15 Insect-borne Diseases

By adopting a more specific means of transmission, some parasitic organisms have become dependent on vectors for carriage to a new host. Several vectors may be used, but often the parasite is restricted to only one kind of vector. This would at first appear to reduce the chance of infection, but instead of the haphazard scattering of large numbers of organisms into the environment, in the hope that one of them will find a new victim, using a vector will have a more certain chance of success. The vector carries the parasite right to the new host and, in many cases, introduces it directly into them. Often a development stage takes place in the vector and the infective stage continues to be produced for the rest of the vector's life. However, transmission depends on the vector being able to find a new host, often within a limited period, a vulnerable step in the life cycle and one where control methods are most likely to succeed.

Vector transmission is one of the commonest methods of spreading disease and many of the infections transmitted this way are of major importance, so large sections of the book are devoted to them. Such is their importance that they are best divided into two: this chapter, which includes all the vectors that use flight, such as mosquitoes and biting flies; and the next chapter on ectoparasites that attach to the host, such as fleas and lice.

15.1 Mosquito-borne Diseases

The mosquito is the most important vector of disease, because it is abundant, lives in close proximity to humans and needs to feed on blood (the female must have a blood meal for the development of her eggs). Incredibly, it is a very delicate insect, being easily blown by the wind, a weak and slow flier and susceptible to climatic change. Its success lies in its opportunism and rapid developmental cycle, allowing large numbers to be produced in a short timespan. Once a suitable breeding place appears, be it a few puddles after a rain storm or a man-made water storage tank, a mosquito will quickly lay its eggs. These develop within a short time into a large number of adults. Each may become a vector, and although many will die, there will be sufficient to seek out suitable blood meals and transmit infection.

Some parasites are specific to certain types of mosquitoes, e.g. malaria and the anophelines, while others, like the arboviruses, are less selective and utilize many different species. Different kinds of mosquitoes may be required in a complex transmission cycle such as yellow fever.

Development of the parasite within the mosquito may be morphological without multiplication (as with filaria), or may involve asexual (arbovirus) or sexual (malaria) reproduction. Each of these methods confers advantages, such as the huge number of organisms produced by asexual reproduction, or the opportunity to develop strains of varying type with sexual reproduction, but if the mosquito does not live long enough for these developmental stages to take place, then all is lost.

There are two main groups of mosquitoes, the anophelines (which include *Anopheles*) and the culicines (which include *Aedes*), which are distinguished by characteristics found in all of the development stages (Fig. 15.1). The adult *Anopheles* mosquito raises its hind legs away from the surface, easily remembered by its stance being like one side of a letter 'A', while the larva lies horizontal to the surface. The eggs are laid singly and have little floats on each side. In contrast, culicine mosquitoes rest horizontal to the surface, their larvae hang down from a single siphon and their eggs have no floats, often being laid in rafts. It is better to try to differentiate an adult male from a female, with its bushy antennae, before subsequently separating anophelines from culicines by the length of the palps. More precise species identification is required to identify which mosquitoes are the principal vectors, but this needs entomological help.

Mosquitoes differ in their habits, some preferring to take blood meals on humans (*anthropophilic*) and

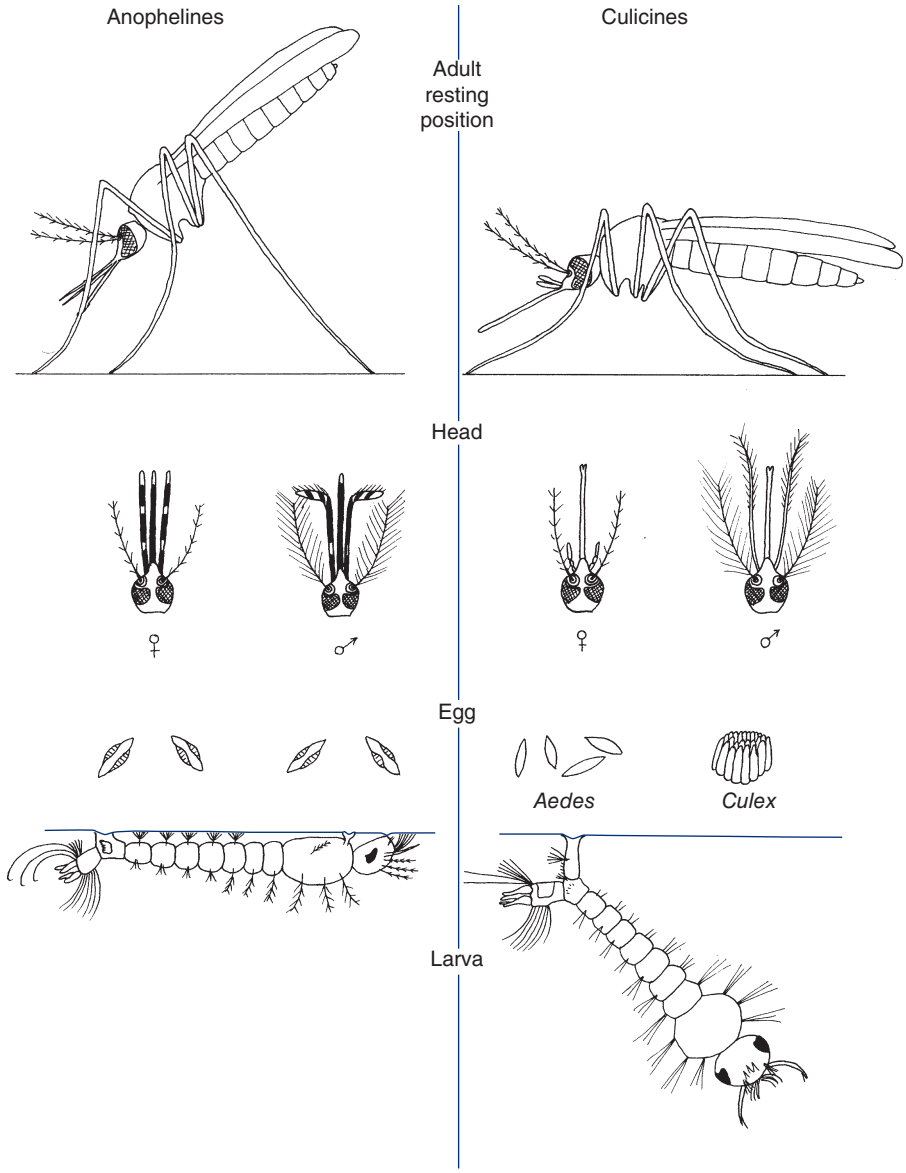

Fig. 15.1. The main differences between anopheline and culicine mosquitoes.

others on animals (*zoophilic*), while some are non-specific, depending on which type of meal is most readily available. They also have particular biting times, either only indoors, only outdoors or a mixture of the two. The biting period can be mainly during the night or predominantly in the daytime. All these different parameters need to be measured in determining the importance of each type of mosquito as a vector.

15.2 Arboviruses

*Ar*thropod-*bo*rne-virus (arbovirus) infections occur in epidemic form in a number of different parts of the world. Many viruses have been identified (see Table 15.1 and Chapter 20), but they are best grouped into three symptom complexes.

Table 15.1. The important arbovirus infections of humans.

Virus	Distribution	Vectors	Reservoir
Mainly fever or arthritis			
Chikungunya	Africa, South and South-east Asia	*Aedes* (*Ae.*) *aegypti*, *Ae. africanus*, *Ae. albopictus*	Baboons, bats, rodents, monkeys
O'nyong-nyong	East Africa, Senegal	*Anopheles* (*A.*) *gambiae*, *A. funestus*	Mosquitoes?
West Nile	Africa, Asia, Europe, USA	*Culex* (*C.*) *pipens molestus*, *C. modestus*, *C. univittatus*	Birds
Oropuche	Trinidad, South America	Mosquitoes, possibly *Culicoides*	Monkeys, sloths, birds
Orungo	West Africa, Uganda	*Ae. dentatus*, *Anopheles* spp.	Humans?
Ross River	Australia, New Zealand, Pacific Islands	*C. annulirostris*, *Ae. vigilax*, *Ae. polynesiensis*	Mosquitoes
Fever and encephalitis			
Western equine	Americas	*C. tarsalis*, *Culiseta* (*Cs.*) *melanura*	Birds
Eastern equine	Americas, Caribbean	*Cs. melanura*, *Aedes* and *Coquillettidia* spp.	Birds, rodents
St Louis	Americas, Caribbean	*C. tarsalis*, *C. nigripalpus*, *C. quinquefasciatus*	Birds
Venezuelan equine	Central/South America, Caribbean, parts of USA	*C. tarsalis* and other *Culex*, *Aedes*, *Mansonia*, *Sabethes*, *Psorophora*, *Anopheles*, *Haemagogus* spp.	Rodents
Japanese	East, South and South-east Asia	*C. tritaeniorhynchus*, *C. gelidus*, *C. fuscocephala*	Birds, pigs
Murray Valley	New Guinea, Australia	*C. annulirostris*	Birds
Rocio	Brazil	Probably mosquitoes	Birds? Rodents
Haemorrhagic fevers			
Yellow fever	South America and Africa	*Ae. aegypti*, *Ae. africanus*, *Ae. simpsoni*, *Ae. furcifer/taylori*, *Ae. luteocephalus*, *Haemagogus* spp.	Monkeys, mosquitoes
Dengue 1, 2, 3 and 4	Asia, Pacific, Caribbean, Africa, Americas	*Ae. aegypti*, *Ae. albopictus*, *Ae. scutellaris* group, *Ae. niveus*, *Ochlerotatus*	Human/mosquito, (monkeys in jungle cycle)
Rift Valley	Africa, South-west Asia	*Ae. caballus*, *C. theileri*, *C. quinquefasciatus* and other *Culex* and *Aedes* spp.	Sheep, cattle, etc., mosquitoes
Kyasanur Forest	South India	*Haemaphysalis* (hard ticks)	Rodents, monkeys
Crimean–Congo	Europe, Africa, Asia	*Hyalomma* spp. (hard ticks)	Domestic animals

15.2.1 Those producing mainly fever or arthritis

Chikungunya, O'nyong-nyong, West Nile, Orungo, Oropouche and Ross River fevers

This group of infections is summarized in Table 15.1. They present as a dengue-like disease (see below) with headache, fever, malaise, arthralgia or myalgia, lasting for a week or less. Rashes are common in Chikungunya, O'nyong-nyong and West Nile fevers. The arthralgia of Chikungunya fever can be debilitating, hence its name 'to become contorted' (from Tanzania) and may present as a haemorrhagic fever in India and South-east Asia. West Nile and Oropouche fevers can present as encephalitides, especially in the elderly. Ross River fever predominantly presents as a polyarthritis and rash. There are many other arbovirus infections that also present as fever listed in Chapter 20.

Diagnosis of all the arbovirus infections is generally made on clinical grounds once the initial cases have been identified by virus isolation in a specialist laboratory. Specific enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase polymerase chain reaction (RT-PCR) can be used. A rise in specific IgM in serum or cerebrospinal fluid (CSF) is a useful diagnostic, if available.

Incubation period. 3–15 days.

Period of communicability of all the arbovirus infections is as long as there are still infected mosquitoes remaining.

Susceptibility is general but infection leads to immunity, probably lifelong. In endemic areas, these are diseases of children, otherwise they are epidemic affecting all age groups and both sexes. In 2002, there were epidemics of West Nile virus in Israel, Canada and the USA (resulting in 3231 cases and 176 deaths in the latter), countries where this infection has not occurred before. While most people suffered minor illness, individuals with weakened immune systems, such as people with chronic diseases, those on chemotherapy or the elderly, suffered more serious effects, including meningitis and encephalitis. Infection has now spread to many countries in Central America, the Caribbean Islands and Colombia in South America. In August 2011, West Nile virus infection reached Europe, with most cases in Greece and Russia. In 2012 a new strain of the virus was identified in Italy.

Outbreaks of Chikungunya fever in the Indian Ocean Islands of Comores, Madagascar, Mayotte, Mauritius, La Réunion and the Seychelles occurred in 2006–2008, with one-third of the population of La Réunion affected and resulting in several cases being imported to Europe. A much larger outbreak developed in India in 2006–2007, with 1.43 million cases (see also Section 19.4). In 2014 Chikungunya infection invaded the Caribbean, and later in the same year spread to the USA and Mexico. Up to March 2015 there were thought to have been in excess of 1.3 million cases in the Americas, with 184 deaths. The present epidemic of Zika, particularly severe in South America, resulting in a feverish illness, is unusual in affecting the fetus in pregnant women.

15.2.2 Those presenting as fever and encephalitis

Western equine, Eastern equine, St Louis, Venezuelan, Japanese, Murray Valley and Rocio encephalitis

This group of diseases presents with a high fever of acute onset, headache, meningeal irritation, stupor, disorientation, coma, spasticity and tremors. Fatality rates are variable, with up to 30% in Japanese, Eastern equine and Murray Valley encephalitis. The distribution, vectors and reservoirs of these viruses are summarized in Table 15.1. Japanese encephalitis (JE) is covered in more detail below.

From the reservoir bird or animal, the organism is often first transmitted to another host, such as horses in the equine arbovirus infections. Humans are then mainly infected from mosquitoes feeding on the horses (but see also Section 16.10.3).

Incubation period is from 5 to 15 days. Susceptibility is highest in the very young and old, with inapparent infection occurring in other age groups.

15.2.3 Haemorrhagic fevers

Yellow fever, Dengue, Rift Valley fever, Kyasanur Forest disease and Crimean–Congo haemorrhagic fever

As well as dengue and yellow fevers, which will be covered in more detail below, a group of generally mild viral fevers including Rift Valley fever, Crimean–Congo haemorrhagic fever and Kyasanur Forest disease, at certain places and on certain occasions take on a severe form resulting in vascular

permeability, hypovolaemia and abnormal blood clotting. Infection commences as an acute fever, malaise, headache, nausea or vomiting, with petechial rashes, severe bruising and bleeding taking place from various sites. Blood can be vomited, passed in the faeces, come from the nose or gums and bleed into the skin. After a few days, sudden circulatory failure and shock may occur, producing a mortality of up to 50%. In Rift Valley fever there are also less fatal forms, ocular (blurring and decreased vision with 50% experiencing permanent loss of sight) and meningoencephalitic (disorientation, convulsions and coma, with low death rate, but often permanent neurological deficit).

Rift Valley fever is normally a disease of cattle, sheep, camels and goats, in which high mortality can cause considerable economic loss, but spread to humans also occurs. A large number of unexplained abortions in livestock is often the first sign of an impending epidemic. The virus infects humans through wounds and broken skin, or can be inhaled from the aerosol produced when an animal is being slaughtered; infection can occur via mosquitoes as well. There is a suggestion that drinking the raw milk of an infected animal can also infect the person.

Incubation period. 3–12 days.

Period of communicability. This lasts as long as there are infected animals and live mosquitoes that have fed on them, but the virus can also be spread transovarially in the mosquito, with the eggs remaining viable for many years. Permanent foci of Rift Valley fever can therefore become established.

Some arbovirus infections can also be spread by non-mosquito arthropods, such as Kyasanur Forest disease and Crimean–Congo haemorrhagic fever. (See Sections 16.10.1 and 16.10.2.)

15.2.4 Control and prevention of arbovirus infections

The main method of control is the destruction of vector mosquitoes and breeding places. The most important vector mosquitoes are *Culex* and *Aedes*, which live in collections of water close to the home. Search is made for larvae and all breeding places destroyed. Water tanks, blocked drains, discarded tin cans or old tyres are favourite breeding places. A simple method is to use schoolchildren, making a game or giving a reward for the number of breeding places found. Large breeding areas (such as water tanks) can be covered, screened, treated with insecticides, or natural predators introduced (e.g. fish or dragonfly larvae). An improvement on just covering water pots and containers is to use an insecticide-treated cover rather than place the insecticide in the container.

Where there is an epidemic in a compact area, such as a town, then the quickest and simplest (although expensive) method of bringing the epidemic to an end is to use fogging or ultra-low volume (ULV) aerial spraying (see Section 3.4.1). Compared to lost working hours, this can be a cost-effective procedure.

Personal prevention with repellents (Section 3.4.1) can protect the individual. The infected case should be nursed under a mosquito net so as not to infect mosquitoes. A vaccine is available for Venezuelan, Eastern and Western equine encephalitis, which can be used for both humans and horses.

Where an animal reservoir is involved, then restriction of animal movement or the reduction of rodents can be of value. In Rift Valley fever, special precautions should be taken in handling domestic animals and their products, including the wearing of gloves and protective clothing. The milk of infected animals should not be drunk, neither must they be slaughtered and their meat consumed. Blood and other body fluids of patients are also infectious, so barrier nursing should be instituted. All animals should be vaccinated prior to the outbreak. During an outbreak, newly infected animals may be viraemic but not display any symptoms, and there is a danger that reuse of needles and syringes may actually increase spread. An inactivated cell culture vaccine for use in humans is available, but has not been fully evaluated.

Treatment. There is no specific treatment, supportive therapy being given. (Ribavirin may be of value.)

Surveillance. Regular checks should be made on mosquito breeding places and control methods instituted where mosquitoes are found. People can be taught to regularly search their home areas for mosquito breeding. (See further under dengue Section 15.4 and yellow fever Section 15.5.) Outbreaks are often associated with heavy rainfall (which provides conditions for mosquito breeding), so can often be forecast.

15.3 Japanese Encephalitis (JE)

Organism. The Japanese encephalitis virus (JEV) is a member of the flavivirus family, the same group of viruses as the West Nile, St Louis, dengue and yellow fever viruses.

Clinical features. Japanese encephalitis (JE) presents as a sudden onset of fever, headache, body aches and pains. Mild cases recover completely, but a high proportion develop encephalitis and progressive coma. Children under 10 years of age may present with gastrointestinal symptoms and convulsions, rapidly leading to death. Those that survive the severe disease may have residual neurological or psychiatric disabilities.

Diagnosis is by finding the specific IgM in cerebrospinal fluid (CSF) or serum. The virus can be cultured in specialist laboratories.

Transmission. The main vectors are *Culex tritaeniorhynchus*, *Culex gelidus* and *Culex fuscocephala*, mosquitoes that predominantly breed in rice fields. The reservoir of infection is probably in wading birds, but domestic pigs also harbour the virus, from which it is transferred to humans. The mosquito breeds when the rice fields are flooded and the first green shoots appear, dying off when the rice grows and shades the water, which produces a marked seasonality, with a peak period in Thailand in July and August, in China in August, and in India/Nepal in September and November. In irrigated areas, mosquito breeding can occur throughout the year, while outbreaks have occurred in urban areas where suitable standing water permits the breeding of vector mosquitoes.

Incubation period. 4–14 days.

Period of communicability. This lasts as long as there are infected mosquitoes continuing to bite people. Mosquitoes can also become infected by feeding on a clinical case at any time during the illness.

Occurrence and distribution. Serological surveys indicate that most people living in endemic areas contract subclinical infection before the age of 15 years. However, young children and adults who have not been infected as children (including visitors) may get clinical disease, and possibly severe disease, with 20–30% mortality. There are about 50,000 cases reported annually and 10,000 deaths.

The endemic area is South and South-east Asia, particularly Cambodia, Laos, Vietnam, Thailand, Malaysia, Myanmar, Indonesia, Philippines, the Indian subcontinent and Russia, with a decreasing incidence in China, Japan and Korea. Risk within any of these countries is greatest during the rice-growing season and when an epidemic is ongoing. JE has recently spread to New Guinea and northern Australia.

Control and prevention. Agricultural methods such as drying out rice fields when no crop is growing or decreasing the number of crops can reduce the period of risk. Personal protection with long-sleeved clothing, the wearing of trousers and use of repellents can reduce mosquito biting. The mosquito bites during the daytime, so babies and young children should be made to sleep under insecticide-treated mosquito nets (Box 3.1). The main method of prevention though is to vaccinate all children in endemic areas, but after the age of 1 year so as not to interfere with remaining maternal antibodies. A booster dose should be given a year later for all types of vaccines and then every 3 years up to 10–15 years of age for the mouse-brain-derived vaccine. An alternative strategy is vaccination of the pig reservoir. In 2012 an Indian inactivated cell-culture-derived vaccine was introduced, which may be preferable to the mouse-brain-derived vaccine.

The World Health Organization (WHO) has recently extended its advice to vaccinate in all areas where JE is recognized as a public health priority. Even if the number of JE confirmed cases is low, vaccination should still be considered. Vaccination, however, only protects the individual and does not lead to herd immunity, so a high coverage is necessary.

Treatment. There is no treatment. A monocyte and macrophage receptor has been used with some success to reduce the severe inflammatory infection of the brain.

Surveillance. Notification of cases should be reported to WHO so that neighbouring countries and visitors can take precautions.

15.4 Dengue

Organism. Dengue virus has four serotypes (1, 2, 3 and 4).

Clinical features. Dengue presents as a sudden onset of fever, retro-orbital headache, joint and muscle pains, and facial signs of flushing, puffy eyelids and red eyes. A maculopapular or scarlatinaform rash usually appears after 3–4 days. Depression and prolonged fatigue often occur following the acute manifestations. Dengue haemorrhagic fever (DHF; recently designated severe dengue), in which there is profound bleeding into skin and tissues, is now a serious feature of many epidemics. After the initial symptoms, the condition suddenly worsens with facial pallor, abdominal pain and cyanosis. The liver may become enlarged and then signs of bleeding occur, such as into the gastrointestinal tract, with concurrent shock.

DHF is probably due to a sensitization with a previous dengue serotype, either acquired at birth or from a previous infection, type 2 being the most potent and types 3, 4 and 1 being responsible in decreasing importance. Differential effects on racial groups suggest that host factors may also have a role, as does the geographical origin of the dengue strain.

Diagnosis. Virus can be isolated from the blood in acute cases. IgM-capture ELISA on a single specimen indicates recent infection, which is confirmed by a rising titre in paired sera.

