olfaction-based anthropophyly in malaria–vector species; and (c) stimulating research in this important area.

We very much hope that this record of the wide-ranging papers presented at this symposium and the lively discussion they stimulated will help to invigorate both basic and applied research, leading to improved strategies and tactics for the prevention of transmission of disease agents to human hosts by vector mosquitoes.

John G. Hildebrand
Chairman of the symposium and open meeting

Boris Dobrokhotov
WHO Special Programme for TDR
Chairman’s introduction

John G. Hildebrand

ARL Division of Neurobiology, 611 Gould-Simpson Building, University of Arizona, Tucson, AZ 85721-0077, USA

I would like to say a few words about the motivation and ideas behind this symposium because it does have a few unconventional elements. First, I do not work in this field, and it is probably unusual to have a chairman of a Ciba Foundation symposium who is not an active participant in the field under discussion. Some of the other participants also don’t work on mosquito olfaction, but that is part of the essence of this symposium as I conceived it from the beginning. Although we all have an interest in the olfactory system of insects and in the behaviour that is controlled by olfactory cues, we each have our own special fields. Some of us study insect olfaction as a model to learn about the principles of olfactory function in general. Others are entomologists who are interested in insect–plant interactions and in the role of olfaction in controlling the interactions of insects with plants that they parasitize. A few of us are interested in insect reproduction and how olfactory cues bring the sexes together for mating. Finally, some of the participants are world experts on the olfactory basis of mosquito–host interactions. The thinking behind the organization of this symposium was that if we brought together people with up-to-date approaches in each of these fields, then perhaps we could summarize the current understanding of mosquito olfaction and identify ideas for future research, with respect to the control of vectors that transmit debilitating human diseases.

I am not going to say anything about the importance of blood-sucking insects as vectors of disease or about mosquitoes in particular because the introductory presentations will bring us up-to-date on these matters. Rather, I would like to pose a few questions that I had in mind during the planning of the symposium, when I was assessing whether this was a worthy enterprise and thinking about which participants to invite. What is the role of olfaction in host location and in the interaction of mosquitoes with their hosts? No one doubts that olfaction is playing a part, but we ought to take stock of the supporting evidence and to what extent olfaction may be the overriding sensory modality for host recognition and host location. What are the necessary cues within an animal’s effluvium that lead to host recognition and interaction of a mosquito with its host? How are those cues detected? How are
they processed by the mosquito’s olfactory system? How do they ultimately generate behaviour? What are the behavioural consequences of those substances? We will be making a mistake if we do not focus from the very beginning on what mosquitoes actually do in the environment in response to cues that interest them and guide them to their hosts. We need to pay attention to the ‘ecophysiology’, or ‘ecosensory biology’, of mosquito behaviour by looking at the nature of the odour cues in the environment, and the behavioural responses of mosquitoes to other cues in the sometimes chaotic conditions of the natural environment. We must think about differences among mosquito groups and pay attention to their biology. We should also pay attention, even within mosquito taxa, to the differences between those groups that are more anthropophilic and those that are more zoophilic, and try to understand whether olfaction plays a significant role in forming the distinctions among mosquito groups. Finally, we must ask ourselves if there are poorly exploited (or even unexploited) targets for chemical intervention, genetic manipulation or behavioural manipulation of mosquitoes. We would miss the mark if we didn’t try to direct future research into this field.

With these questions in mind, I believe that there are some clear purposes of this symposium. The first is to summarize and assess the state of this field. Second, it is valuable to put together a coherent account of the state of the field, so that all of our colleagues and students throughout the world will have the opportunity to join us in taking stock of the subject. Finally, it is a worthy goal to try to identify and draw attention to important problems yet to be explored by investigators—and especially by those who are new to the field.

To achieve these goals, I believe that it is important to mix together the experts in this field with those of us who bring expertise in allied areas, but who are not actually working directly on mosquitoes. I hope that this will result in an outcome different from that of other meetings that have considered mosquito olfaction and behaviour. I believe firmly that hybrid vigour is desirable in science, and that it is beneficial to bring together molecular geneticists, biophysicists, physiologists and behavioural biologists, because they will have provocative ideas about mosquito research.