Transmission. Mosquitoes of the *Aedes* group, especially *Ae. aegypti*, *Ae. albopictus* or a member of the *Ae. scutellaris* group are responsible for transmission. These mosquitoes are more easily identifiable than most by their black colour, with distinctive white markings (Fig. 15.2). They like to breed close to humans, taking advantage of any water containers, old tyres, empty tins or other small collections of water in which they can breed. They are daytime biters and can be found in large numbers in urban and peri-urban areas. *Ae. albopictus* has comparatively recently become established in the USA, Central America and the Caribbean owing to the trade in used tyres.

Virus is maintained in a human/mosquito cycle in many parts of the world, but in Africa and South-east Asia a monkey/mosquito cycle is involved.

Incubation period. 3–15 days (commonly 4–6).

Period of communicability. The mosquito is able to transmit infection 8–12 days after taking an infective blood meal and remains infective for the rest of its life. Humans and monkeys are infectious during and just before the febrile period.

Occurrence and distribution. Dengue is now endemic in South and Central America, sub-Saharan Africa and South and South-east Asia (Fig. 15.3). In more isolated communities, large epidemics have occurred, especially in island countries of the Caribbean and Pacific, with devastating effect. The epidemic can be so massive as to immobilize large segments of the population, disrupt the workforce and cause a breakdown in organization. The development of DHF has been variable, producing a number of deaths. It is estimated that there are about 50 million cases of dengue and 0.5 million of DHF, with 12,000 deaths due to dengue every year. Children are the main sufferers of both dengue and DHF.

Control and prevention. The main method of control is to reduce mosquito breeding, especially of the *Aedes* mosquito, by depriving it of collections of water or covering them so that mosquitoes cannot enter. All water tanks, pots or other containers must be covered at all times, treating the covers with insecticides if there is not a perfect fit. Guttering around the roof can also allow pools of water to collect, so should be of sufficient slope for good drainage and be cleaned out regularly. Old tyres should have holes cut in them or be removed altogether (one answer to the disposal problem is to weight them and bury them at sea to form artificial reefs).

People should check round their gardens and the immediate vicinity at regular intervals to remove any cans, coconut shells or other temporary collections of water. Children are very effective at doing this and can be encouraged with a marks or reward scheme.

Screening of houses and mosquito nets are of little use because people are often outside their houses when the mosquito bites, but these measures are of value for young children. ULV spraying, either by fogging or by aircraft, is of value in the presence of an epidemic, but only adult mosquitoes are killed, which are soon replaced by young adults, unless simultaneous larval control is also in operation.

A dengue vaccine is being tested, but there is concern that it may sensitize the individual and produce DHF.

Treatment. There is no specific treatment, but hypovolaemic shock must be treated with rapid fluid replacement and oxygen therapy.

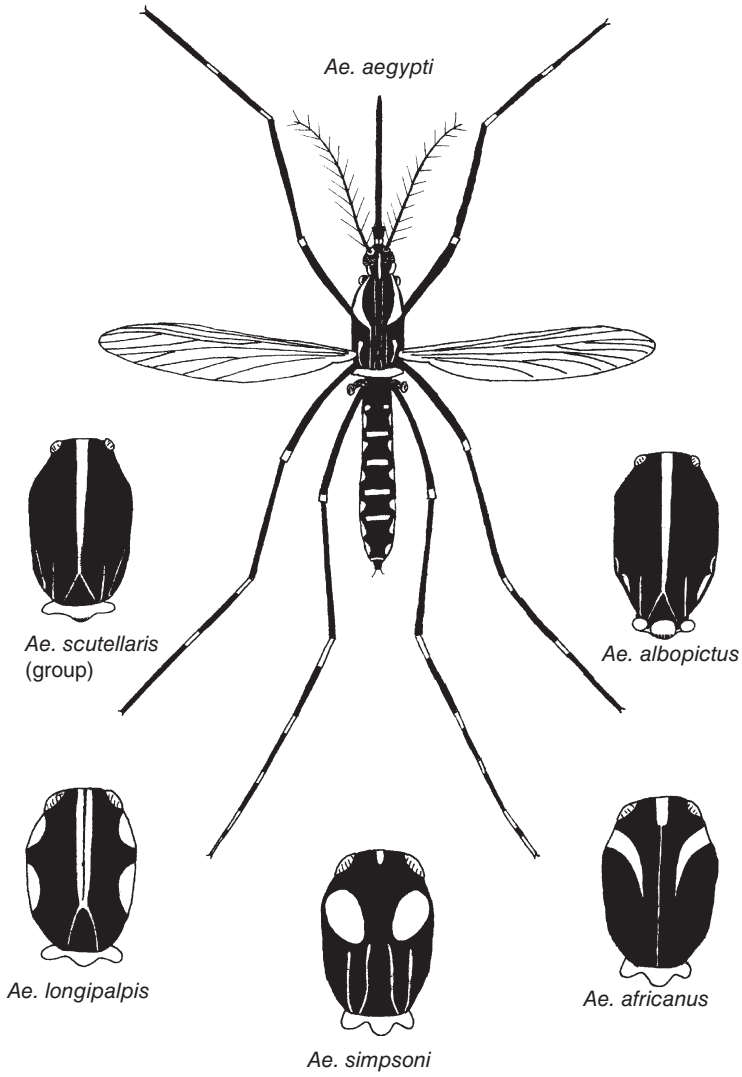

Fig. 15.2. *Aedes*, the black and white mosquitoes. Note the thorax markings of the different species.

Surveillance. Regular checks should be made on mosquito breeding, especially of *Ae. aegypti*. Samples are taken and the number of larvae breeding is counted to give an indication of the risk of transmission. Further details will be found in Section 15.5.

15.5 Yellow Fever

Organism. The yellow fever virus is a flavivirus.

Clinical features. One of the haemorrhagic group of arbovirus infections, yellow fever presents with a sudden onset of fever, headache, backache, prostration and vomiting. Jaundice commences mildly at first and intensifies as the disease progresses. Albuminuria and leucopenia are found on examination, while the haemorrhagic symptoms of epistaxis, haematemesis, melaena and bleeding from the gums can all occur. In endemic areas, the fatality rate is low except in the non-indigenous. The death rate may reach 50% in epidemics.

Diagnosis is made on clinical grounds after initial identification of an outbreak. Virus can be isolated

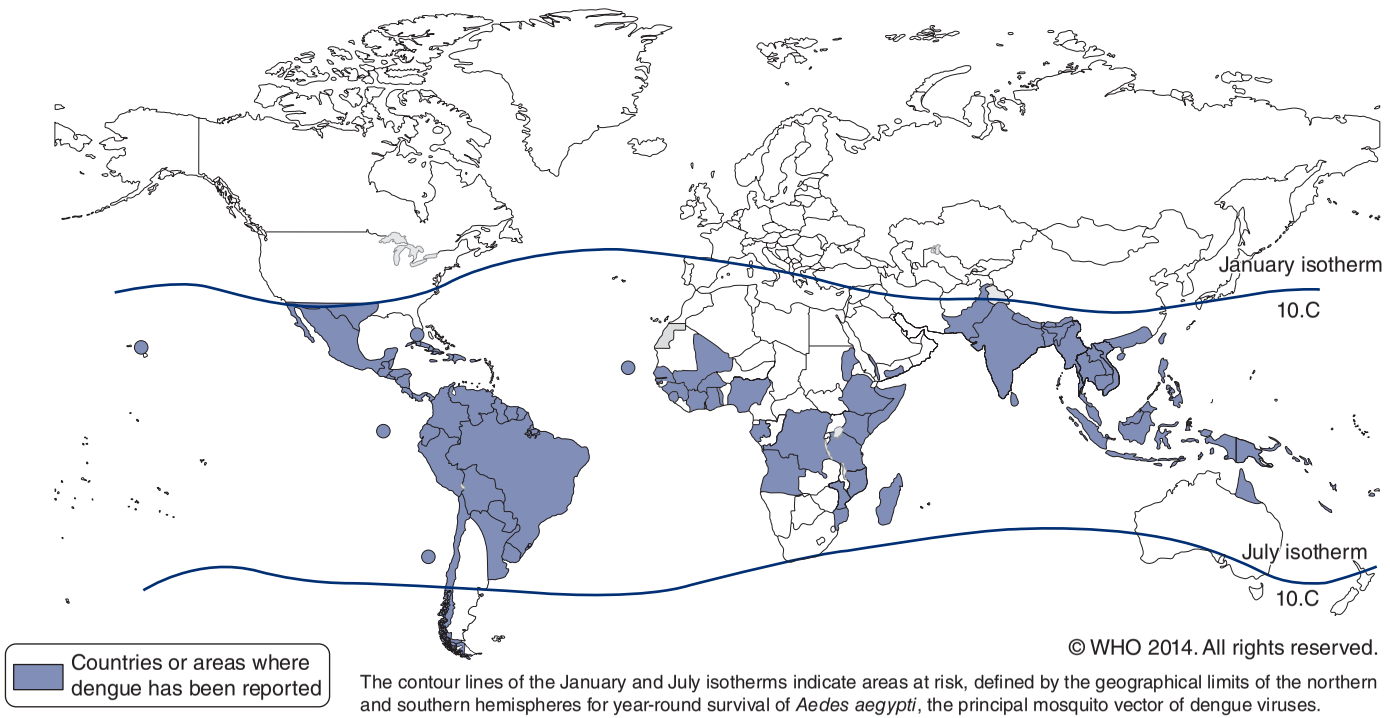

Fig. 15.3. Dengue, countries or areas at risk, 2013. (Reproduced by permission of the World Health Organization, Geneva.)

from blood in specialist laboratories, such as the Pasteur Institute in Dakar, and IgM tested by ELISA techniques. Viral isolation and typical liver histology from fatal human cases and in monkeys thought to have died from the disease can assist in the evaluation of epidemics. A revised case definition developed by WHO is:

- **Suspected**, acute onset of fever, with jaundice appearing within 14 days. (See Table 8.2 for differential diagnosis of jaundice.)
- **Probable**, presence of yellow fever IgM in the absence of yellow fever immunization within 30 days. Epidemiological link to a confirmed case or an outbreak.
- **Confirmed**, detection of yellow-fever-specific IgM or fourfold increase of yellow fever IgM or IgG antibody titres or detection of yellow-fever-specific neutralizing antibodies in the absence of yellow fever immunization within 30 days. If no yellow fever immunization within 14 days, then either the detection of yellow fever virus genome in blood or other organs by PCR or of antigen in blood or other organs by immunoassay or the isolation of yellow fever virus.

Transmission. Yellow fever is a disease of the forest, maintained in the monkey population by the sylvatic transmission cycle, which involves *Haemagogus*, *Sabethes* and *Aedes* mosquitoes in America, and *Aedes* in Africa (Fig. 15.4). The monkeys are generally not affected by the disease but occasionally start dying, indicating that spread to the human population may soon begin. In South America, it may be a reduction in the monkey population that will make the canopy mosquito look for another blood meal and perhaps feed on humans. More commonly, it is the person who goes into the forest to cut wood or hunt that becomes bitten incidentally. When they return to their village or town, they are fed on by *Ae. aegypti*, and an urban yellow fever transmission cycle is set up (see Fig. 15.4). In Africa, three different kinds of mosquitoes are involved. *Aedes africanus* remains in the jungle canopy rarely feeding on humans, but should the monkey descend to the forest floor or even enter areas of human habitation, it is fed on by *Aedes simpsoni*, *Aedes furcifer-taylori* or *Aedes luteocephalus*. The mosquito then bites a person on the edge of the forest (the rural cycle), who returns to the village soon to suffer from yellow fever. Fed upon by the peri-domestic mosquito *Ae. aegypti*, an urban cycle is started (Fig. 15.4). The extrinsic (within-mosquito) cycle of infection takes 5–30 days, depending on the temperature and type of mosquito. Transovarian (transovarial) infection can also occur.

Incubation period. 3–6 days.

Period of communicability is from before the fever commences to 5 days after, so the patient should be nursed under a mosquito net to prevent new mosquitoes from becoming infected.

Occurrence and distribution. Yellow fever nearly always presents as an epidemic in humans, affecting all ages and both sexes, although adults (particularly males) who go into the forest are likely to be the first to contract the disease. Yellow fever is restricted to the areas of Africa and South America shown in Fig. 5.1. WHO has established a special initiative to assist Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria, Senegal, Sierra Leone and Togo, the 12 highest risk countries (see further below).

Control and prevention. The most important part of the complex mosquito transmission cycle is *Ae. aegypti*. With its proximity to humans, it is capable of infecting a large number of people as well as being the easiest mosquito species to control. It breeds in small collections of water near to people's houses, so a careful search for larvae and the destruction of breeding places can do much to reduce the danger. Simple clearance is the most effective method of reducing the mosquito population (see under dengue above), but insecticides such as temephos (Abate) can be used where collections of water cannot be destroyed or covered. In the event of an epidemic, then emergency reduction by fogging or ULV spray from aircraft will rapidly destroy the adult population (but not the larvae).

One attack of yellow fever confers immunity for life if the person survives the disease. Inapparent infections can also occur. A very effective vaccine has been developed, which provides immunity for at least 10 years and probably longer, so all those at risk in the known endemic areas should be vaccinated (Fig. 5.1). This has been attempted by offering vaccination at markets and meetings, or systematically offering it to schoolchildren. WHO now recommend that yellow fever vaccination be

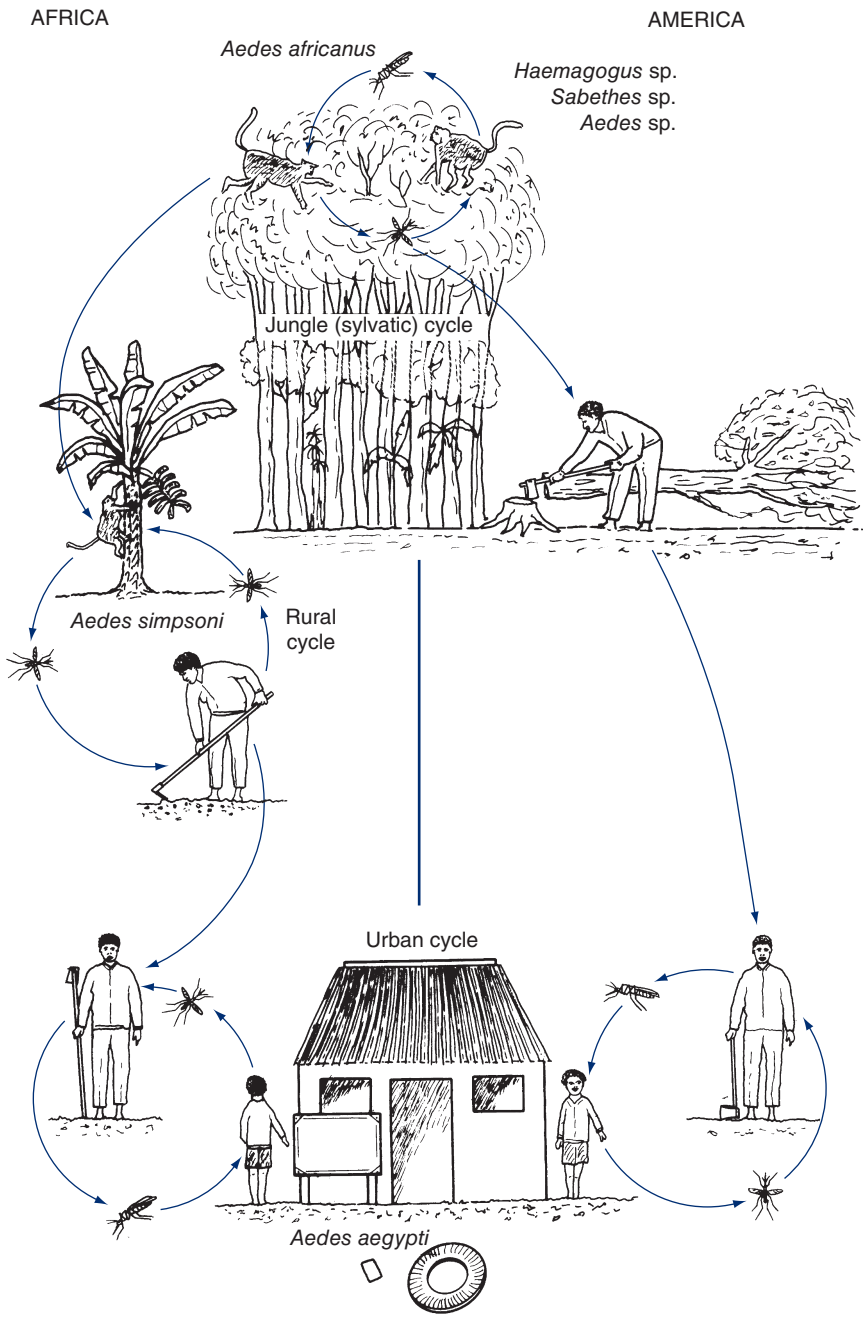

Fig. 15.4. Yellow fever transmission cycles in Africa and South America (including Panama).

included in the childhood vaccination programme in the 33 countries of Africa in the yellow fever zone; the vaccine is to be given at the same time as the measles vaccine. The countries of South America have already implemented childhood vaccination programmes. In the event of an epidemic, then ring vaccination can be performed; the epidemic is surrounded by a circle of vaccinated persons,

progressively closing in on the centre of the outbreak. Areas of Africa and South America have been designated as yellow fever areas (Fig. 5.1) and all visitors to this zone require vaccination. If a person has visited a country where there is a risk of transmission and they are not vaccinated and then enter another country where the vector of yellow fever is present, then the authorities can quarantine that person for 6 days.

In view of the rapid urbanization of African cities and the increase in migration, WHO is concerned that major outbreaks could occur, exhausting vaccine supplies, so is proposing to pre-emptively vaccinate some 48 million people (17% of the population) in the 12 high-risk countries. The priority groups for vaccination will be determined from the past history of yellow fever outbreaks in the particular district or its proximity to an outbreak, and the proportion of vaccinated persons in the district (the lower the proportion, the higher the priority). In order to do this, WHO has established a stockpile of vaccine that can be drawn on for preventive mass vaccination and emergency use.

WHO now recommends that a single dose of yellow fever vaccine is sufficient to confer substantial immunity and life-long protection against yellow fever, and a booster dose of yellow fever vaccine is not needed. However, some countries might still require evidence of a booster every 10 years. From June 2016, life-long protection from a single vaccination will be accepted for certification purposes.

In these days of rapid air transport, it has always been surprising that yellow fever has not been transported to Asia, where there are the vectors and conditions for transmission. A suggested reason is that there is some cross immunity with other Group B arboviruses (flaviviruses), and that the level of such induced immunity may be sufficient to prevent epidemic spread. A precaution is to spray all aircraft coming from a yellow fever area.

Treatment. There is no specific treatment, but supportive therapy is given to combat shock and renal failure.

Surveillance. All cases of suspected or confirmed yellow fever should be reported to WHO as an event of international public health importance. The prevalence of the urban vector can be measured by the *Ae. aegypti* index. This is the number of houses found with *Ae. aegypti* breeding within a specified area of 100 houses. Alternatively, the Breteau index can be used, which is the number of containers in which larvae are found out of 100 samples. If this is kept below 5%, or preferably 1%, then the danger of an epidemic is minimized.

15.6 Malaria

Organism. There are four human malaria parasites, *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. *P. falciparum* causes the most serious disease and is the commonest parasite in tropical regions, but differs from *P. vivax* and *P. ovale* in having no persistent stage (the hypnozoite) from which repeat blood-stage parasites are produced. *P. vivax* has the widest geographical range, being found in temperate and subtropical zones as well as in the tropics. *P. vivax* infection will lead to relapses if a schizontocidal drug only is used for treatment, and some strains, e.g. the Chesson strain in New Guinea and Solomon Islands, require a more prolonged radical treatment. *P. malariae* produces a milder infection but is distinguished from the fever caused by the other three species by having paroxysms of fever every fourth day. *P. malariae* can persist as an asymptomatic low-grade parasitaemia for many years, to multiply at a future date as a clinical infection. *P. ovale* is the rarest of the parasites and is suppressed by infections with the other species. A few cases of malaria have been found to be due to *P. knowlesi*, which normally infects monkeys in South-east Asia.

The malaria parasite *Plasmodium* may be the cause of one of the oldest parasitic infections of humans, dating from at least 60 million years ago when it inhabited the guts of reptiles. The parasite was transferred to bird and mammalian predators where forms evolved that entered the bloodstream. At some time, it adapted to the mosquito, with separate species evolving to parasitize different kinds of birds and mammals, including humans. While most species of *Plasmodium* are considered to have arisen in Africa, *P. vivax* was thought to have originated in Asia due to its genetic similarity to the species infecting Asian macaques; however, a closer link has now been found with chimps and gorillas, confirming its African origin.