We must endeavour to inspire and attract new, young investigators into this area. It is no accident that some people of that description have been invited to participate in this symposium. I hope that this symposium and the published volume will not only attract other young researchers, but also stimulate interest among researchers who work with Drosophila and other insect species, and develop greater vigour and diversity in this field.
Every few years the question ‘what is the most dangerous animal in the world?’ is raised on BBC Children’s Television. The young questioner presumably expects the answer to be a lion, a tiger or perhaps a spitting cobra. However, we always advise the presenters to answer ‘the African malaria mosquito, *Anopheles gambiae*’. The overwhelming importance of malaria as a vector-borne disease and of African children as its victims has only been fully recognized comparatively recently. Recent estimates (WHO 1993) are that 50% of the African rural population are infected with *Plasmodium falciparum* at any one time (often without symptoms because of immunity): there are 250–450 million clinical cases in Africa per year (80% of the world’s total) and 1–3 million deaths are partly or wholly due to malaria. Almost all of these deaths occur in children under the age of five, before they have had a chance to build up a sufficient level of protective immunity as a result of repeated malaria attacks.

The reasons for the predominance of tropical Africans as malaria victims are partly politicoeconomic and climatic, but are mainly because of the high efficiency of *An. gambiae* as a vector. The importance of this factor was demonstrated by the accidental introductions of *An. gambiae* into Brazil and Egypt in the 1930s and 1940s, which led to malaria epidemics far worse than the levels of malaria endemic in those countries before the invasions and after their eradication (Soper & Wilson 1943, Shousa 1948).

The exceptional danger of *An. gambiae* arises from its strong tendency to feed on humans (anthropophily) and its long life. Both of these parameters have a strong influence on the vectorial capacity of an insect population (Macdonald 1957, Garrett Jones & Grab 1965) because, to be a vector of malaria, a mosquito must pick up gametocytes from one human, live 12 more days for them to mature to sporozoites and then bite another human whom the sporozoites can infect.

There are other highly anthropophilic and long lived anophelines, such as *Anopheles dirus* in the areas of multidrug-resistant *P. falciparum* in South-East
Asia. Fortunately, *An. dirus* breeds in small forest pools and does not appear in villages at high densities, but *An. gambiae* is well adapted to breeding sites created by the activities of humans and domestic animals in and around villages, e.g. footprints and hoofprints in marshy or irrigated land. Thus, 50–100 *An. gambiae* (about 5% of which are likely to be carrying sporozoites) may bite each villager each night. *An. gambiae* rest after blood feeding on the walls of the house (i.e. they are endophilic); therefore, they are vulnerable to the standard method of malaria vector control, i.e. house spraying with a residual insecticide. By contrast, *An. dirus* exit immediately after feeding indoors and are therefore difficult to kill.

Little is known of the mechanisms by which gravid females of different species seek out different types of site for oviposition, or how blood-fed females choose their places for resting and digestion. *An. gambiae* are found at lower densities in houses than *Culex quinquefasciatus*, which are found in urbanized areas all over the tropics or subtropics. They breed in wet pit latrines, incompletely sealed cesspits or open drains. We recorded a pit latrine in Zanzibar yielding 13 000 *Cx. quinquefasciatus* per night (Maxwell et al 1990) and Gubler & Bhattachariya (1974) recorded about one bite/person per minute throughout the night in Howrah, near Calcutta. These mosquitoes are also anthropophilic (but will sometimes bite birds as an alternative) and are the cause of most mosquito nuisance, as well as being the vectors that initiated most of the world's 90 million chronic filariasis infections (Knudsen & Sloof 1992). Some of these infections lead to grossly deforming elephantiasis but apparently not to death, except by suicide.

The other mosquito-borne disease of major public health importance is dengue, for which there are recent estimates of 30–60 million infections and 100 000 acute clinical cases/year (Knudsen & Sloof 1992). The main vector is *Aedes aegypti*, which is localized around its domestic breeding sites in water accumulated in storage jars and discarded tyres, for example. Here it readily encounters humans for biting, but unlike *An. gambiae* and *Cx. quinquefasciatus*, it does so during the day. We may hear more at this symposium about the mechanisms by which mosquitoes locate humans for biting and therefore become dangerous vectors and/or a nuisance. Whether the same mechanisms are involved in species that bite during the night, evening and day has not, to my knowledge, been investigated.

A proper understanding and ability to manipulate olfactory (or other) searching mechanisms for human hosts or breeding sites might be exploited in the following ways.