The malaria parasite reproduces asexually in the human and sexually in the mosquito (Fig. 15.5). A merozoite attacks a red blood cell (RBC), divides asexually, rupturing the cell, and each newly formed merozoite attacks another RBC. Toxins are liberated when the cell ruptures, producing the clinical paroxysms. After several asexual cycles, male and

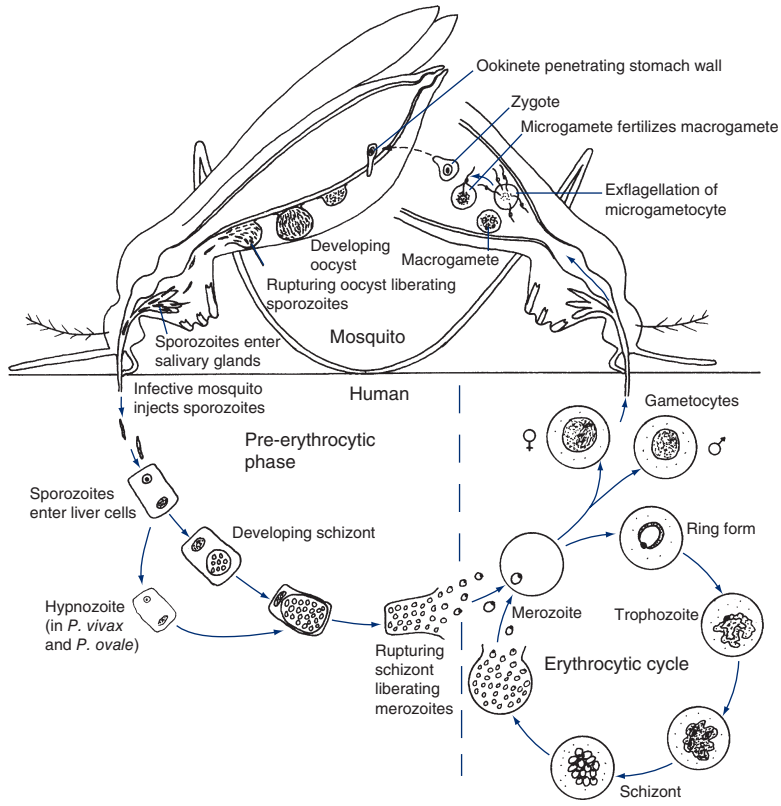

Fig. 15.5. The malaria (*Plasmodium* spp.) life cycle.

female gametes (gametocytes) are produced, which are ingested when a mosquito takes a blood meal. These go through a complex developmental cycle in the stomach wall of the mosquito, culminating in the production of sporozoites, which migrate to the salivary glands ready to enter another person when the mosquito next takes a blood meal.

The sporozoite enters a human liver cell, in which development to a schizont takes place. This ruptures, liberating merozoites, which attack RBCs, so starting an erythrocytic cycle all over again. In *P. vivax* and *P. ovale*, a persistent liver stage, the hypnozoite, is formed, meaning that if parasites are cleared from the blood, relapses can occur, often continuing for many years unless radical treatment is given.

Clinical features. Infection commences with fever and headache, soon developing into an alternating pattern of peaks of fever followed by sweating and profound chills. Classically, these take on a pattern of either 3 days (tertiary malaria) or 4 days (quaternary malaria). However, falciparum malaria can present in many different forms, including cerebral malaria (encephalopathy and coma), and acute shock, haematuria (blackwater fever) and jaundice. The higher the parasitaemia, the more severe the morbidity and the higher the mortality. Cerebral malaria in children presents as febrile seizures, making it difficult to differentiate it from other causes, but malaria should be considered the most likely diagnosis and treatment started without delay.

Partial treatment leads to recrudescences of fever, whereas relapses can occur many years after initial infection with *P. vivax* and *P. ovale*.

Interaction between malaria and HIV infection has now been shown to produce more severe clinical disease in persons already infected with human immunodeficiency virus (HIV), as well as an excess of cases.

Diagnosis is from a thick blood smear (to detect parasites) and a thin smear (to determine species) (Fig. 15.6). Rapid diagnostic test (RDT) dipstick

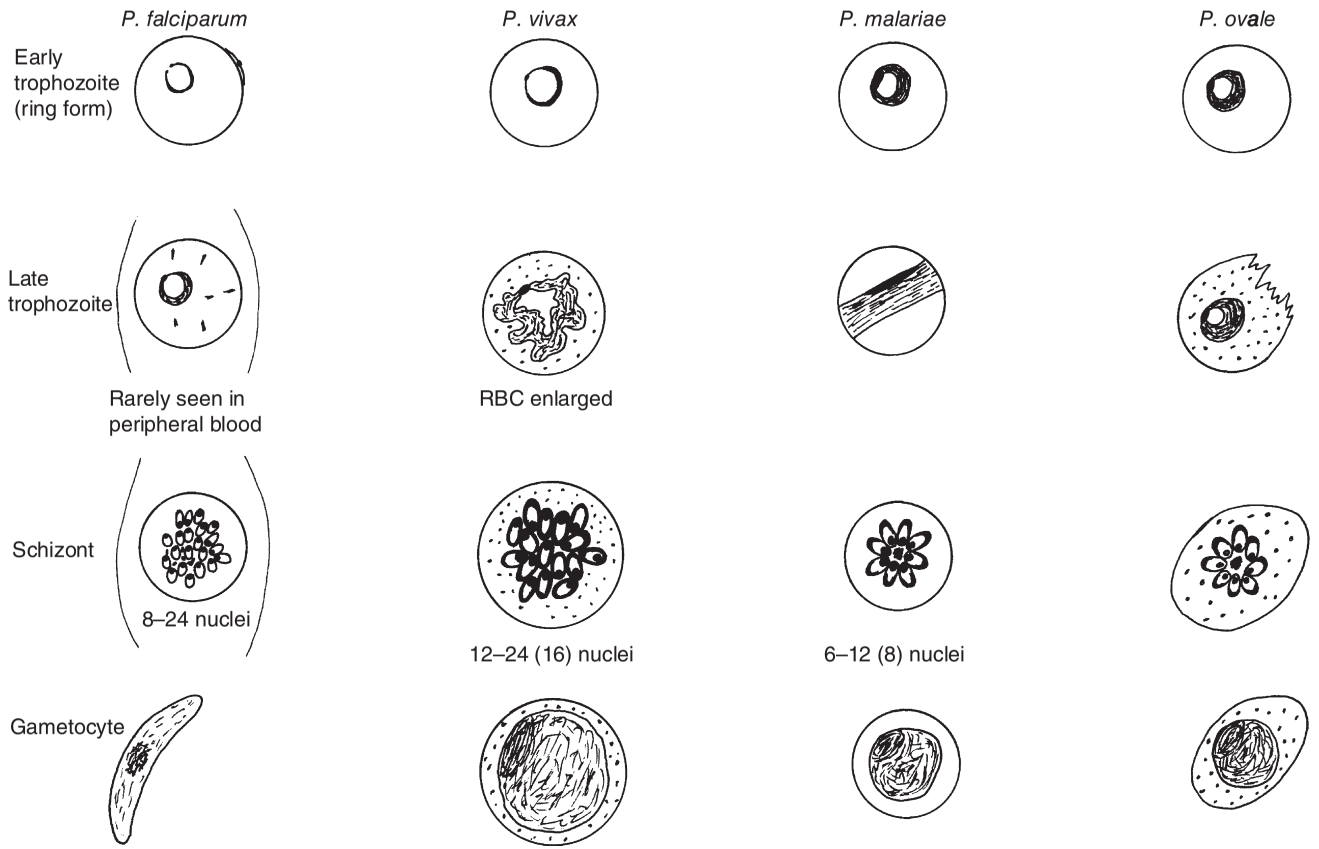

Fig. 15.6. Differential diagnosis of *Plasmodium* spp. RBC, red blood cell.

methods have made the diagnosis of malaria simpler, but need to be evaluated for each country in which they are to be used. They are particularly useful for surveys.

Transmission is by *Anopheles* mosquitoes (Table 15.2). The efficiency of the vector will depend on the species of *Anopheles*, its feeding habits and the environmental conditions. This varies widely, from *A. gambiae*, the most efficient of all malaria vectors, to a species such as *A. culicifacies*, which is comparatively inefficient. Vector efficiency is determined by a number of factors, such as the preferred food source (human or animal), the time of biting (easier

Table 15.2. The main malaria vectors and their behaviour in relation to control.

Geographical area	*Anopheles* species	Behaviour in relation to control
More arid areas of sub-Saharan Africa and western Arabia	*A. arabiensis*	Feeds on animals and humans depending on availability. Some exit after feeding.
More humid parts of sub-Saharan Africa	*A. gambiae s.s.*	Bites humans in the middle of the night. Rests indoors after feeding. Breeds in temporary puddles, increasing considerably in wet season and declining in dry.
Sub-Saharan Africa, including highlands	*A. funestus*	Bites humans in middle of the night. Rests indoors after feeding. Breeds in more permanent water bodies, remaining a constant vector all year.
Turkey, Central Asia, Afghanistan	*A. sacharovi*, *A. superpictus*	Bites humans indoors.
Rural areas of Indian subcontinent and South-west Asia	*A. culicifacies*, species A, C, D and E	Feeds predominantly on animals but bites humans sufficiently to be the main rural vector in India and Sri Lanka. Tends to bite early in the night. Breeds in water tanks and pools, but not rice fields.
Urban areas of Indian subcontinent and South-west Asia	*A. stephensi*	Feeds on humans and animals throughout night except in cold weather, when biting is early. Breeds in wells and water tanks.
Indian subcontinent	*A. fluviatilis* species S	Bites humans and rests indoors. Associated with hill streams.
South and South-east Asia	*A. sundaicus*	Mainly bites cattle, but also humans sufficiently to be a vector. Breeds in saltwater lagoons.
South-east Asia (including north-east India and south-west China)	*A. minimus*	Feeds on humans and rests indoors, but due to prolonged insecticide spraying has changed to outdoor resting and animal biting in some areas.
South-east Asia	*A. dirus*	Bites humans indoors, but then exits. Associated with forests.
	A. aconitus	Lives indoors. Breeds in rice fields.
Nepal, Malaysia, Indonesia	*A. maculatus*	Bites humans indoors. Breeds in rice fields.
Indonesia	*A. leucosphyrus*	Bites humans and rests indoors.
Philippines	*A. flavirostris*	Bites humans and rests indoors.
China	*A. sinensis*	Mainly bites animals, inefficient vector.
	A. anthropophagus	Bites humans, efficient vector. Both *A. sinensis* and *A. anthropophagus* breed in rice fields.
Melanesia	*A. farauti*, *A. punctulatus*, *A. koliensis*	Bites humans indoors and rests indoors. Breeds in temporary rainwater pools.
Central America, western South America and Haiti	*A. albimanus*	Bites outside and early in the night. More abundant during rainy season.
Central and northern South America	*A. pseudopunctipennis*	Bites humans indoors.
North urban South America	*A. darlingi*	Bites humans and rests indoors. Biting time variable in different parts of its range. More abundant during rainy season.
Northern South America	*A. nuñeztovari*	Bites humans indoors but exits during night.
	A. aquasalis	Bites outside early in the night. Breeds in brackish water.
South America	*A. albitarsis* complex (*A. marajoara*)	Bites humans outdoors. Associated with gold mining.

in the middle of the night when people are sleeping) and whether the mosquito lives inside the house or outside; but the most important factor is the mosquito's length of life. Only a few *A. culicifacies* will survive longer than 12 days and so become infective (i.e. most die before completion of the extrinsic cycle), whereas 50% of a population of *A. gambiae* will live longer than 12 days. Longer-living mosquitoes are better vectors.

A female mosquito must have a blood meal before it can complete its gonotrophic cycle and lay a batch of eggs. The gonotrophic cycle is normally about 2–3 days but varies with temperature, species and locality. Long-living mosquitoes will be able to lay several batches of eggs, and this characteristic is used to estimate longevity of a mosquito species.

Another factor is mosquito density. A large number of mosquitoes have a greater transmission potential than a few. Some mosquitoes are produced in large numbers at certain favourable times of the year, while others maintain more constant populations. The environment largely determines mosquito density.

The most important environmental factors are temperature and humidity, with wind, phases of the moon and human activity having lesser effects. Temperature determines the length of the development cycle of the parasite and the survival of the mosquito vector. This means that in temperate climates malaria can only be transmitted in brief periods of warm weather when the right conditions are available. In tropical regions, altitude alters the temperature, and highland areas will have less (although possibly epidemic) malaria.

Water is essential for the mosquito to breed. In arid desert countries, the mosquito cannot survive, but wells and irrigation have allowed mosquitoes to breed and malaria to appear. Rainfall generally increases the number of breeding places for mosquitoes, so there is more malaria in the wet season. However, the rain may be so great as to wash out breeding places, thereby instead producing a decrease in the population.

The mosquito, being a fragile flyer, is easily blown by the wind, sometimes to its advantage, but generally to its disadvantage. On windy evenings, mosquito biting may decrease considerably.

Nocturnal mosquitoes are sensitive to light, so on a moonlit night there is a reduction in numbers. Measurements of mosquito density must be made on several nights, or ideally over a period of months.

Where the mosquito species is mainly zoophilic (feeds on animals), keeping domestic animals in proximity to the household will encourage mosquitoes to feed on them instead of on the human occupants. It is these environmental factors that determine whether malaria is *endemic* or *epidemic*. Where conditions of temperature and moisture permit all-year-round breeding of mosquitoes, then endemic malaria occurs, but if there is a marked dry season or reduction in temperature, then conditions for transmission may only be suitable during part of the year, resulting in seasonal malaria. If conditions are marginal and only favourable every few years, then epidemic malaria can result. Epidemic malaria is devastating as large numbers of people who have no immunity are attacked. Endemic and epidemic malaria call for quite different strategies of control.

Malaria can also be transmitted by blood transfusion, from needles and syringes and rarely congenitally.

Incubation period depends on the species and strain of the parasite:

- *P. falciparum* 9–14 days
- *P. vivax* 12–17 days, but in temperate climates it can be 6–9 months
- *P. malariae* 18–40 days
- *P. ovale* 16–18 days

Period of communicability is as long as there are infective mosquitoes. For a mosquito to become infective it must live long enough for the parasite to complete the developmental cycle (the extrinsic cycle), which depends on the temperature and species. *P. vivax* completes this more quickly than *P. falciparum*.

	Development time (days) at mean ambient temperature		
Species of parasite	30°C	24°C	20°C
P. vivax	7	9	16
P. falciparum	9	11	20
P. malariae	15	21	30

At 19°C, *P. falciparum* takes in excess of 30 days (beyond the life expectancy of the average mosquito), whereas *P. vivax* can still complete its cycle in less than 20 days; 17°C is the absolute minimum temperature for *P. vivax*, but the extrinsic cycle is longer than the lifetime of the mosquito.

Occurrence and distribution. In a non-immune population, children and adults of both sexes are affected equally. In areas of continuous infection with *P. falciparum*, malaria is predominantly an infection of children, in whom mortality can be considerable. The survivors acquire immunity, which is only preserved by the maintenance of parasites in the body, due to reinfection. Should the individual leave an area of continuous malaria, immunity may be reduced. The other time when immunity is reduced is during pregnancy, and severe malaria can occur in the pregnant woman, even one that has lived in an endemic area. This is worse in the first pregnancy than subsequently. (See also Section 18.2.9.)

The body responds to malaria by an enlargement of the spleen. The degree of enlargement and the proportion of the population with palpable spleens has been used as a measure of malarial endemicity:

- *Hypoendemic*. Spleen rate in children (2–9 years) not exceeding 10%.
- *Mesoendemic*. Spleen rate in children between 11 and 50%.
- *Hyperendemic*. Spleen rate in children constantly over 50%. Spleen rate in adults also high (over 25%).
- *Holoendemic*. Spleen rate in children constantly over 75%, but spleen rate in adults low.

In endemic areas, the gametocyte rate is highest in the very young, but in epidemic malaria or areas where transmission has been considerably reduced, gametocytes occur at all ages.

Malaria is found in the tropics and subtropics of the world (Fig. 15.7 and Table 15.2), mostly *P. falciparum*, but *P. vivax* is the predominant species in the Indian subcontinent. The disease used to be more extensive, with seasonal malaria in temperate regions, but extensive control programmes have confined it to its present limits. However, increase in population and the development of resistance, both by the parasite and the mosquito, means that malaria is still the most important parasitic disease in the world. Control methods, especially the use of insecticide-treated mosquito nets, have recently

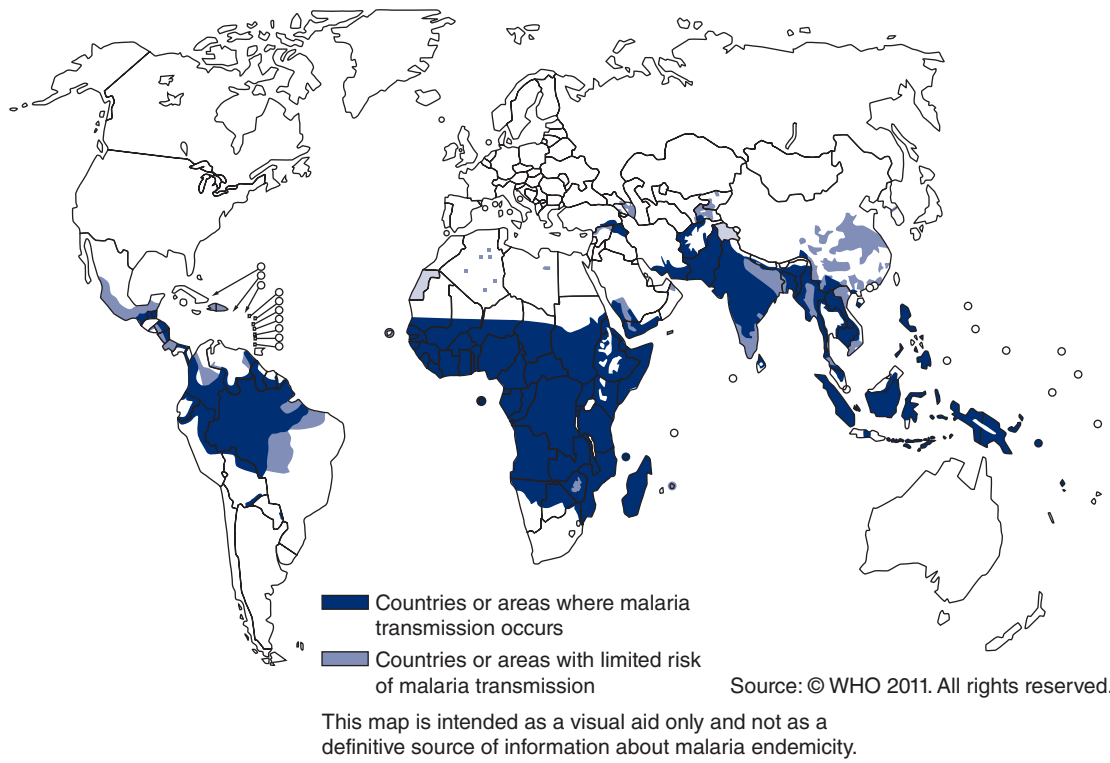

Fig. 15.7. Malaria, countries or areas at risk of transmission, 2010. (Reproduced by permission of the World Health Organization, Geneva.)

brought down the number of cases from some 300 million and over 1 million deaths each year, to 214 million cases and 438,000 deaths in 2015. Unfortunately, an interaction between HIV infection and malaria has meant that HIV-infected people are more likely to contract malaria and to die from it.

Certain genetic traits such as sickle cell anaemia and the Duffy minus mutation offer protection from malaria in Africa, particularly in West Africa where these conditions are more common. A similar effect is produced by alpha thalassaemia found in Papua New Guinea and Irian Jaya (part of Indonesia). Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is more widespread, but reaction with primaquine in the radical treatment of *P. vivax* can cause severe drug reactions.

Global climatic change has resulted in an increase in epidemic malaria (infecting new or infrequently involved areas), and in the development of endemic malaria in highland areas which were normally protected by their lower temperatures (see also Section 1.5.3).

Control and prevention. Mathematical models were introduced in Section 2.4, malaria being one of the best examples in which they can be used to work out the strategy for control. The parasite life cycle was described above and is illustrated in Fig. 15.5, while each of these stages can be represented mathematically on a diagram as shown in Fig. 15.8. The stages and values for each of the places where the life cycle can be interrupted are:

1. In *humans*:

- Reduction of the duration of infection ($1/r$) by chemotherapy.
- Prevention of infections with gametocytes (b) by chemoprophylaxis and vaccination.

2. In *mosquitoes*:

- Prevention of human biting ($a \times a = a^2$) by personal protection and mosquito nets.
- Decreasing mosquito density (m) with larviciding and biological control.
- Reduction of the proportion surviving to infectivity (p^n) by residual insecticides and treated mosquito nets.
- Reduction of the mosquito expectation of life ($1/-\ln p$) by knock-down and residual insecticides, where p is the probability of a mosquito surviving through one day, n the time taken to

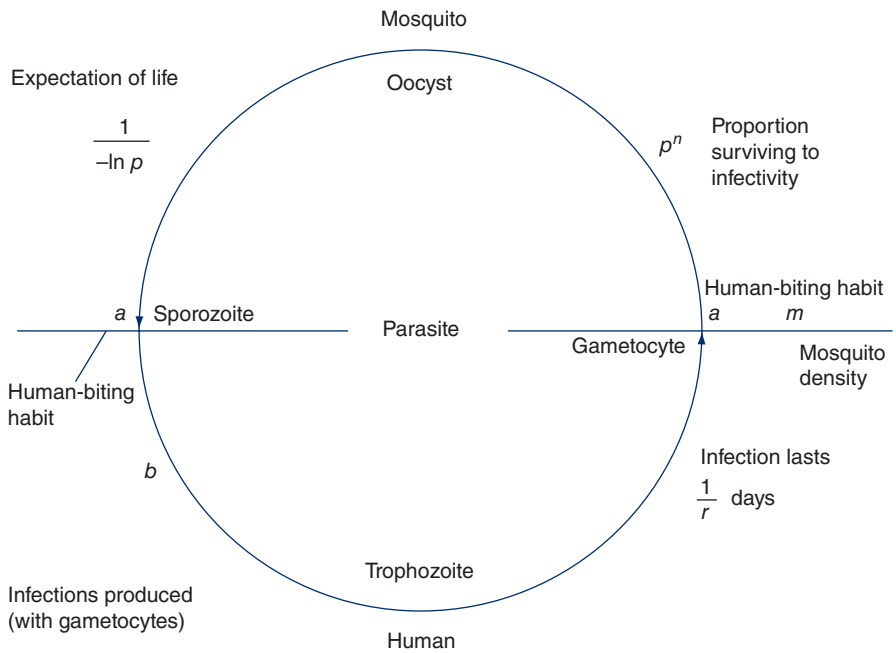

Fig. 15.8. Mathematical model of malaria based on the schematic life cycle of the parasite. See text for explanation of variables.

complete the extrinsic cycle, and ln the natural logarithm).

The complete formula becomes

$$z_0 = \frac{ma^2bp^n}{-r(\ln p)}$$

where z_0 is the basic reproductive rate (see Section 2.2.3). Each of the parameters can be given values that have been measured in the field so that the level of control required to interrupt transmission can be calculated (reduce the basic reproductive rate below 1).

Some useful modifications of the formula are for the vectorial capacity:

$$\frac{ma^2p^n}{-r(\ln p)}$$

and for the critical density of mosquitoes below which the infection will die out:

$$\frac{-r(\ln p)}{a^2bp^n}$$

More complex models have been developed to overcome some of the shortcomings of this model, such as the development of immunity, but even in this limited form it is very valuable.

The effectiveness of any potential strategy can be estimated from the algebraic expression given to each part of the formula without making any calculations:

- $1/r$, the duration of infection reduced by chemotherapy, which demonstrates the small effect of just treating malaria cases, and that control efforts such as mass drug administration used in malaria eradication programmes, needs to be total, covering every single person – virtually impossible to achieve.
- b, actually a notation normally applied to mosquitoes, being the proportion that ingest gametocytes so that the parasite sexual cycle can take place, but can be applied to the human part of the cycle as any method which prevents the production of gametocytes. This can either be by preventing infection in the first place with vaccination or chemoprophylaxis, the use of gametocidal drugs, or preventing the mosquito feeding on a malaria case by keeping the case under a mosquito net. However, b is only a unitary factor, so all of these methods will need to be nearly perfect to work.
- a, the number of bites that need to be made by the mosquito. One bite is needed to introduce infection and another to take up gametocytes, so the interruption of mosquito biting could be quite an effective strategy. Therefore, personal protection with clothing, repellents and mosquito nets is a valuable method of control.
- m, the density of mosquitoes, is only a unitary factor demonstrating the poor results of larviciding and biological methods in malaria control.
- p, mosquito survival, consists of two factors, the mosquito's expectation of life (short-lived vectors are poor transmitters) and the number of mosquitoes living long enough to complete the extrinsic cycle. In this, p is raised to the nth power, showing that reducing the length of life of the mosquito (mainly by the use of insecticides) is the best control strategy.

Personal protection. Methods of personal protection have been covered in Section 3.4.1. They include clothing, mosquito nets and repellents. Items of clothing such as socks and shawls can be treated with repellents, which retain activity for some time, or repellents can be applied directly to the skin. Some naturally occurring plants have repellent properties, such as *Tegetes minuta* in East Africa.

Mosquito nets are most effective if used properly. Providing subsidized mosquito nets can be used as a method of malaria control, especially for mothers and children who are liable to go to bed early (before mosquito biting starts). This can be improved by treating the nets with synthetic pyrethroid insecticides (such as permethrin, deltamethrin, alpha-cypermethrin or lambda-cyhalothrin). This repels mosquitoes and kills those that come into contact with the net. When used on a community scale, the concentration of insecticide-treated mosquito nets (ITNs) can produce a mass effect, reducing the mosquito population and the sporozoite rate. An improved technology is the manufacture of mosquito nets with the insecticide already in the net, known as long-lasting insecticidal nets (LLINs). These retain activity for at least 4 years, which avoids the regular retreating of nets, and are now the main method of malaria control. The method of treating mosquito nets and more on their use will be found in Box 3.1.

Mosquito bed nets are more effective and cheaper to maintain than screening the whole house, which is only recommended for people with a high standard of living. A small hole in the netting can render the rest ineffective. A knock-down spray can be used to kill mosquitoes that have entered a screened house.

The use of smoke from mosquito coils or vaporizing mats can be surprisingly effective and has the advantage that it is a cheap personal protection. Coils are easily manufactured locally and naturally occurring substances, such as incorporated pyrethrum. People often sit around fires in the evening and by the addition of certain plants a repellent smoke can be produced.

Mosquitoes can be encouraged to bite other animals if they are the preferred blood meal; however, if the animals are taken away, such as to market, then the mosquitoes may be forced to take their blood meals on humans. The habits of the malaria vectors will need to be known before encouraging this practice.

Residual insecticides. Use of residual insecticides has been covered in Section 3.4.1. These are applied to the inside surface of houses so that the resting mosquito (after it has taken its blood meal), absorbs a lethal dose of insecticide and dies before the parasites it has taken up in the blood can complete development. This was the main method of the malaria eradication programmes used in many countries of the world. Unfortunately, insecticidal resistance, organizational breakdown and reluctance by people to have their houses sprayed resulted in an abandonment of the goal of eradication. This has been replaced by a policy of malaria control in which house spraying may be a component.

Larviciding and biological control. The number of larvae determines the density of mosquitoes, so any method which reduces the larval numbers inadvertently reduces the potential number of adults. The larvae can be attacked by several different methods:

- using insecticides and larvicidal substances;
- modification of the environment; and
- biological control.

Larvicidal substances can be oils that spread over the water surface and asphyxiate the larvae or have insecticidal properties. The size and flow of the body of water will determine which is the preferred method to use. Modification of the environment by drainage or filling in is the most permanent and effective, but is an expensive undertaking. It is worth spending money on engineering methods in areas of dense population such as towns, while in rural areas much can be achieved by using self-help schemes. The considerable advantage of this method is that once done, it lasts for a long time, if not permanently, and in these days of resistant mosquitoes it is seen as an economic proposition in some circumstances (see also Section 3.4.1).

Biological control using fish or bacilli (*Bacillus thuringiensis* or *Bacillus sphaericus*) will reduce mosquito larvae to a certain extent, but a balance, as with much of nature, often results. Biological control can also be used directly against adults with the sterile male technique. This has not been successful with mosquitoes because of the very large numbers involved and their short period of life. Another method that is being considered is species competition, whereby a non-malarial mosquito from another part of the world is introduced to compete with the resident vector. This has not met with any great success.

In epidemic malaria, using a fogging machine or ULV spray from aircraft can rapidly reduce adult mosquito density. This will cut short the epidemic by killing off flying adults, but needs to be repeated regularly as new adults will continually be produced from larvae that are not affected by the knock-down sprays.

Chemoprophylaxis. Attempts to use chemoprophylaxis on a large scale for pregnant women and young children have not met with much success, except in areas of seasonal malaria chemoprophylaxis (SMC, see Section 18.2.9), but could be given to persons at particular risk, such as non-immune immigrants or migrant workers. Chloroquine 300 mg (two tablets) weekly can be used where chloroquine resistance is not a major problem, but local advice should be sought. It is preferable to give pregnant women and young children priority in the distribution of ITNs or LLINs, or to use chemoprophylaxis in combination with these.

Reducing the number of gametocytes. Quinine, chloroquine and amodiaquine are active against the gametocytes of *P. vivax* and *P. malariae*, but not against the more important *P. falciparum*. Proguanil and pyrimethamine act on the development of gametocytes within the mosquito on all four *Plasmodium* parasites. Primaquine has a highly active and rapid action on gametocytes of all species, whether in the blood or mosquito, and is used in combination with treatment in the individual. It has also been proposed as a method of reducing the level of gametocytes within the population, but would require an almost perfect mass treatment, as well as consideration of the danger of toxicity (especially

with glucose-6-phosphate dehydrogenase deficient individuals), so is not considered a suitable method of malaria control. Surprisingly, Viagra has been found to have an effect on the gamete by stiffening it, facilitating its destruction by the spleen.

Any person found to have malaria should, where possible, be protected by a mosquito net so as not to infect new mosquitoes. This is a particularly important measure during eradication and control campaigns, especially when endemicity is brought to a low level.

Vaccines. Attempts to produce a vaccine against malaria have been in progress since 1910. A vaccine made from killed sporozoites by irradiating mosquitoes is reasonably effective, but cannot be produced on a large scale. Easier to produce are vaccines made by isolating the DNA fragments of the circumsporozoite antigen and cloning them through bacteria or yeasts. This has allowed large quantities of pure antigen to be produced, and trials of candidate vaccines. RTS,S vaccine given to children in three doses plus a booster had a 36% efficacy, but there was an increased incidence of meningitis. Pilot implementation studies have started to reveal how best to use the vaccine. It could be added to but not replace existing methods of malaria prevention. One of the strategies suggested is, in areas of seasonal malaria where SMC is used, to reduce the quantity and length of chemoprophylaxis. However, even if a vaccine is used, there will still be all the problems of vaccination programmes, such as coverage, administrative difficulties and response of the public (see Section 3.2).

Prospects for malaria control. Malaria attracts the wonder cure; first it was the eradication programme, now all hope is pinned on the vaccine, but the disease is more likely to be controlled by simple, non-dramatic methods, where care to detail is applied. It is the encouragement of simple protective methods that everybody can follow, like using ITNs (or LLINs), or community action to modify the environment to make it unsuitable for mosquitoes to breed (see Table 15.2 for the main vectors). A multiplicity of simple methods, carried out by many responsible people, is likely to be more successful in the long term than more complex methods.

WHO has initiated a malaria elimination programme and the United Arab Emirates was declared free of malaria in 2007, Morocco and Turkmenistan in 2010 and Armenia in 2011.

Treatment of the uncomplicated case of *P. vivax*, *P. malariae* and *P. ovale* malaria is with chloroquine:

- 600 mg of chloroquine base as an initial dose,
- 6 h later, 300 mg chloroquine base,
- followed by 300 mg chloroquine base for 3 or more days.

However, chloroquine-resistant *P. vivax* has been reported from the Western Pacific islands, including the island of New Guinea, as well as from Guyana in South America.

P. falciparum is resistant to chloroquine and many other antimalarials, largely as a result of their indiscriminate use. The artemisinin group of compounds, especially artesunate, artemether and dihydroartemisinin, are mostly effective, and WHO recommends that they be used in combination with other antimalarials as an artemisinin combination therapy (ACT) to reduce the development of resistance. Unfortunately, the first cases of artimisinin-resistant malaria have appeared in Cambodia and Thailand, and a new genetic mutation in Africa indicates developing resistance to artemisinin and quinine. Intense efforts are being made to contain and eliminate these pockets of resistance before they spread more widely. In the main focus of resistance in Cambodia, atovaquone-proguanil is used to treat resistant cases. ACT still remains effective in most places and one of the following regimes can be used:

- artemether/lumefantrine;
- artesunate plus amodiaquine (in areas where the cure rate of amodiaquine monotherapy is greater than 80%);
- artesunate plus sulfadoxine/pyrimethamine (in areas where the cure rate of sulfadoxine/pyrimethamine is greater than 80%);
- artesunate plus mefloquine (insufficient safety data to recommend use in Africa); and
- dihydroartemisin plus piperaquine.

The addition of a single dose of primaquine (0.75 mg/kg body weight) will accelerate the removal of gametocytes, but care must be used in glucose-6-phosphate dehydrogenase deficiency areas.

While the microscope slide is being read (in many situations it may need to be sent to a centre for confirmatory microscopy) and the health worker has excluded other possible causes of fever, then presumptive treatment can be given. This is with a full course of therapy, which can be discontinued if the slide result is negative.

In *P. vivax*, chloroquine will only clear parasites from the blood, and to effect radical cure, primaquine is administered in a dose of 15 mg base daily for 14 days (except in the island of New Guinea and other Western Pacific Islands, where more prolonged treatment is required).

Case finding and treatment is an effective control strategy where there is a low level of malaria, but it needs to be used in combination with other methods.

Surveillance. In all areas where malaria is found, a blood slide should be taken from anyone with a fever. Where attempts are being made to eradicate or reduce the level of malaria, then an active system of surveillance may be instituted as described in Section 4.5.2.

Where a control method is in operation, then regular checks should be made, such as the proportion of houses with ITNs and the number of people sleeping under them. More will be found on malaria programmes in Sections 4.2, 4.3 and 4.5.

15.7 Lymphatic Filariasis

Organism. *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, nematode worms. The life cycle is illustrated in Fig. 15.9. Microfilariae, the larval nematode form present in the peripheral blood, are taken into a mosquito's stomach when it feeds on humans (or an animal reservoir in *B. malayi*). The larva loses its sheath inside the mosquito, migrates through the stomach wall and burrows into the muscles of the thorax. It becomes shorter and fatter, commonly described as sausage shaped. Developmental changes take place and it elongates to a third-stage, infective larva. Leaving the thoracic muscles, it migrates to the proboscis, where it waits for the mosquito to feed. Forcing its way out of the proboscis, it falls on to the human (or animal) skin, finding a way into the tissues, generally through the wound made by the mosquito. (This differs from malaria, in that the infective larva is *not* injected when the mosquito takes a blood meal.) This developmental stage in the mosquito, from the time of the blood meal until reinfection, takes 11–21 days (average 15) at an optimum temperature of 26–27°C (extremes are 17 and 32°C), a very similar length of time to the development of *Plasmodium*.

When the larva brakes out of the mosquito to enter the skin, this is a very precarious time for the parasite and only 20–40% are successful. No multiplication has taken place in the mosquito, so one larva that was taken up in the blood meal becomes one adult in the human. However, many larvae are lost, with only about 1 in 700 succeeding. Because there are male and female worms, it is necessary for the two sexes to meet if the female is to be fertilized. Many are unsuccessful in finding a mate of the opposite sex and it is only when there is a heavy infection that the probability of them doing so is increased. So intensity of infection will determine the outcome. Once the worms mate, the female produces huge numbers of microfilariae into the lymphatic system, and these reach blood vessels via the thoracic duct.

The parasite has timed its production of microfilariae to coincide with the biting time of the vector mosquito, a phenomenon called periodicity. Mostly this is a nocturnal cycle, with a peak around midnight, but it can also be diurnal, or in the Central and Eastern Pacific Islands it is aperiodic, with similar levels of microfilariae being found throughout the 24 h period.

Microfilariae live for about 6 months and adult worms 7–12 years, although they probably only produce microfilariae for 2–3 years.

Clinical features. In the human body, the larva reaches the lymphatics and settles down in a lymphatic node to develop into an adult. It is the obstruction of the lymphatic drainage system by the adult worms, especially the fibrotic reaction when they die, that causes the series of disease manifestations. A range of conditions result including fever, lymphangitis, lymphoedema, hydrocele, elephantiasis and chyluria. Night sweats are a common early indication of infection, with high eosinophilia counts. An allergic reaction, tropical pulmonary eosinophilia syndrome, can also result. Although the signs and symptoms are diverse and variable, in an endemic area they are often known, and a blood sample will soon confirm the diagnosis.

Diagnosis used to be by finding microfilariae in a measured sample of blood using a thick blood smear, counting chamber or filtration technique, taken during the peak microfilarial output, which generally means collecting samples at night time. These laborious methods have now largely been replaced by circulating filarial antigen (CFA) detection either based on ELISA or on an immunochromatographic card. However, the card test only diagnoses positive or negative, while the ELISA is

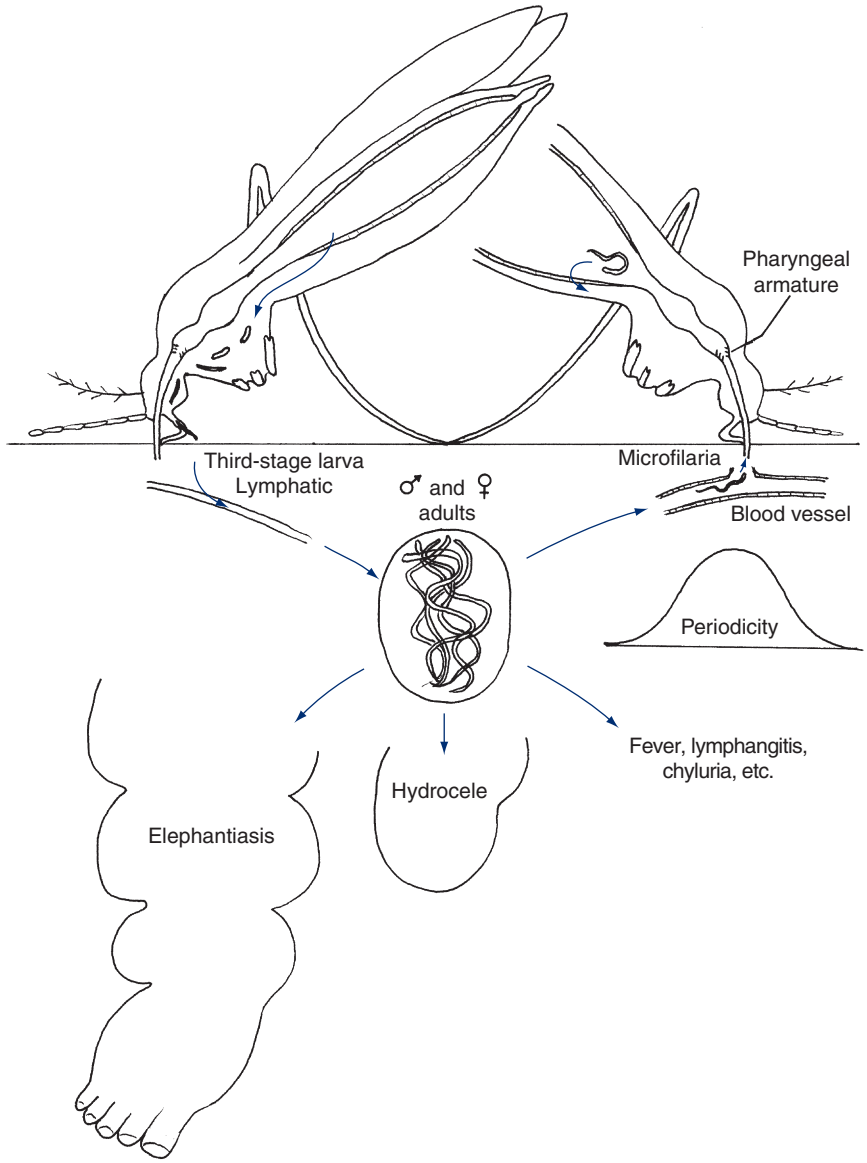

Fig. 15.9. Life cycle and clinical features of lymphatic filariasis.

semi-quantitative, so where full quantitative measures are required, the measured blood sample methods will still need to be used. This will be the case in assessing control programmes, as a decrease in the number of microfilariae occurs before conversion to negativity. A new method, the Alere Filariasis Test Strip (FTS), can be used for mapping and evaluation. CFA detection is also not available for *B. malayi* or *B. timori*. Different microfilariae need to be differentiated, as seen in Fig. 15.10, as several filarial infections may be present in the same locality.

Transmission is by both culicine and anopheline mosquitoes (Table 15.3), producing quite different patterns of infection and, as a result, different strategies for control. If *Anopheles* mosquitoes are the vectors, they are nearly always the same vectors as

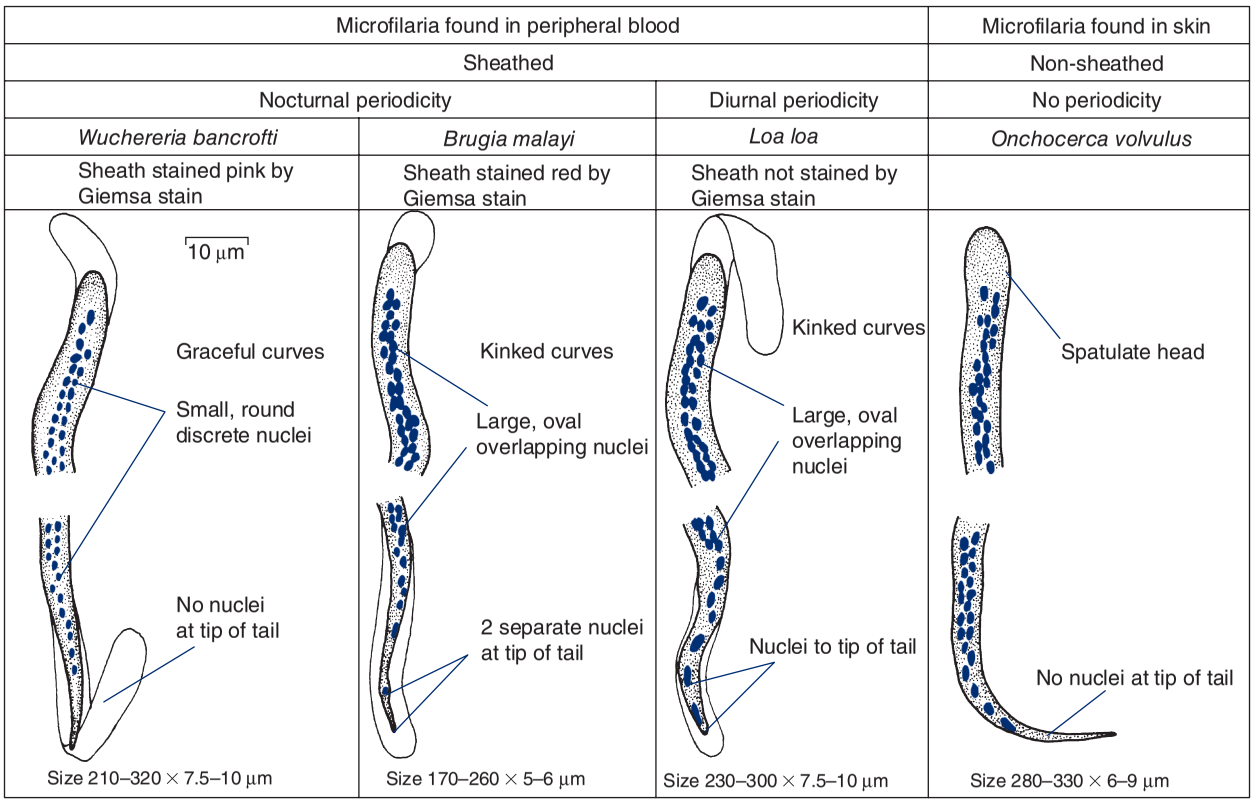

Fig. 15.10. Differential features of microfilariae of medical importance. (Courtesy Department of Medical Parasitology, London School of Hygiene and Tropical Medicine.)