(1) It may be possible to use traps for blood-seeking mosquitoes that are comparable to odour- and colour-baited tsetse traps (Lavessière et al 1991). One might envisage a mosquito trap that could outcompete one's own mosquito-attractive stimuli (without itself smelling intolerable). Perhaps
more immediately realizable would be improvements in the light traps that are currently used for monitoring mosquito populations (Lines et al. 1991). This is especially needed for certain species that do not respond well to light traps, and where the standard method of monitoring by teams of human baits/catchers is becoming increasingly unethical because of the spread of drug-resistant malaria.

(2) Alternatively, we may be able to divert gravid females from their normal breeding sites to ovitraps in which larval development can be prevented (McCall & Cameron 1995).

(3) At present $N,N$-diethyl-$m$-toluamide (DEET) is used in most commercially available brands of insect repellent. It is effective for several hours but not overnight. Rare cases of poisoning do occur but it is considered to be less dangerous to have around the house, where children might misuse it, than household bleach (Veltri et al. 1994). However, it does attack certain plastics and paintwork. Effective plant-based repellents are now becoming commercially available, but an effective dose has a strong smell. A repellent that would remain effective overnight without being rubbed off on bedclothes and is as effective as, but cheaper than, a bednet could make a real contribution to malaria and mosquito nuisance control.

(4) A system for genetically manipulating a vector population so that it changed its food preference to animals (zoophily) would be helpful (Curtis 1994). This might be more sustainable than attempts to make vectors refractory (genetically non-susceptible) to pathogens, as the latter might lead to the evolution of a pathogen strain that could evade the refractoriness gene which had been introduced into the mosquito population. Closely related mosquito species may differ sharply in anthropophily/zoophily but may sometimes be crossed successfully in the laboratory. By an appropriate backcrossing programme, with selection of the zoophilic segregants at each generation, one might produce a strain for release that was zoophilic, but genetically and behaviourally compatible with a dangerous anthropophilic species. The sibling species *Anopheles quadriannulatus* and *An. gambiae sensu strictu* seem to be the obvious targets for this approach.

It may be useful at this symposium to speculate about fancy ways of controlling mosquito-borne disease. However, one should not get carried away and, in particular, one should keep in mind the following two opposing constraints in the real world.

First, the problem of insecticide resistance is not yet so widespread in *Anopheles* as is sometimes implied in the introductions to grant applications and other blatantly propagandist literature. Pyrethroids for house spraying or bednet impregnation provide highly effective methods for malaria vector and
nuisance control. For olfactory traps to be a useful alternative, they would have to be cheaper or otherwise more attractive than established methods so as to encourage communities to use them more widely and consistently.

Second, in the most highly malarious areas of tropical Africa, transmission may be far above the level of 'saturation'. Snow et al (1994) have compared areas that have high levels of transmission with those that have 30-fold lower levels, and they have suggested that severe malaria rates might actually be made worse by vector control, short of virtual eradication, by delaying the build up of immunity in growing babies to an age at which they are apparently more prone to cerebral malaria. In such circumstances one should be cautious about advocating vector control methods that are not known to be able to produce massive and sustainable reductions in the vectorial capacity of mosquito populations (Snow & Marsh 1995). These may need to be backed up by improvements on existing malaria vaccines that could sustain immunity levels without the need for a child to suffer malaria attacks to acquire the immunity.

References


WHO 1993 A global strategy for malaria control. World Health Organization, Geneva
Vector insects and their control

M. J. Lehane

School of Biological Sciences, University of Wales, Bangor, Gwynedd LL57 2UW, UK

Abstract. This paper emphasizes the huge influence that vector-transmitted disease has on humans using plague, epidemic typhus and nagana as examples. The continuing need for vector control in campaigns against insect-transmitted disease is shown by reference to current control programmes mounted against Chagas' disease, onchocerciasis, lymphatic filariasis and nagana. These successful campaigns have not been reliant on new breakthroughs but on the forging of available tools into effective strategies widely and efficiently used by the control authorities, and the long-lasting political commitment to the success of the schemes in question. A brief mention is made of current fashions in vector control research and that great care needs to be taken by policy-makers to achieve a balance between long-term research aiming at the production of fundamentally new control technologies and operational research aiming to forge the often highly effective tools we already have into sound control strategies.

1996 Olfaction in mosquito–host interactions. Wiley, Chichester (Ciba Foundation Symposium 200) p 8–21

Importance of blood-sucking insects

At present, only 750 000 species of insect have been described; the total number of insect species, however, is likely to lie between one and 10 million species. Further, it has been suggested that as many as $10^{18}$ individual insects are alive at any one instant, giving 200 million insects for each man, woman and child on earth. This makes the insects the pre-eminent form of life on land. Insects make a living in a variety of ways but thankfully only a few (300–400 species) have developed the habit of blood feeding. Despite being only a small fraction of the total number, these insects transmit diseases that have played an important role in shaping the course of human history (e.g. Duffy 1953, Bruce-Chwatt 1988, Harrison 1978) and they continue to have a major influence on economic development and human welfare over large areas of the earth.