Table 15.3. The vectors of lymphatic filariasis (*A*., *Anopheles*; *Ae*., *Aedes*; *C*., *Culex*; *M*., *Mansonia*; *O*., *Ochlerotatus*).

Geographical area	Species transmitting *Wuchereria bancrofti*	Species transmitting *Brugia malayi*
West Africa, rural East Africa, Madagascar	*A. gambiae*, *A. funestus*, *A. arabiensis*, *A. melas*, *A. merus*	
Urban East Africa	*C. quinquefasciatus*	
Egypt	*C. pipiens molestus*	
India, Sri Lanka and Maldive Islands	*C. quinquefasciatus*, *A. minimus*, *Ae. niveus*, *O. harinasutai*	*M. amulifera*, *M. indiana*, *M. uniformis*, *M. annulata*, *M. bonneae*, *M. dives*
China	*Ae. togoi*, *A. sinensis*, *A. anthrapophagus*	*Ae. togoi*, *A. lesteri*, *A. sinensis*, *A. anthrapophagus*
Vietnam	*A. jeyporiensis*	
Rural Thailand	*O. hariniasutai*	*M. annulata*, *M. bonnae*, *M. uniformis*, *M. indiana*
Malaysia	*A. letifer*, *A. whartoni*, *A. maculatus*, *A. dirus*, *A. donaldi*, *A. letifer*	*M. annulata*, *M. annulifera*, *M. bonnae*, *M. dives*, *M. uniformis*, *A. campestris*, *A. donaldi*
Indonesia	*A. balabacensis*, *A. leucosphyrus*, *A. maculatus*	*M. annulata*, *M. bonnae*, *M. dives*, *A. barbirostris* (*B. timori*)
Philippines		*M. dives*
New Guinea (Papua New Guinea and Irian Jaya)	*A. farauti*, *A. punctulatus*, *A. koliensis*, *C. annulinostris*, *C. bitaneniorhynchus*, *M. uniformis*	
New Caledonia	*Ae. vigilax*	
Fiji	*Ae. polynesiensis*, *Ae. fijiensis*, *Ae. pseudoscutellaris*, *Ae. oceanicus*	
Polynesian Islands	*Ae. polynesiensis*, *Ae. samoanus*, *Ae. upolensis*, *Ae. kesseli*, *Ae. tutuilae*, *Ae. tabu*, *Ae. cooki*	
North-east Brazil	*C. quinquefasciatus*	

transmit malaria, so the mosquito might well have a double infection or its expectation of life be affected by being parasitized by filariasis and malaria.

As the microfilaria is quite large, it causes damage to the mosquito when it bores into the thoracic muscles, so the more microfilariae the mosquito ingests, the more likely it is to be killed by a heavy infection. (In *Culex* and *Aedes* mosquitoes, this occurs when the microfilarial density exceeds 50/20 mm^3 of blood.) This is seen in Fig. 15.11 at point E for both culicine mosquitoes (upper figure) and anopheline mosquitoes (lower figure). The line P represents the equilibrium level (basic reproductive level of 1), whereby above the line transmissions will increase and below it infection will die out, so when infection is excessively heavy, mosquito mortality occurs and the infection dies out. In reality, the number of microfilariae will decrease below the point E, mosquitoes will survive sufficiently to transmit again and the level will approach E, or the level of equilibrium, again. This is always the case with culicine transmission, but in the bottom figure it will be noticed that there is also a lower point I, below which transmission is not sustained for anopheline mosquitoes. In other words, at low levels of microfilariae, the anopheline mosquito seems to be able to prevent itself from becoming infected. This is probably due to the pharyngeal armature in anopheline mosquitoes, which damages microfilariae. When there are many microfilariae ingested by the mosquito, sufficient will remain undamaged to produce infection, but at low levels of microfilariae, every microfilaria will be damaged. This applies to both *W. bancrofti* and *B. malayi*, so for control purposes, the type of mosquito is more important than the species of parasite.

Filarial infection is determined by the number of infected bites, which can either be the result of a high intensity over a short period or of constant bites over a long period. Mosquito mortality occurs when density of microfilariae is excessive, so the chronic, long-term pattern is more common.

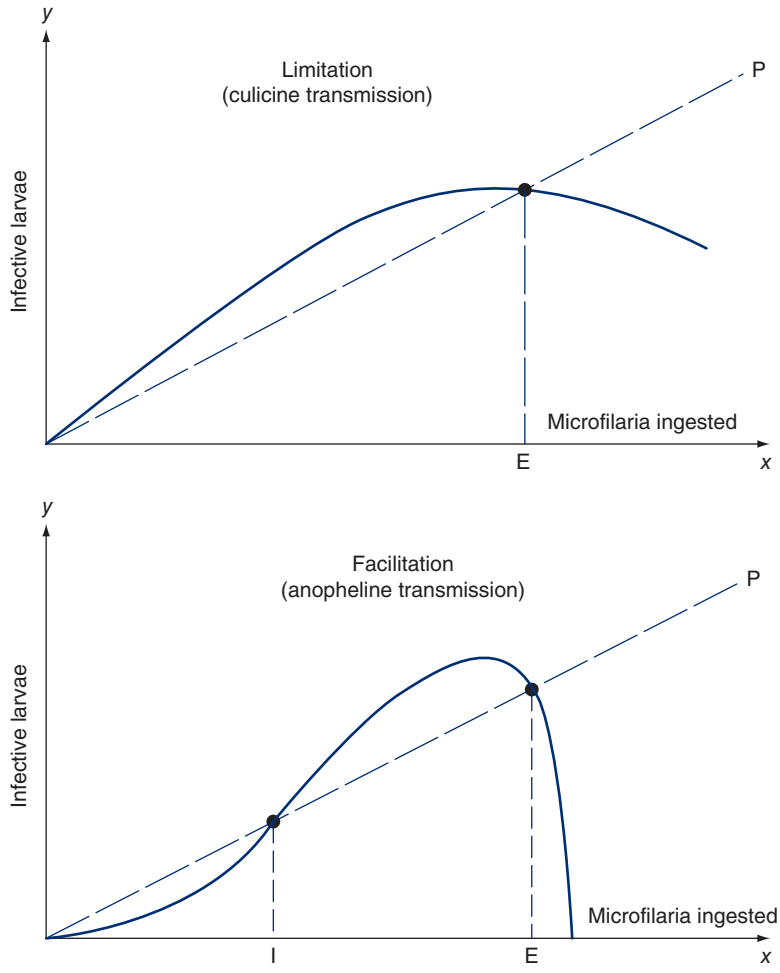

Fig. 15.11. The dynamics of culicine and anopheline transmitted filariasis. (Reproduced, by permission, from Pichon, G., Perrault, G. and Laigret, J. (1975) *Rendement parasitaire chez les vecteurs de filarioses*. (WHO/FIL/75.132), World Health Organization, Geneva.) See text for explanation of variables.

Incubation period. From infection to the development of adult worms is about 1 year, but the first symptoms may not occur until microfilariae are produced (fever) or worms die to produce lymphatic obstruction some years later.

Period of communicability. Because many infective bites are required to produce infection in humans, there will need to be a continuous supply of infected mosquitoes. The development cycle in the mosquito is 11–21 days (mean 15 days). The infected person can continue to produce microfilariae for in excess of 10 years, although maximum output is in the first 3 years.

Occurrence and distribution. Humans only are infected by *W. bancrofti*, but an animal reservoir exists for *B. malayi* in monkeys, cats and several other animals. All races, both sexes and all ages of persons are equally susceptible to infection. (There are marked differences between individuals developing elephantiasis, but these are immunological rather than ethnic.)

Three types of filariasis are seen: *rural* filariasis transmitted by nocturnal *Anopheles* mosquitoes with a generalized distribution similar to that of malaria; *urban* filariasis transmitted by *Culex*, with a tendency to invade new areas; and the Pacific Island variety, which has a homogeneous (rural)

distribution but is transmitted by day- and night-biting *Aedes* mosquitoes.

W. bancrofti is found in the tropical regions of the world, but with only a few foci in South America and the Caribbean. *B. malayi* is restricted to East and South-east Asia, overlapping with *W. bancrofti* in part of its range. *B. timori* is only found in the islands of Timor, Flores, Alor and Roti (Fig. 15.12). In 2010, there were estimated to be 1.39 billion people at risk of filarial infection in 72 countries and territories, approximately 18% of the world population. Some 120 million people in the world are infected and 40 million with disabling disease.

Control and prevention. A similar process to that used for malaria for identifying the best strategies for control can also be applied to filariasis. The various places at which control can be implemented are:

- reduction of the number of infective bites by mosquitoes;
- decreasing the number of microfilariae in the human host;
- reduction of the mosquito's expectation of life;
- decreasing the mosquito density;
- alteration of the mosquito biting time; and
- reduction of the number of adult worms.

Reducing the number of infective bites. Multiplication does not take place when the larva enters the host, so the disease process and its severity depends on repeated entry of parasites to the body, many of which will be unsuccessful. The transmission process is surprisingly inefficient, requiring some 15,500 infected bites to produce a reproducing adult. This means that for *Anopheles* mosquitoes, approximately eight bites per person per day can take place without the disease being transmitted.

The number of bites can be reduced by taking simple precautions of personal protection: mosquito nets, repellents, protective clothing, etc. ITNs or LLINs are effective in nocturnally periodic filariasis transmitted by anopheline mosquitoes (Box 3.1). This would be an additional benefit of a malaria control programme.

Decreasing the number of microfilariae (mass chemotherapy). Mass drug administration (MDA) is the main method used in the filariasis elimination programme. This is given as an annual single dose treatment to all the population for at least 5 years, preferably 7 years. Two regimes are used:

- albendazole 400 mg plus ivermectin 150–200 mcg/kg, or
- albendazole 400 mg plus diethylcarbamazine (DEC) 6 mg/kg.

An alternative is to use DEC-fortified salt (or fortified soy sauce in China) for 6–12 months, if total compliance can be assured. DEC cannot be used in an area that also has onchocerciasis.

This strategy is likely to work in areas in which filariasis is transmitted by *Anopheles* mosquitoes if the number of microfilariae can be maintained below the critical threshold (I in Fig. 15.11). One estimate suggests that this level is about 12 microfilariae/60 mm^3. However, as *Anopheles* is also a vector for malaria, reducing the number of parasitizing microfilariae, which cause damage to the mosquito, will increase the mosquito's expectation of life and improve its chance of transmitting malaria. Precautions should therefore be taken at the same time to prevent this from happening by the use of ITNs or LLINs (Box 3.1).

In areas in which culicine mosquitoes are the vectors, it is unlikely that MDA alone will succeed in eliminating filariasis, as can be seen from Fig. 15.11, and from past experience in control programmes in Samoa and Tahiti. Control of the mosquito also needs to take place, a simple strategy being the use of expanded polystyrene beads, as was used in latrines in Zanzibar and soakage pits in south India (see also below).

Before mounting a mass drug treatment control programme, a complete survey is needed. Follow-up surveys of samples of the population are made at annual intervals; 30% of the treated population should be sampled. Children less than 1 year old, pregnant and nursing mothers, the sick and the very old should be excluded from mass treatment. Side effects, especially itching, can be most unpleasant, and a pilot control study should precede the main campaign. Considerable care should be taken in areas where both filariasis and onchocerciasis co-exist. *Loa loa* infection in parts of West Africa may make it impossible to use the standard MDA regimes; instead, a 4–8 week course of doxycycline can be used.

Reduction of the mosquito's lifespan (vector control). By reducing the lifespan of the mosquito to below that of the developmental period of the parasite within the mosquito (range 10–15 days), transmission of infective larvae will be halted.

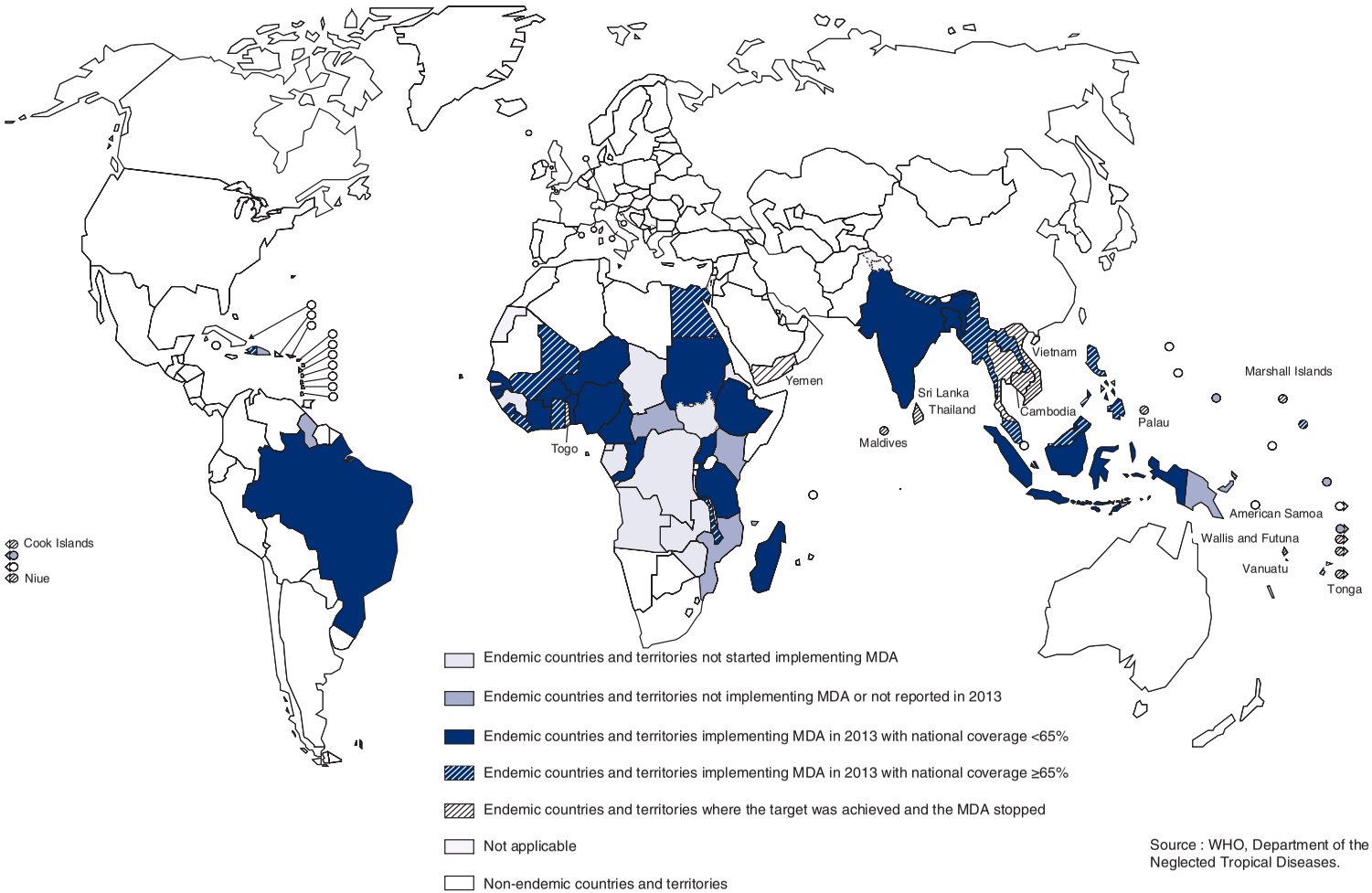

Fig. 15.12. Countries where lymphatic filariasis is endemic and status of mass drug administration (MDA) in those countries, 2013. (Reproduced by permission of the World Health Organization, Geneva.)

This can be done by spraying residual insecticides inside houses or treating mosquito nets.

Where the same vectors transmit both malaria and filariasis, then a joint control programme is cost-effective. ITNs or LLINs are particularly suitable for filariasis control where there is an anopheline vector and could be used as the only strategy or combined with MDA (see above). The degree of mosquito reduction required is much less for filariasis than it is for malaria; however, mosquito control needs to be for a prolonged period, at least 7 years and preferably 10 years.

Decrease mosquito density (larviciding). The number of mosquitoes able to bite humans is dependent on the number of larvae that develop into adults, so by reducing the number of larvae, mosquito density is also diminished. This is a supplementary method of malaria control and has also been covered in Section 3.4.1 on vector control. Various methods can be used, larvicides, genetic modification, and environmental or biological control. These methods are particularly appropriate to culicine-transmitted urban filariasis, although the degree of larval reduction required is often difficult to achieve. In enclosed areas of water such as latrines and septic tanks, expanded polystyrene beads are very effective.

B. malayi is transmitted mainly by *Mansonia* and *Anopheles* mosquitoes, *Mansonia* being particularly difficult to control because the larvae attach themselves to the underside of water plants (especially *Pistia*), where they are immune to surface oils and larvicides. Removal of these water plants by hand or with herbicides has produced some effect.

Alteration of mosquito biting pattern. The parasite has developed a periodicity of its microfilariae which coincides with the biting pattern of the vector mosquitoes. If it is possible to alter the time mosquitoes bite, then the chance of them taking up microfilariae will also be reduced. This has happened in some places owing to the prolonged use of residual insecticides, and although it is probably not possible to utilize this as a main control method, it could be of subsidiary value.

Reduction of the number of adult worms. Unfortunately, there is no specific drug that kills adult worms, although DEC causes substantial mortality, a valuable secondary action to killing microfilariae. The worms lie embedded in the lymphatics so cannot be removed surgically, as practised in onchocerciasis control.

Adult worms live for approximately 10 years (range 7–12 years), so if reinfection can be prevented for this period, they will die off and there will be no reservoir of infection. It is maintaining control methods for this period that is crucial with filariasis.

A vaccine is being developed and has shown initial success in mouse models. It appears to be effective for both *W. bancrofti* and *B. malayi*.

Treatment for established elephantiasis is unsatisfactory, with mutilating surgical procedures. If discovered in its early stages of intermittent swelling, before tissue damage has occurred, then pressure bandages can prevent gross elephantiasis from developing. In *B. timori*, repeat doses of DEC reduce lymphoedema and, to a certain extent, elephantiasis. In other areas, a single dose of DEC plus albendazole or a multi-week course of doxycycline (by its action on the endosymbiotic *Wolbachia* organisms and also as a macrofilariacide) may be tried. Moxidectin, which is used in veterinary practice, is being tried in humans against adult worms in onchocerciasis and could, theoretically, also kill adult *W. bancrofti*.

Surveillance. Hydrocele or lymph-node surveys can be of value in rapidly defining the area of filariasis. Detailed blood surveys are then made.

The year 2020 has been designated as the target for elimination of lymphatic filariasis worldwide. Surveillance and search for new cases will need to continue for a considerable period, and for several years after a country has been found to be free of infection.

15.8 Onchocerciasis

Organism. *Onchocerca volvulus*, a nematode worm that has a predilection for the skin and eye, is transmitted by *Simulium* flies. Microfilariae are taken up by the fly when it bites the human, and undergo larval changes within the thoracic muscles, migrating to the head of the fly as infective larvae. When the fly bites again, microfilariae break out on to the skin to enter via any abrasion, especially the bite wound.

Clinical features. The microfilariae, as they migrate through the skin, cause itching and damage resulting

in skin changes, loss of elasticity and discoloration, the so-called 'leopard skin'. As well as migrating through the skin, they also enter the eye, where the reaction caused by their death leads to eye damage, the person in time going blind, giving onchocerciasis its other name of 'river blindness'. Adult worms settle in subcutaneous nodules, making this a ready method of diagnosis. Lymphadenopathy is also a feature, sometimes being gross, e.g. 'hanging groin'.

Diagnosis is made by taking skin snips, which are placed in saline, and the liberated microfilariae identified (Fig. 15.10). Taking a measured area of skin with a special punch allows density measurements to be made. Slit-lamp examination of the eye may observe microfilariae in the anterior chamber or reveal characteristic eye damage. The adult worms live in palpable nodules in the skin, so their presence and characteristic skin changes can suggest a clinical diagnosis.

Transmission. The vector *Simulium*, also called the blackfly, breeds in fast-flowing streams, where it is found in huge numbers. The female fly attaches its eggs to the leaves of water plants in fast-flowing water, where they have the high oxygen levels they require for their development (Fig. 15.13). The fly has a painful bite and is persistent, making it a

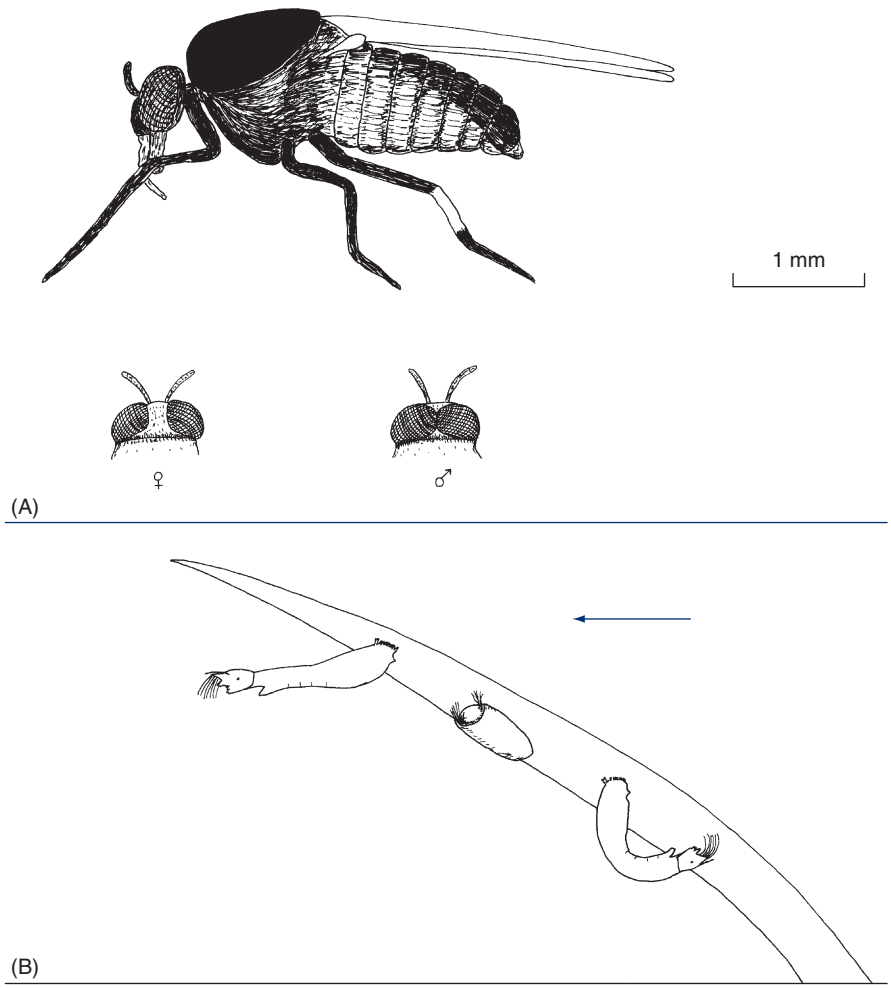

Fig. 15.13. *Simulium*, the vector of onchocerciasis. (A) Adult. (B) Larvae and a pupa attached to a water plant, the stream flowing in the direction of the arrow.

considerable nuisance, but is also a powerful flier, and assisted by the wind can travel up to 100 km in search of a blood meal.

The *Simulium* vectors and their usual breeding places are listed in Table 15.4. The African flies prefer to bite the lower body, whereas the South American flies attack the upper body. Although they can fly great distances, maximum density is at the breeding place, resulting in focal infection. They are outdoor, daytime biters, but each species prefer different times of day to seek their blood meal. South American *Simulium* species have pharyngeal armatures, whereas African species do not, but mortality due to superinfection by *Onchocerca* is not important. The adult flies live for 2–3 weeks (with a maximum of 3 months) but prefer to feed on animals rather than humans. However, people need to collect water, so it is when they come to the river, to wash or collect drinking water, that they stand the greatest chance of being infected.

O. volvulus only infects humans (and epidemiologically insignificant chimpanzees and gorillas). Eye and skin pathology is related to the proximity of the nodules, so more nodules on the upper part of the body produces a higher prevalence of blindness. In Africa, the savannah infection produces more blindness than that acquired in forests.

Microfilariae are found only in the skin, a high density leading to the more severe clinical manifestations, as well as producing greater opportunity to infect flies. They survive for up to 2.5 years and have a periodic cycle with peak at 16.00–18.00 h, but this is relatively unimportant.

Incubation period is prolonged, normally taking about 1 year for symptoms to start following infection.

Period of communicability is some 16–17 years, adult worms producing microfilariae into old age. *Simulium* becomes infective after 6–13 days, depending on temperature.

Occurrence and distribution. Onchocerciasis is found only in tropical Africa, Yemen and South/Central America, with well-marked foci in much of this area (Fig. 15.14). In West and much of Central Africa, the infection is more widespread, with the most westerly part of the region covered by the Onchocerciasis Control Programme (OCP, see below).

Repeat infection and progressive damage from dying microfilariae means that blindness is more common in adults, children then having to lead them around until their turn comes to go blind. Because of these severe consequences, abandonment

Table 15.4. *Simulium* vectors of onchocerciasis.

Geographical area	*Simulium* species	Breeding place	Habitat
West Africa, Central African Republic (CAR), Sudan, Uganda, Ethiopia (Yemen?)	*S. damnosum* species complex	Large rivers	Savannah, sometimes forest
West Africa, CAR, Sudan	*S. sirbanum*	Large rivers	Savannah
West Africa, CAR, Congo	*S. squamosum*	Small- to medium-sized rivers in hilly areas	Forest, savannah, mosaic
West Africa	*S. soubrense*	Large rivers	Forest, savannah
West Africa	*S. sanctipauli*	Large rivers	Forest
West Africa	*S. yahense*	Small watercourses	Forest
Cameroon, CAR, Tanzania	*S. mengense*	Large rivers	Forest
Congo, Burundi, Uganda, Tanzania, Malawi	*S. kilibanum*	Large rivers	Forest
Congo, Burundi, Rwanda, Uganda, Sudan	*S. naevi* species complex	Heavily shaded, small permanent rivers in forest	Forest
Ethiopia	*S. ethiopiense*	Heavily shaded, small permanent rivers in forest	Forest
Tanzania	*S. woodi*	Heavily shaded, small permanent rivers in forest	Forest
Guatemala, Mexico	*S. ochraceum*	Small mountain streams	Highlands
Guatemala, Mexico, Venezuela	*S. metallicum*	Small streams	Highlands
Colombia, Ecuador, Venezuela	*S. exiguum*	Large rivers	Lowlands
Brazil, Venezuela	*S. guianense*	Large, fast-flowing rivers	Highlands
Brazil, Venezuela	*S. oyapockense*	Large rivers	Lowlands

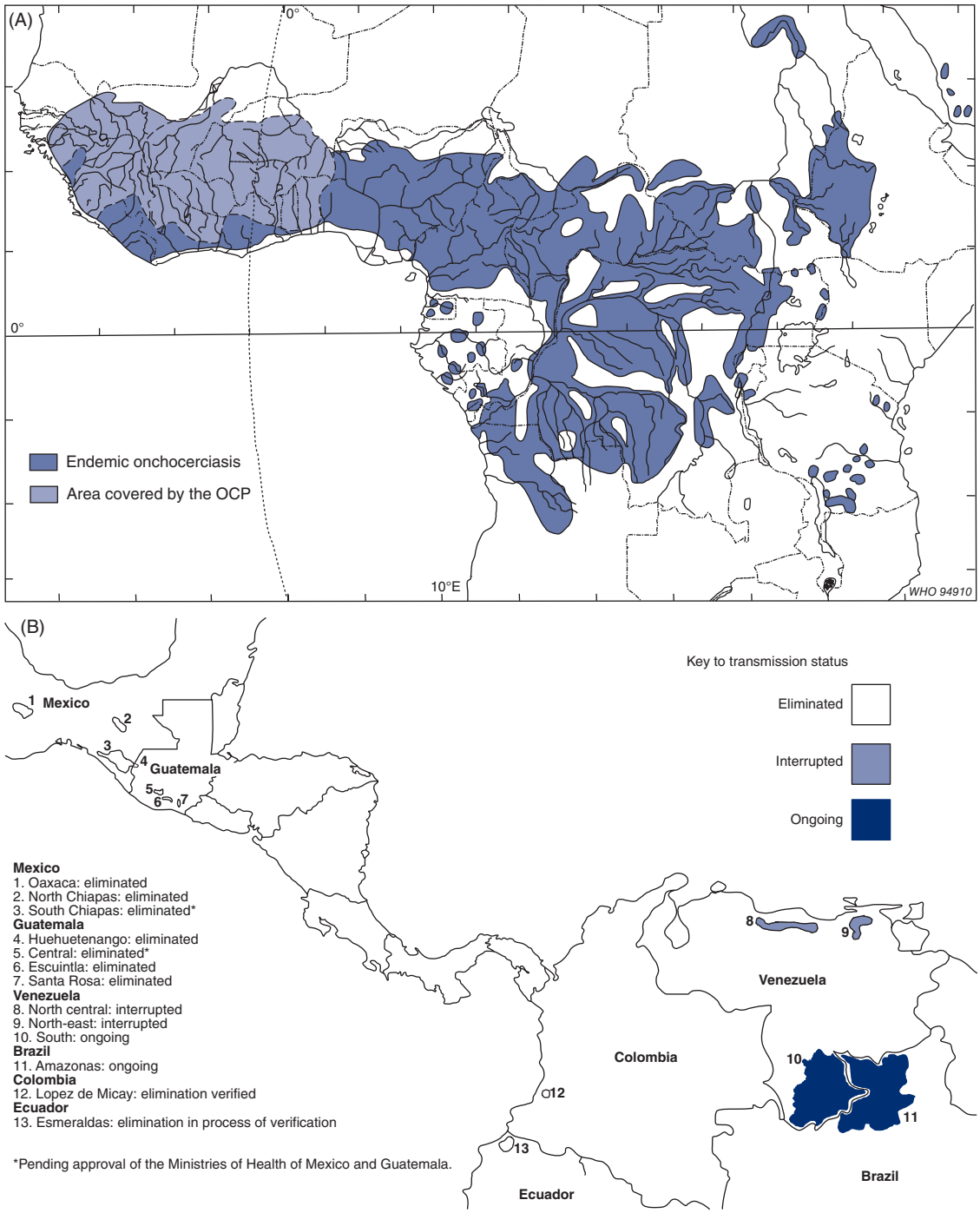

Fig. 15.14. Distribution of onchocerciasis. (A) Africa and Yemen. (B) the Americas. OCP, former Onchocerciasis Control Programme area. NB some of these foci have since been eliminated. (Part A from World Health Organization (1995) *Onchocerciasis and its Control*. Technical Report Series No. 852. Part B from Weekly Epidemiological Record No. 37, 12 November 2014. Both reproduced by permission of the World Health Organization, Geneva.)

of good village sites close to rivers has frequently resulted, although control programmes have largely reversed this trend.

Control and prevention. Various approaches to control can be tried, as with lymphatic filariasis. These are:

- reducing the fly density;
- avoidance of fly breeding places;
- reducing the microfilarial density;
- reduction of the number of adult worms; and
- reduction in the number of *Simulium* bites.

Reducing the fly density (larviciding). The larvae breed in water, so insecticide is sprayed on streams and rivers. They are relatively sensitive to insecticides, so low-dose applications, 0.05–0.1 mg/l are effective. Temephos (Abate) is suitable as it is effective in a very low dose, is relatively non-toxic to fish and retains some residual action. It exerts its effect for some 20–40 km downstream in the wet season. The main difficulty with larviciding is to ensure that every watercourse is treated. Owing to the flies' ability to cover large distances, recolonization soon takes place when insecticidal applications are discontinued. Although expensive, the extra cost of using aircraft and helicopters can be justified if many watercourses, spread over large areas of countryside, have to be covered.

Unfortunately, insecticidal resistance has occurred in a number of areas, so biological control with *B. thuringiensis* is an alternative. This does not have the spreading power of insecticides, so greater concentrations need to be used (in the order of 0.9 mg/l), and it has to be mixed with water before it can be applied.

Avoidance of fly breeding places. Maximum contact between humans and flies occurs near rivers where *Simulium* breeds, but these can be avoided by providing alternative water sources, such as wells or a piped water supply.

Reducing the microfilarial density. Ivermectin immobilizes microfilariae, which are flushed out of the skin and eye and killed in the lymph nodes. As microfilarial death occurs away from the skin and eye, irritation is minimized and ocular reaction reduced. Ivermectin can be given as a single dose of 200 mg/kg, with retreatment at 6- and 18-month intervals. This means that MDA for onchocerciasis can be used as an adjunct to vector control.

MDA given twice a year has been found to eliminate infection if continued for 15–17 years. However, it cannot be used in areas where *Loa loa* infection is also found, in which case doxycycline can be used for 4–8 weeks.

Reducing the number of adult worms. Because the adult worms live for a considerable length of time, during all of which they are producing microfilariae, specific attack on the adult parasites can reduce both the symptoms and the potential for transmitting infection. Nodulectomy, or the surgical removal of adult worms from skin nodules, can be a relatively effective procedure, practised particularly in the onchocercal areas of South America, where nodules are more common in the upper parts of the body. Doxycycline continued for 6 weeks kills endosymbiotic Wolbachia on which the *O. volvulus* obtains nutrition, so that it also dies; it should be used on a selective basis and not given to pregnant women or children.

Reducing the number of *Simulium* bites. Personal protection is less effective against *Simulium* than with mosquitoes, with nets being inappropriate, although repellents have some effect. The wearing of long-sleeved shirts and long trousers with hat and net can be used by individuals investigating the disease, but are not methods that can be developed for mass use. Avoiding passage through breeding sites will reduce fly biting.

Onchocerciasis control programmes. As adult *O. volvulus* can live for 15–17 years, any control programme would need to be maintained for this length of time before eradication could take place. However, most programmes seek to reduce the intensity of infection to a level where symptoms are absent. The criteria used in the OCP in West Africa were:

- less than 100 infective larvae/person a year; and
- annual biting rates of less than 1000.

After many years of operation, the OCP finished in 2002, with delegation to individual countries to detect and treat all new cases.

The main method of control was larviciding, which can be extremely effective if carried out thoroughly. Species eradication of *Simulium naevi* was achieved in Kenya by methodically treating every watercourse with DDT. Where the disease covers a limited area, then such an intense programme could be considered. In a more diffuse focus, the borders of control need to be extended sufficiently to prevent reinvasion by *Simulium* flying in

from outside. While resistance is a serious problem, resistant *Simulium* is less important in transmission.

Mass drug therapy, or selective therapy to persons with heavy infections, can be given right from the start of the programme. This will rapidly reduce the level of microfilariae and the potential for infecting flies. Preventing blindness (with ivermectin) has been particularly valuable in obtaining the cooperation of people. As lymphatic filariasis and onchocerciasis occur in the same areas in a number of countries (mainly in West Africa), and ivermectin is used to treat both diseases, then joint programmes (with the addition of albendazole) are cost-effective.

The mass drug therapy approach has been particularly valuable in the areas formerly covered by the OCP in Africa. Ivermectin therapy, which had been used for 15–17 years in Mali and Senegal, was stopped and no further infections were detected after 2 years, showing that the disease can be eliminated.

Mass drug administration with ivermectin is also used in the South/Central America Onchocerciasis Elimination Programme, with good progress being made in reducing foci in all countries. Colombia was declared free of onchocerciasis in 2013 and Mexico in 2015, with continuing good progress being made in Ecuador, Guatemala, Venezuela and Brazil.

Treatment. Ivermectin has been very effective, especially in the reduction of blindness. A 6-week course of doxycycline is effective in killing adult worms.

Surveillance. Skin and nodule surveys can be used to indicate areas that need more intense skin-snip examination. (See also the OCP programme above.)

15.9 Loiasis

Organism. *Loa loa*, a nematode worm. The life cycle of the parasite is essentially the same as that of *W. bancrofti*, except that the vectors are tabanid flies.

Clinical features. The disease is characterized by Calabar swellings (named after a town in eastern Nigeria) which are transient, itchy and found anywhere on the body. Fever and eosinophilia suggest that they have an allergic aetiology. *L. loa* is often confusingly called the eye worm (to be differentiated from *O. volvulus*), as the worm is sometimes seen migrating across the conjunctiva, but it produces no pathology in the eye.

Diagnosis. *L. loa* is diurnally periodic and diagnosis is made by examining daytime blood in which the microfilaria (Fig. 15.10) will be found. *Mansonella ozzardi, Mansonella perstans* and *Mansonella streptocerca* are also commonly found in blood and skin smears in the same area and need to be differentiated from *L. loa* as well as from *W. bancrofti* and *O. volvulus*.

Transmission. The vector is *Chrysops*, a large, powerful fly which inflicts a painful bite, attacking either within the forest or at the forest fringe.

Incubation period. Although microfilariae may appear in the blood after about 6 months, the first symptoms may take years.

Period of communicability. Like *O. volvulus*, the adult can live for up to 17 years, producing microfilariae all this time. *L. loa* takes 10–12 days to produce infective larvae in the fly.

Occurrence and distribution. Loiasis is found in west and central African rainforests, and especially in the Congo River basin.

Treatment. Both adult worms and microfilariae are killed by diethylcarbamazine, but caution needs to be exercised as allergic reactions can be profound. Low dosages of 0.1 mg/kg can be used to initiate treatment, gradually building up over 8 days to 6 mg/kg, which is continued for 3 weeks. Steroid cover may be required in those cases with more than 30 microfilaria/mm^3. Ivermectin will also reduce the microfilarial stage and produces less reaction, so is more suitable for mass control programmes. However, reactions do still occur, especially in those in whom the worm is seen crossing the eye, so a useful preliminary is to show people a picture of the worm in the lower eye and exclude those in which it has been seen.

Control and prevention. Extensive control measures are generally not warranted, the main preventive action being against the bites of *Chrysops* with protective clothing and repellents. Clearing the forest canopy, oiling of pools and mass treatment (with ivermectin) are methods that have been practised in areas of high transmission. Diethylcarbamazine can be used as a prophylactic by expatriate workers entering areas of high endemicity.

Surveillance. Surveys for Calabar swellings or a history of them will indicate the area in which to take a blood-smear survey.

15.10 African Trypanosomiasis (Sleeping Sickness)

Organism. There are two forms of human sleeping sickness in Africa, that due to *Trypanosoma brucei gambiense* and that due to *Trypanosoma brucei rhodesiense*. A third form (nagana), caused by *Trypanosoma brucei brucei*, is found in cattle, and causes considerable economic loss. (See Fig. 15.15.)

The trypanosome exists in several different forms during its life cycle. When seen in human blood, the trypomastigotes are long and slender, short and stumpy, or intermediate between the two, probably representing a cycle of antigenic variation (Fig. 15.19). They are introduced into the blood by the bite of the tsetse fly and multiply locally. After being disseminated round the body, they continue to multiply, rapidly in *T. b. rhodesiense*, less so in *T. b. gambiense*. They are infective to any tsetse fly when it bites, being taken up into the midgut. They multiply, migrate into the space between the peritrophic membrane and the gut wall, and pass forward to the salivary glands. The epimastigote developmental form changes into a trypomastigote, to infect the next person that is bitten.

Clinical features. The bite of a tsetse fly generally causes a local reaction, but 7–10 days after this initial reaction has subsided the site becomes red and inflamed, the first sign of infection having become established. Trypanosomes multiply at the bite site and aspirated fluid will contain the dividing forms. In *T. b. gambiense*, an enlargement of the lymph glands also takes place, especially those in the cervical region. This rarely occurs in *T. b. rhodesiense*, the disease progressing rapidly to involve the central nervous system (CNS), with invariably a fatal outcome, often from cardiac failure. The main

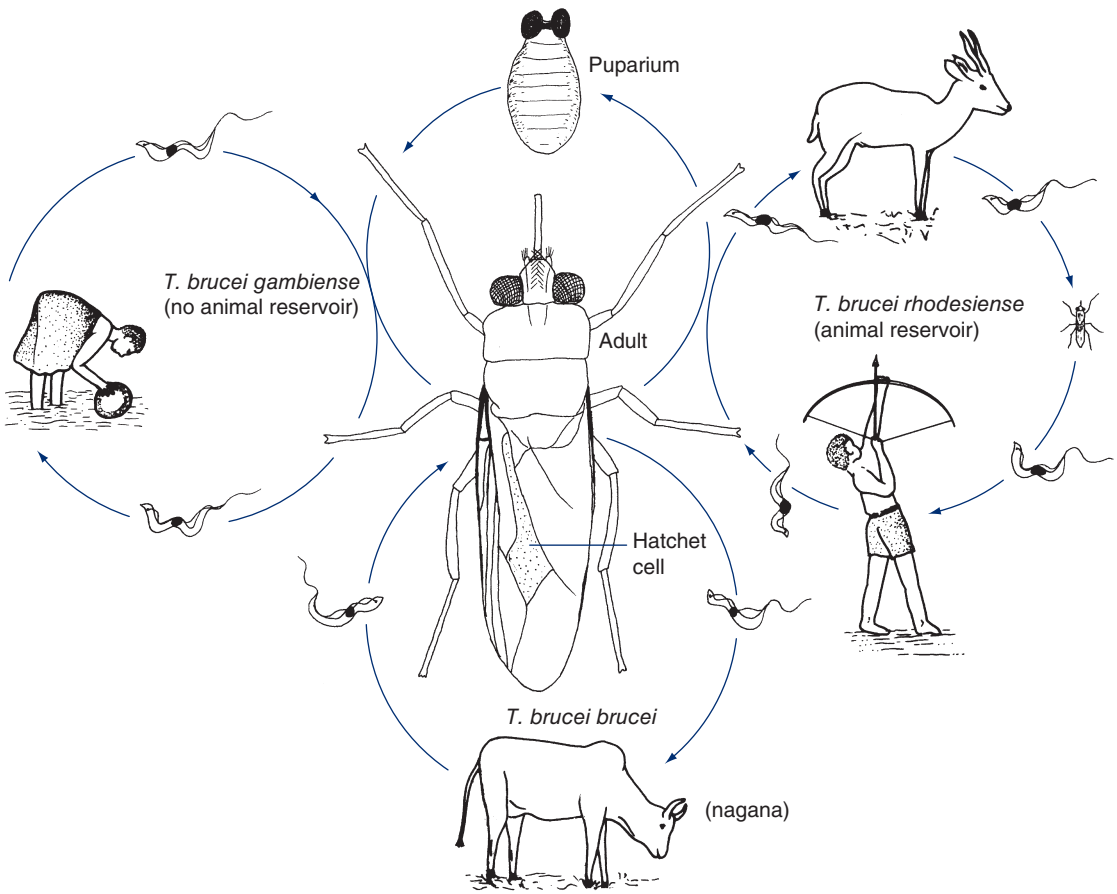

Fig. 15.15. African trypanosomiasis (caused by three subspecies of *Trypanosoma brucei*) life cycles and the tsetse fly.

clinical signs are fever and protracted headaches. In *T. b. gambiense*, the course is much more prolonged and personality changes may be the indication of infection, but inevitably the disease leads to progressive lethargy, emaciation, coma and death.

Diagnosis is by finding trypomastigotes in the blood, CSF or gland puncture. The blood smear should be repeated several times before a negative diagnosis is made. Parasite concentration techniques, such as capillary tube centrifugation or mini-anion exchange centrifugation, are valuable. Antibodies may be detected by serological techniques, while a circulating antigen assay using the card agglutination test (CATT) in which a drop of finger-prick blood is mixed with a suspension of trypanosomes has revolutionized diagnosis for *T. b. gambiense*. This technique is particularly useful for surveys in the field.