Malaria, African trypanosomiasis (sleeping sickness), Chagas' disease (American trypanosomiasis), leishmaniasis, onchocerciasis (river blindness), filariasis (elephantiasis and loaiasis), bubonic plague, epidemic typhus, yellow fever, dengue and many other diseases are transmitted to man by insects. The
numbers afflicted are colossal and the numbers considered at risk are staggering (Table 1). Although mosquitoes are the most important vectors, we should not forget that other insects are also of great importance. For example, Chagas' disease is transmitted by triatomine bugs, African trypanosomiasis by tsetse flies, onchocerciasis by blackflies, leishmaniasis by sandflies, epidemic typhus by lice and bubonic plague by fleas.

Bubonic plague can be used to illustrate the huge influence vector-borne disease has on humans. It is caused by the bacterium *Yersinia pestis* and is transmitted from its normal rodent host to humans by the bite of fleas. Subsequently, it can spread in the form of pneumonic plague from human to human via droplets produced by coughing and sneezing. In the pre-antibiotic era, diseases caused by flea bites had a mortality rate of 30–90%, and in some instances pneumonic plague was reported to have a mortality rate of 100%. The disease is endemic in the Eurasian steppe and there are three major epidemics recorded in history. The first was the plague of Justinian, which was at its peak from A.D. 542 until about A.D. 590 but carried on intermittently until A.D. 750. The devastation caused appears to have been as great as in the later, better documented epidemics (McNeill 1976)—10 000 people a day were dying in Constantinople at the height of the plague and a large proportion of the urban populations in the Mediterranean were lost to it. The plague is seen as a major factor in the last decline of the Roman Empire, in the successes of the Moslem armies against its remnants in A.D. 634 (Dols 1974) and in the movement of the centre of European civilization from the Mediterranean to more northerly lands. The second great epidemic originated in central Asia. Spreading eastwards to China and south to India it spread to Europe with a Mongol army laying siege to the trading city of Caffa in the Crimea in 1346. From here the disease spread by ship through the Mediterranean ports and then rapidly northwards through Europe. The best estimates suggest that

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated number of people infected</th>
<th>Estimated number of people at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>365</td>
<td>2217</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>90</td>
<td>905</td>
</tr>
<tr>
<td>African trypanosomiasis</td>
<td>&gt;0.025</td>
<td>50</td>
</tr>
<tr>
<td>Chagas' disease</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>12</td>
<td>350</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>50</td>
<td>100s</td>
</tr>
</tbody>
</table>
between 1346 and 1350 a third of the population of Europe died. Historians suggest that this initial wave of the ‘Black Death’ and recurrent episodes of plague through the second half of the fourteenth century led to a profound change in the course of European history driven by the socioeconomic effects of depopulation. The disease continued to ravage Europe sporadically through the next three centuries. For example, it is estimated that a million Spaniards died of plague in the seventeenth century, and this has been seen as a major factor in the decline of Spain as an economic and political power (Bennassar 1969). The next great outbreak of plague was the great Indian epidemic of 1898–1918, in which it has been estimated that between 10 and 13 million lives were lost. Originating deep in the interior of China in 1855 on the back of a military rebellion (McNeill 1976), it spread to Hunan Province in 1892, to Canton in 1894 and from there to Hong Kong, Calcutta and Bombay. Having spread through India, where the worst of its effects were felt, it passed by the shipping lanes to ports in Java, Japan, Asia Minor, South Africa, Mediterranean Africa and parts of the Americas; thankfully in these regions it remained largely confined to seaports. This third pandemic is now coming to an end: 6004 cases were reported to the World Health Organization in 1967, and there were less than 1000 reported cases in 1992 (Knudsen & Sloof 1992). In 1943, with the advent of modern antibiotics, plague became an easily treatable disease and will remain so unless antibiotic resistance once more places us at the mercy of this dreadful, history-changing zoonosis.

Insects also have an indirect effect on human welfare because they transmit diseases to domesticated animals. Nagana (sleeping sickness of animals in Africa), surra, bluetongue, African horse sickness, Akabane virus, rift valley fever and many other diseases are caused by parasites transmitted to domesticated animals by insect vectors. In addition, the massively important piroplasms causing red water fever (Babesia) (and the now eradicated Texas fever in the USA) and East Coast fever (Theileria) are transmitted by ticks (acari). These vector-borne diseases are largely confined to the tropics and subtropics. Given that the carrying-capacity has been reached for most agricultural livestock systems in the developed world, if future expansions in production are required they will need to be in these regions blighted by vector-borne disease. This will mean both increasing productivity of land already in use by minimizing disease impact and making new areas available for exploitation through disease control. One of the most celebrated examples of agricultural constraints caused by vector-borne disease is nagana. Caused by trypanosome species transmitted by tsetse flies, this disease prevents the use of about 10 million km² of Africa for cattle rearing (Steelman 1976). An estimate, now over 20 years old, suggested that trypanosomiasis cost the cattle industry US$5 billion per year (Goodwin 1973). Of course the arguments for control and the agricultural expansions this will permit are not straightforward because control of the tsetse and the trypanosomiasis it transmits may well, in the
Vector insects

minds of many commentators, lead to widespread losses of African game animals and heighten African overgrazing problems. The arguments have been clearly outlined by Jordan (1986).

In addition to the diseases they transmit to livestock, blood-sucking insects also cause considerable direct losses in meat and milk yields through the annoyance of their bites (Steelman 1976). The question of the direct annoyance to man caused by blood-sucking insects is more difficult to address because it is difficult to quantify. It is best addressed as tolerance thresholds and I would contend that our tolerance in western society has decreased considerably over the last century largely because an increasingly urban and affluent population encounters blood-sucking insects increasingly rarely. Over the same period increasing leisure time and income levels have made national and international tourism one of the world’s most important industries. The combination of the two trends have made nuisance insects a constraint to the development of tourism in many parts of the world—notably in the Camargue region of southern France, the Scottish highlands, the Bahamas, Florida and many parts of the Caribbean (Linley & Davies 1971)—although it is rare to find the tourism industry making public statements of this kind for obvious reasons. The Marquesas islands in French Polynesia are one specific example that has been studied recently. The day-biting midge *Leptoconops albiventris*, called the nono by local people, plagues the islands’ beaches, preventing development of tourism and forming a serious impairment to economic development (Aussel 1993).

**Control of blood-sucking insects**

Clearly, effective vector control is essential if we are to deal with problems caused directly by blood-sucking insects. But have other control agencies rendered vector control unnecessary? Most certainly not. For most of the diseases listed above, vector control plays a significant role and for some—such as South American sleeping sickness, where no vaccines or drugs for public health use are available—it is the major control strategy. What vector control strategies are available? At the beginning of the twentieth century, when the role insects play in disease transmission was first being appreciated, the tools available for vector control were poor. For the first four decades of the century the most important advances in control were due to a rapid advance in our understanding of the biology of the insects, which permitted more efficient use of the rather limited tools available. Since 1941, with the discovery of the insecticidal properties of dichlorodiphenyltrichloroethane (DDT) by Müller in the laboratories of Ciba Geigy, we have had infinitely more powerful tools at our disposal. To illustrate this we can compare the anti-malaria operations in Mian Mir, a British army encampment in India in the early 1900s, with the campaign to rid Italy of malaria immediately after
the Second World War. In the pre-insecticide era Christophers and colleagues used 500 British and Indian soldiers to control mosquito breeding within a half mile of the soldiers’ living quarters in Mian Mir. Despite continuing intensive operations over a five-year period by a highly disciplined workforce and the very limited objective of preventing malaria transmission in the encampment, there was no success: the enlarged spleen rate in children remained at 66% and the number of adult mosquitoes in the encampment was undiminished. In contrast to this monumental failure, the Italian government and the health division of the United Nations relief organization, armed with the new insecticide DDT, took just two years from 1945 to sweep malaria from Italy (excluding Sardinia) (Harrison 1978). The power of these new tools was driven home to the control community by their effect on the epidemic typhus outbreak in Naples in 1943. Epidemic typhus is transmitted by lice and its huge influence on humans is famously documented by Zinsser (1935). The disease is credited with a major role in the defeat of Napoleon’s armies in Russia. In Europe and Russia between 1917 and 1923 it is estimated that there were three million deaths among the 30 million who suffered from the disease. The epidemic in Naples in 1943 was the last and was brought to an abrupt end by DDT and other anti-louse measures—the first time this ancient scourge of man was halted in mid-epidemic. The immense power of these insecticidal tools was obvious to all and they were seen by many (but certainly not all) at the time as a magic bullet, capable of dealing at a stroke with long-standing problems with vector-borne disease. Many of the earlier lessons of species sanitation were set aside. This view of insecticides as a panacea lasted perhaps 10 years among the optimistic but was finally dispelled by the perceived ‘failure’ of the global malaria eradication campaign. (Despite its supposed failure it should be remembered that largely because of this campaign malaria was reduced from a threat to 64% of the world’s population in 1950 to 38% in 1972.) The dispelling of the idea that insecticides were the magic bullets, and the realization that insecticide usage strategies must be planned carefully to be successful, leads us to the modern age in which there are several impressive success stories. All are characterized by the forging of available tools into sensible and sustainable control strategies and by political will to continue the control effort to its conclusion despite the economic pressures to switch scarce resources which inevitably arise once a degree of control has been achieved. I will outline some of these recent successes.