Transmission is from the bite of the tsetse fly, in which the parasite goes through a developmental stage. However, as the infective form for the fly and the human is the same (the trypomastigote), mechanical transfer can occasionally happen if a contaminated fly bites another person within a short space of time. The trypanasome can cross the placental barrier, so infection of the fetus can occur.

The tsetse fly (*Glossina*) is easily recognized by its characteristic stance and behaviour. A large and powerful fly, it rests on a surface with wings folded like a pair of scissors. Within the venation of these wings a characteristic hatchet cell (Fig. 15.15) can be defined, which helps in identification. However, when passing through 'fly' country, there is normally no doubt about its presence, as tsetse flies attack any moving object in large numbers, rendering the most painful bite. They are attracted by movement and will cling to the side of a vehicle travelling at 30–40 kph without being dislodged. They prefer dark colours, and if there is a large object, they will fly to that in preference. They are more abundant near their preferred breeding place in the sandy soil beside rivers.

The distribution of tsetse flies is shown in Fig. 15.16, in which it will be noticed that distinct species are often related to particular sleeping sickness areas (compare with Fig. 15.17). Table 15.5 is a simplified guide to

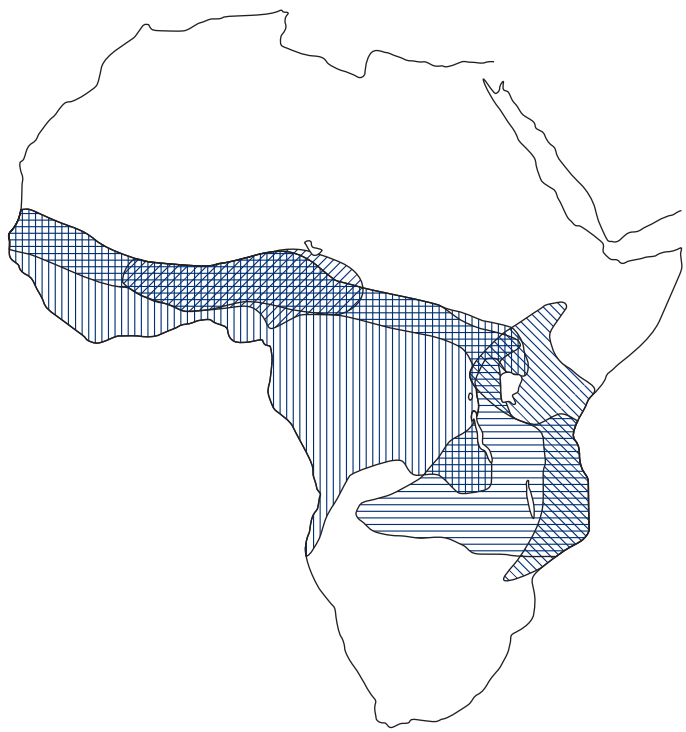

Fig. 15.16. Tsetse fly distribution in Africa. ▤, *Glossina morsitans*; ▨, *Glossina pallidipes*; ▥, *Glossina palpalis* and *Glossina fuscipes*; ▨, *Glossina tachinoides*.

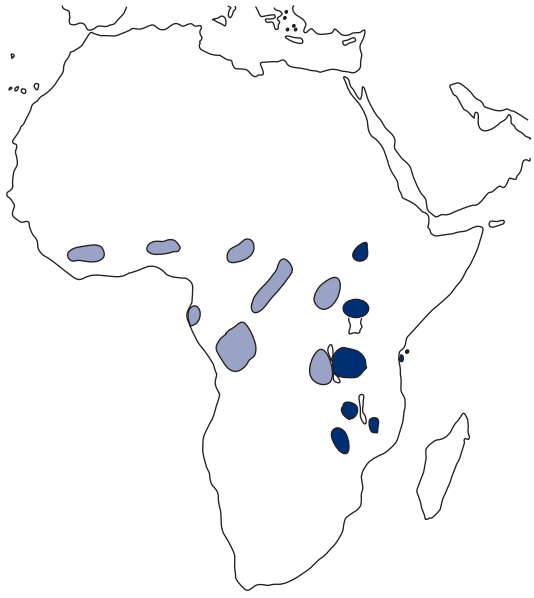

Fig. 15.17. Sleeping sickness foci in Africa. Light blue, *Trypanosoma brucei gambiense*; dark blue, *Trypanosoma brucei rhodesiense*.

assist in identifying the species of *Glossina*, but professional confirmation should always be obtained.

Incubation period. 3 days to 3 weeks in *T. b. rhodesiense*, months to years for *T. b. gambiense*.

Period of communicability. The trypanosome takes 12–30 days to complete its developmental stage in the tsetse fly, depending on temperature, the fly then remaining infected for life. Humans can be infected for many years with *T. b. gambiense*, but due to the shorter life history with *T. b. rhodesiense*, the animal reservoir is probably more important.

Occurrence and distribution. Around half a million people live in sleeping sickness areas with an estimated 100,000 new cases each year. *T. b. gambiense* mostly occurs to the west of the Central Rift Valley of Africa, containing the lakes of Tanganyika, Kivu, Edward and Albert, while *T. b. rhodesiense* is found mainly to the east (Fig. 15.17). *T. b. gambiense* infection is particularly prevalent in the Democratic Republic of the Congo (DRC), with over 70% of cases, and *T. b. rhodesiense* in Tanzania and Uganda (where there might

Table 15.5. A simplified key to *Glossina* of medical importance and their favoured habitats.

Hind tarsi	All segments dark above	*G. palpalis* group (1)
	Only 2 distal segments dark above	*G. morsitans* group (2)
	1. Abdomen obviously banded dorsally	*G. tachinoides*
	Abdomen dark, unbanded dorsally	*G. palpalis* (W. Africa)
		G. fuscipes (E. Africa)
	2. Distal 2 segments of front and middle tarsi *without* dark tips	*G. pallidipes*
	Last 2 segments of front and middle tarsi *with* dark tips	(3)
	3. Bands of abdomen very distinct and sharply rectangular	*G. swynnertoni*
	Bands on abdomen rounded medially and less distinct	*G. morsitans*
In summary, the vectors of *Trypanosoma brucei gambiense* are:		*G. palpalis*
		G. tachinoides
		G. morsitans
and those of *Trypanosoma brucei rhodesiense* are:		*G. morsitans*
		G. pallidipes
		G. fuscipes
		G. swynnertoni
		G. tachinoides (SW Ethiopia)
Favoured habitats are:		
	a. Lake and riverside fringing forest	*G. palpalis*
		G. tachinoides
		G. fuscipes (near Lake Victoria)
	b. Fringing forest without permanent water	*G. pallidipes*
	c. Miombo woodland, thickets and ‘game’ savannah woodland	*G. morsitans*
	d. Restricted to Northern Tanzania ‘game’ savannah woodland	*G. swynnertoni*

be overlap of the two types). These two diseases differ markedly in their epidemiology and control.

Gambian sleeping sickness. Sleeping sickness, as with other vector-borne diseases, is determined by the habits of the vector. In the gambiense type, the tsetse fly breeds in the tunnel of forest along the course of rivers (Fig. 15.18). Although powerful flyers, they do not range far from this shaded protection, but travel extensively through this tunnel of forest in search of blood meals. Any mammals, including humans that come to the river to drink or cross it, are attacked and fed upon.

Humans are the main reservoir of *T. b. gambiense* infection (although the domestic pig may be involved) and people whose jobs bring them into contact with the infected fly are more likely to succumb to infection. As women are involved in the collection of water, the preparation of food and the washing of clothes, they are more commonly infected in Gambian sleeping sickness.

The disease can occur in endemic and epidemic form. There are well-known foci from which people become infected at a constant rate (Fig. 15.17), but movements of infected flies or, more commonly, people into new areas can initiate epidemics. Generally, infected flies are comparatively few in number, so that a large number of bites are required before a person becomes infected. Where the community that is fed upon is small and stable (less than 10 persons/km^2), then a few cases will only occur. When the community is much larger (above 10 persons/km^2), as when an infected person travels to a more densely populated area, then the infection can be transmitted to other people who, in turn, form a reservoir to infect more flies, and an increasing number of cases occurs. Epidemic sleeping sickness is more likely in *T. b. gambiense* infection as it is a more chronic disease and cases provide a reservoir (to infect flies) before symptoms cause them to seek medical attention. While endemic foci are difficult to eradicate, control measures should prevent epidemics from occurring.

In 1998, almost 40,000 cases of *T. b. gambiense* infection were reported, although there were probably more like 300,000 cases. By 2005, after coordinated effort, the estimated number of cases had declined to 60,000 and by 2009 to 30,000.

Rhodesian sleeping sickness. The principal vector of *T. b. rhodesiense* is *Glossina morsitans*, which breeds along watercourses, but then travels widely throughout the extensive shade cover provided by the forest belt. This open type of forest, commonly called 'miombo' (mainly *Brachystegia* and *Julbernardia* spp.), is found in large areas of East Africa. Smaller wild animals inhabit it, especially the bushbuck, which forms a reservoir of infection. Towards the margins of this forest belt, the cover breaks up into thickets separated by savannah grassland in which large numbers of wild animals are found.

Fig. 15.18. Tunnel of forest along the banks of a river with selective clearance (leaving the big trees).

The tsetse fly ranges widely over these areas, feeding mainly on animals and using the thickets for cover and shade. It is, therefore, humans that travel through the forest and fringing savannah in their occupational pursuits – the hunter and honey collector – that become infected. Adult males are then the main victims in Rhodesian sleeping sickness.

T. b. rhodesiense infection is not a focal disease, and because of its short clinical course, epidemics are uncommon. However, movements of people, such as the development of new settlements in forest areas, will expose a large number of people to infected flies all at the same time, so allowing an epidemic to start. The first signs that this is happening is where women, and especially children, become infected.

Although these are the main patterns for the two diseases, sometimes a riverine tsetse fly becomes the vector of Rhodesian sleeping sickness.

Sleeping sickness was far more widespread in former times, and in early history is thought to have extended as far as the Nile Valley. A major epidemic in Uganda between 1900 and 1920 claimed at least a quarter of a million lives, and resulted in major resettlement and movement of the population. While there were probably many causes for this epidemic, it was preceded by several years of drought, followed by heavy rains, so that climate change might well have an impact on this disease in the future.

Control and prevention

Vector control. Knowledge of the habits and behaviour of the local vector is necessary before embarking on methods of vector control. The principle is to modify the environment so that it is unsuitable for the fly, but not to make so much damage that the water table is affected or soil erosion results. With the riverine type of habitat, areas of the forest tunnel are cleared, removing all the dense undergrowth but leaving the big trees with their extensive root systems to prevent erosion of the riverbank (Fig. 15.18). Clearance should be continued for half a kilometre on either side of a river crossing, water collection place or inhabited area.

In East Africa, where extensive forest provides a habitat for the fly, the forest margin is pushed back from any place of habitation. A band of at least 1 km, preferably 2 km, should be left between the area of habitation and the forest. This must also include any cultivated area, and regulations are required to prevent people from moving into the cleared part to start new cultivation. Ring barking is a more economical method of forest clearance than cutting down every tree.

Where forest clearance is impractical, then insecticides can be used. This is easiest along the course of substantial rivers using a boat, spraying the forest on either side. In the savannah-type habitat, isolated thickets can be treated. Extensive insecticidal application to miombo forest is inappropriate. Insecticide applications have to be repeated, whereas forest clearance is permanent, and the relative costs of these two techniques need to be considered.

Trapping can also control the vector. A well-designed trap will collect enough flies to considerably reduce the biting risk. An effective trap has a fine metal mesh treated with insecticides, which is shaded to attract tsetse flies. These are rapidly killed when they touch the screen, but this must be cleaned regularly to work efficiently.

The fly can bite through thin clothing, so taking preventive action from being bitten in a tropical climate is difficult.

Alteration of the human habitat. Sleeping sickness has been responsible for large movements of people from their traditional homelands either by self-choice or by government action to avoid an epidemic. Moving people away from the sleeping sickness areas is the ultimate method of control, but one to be taken only when all else fails.

The preferable alternative to moving populations is to modify the habitat so that it is unsuitable for disease transmission. Methods of forest clearance have already been described, while providing water supplies will remove the reliance on obtaining water from rivers.

The density of population largely determines the endemicity, as mentioned above. Two different approaches can be taken:

- Keep the population close together and clear an area of forest around them.
- Encourage the people to spread out very widely so that they partially clear a large area of forest.

In the first method, the people are safe as long as they remain within the village, but once they pass through the forest they are subjected to a considerable number of bites. In the second alternative, people will become infected in the initial stages of forest clearance, but once this has been done then protection will be much greater and more use can

be made of the land. In the initial period of forest clearance, a surveillance service will be required to find the pioneer cases. The most unsatisfactory solution is a moderately large population spread evenly over the area, as this is the potential situation for an epidemic.

Parasite reduction. A surveillance service should be set up and all cases treated (see below). Finding cases in the early stages of the disease not only increases the chance of successful treatment, but also removes a potential source of infection to tsetse flies.

Another approach to reducing the parasite reservoir in *T. b. rhodesiense* is to destroy the animal population. This used to be practised on a wide scale, but animal conservation has now questioned the wanton slaughter of animals. In most cases, it will be found that the human reservoir is more important than the animal reservoir, but where there is evidence that flies are becoming infected from this alternative source, then game can be killed or driven off.

Treatment of cases requires hospitalization as the drugs used are highly toxic.

- First-line treatment (when the trypanasome has not crossed the blood–brain barrier) is with pentamidine for *T. b. gambiense* and suramin for *T. b. rhodesiense*.
- When the CNS is involved, then melarsoprol can be used for both, but is toxic, while eflornithine is very effective against all stages of *T. b. gambiense*.
- A combination of nifurtimox and eflornithine can also be used against *T. b. gambiense*, but not against *T. b. rhodesiense*.

Pentamidine has been used as a prophylactic against *T. b. gambiense* infection in people at special risk. There is no prophylactic against *T. b. rhodesiense* infection.

Surveillance. A surveillance service should be set up in a sleeping sickness area. Sleeping sickness workers are recruited more on their knowledge of the local community than on their medical skills, as the simple techniques of gland puncture or making a blood slide can easily be taught. The workers cover a set area and take slides from people with symptoms of persistent fever and headache, or those who pursue a particular occupation, such as hunters, honey collectors or woodcutters. In *T. b. gambiense* infection, palpation of the neck glands can provide a useful estimate of prevalence. In an epidemic of *T. b. rhodesiense*, a mass blood-slide examination can be performed in the worst affected areas to detect asymptomatic cases.

The illness in animals is more extensive than in the human population, and veterinary services often set up extensive surveillance and control programmes, so combining efforts with them can be of value.

15.11 American Trypanosomiasis (Chagas' Disease)

Organism. *Trypanosoma cruzi*. The trypanosome in American trypanosomiasis undergoes a development cycle both in the vector bug and the vertebrate host, with trypomastigotes, the infective form, and pseudocysts forming in the muscle. The pseudocysts contain amastigotes, which grow a flagellum and become promastigotes and epimastigotes (Fig. 15.19) when the pseudocyst ruptures, finally developing into infective trypomastigotes (Fig. 15.20). The trypomastigote of the American disease has a larger kinetoplast and is more curved than that of the African one. The infection differs in that repeat cycles take place in the host's muscles, producing a chronic disease state.

Clinical features. American trypanosomiasis presents as an acute infection, generally in children, with fever, local swelling at the site of inoculation and enlargement of the regional lymph nodes. Muscular tissues are attacked, so that in adult life chronic conditions such as enlargement of the heart, oesophagus or colon develop. Heart failure and cardiac irregularities are common manifestations that lead in time to disability and an early death. The HIV-infected person can also develop acute myocarditis or meningoencephalitis. Oesophageal cancer can occur in a small proportion of patients with megaoesophagus. Congenital Chagas' disease results in small-sized infants with CNS and cardiac involvement.

Diagnosis is by finding the organism in the blood in the acute stage. Methods of concentrating the erythrocytes or xenodiagnosis (feeding of laboratory-reared clean bugs on the patient) are often required. In the chronic case, serological tests may be positive. ELISA and PCR can be used to differentiate different strains of *T. cruzi*.

Transmission is from the faecal deposit after the bug has fed, which is generally scratched into a wound or enters through the conjunctiva. The main genera

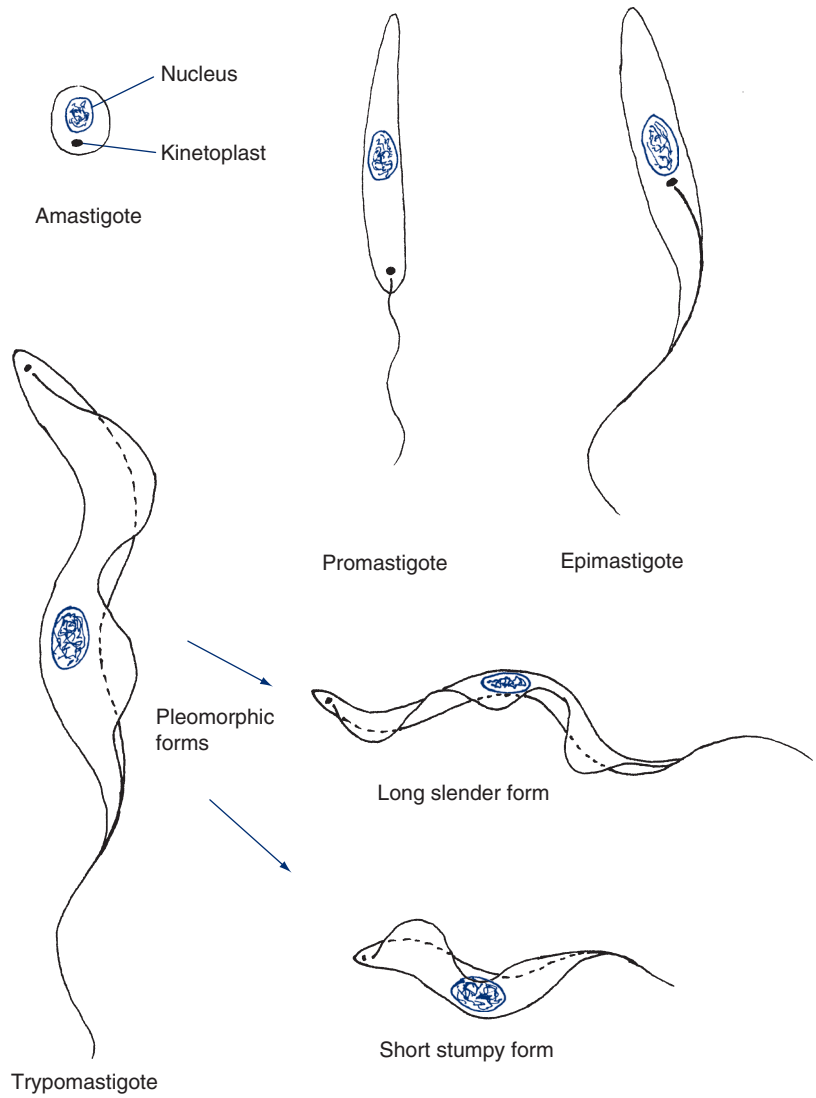

Fig. 15.19. Different forms of trypanosomes.

of bugs are *Triatoma*, *Rodnius* and *Panstrongylus*, which can be differentiated from each other by their antennae and mouthparts (Fig. 15.20). Essentially there are two cycles, a wild and a domestic, which are illustrated in Fig. 15.21.

In the wild cycle, armadillos, opossums, raccoons and a number of other animals have been found to be infected, living in close proximity to the burrow-inhabiting bugs. This infection remains as a zoonosis until disturbed by a domestic animal, commonly a dog ferreting around the burrows of these wild animals. They are attacked by the bugs and acquire the infection. On returning to the house, the dog becomes a reservoir for the domestic bugs, which transmit the infection to any humans living or staying in the house.

In Central America, the cycle is semi-domestic with the reservoir maintained in the domestic rat (*Rattus rattus*) from which house-haunting bugs pass on the infection to people in the house. Although the bugs feed on people, it is the passage of trypanosomes in the bug faeces, which are rubbed into the wound or conjunctiva that produces the infection.

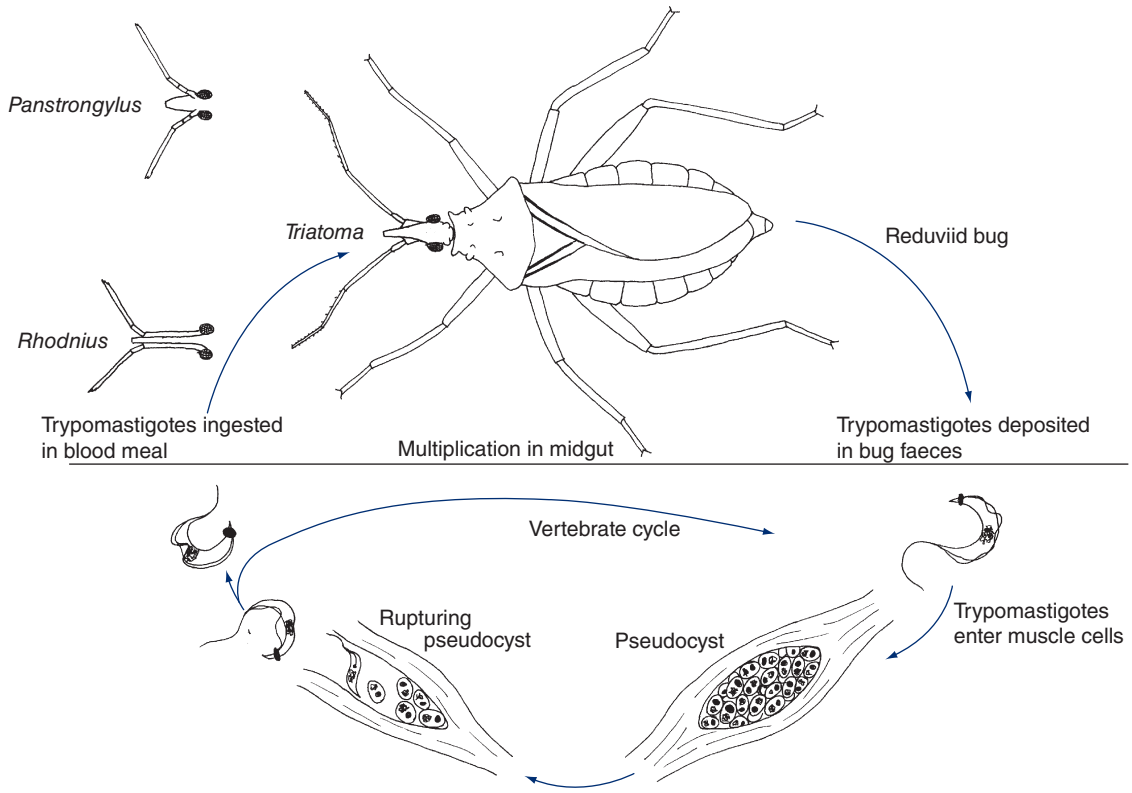

Fig. 15.20. Life cycle and vectors of American trypanosomiasis (Chagas' disease).