It is estimated that two-thirds of the 16–20 million people infected with Chagas’ disease live in Argentina, Chile, Uruguay, Paraguay, Bolivia, Brazil and Peru (WHO 1991). In these seven countries the major vector is *Triatoma infestans*. For all practical purposes, this bug is only found in the domestic and peridomestic environment. It has slow population growth and is susceptible to modern insecticides; therefore, it is readily accessible to insecticidal control
measures. The Southern Cone initiative, a co-ordinated effort of six of the seven countries (Peru is a non-participant) with support funding from the developed world, was established in 1991. It is attempting the elimination of *T. infestans* by house spraying with synthetic pyrethroids, and this attack on Chagas’ disease is supported by efforts against transmission of the disease through blood transfusion services (PAHO 1993, Schofield 1992). Expenditure from 1991–1995 is estimated at US$156 million. Uruguay and Chile are virtually free of transmission, and Argentina, Paraguay and particularly Brazil are making good progress (C. J. Schofield, personal communication 1995). This successful campaign did not rely on a remarkable new breakthrough in control technology. It just required political will fostered and stimulated by interested and persistent individuals.

The same is true of onchocerciasis control. Onchocerciasis afflicts about 18 million people, mainly in 27 African countries. It causes blindness in about 340 000 people, including up to 40% of the adult male work force in some areas in the sub-Saharan savannah belt. In the past, onchocerciasis had a disastrous socioeconomic effect in this region because it forced people to abandon fertile land near rivers. The onchocerciasis control campaign started in 1974 and relied until the late 1980s on direct vector control through larviciding of rivers over a 1.3 million km² area in 11 countries to kill the vector *Simulium damnosum*. This audacious and brilliantly executed vector control programme has been remarkably successful, achieving disease control over most of the area concerned (Molyneux 1995). Since 1988, vector control has been supplemented with the drug ivermectin (Mectizan) which, like vector control, interrupts transmission but in addition helps with the treatment of the disease because it rapidly kills the microfilaria which are the cause of the eye pathology (Tsalikis 1993). Although eradication of *Onchocerca volvulus* is currently an unrealistic prospect (Duke 1990), the onchocerciasis control campaign, costing approximately US$27 million per annum, has proven that disease control is achievable. The question is will the political will be there to continue control operations indefinitely, particularly with rates of blindness falling markedly and other health priorities coming to the top of the political agenda?

Well-planned and well-executed control operations, commonly incorporating vector control, are proving exceptionally effective in dealing with lymphatic filariasis (Ottesen & Ramachandran 1995). These strategies have eliminated filariasis from Japan, Taiwan and South Korea, and China is on the road to a similar success. Control is based on the interruption of disease transmission through drug and vector control programmes. The extremely safe drug diethylcarbamazine (DEC) (probably soon to be supplemented by ivermectin) is the major tool, delivered in cost-effective ways either as an additive to table salt or in once-a-year doses. The drug kills the microfilarial stage, preventing infection of mosquitoes and the transmission of the disease. Vector control plays an
effective supporting role for these drug-based campaigns and can often be integrated with anti-mosquito measures aimed at other diseases. Vector control is particularly effective where the disease is transmitted by endophilic mosquitoes, such as *Culex quinquefasciatus* and *Anopheles*, and least effective for vectors such as the *Aedes scutellaris* complex where the adults are exophilic and larval breeding sites are too small and disparate for effective control to be instigated. The remarkable success of these campaigns means that lymphatic filariasis has been identified by the International Task Force for Disease Eradication as one of only six potentially eradicable diseases (Center for Disease Control 1993).

A final example is the control of nagana in African livestock. The trypanosomes causing the disease are transmitted by tsetse flies. Despite widespread drug resistance, available trypanocidal drugs can be effective in controlling disease in sedentary, well-managed herds even when kept in areas of high challenge. But this is not typical of cattle rearing across most of Africa where pastoralism, poor herd management and lack of veterinary services suggest that prospects for the widespread success of the drug-based approach to trypanosomiasis control are poor, particularly for economically sound cattle-rearing operations (Jordan 1986). However, the tsetse fly is present at low densities and has a low reproductive rate. Removal of significant parts of the population can cause the disappearance of flies from an area. Since the early 1970s, when biconical traps were introduced for sampling tsetse populations (Challier & Laveissière 1974), trap technology for tsetse control, including the use of natural baits, has taken considerable steps forward and is now widely and successfully used for control purposes (reviewed by Green 1994). For example, a campaign run in Côte d'Ivoire since 1980 has cleared 60,000 km², which is 19% of the total area of the country, of tsetse fly (see Green 1994).

Looking in from the outside, one might be misled into thinking that fundamentally more effective insecticides and drugs had suddenly emerged in the last decade or so to make such successes possible. Neither is true. There have been advances (such as the emergence of ivermectin as a safe drug for use in onchocerciasis control, for example) but most of the tools have been available for a long time—DEC was first used clinically in 1947 and traps were first used against tsetse in the 1930s. The insecticidal control tools are mostly long standing. Thus, the major environmental management treatments, including source reduction, house or personal screening, date back at least to the beginning of the century, and even the introduction of synthetic pyrethroids in the form of allethrin came in 1969. What has happened is that the tools available have been forged into effective strategies, which have been widely and efficiently used by the control authorities; and, of particular importance, there has been a long-lasting political commitment to the success of the schemes in question.
**Future trends in vector control**

Finally I would like to mention the current fashion in vector control research. Many laboratories are using molecular techniques to try to devise means for the eventual introduction of refractory genes into vector populations (Crampton 1994). Others are attempting to develop vaccination strategies against vector insects (Jacobs-Lorena & Lemos 1995) or the parasites within them. These elegant technologies hold the promise that radical, new control tools will be developed, but it is generally accepted that this is unlikely to happen within a decade. When they arrive such tools will probably fill a useful role within well-designed and well-organized control programmes, but they are unlikely to be the magic bullet some might suggest. It should be clear from the examples above that much can be achieved if available resources are concentrated on operational research designed to forge the tools we have into ever more effective control strategies suited to local conditions (e.g. Curtis 1994). Combining this with funding and training strategies, which ensure that these are implemented efficiently, and effective lobbying to gain full and lasting political backing for the control operations undertaken can achieve much for human welfare in the immediate future.

**References**


Bennassar B 1969 Recherches sur les grandes epidemies dans le nord de l'Espagne a la fin du XVI siecle. Service d'édition et de vent des publications de l'éducation national, Paris


Center for Disease Control 1993 Morb Mortal Wkly Rep 42:1–38


Duffy J 1953 Epidemics in colonial America. Louisiana State University Press, Baton Rouge, LA

Duke BOL 1990 Onchocerciasis (river blindness): can it be eradicated? Parasitol Today 6:82–84


DISCUSSION

Hildebrand: Finding a solution for these devastating diseases has important political and economic ramifications that are probably more problematic than the biology that we’re discussing here. Several years ago, I read an editorial in a medical journal arguing that the majority of the most devastating and debilitating diseases of humans are vector-borne diseases. Diseases such as cancer and heart disease were characterized as barely significant in comparison.

At that time the total world investment and research on those ‘great, neglected diseases of mankind’ was in the order of US$40 million, or more than an order of magnitude less than the budget of the National Cancer Institute of the National Institutes of Health in the USA. My own interest in this field was initiated by reading that editorial and thinking about how distorted the priorities of our governments are. I hope that we won’t forget, as we talk about the biology of olfactory-mediated, mosquito–host interactions, about economic and political issues.
Brady: Louis Miller (personal communication) has pointed out that the National Institutes of Health spends at least US$1.4 billion on AIDS research compared with about US$30 million on malaria.

Steinbrecht: If AIDS did not affect the European and industrialized Northern hemisphere, there probably wouldn’t be much spent on research into AIDS either. Vector-borne diseases occur primarily in the developing countries, and they seem to be left alone to deal with them.