The bugs live in cracks in the walls and floors and within thatch in the roof. The mud and wattle type of structure is particularly suited to the conditions required. The number of bugs hiding within the cracks and crevices can be several hundreds.

Infection can also be transmitted by blood transfusion and by breastfeeding. Small epidemics in a group of people sharing the same food suggests that contamination of food by bug faeces could lead to transmission by the oral route.

The infected mother can pass infection on to her newborn either during pregnancy or childbirth. Organ transplants and laboratory accidents are rarer methods of transmission.

Incubation period. 5–14 days.

Period of communicability. Bugs become infected after 8–10 days and remain so for life, which lasts about 2 years. Infected persons have circulating trypanosomes in the acute and early chronic stages of the disease, but these may persist in small numbers for the life of the individual.

Occurrence and distribution. Chagas' disease is found throughout Central America and South America, with a prevalence of 8–10 million, annual incidence of 40,000 new cases and 10,000 deaths. Due to population movements, cases are now found in the USA, Canada, Europe and Western Pacific countries. Unfortunately, progress in the control of the disease has reversed due to insecticidal resistance, with reinfection of areas that were formerly thought to have eradicated the disease. Chagas' disease is found in Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guyana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Venezuela and Uruguay.

Control and prevention. The methods of control are to reduce the number of bugs that come into close proximity with humans and remove the reservoirs

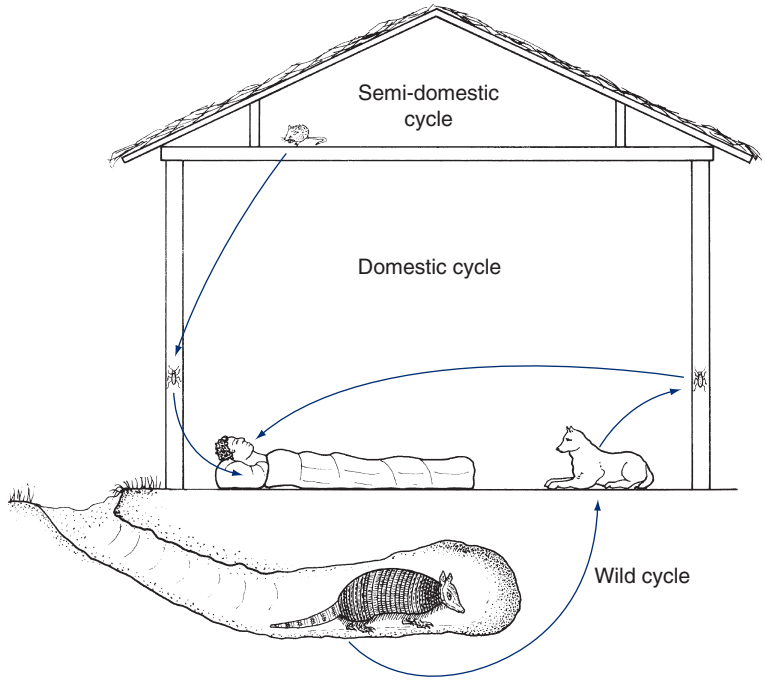

Fig. 15.21. Transmission cycles of American trypanosomiasis.

of disease. These requirements are both satisfied by improvements to housing. Unfortunately, trypanosomiasis is a disease of poverty, and building new and better houses is rather impractical in this segment of the population. If assistance can be given, then proper foundations and cement walls will not only deny a place for the bugs to live, but also prevent rats and armadillos from making their burrows underneath them. Even with existing houses, much can be done by applying a layer of mud plaster to the walls and erecting a simple ceiling. Where cost prohibits any of these methods, then residual insecticides can be sprayed on to the walls and ceilings. This can effectively be carried out as a control programme, using a similar methodology to that for malaria.

First, a pyrethrum spray is administered which draws the bugs out of their hiding places and marks the infected houses. In the attack phase, a residual insecticide is sprayed on all houses in an infected locality (not just applied to infested houses). A second spraying is made 90 days after the first to houses where bugs have been found either in the preliminary or attack phases. Spraying continues at this time interval until the number of infested houses falls below 5%. Maintenance is achieved by regular house searches and by instituting focal spraying when reinfestation is discovered.

The use of pyrethroid fumigant cans which release insecticide when lit, and of insecticidal paints, are simpler methods than residual spraying. An alternative is to protect the individual from being bitten by the use of insecticide-treated mosquito nets (see Box 3.1).

The dog is probably the most important domestic reservoir of the disease and householders should question the value of maintaining such animals if they are proving a threat to the health of the family. Good hygiene, trapping and poison will keep down rats (see Box 16.1). Control of the wild reservoir is unlikely to be successful.

In areas of high endemicity, screening of blood donors is required and gentian violet (a trypanosomicidal agent) can be added to the blood. Pregnant women should be questioned about possible infection and tested where necessary.

Treatment. Nifurtimox and benznidazole are effective in the acute and early chronic phase of the disease, but are still worth trying in the chronic disease as they

can delay the onset of cardiac damage. Survival rates have been increased by the use of cyclosporin.

Surveillance. Regular monitoring of houses for signs of infestation or reinfestation should be maintained (see above).

15.12 Leishmaniasis

Organism. There are seven species of *Leishmania* and a number of subspecies:

Visceral leishmaniasis	*L. donovani* (*donovani*)
	L. infantum (*infantum*, *chagasi*)
Mucocutaneous	*L. braziliensis* (*braziliensis*, *peruviana*, *guyanensis*, *panamensis*)
New world cutaneous	*L. mexicana* (*mexicana*, *amazonensis*, *pifanoi*, *garnhami*, *venezuelensis*)
Old world cutaneous	*L. major*
	L. tropica (*tropica*, *killicki*)
	L. aethiopica

The parasites are all transmitted by the bite of the sandfly and undergo the same simple life cycle. Promastigotes enter humans with the bite of the sandfly, change into amastigotes (Fig. 15.19) and are engulfed by macrophages. They multiply and finally rupture the cell, invading other macrophages. When the sandfly takes a blood meal, the amastigotes change into promastigotes. These multiply continuously so that the number produced can be so large as to block the foregut of the sandfly. When the insect next bites, it is forced to regurgitate promastigotes into the host before it can take a blood meal (Fig. 15.22).

In cutaneous leishmaniasis, the amastigotes remain at the site of introduction, contained by the macrophages of the skin. In visceral leishmaniasis, large mononuclear cells and polymorphonuclear leucocytes become invaded and subsequently carry the parasites to the viscera, especially the liver, spleen and bone marrow. The mucocutaneous form is intermediate, the parasite restricting its attack to the reticuloendothelial system of the mucus membranes of the mouth, nose and throat.

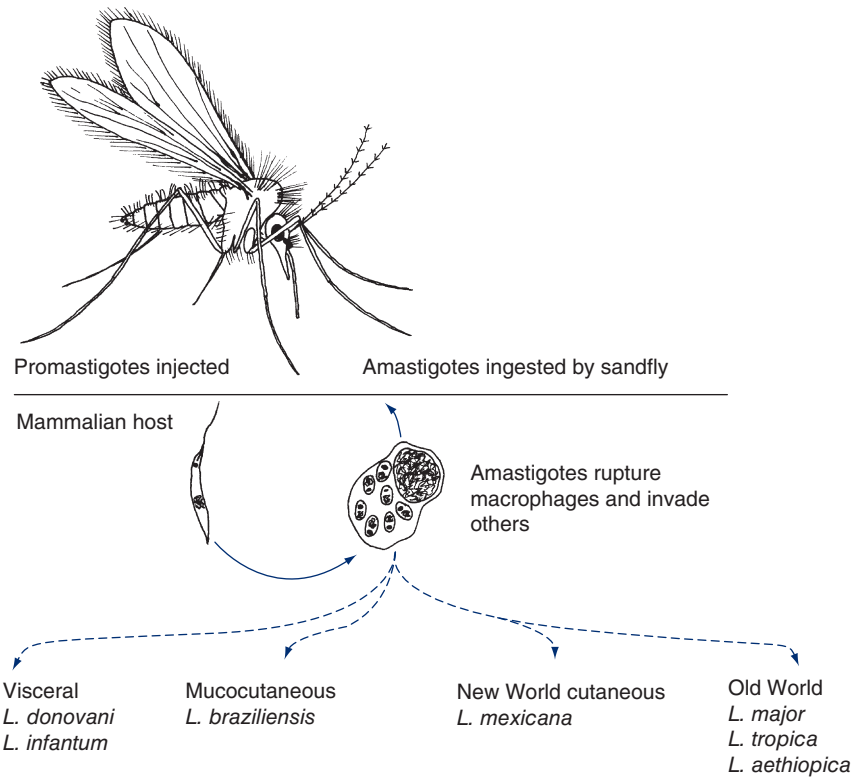

Fig. 15.22. *Leishmania* vector, parasite and life cycle.

Clinical features. There are four main clinical forms of the disease: cutaneous, mucocutaneous, visceral (kala-azar) and post-kala-azar dermal leishmaniasis. The cutaneous infection starts with a papule and enlarges to become an indolent ulcer, which either heals or persists for many years. In the New World infections, a more aggressive form of mucocutaneous leishmaniasis (espundia, Chiclero ulcer) results in nasopharyngeal destruction and hideous deformities. The visceral form is a chronic infection with fever, progressive weakness, hepatosplenomegaly, lymphadenopathy and anaemia. There is progressive emaciation and weakness, with generally a fatal outcome if not treated. Post-kala-azar dermal leishmaniasis produces nodular lesions and can occur after apparent cure of the visceral case. It is due to host response rather than to the parasite.

As in leprosy, host response largely determines the outcome of the disease and in any condition in which this is minimized, a more florid disease results. Cutaneous leishmaniasis is normally a self-limiting condition, but in some individuals diffuse cutaneous leishmaniasis, in which metastatic lesions are disseminated around the body, can occur. The resulting nodular lesions resemble those of lepromatous leprosy and respond poorly to treatment. So any condition that compromises the host response, such as HIV infection, may lead to reactivation of latent disease or cutaneous disease progressing to visceral illness. Leishmaniasis, like tuberculosis (TB), is intertwined with HIV infection, so that in areas where leishmaniasis is found both conditions have a more serious outcome.

Diagnosis is by the detection of the intracellular Leishman–Donovan bodies in infected macrophages in the liver, spleen and bone marrow, or in cutaneous lesions, by stained smear or culture. PCR techniques can also be used. A dipstick method, K39, can be used for serological diagnosis and will be particularly valuable for field surveys.

Transmission is by the minute and fragile phlebotomine sandflies *Phlebotomus* and *Lutzomyia*. They are weak fliers, utilizing a hopping flight that only carries them a short distance from their habitat. This requires conditions of high humidity, as found in animal burrows and moist tropical forests. Typical habitats are tree holes, new or old animal burrows, termite hills, rock crevices, foliage clumps and fissures that develop in the ground during the dry season.

The life cycle, from oviposition to emergence of the adult sandfly, can take 30–100 days depending on species and temperature, while the adult lives for approximately 2 weeks. Only the female sucks blood, and lizards, birds and mammals are satisfactory alternative food sources to humans.

Most species of sandfly feed out of doors during the evening and night, but will do so in the day when there is shade, or the weather is overcast. If it is windy, they are unable to fly. They are not able to bite through clothing and mainly attack the lower parts of the body. The main vectors are summarized in Table 15.6.

A range of reservoirs are found in this complex of diseases. In Central Asia, cutaneous leishmaniasis is a zoonosis, the gerbil being the main reservoir. In India, there is a domestic reservoir, mainly of dogs, but direct human-to-human transmission also occurs. The vectors and reservoirs involved are summarized in Table 15.6.

Transmission can also take place directly through needles and other instruments contaminated with blood of an infected person. Sadly, this is also the method by which HIV is transmitted in many developing countries.

Incubation period. 2 weeks to 6 months, but can be years.

Period of communicability. The untreated case can remain infectious to sandflies for up to 2 years.

Occurrence and distribution. Leishmaniasis is found in Central/South America, Africa, the Mediterranean, South-west, Central and South Asia, and part of China, as shown in Fig. 15.23 and Table 15.6. Some 90% of all visceral cases are found in Bangladesh, Brazil, India, Nepal and Sudan; the majority of mucocutaneous cases are in Brazil, Bolivia and Peru; and 90% of cutaneous cases are in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria.

Population movements, both of persons from endemic rural areas into towns and during large man-made projects such as dams in endemic foci, have brought an increasing number of people into contact with leishmaniasis. Several large-scale development projects have been seriously hampered by epidemics of the diseases. Also, the spread of HIV infection has made what was largely a curable condition into a persistent source of parasites for the vector sandfly and a resulting more serious disease. It is estimated that 12 million

Table 15.6. The vectors and reservoirs of leishmaniasis.

Type and parasite (*Leishmania* species)	Geographical area	Main vector (*Phlebotamus* or *Lutzomyia* species)	Reservoir
Visceral			
L. donovani	Mediterranean, SW Asia	*P. peniciosus*, *P. ariasi*, *P. major syriacus*, *P. longicuspis*	Dogs, foxes
	Central Asia	*P. major syriacus*, *P. smirnovi*, *P. longiductus*	Dogs, jackals, foxes
	China	*P. chinensis*	Dogs
	India, Bangladesh	*P. argentipes*, *P. papatasi*	Humans
	Sudan, Chad	*P. orientalis*, *P. martini*	Wild rodents and carnivores
	Kenya	*P. martini*	Dogs
	Central and South America	*L. longipalpis*	Dogs, foxes
L. infantum	Mediterranean	*P. peniciosus*	Dogs, foxes
Mucocutaneous			
L. braziliensis	Central and South America	*L. wellcomi*, *L. umbratilis*, *L.trapidoi*	Rodents and forest animals
Cutaneous (New World)			
L. mexicana	Mexico, Belize, Guatemala	*L. olmeca*	Forest rodents
	Amazon Basin	*L. flaviscutellata*	Forest rodents
	Peru	*L. peruensis*, *L. verrucarum*	Dogs
Cutaneous (Old World)			
L. major	Mediterranean	*P. papatasi*	Rodents, dogs, gerbils
	SW Asia	*P. papatasi*, *P. sergenti*	Dogs, rodents
L. tropica	Central Asia	*P. papatasi*	Rodents, gerbils
	India	*P. sergenti*	Dogs
	West Africa	*P. duboscqi*	Dogs, rodents
L. aethiopica	Ethiopia	*P. longpipes*	Hyraxes
	Kenya	*P. pedifer*	Rodents

people are infected worldwide, with 2 million new cases occurring annually.

Immunity develops following infection with the parasite, but there is little cross immunity. *Leishmania tropica* has been used for a long time as an inoculum to induce a sore on a hidden part of the body so as to prevent a more disfiguring lesion developing on the face. *Leishmania major* will protect against *L. tropica* as well as *L. major* lesions, and suspensions of living organisms have been prepared for this purpose. There is no cross immunity with kala-azar and the other species of *Leishmania*, but an attack of kala-azar will protect against developing kala-azar in any other part of the world.

Control and prevention. Cases of the disease are normally sporadic so should be treated to prevent flies from becoming infected. Early diagnosis via an adequate health infrastructure is an essential part of control, as well as reducing the morbidity and mortality of the disease.

Repellents and personal protection adequately protect the individual from being bitten. Sandfly nets can be used, but a more effective solution is ITNs or LLINs (see Box 3.1). Insecticide-treated sheeting in refugee shelters was found particularly useful in an epidemic in Afghanistan. The use of residual insecticides has been effective in areas where leishmaniasis overlaps with malaria, but owing to insecticide resistance and the replacement of this strategy by the use of insecticide-treated materials, it is not justified to use this method except under epidemic conditions.

Because of the fragile nature of the vector, it is easily attacked with insecticides either as a residual house spray if the vector comes indoors, or by insecticide powder blown into mammal burrows, ant hills and similar microhabitats. A longer-term solution is to alter the microenvironment, such as by the destruction of termite hills and killing of rodents. Proper control of domestic animals, especially dogs, can be effective where they are important reservoirs.

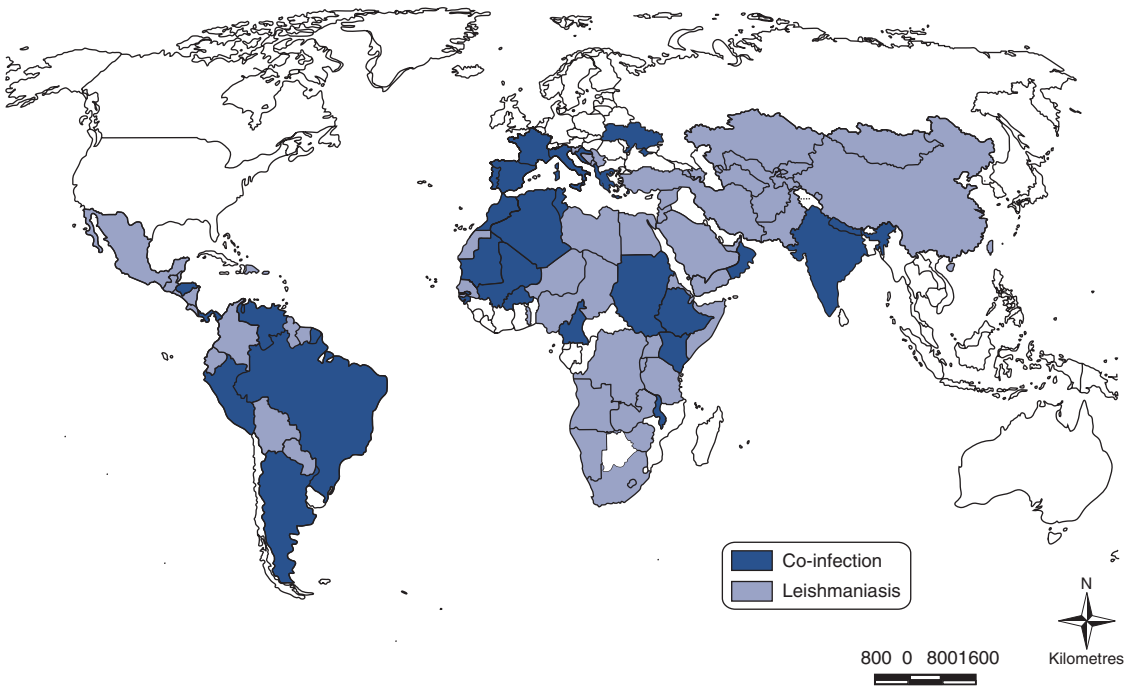

Fig. 15.23. The worldwide distribution of leishmaniasis and countries reporting *Leishmania*/HIV co-infection, 2000. (Reproduced by permission of the World Health Organization, Geneva.)

The use of deltamethrin-treated collars has been found to be effective. A vaccine for use in dogs would be valuable.

Low-dose inocula and attenuated vaccines have been developed to minimize the severity of disease in some endemic areas. The concomitant problem of HIV infection has added to the seriousness of dual infection, so a simultaneous programme of sexually transmitted infection (STI) control is required with information produced on how to avoid both diseases.

Due to the lack of an animal reservoir in India, the availability of new diagnostic tests (the K39 dipstick) and effective treatment (with miltefosine), there is a real possibility of eliminating visceral leishmaniasis from the subcontinent based on the following strategy:

- early diagnosis and complete treatment of cases;
- integrated vector management;
- effective disease surveillance through passive and active case detection;
- social mobilization and partnership building at all levels; and
- clinical and operational research, as required.

Treatment has been with sodium stibogluconate or meglumine antimonate, but pentamidine or liposomal amphotericin B may be required in cases that do not respond, especially in mucocutaneous leishmaniasis. Because of the toxicity of the preparations, treatment should be undertaken in hospital. Miltefosine has shown considerable promise in the treatment of visceral leishmaniasis, with high cure rates and in those cases resistant to antimony therapy. Its other advantage is that it can be administered orally, but it should not be given to pregnant women because of its teratogenicity. Miltefosine may be particularly valuable in the treatment of leishmania patients who also have HIV.

Paromomycin has been shown to be a safe and effective drug, possibly best given in combination with sodium stibogluconate, as the development of resistance to single-treatment regimes has a high probability. Other dual therapies are liposomal amphotericin B and miltefosine.

Surveillance. Outbreaks should be reported to neighbouring countries so that they can take control measures in border areas. Patients with HIV infection should be examined for reactivated leishmaniasis.

Summary

- Vectors are a more specific way of carrying the infective organism direct to the host.
- The most important flying vector is the mosquito, but *Simulium*, tsetse flies, sandflies and the reduviid bugs transmit other serious infections.
- The dynamics of the vector need to be understood in defining the parameters of the infection and how to control it.
- Control is aimed at reducing the vector numbers, the biting rate and length of life to below a level where the parasite is unable to develop or is of a sufficiently small number to be unable to propagate the infection.
- Insecticide-treated nets are the main method of control, with residual spraying, larviciding, environmental modification and MDA also being used.

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