Hildebrand: Perhaps we could go further and suggest that so little is spent on vector-borne diseases because they usually do not afflict the families of congressmen and members of Parliament.

Lehane: It even goes beyond that because the money which is available for disease research is often not aimed directly at control: it’s often aimed at supporting western laboratories, and there is a difference. We sometimes consider our best interests when we’re using this money, which is an extremely difficult dilemma for a scientist. One has to do one’s best for the laboratory, but we shouldn’t get carried away with the idea that this is always the best route to control diseases. I’m not sure how to communicate this message to politicians. It’s interesting to note that two of the most successful campaigns that I have outlined here—the onchocerciasis (river blindness) campaign and the Chagas’ disease campaign—were started by the enthusiasm of just a few interested entomologists.

Curtis: I share John Hildebrand’s sentiments about the importance of vector-borne diseases in developing countries, but the point may have been slightly overstated. For example, diseases such as tuberculosis, acute respiratory diseases and diarrhoea may kill more people than malaria, and they are not vector borne, although they are primarily diseases of developing countries and are therefore grossly under funded.

Hildebrand: Both Chris Curtis and Mike Lehane have stressed the importance of giving due respect to the use of pesticides. Even if traditional pesticides can still be used effectively, don’t you agree that the inevitable problem of biological resistance has to be faced in the long run, so that it’s also important to develop a better understanding of the biology of mosquitoes and their interactions with hosts for a long-term solution?

Lehane: But pesticide resistance has not been described for triatomine bugs or tsetse flies, although it is more of a concern for mosquitoes.

Brady: Could I make a point about tsetse flies, because they represent a model that we may refer to several times over the next couple of days. The European Economic Community was going to eradicate tsetse flies by an aerial spraying programme covering 350 000 km² of the South African bush with ULV endosulfan, but decided to switch to using odour-baited, insecticide-treated targets instead, partly because of ‘green’ pressures. Also, in contrast to the point which Mike Lehane mentioned that the western countries spend
much of their research money on supporting their own laboratories, this target
technology was developed completely endogenously within a Third World
country, i.e. Zimbabwe.

**Dobrokhotov:** Vector control based on the use of insecticides was a key
element for many World Health Organization (WHO) support disease control
programmes. All of them are now facing serious problems due to the rapid
increase in insecticide resistance. Many developing countries cannot afford the
new, more effective insecticides. The same problems occur with the use of tsetse
traps. Despite their efficiency, there is not a single example of a self-supported
trap programme in Africa—all of them depend on external funding. The well-
known success of the onchocerciasis control programme, which practically
eliminated onchocerciasis in West Africa, was achieved by means of
international multi-donor support managed by the WHO. Further sustain-
ability of the programme will depend on the combination of black fly control
with the treatment of patients with drugs (ivermectin).

**Guerin:** May I just raise the point regarding the consequences of
controlling the behaviour of individuals on the vector population. Mike
Lehane provided the example of the direct treatment of houses infested by
triatomines. In the case of onchocerciasis, where rivers act as the reservoir for
the vector, the control programme outlined is probably the only way of
handling an acute situation using an ‘environmentally acceptable’ approach. In
the onchocerciasis control programme, was just one species targeted or was it a
series of species?

**Lehane:** At the start of the campaign, no one anticipated the number of
problems that they would face with *Simulium* because it is a species complex,
and different members of the complex may have subtle variations in their
lifestyle that make control of one member of the complex more difficult than
others. The aim of the campaign was not to remove the population, but to
interrupt the transmission for a set period of time, i.e. until the adult worms
died out in the human population, which was estimated to take about 20 years.
However, it's quite clear now that it's going to have to be a continuing
programme, either based on interrupted transmissions using insecticides or
ivermectin if it's going to be successful.

**Galun:** I agree with Mike Lehane that insecticides are going to remain our
major means of insect control. In a recent lecture delivered by Perry Atkinsson
in Israel upon receiving the Wolf Prize, he described a 30-year effort to
integrate pest management, aimed at reducing the use of insecticides in cotton.
So far they have achieved a 15–20% reduction.

Even the example given by Mike Lehane concerning the development of
traps for the control of tsetse flies still involves insecticides. The traps used are
basically blue screens impregnated with permethrins and accompanied by a
source of acetone and octenol. Thus, we are dealing with visual and chemical
attractants that bring the flies to the insecticide. This method is much safer to