1

Animal Associations and the Importance of Parasites

CONTENTS

1.1 Introduction

In this chapter, we introduce the concept of parasitism as a lifestyle and explain why it is such a difficult term to define. We also introduce some of the terms commonly used by parasitologists. Like all branches of science, parasitology uses specialist terms such as 'intermediate host', 'definitive host' and 'zoonosis' that one must understood before one can make sense of the literature. We explain why the study of parasites is so important and why parasitic infections will remain a problem in human and veterinary medicine for many years yet to come.

1.2 Animal Associations

All animals are in constant interaction with other organisms. These interactions can be divided into two basic types: intra-specific interactions and inter-specific interactions.

Parasitology: An Integrated Approach, Second Edition. Alan Gunn and Sarah J. Pitt.

Companion website: www.wiley.com/go/gunn/parasitology2

Intra-specific interactions are those that occur between organisms of the same species. They range between relatively loose associations such as those between members of a flock of sheep and highly complex interactions such as those seen in colonial invertebrates. For example, the adult (medusa) stage of the Portuguese man o' war 'jellyfish' (*Physalia physalis*) may appear to be a single organism but is actually composed of colonies of genetically identical but polymorphic individuals. These colonies divide labour between themselves in a similar manner to that of organ systems within a non-colonial organism. For example, some colonies are specialised for reproduction, whilst others are specialised for feeding. The term 'jellyfish' is in inverted commas because although *P. physalis* superficially resembles a jellyfish and is a member of the Phylum Cnidaria, it is taxonomically not a true jellyfish. Instead, it belongs to the order Siphonophora within the class Hydrozoa. The true jellyfish belong to the Class Sycphozoa within which there are several orders but in all of these, the medusa stage is a single multicellular organism.

Inter-specific interactions are those that take place between different species of organism (Figure 1.1). As with intra-specific interactions, the degree of association can vary between being extremely loose and highly complex. Odum (1959) classified these interactions on the basis of their effect on population growth using the codes '+' = positive effect, '−' = negative effect, and '0' = no effect. This leads to six possible combinations (00, 0−, 0+ etc.), and these too can be broken down into further subdivisions. Some authors also include a consideration of the direction and extent of any physiological and biochemical interactions between the two organisms. Many terms have been suggested to compartmentalise these interactions (e.g., phoresis, mutualism, predation), but these are merely convenient tags, and they cannot be defined absolutely. This is because there is a huge diversity of organism interactions, and even within a single interaction there are many variables, such as the relative health of the two organisms, that will determine the consequences of the interaction for them both. It is therefore not surprising that there is a multiplicity of definitions in the scientific literature, and it is not unusual for two authors to use different terms for the same type

Figure 1.1 Different species will sometimes co-operate for mutual benefit.

of interaction between species. In this section, we will discuss symbiosis, commensalism, phoresis, mutualism and finally parasitism, with some examples of each.

1.2.1 Symbiosis

The term symbiosis derives from the Greek *συμβίωση* and is usually translated as 'living together'. It was originally used in 1879 by Heinrich Anton de Barry to define a relationship of 'any two organisms living in close association, commonly one living in or on the body of the other'. According to this definition, symbiosis covers an extremely wide range of relationships. Some authors state that both organisms in a symbiotic relationship benefit from the association (i.e., it is [++]) although this is clearly a much more restrictive definition, and it is more appropriately referred to as mutualism. However, some authors consider symbiosis and mutualism are synonymous – this only adds to the confusion. For the purposes of this book, we will keep to de Barry's original definition.

1.2.1.1 Symbionts

Strictly speaking, a 'symbiont' is any organism involved in a symbiotic relationship. However, most scientists tend to restrict the term to an organism that lives within or upon another organism and provides it with some form of benefit – usually nutritional. The association is therefore referred to as a host: symbiont relationship and most symbionts are microorganisms such as bacteria, algae, or protozoa. Where the symbiont occurs within the body of its host, it is referred to as an endosymbiont, whilst those attached to the outside are referred to as ectosymbionts. There are two types of endosymbiont: primary endosymbionts (or p-endosymbionts) and secondary endosymbionts. Primary endosymbionts form obligate relationships with their host and are the product of many millions of years of co-evolution. They are usually contained within specialised cells and are transferred vertically from mother to offspring. Consequently, they undergo co-speciation with their host and form very close host-specific relationships. By contrast, secondary endosymbionts probably represent more recent host: symbiont associations. In the case of insects, these symbionts live within the haemolymph (blood) rather than specialised cells or organs. Secondary endosymbionts tend to be transmitted horizontally and therefore do not show a close host: symbiont relationship. Horizontal transmission occurs when a symbiont (or parasite) is transmitted from one host to another that is not necessarily related to it.

It is uncertain how endosymbionts begin their association with their hosts, but some authors suggest that they arise from pathogens that attenuated over time. The suggestion that a parasite–host relationship tends to start off acrimoniously and then mellows with time is widespread in the literature, and whilst this may sometimes occur it is not a foregone conclusion.

1.2.1.2 The Importance of Symbionts to Blood-feeding Organisms

Although vertebrate blood contains proteins, sugars, and lipids, as well as various micronutrients and minerals, it lacks the complete range of substances most organisms require to sustain life and to reproduce. Consequently, many of the animals, which derive most or all their nutrition from feeding on blood (haematophagy), have symbiotic relationships with bacteria that provide the missing substances, such as the B group of vitamins. The need for supplementary nutrients is particularly acute in blood sucking lice (sub-order Anoplura) because they have lost the ability to lyse (break up) red blood cells, and therefore many nutrients will remain locked within these cells. In many cases, the symbiotic bacteria are held within special cells called mycetocytes that are grouped together to form an organ called a mycetome. Although these terms appear to indicate the involvement of fungi, they originate from a time when scientists could not distinguish between

the presence of yeasts and bacteria within cells. Many scientists continue to use the term 'mycetocyte' regardless of the nature of the symbiont, but others use the term 'bacteriocyte' where it is known that the cells harbour only bacteria.

In blood-feeding leeches belonging to the order Rhynchobdellida (there is a popular misconception that all leeches feed on blood; many of them are predatory), mycetomes surround or connect to the oesophagus. Mycetomes do not form in all blood-feeding leeches, and in the medicinal leech, *Hirudo medicinalis* (Figure 12.1), the symbiotic bacteria live within the lumen of the gut (Graf et al. 2006). The bacteria present in *H. medicinalis* are *Aeromonas veronii*; earlier work on leeches often refers to this bacterium as *Aeromonas hydrophila*. *Aeromonas veronii* also forms associations with other blood-feeding invertebrates, as well as vampire bats, but it can also live independently as a free-living organism. Interestingly, both *H. medicinalis* and *A. veronii* produce antimicrobial peptides that suppress the growth of other microbes in the leech's gut (Tasiemski et al. 2015). This reduces the diversity of the gut microbial flora and emphasises the close relationship between the two organisms. *Aeromonas veronii* is not always beneficial: in humans, it causes wound infections, septicaemia, and gastroenteritis. Blood-feeding leeches are useful in modern medicine, particularly to aid wound drainage following reconstructive surgery, but there is a risk of them facilitating an *Aeromonas* infection in the patient. The infections are often trivial, but they can become serious and lead to abscesses or cellulitis. This is a difficult problem to solve because the symbiotic bacteria are essential for the long-term survival of the leech. One cannot develop a strain or culture of *Aeromonas*-free leeches. However, treating the leeches 1–4 weeks before use with an antibiotic such as ciprofloxacin removes the bacteria without compromising the willingness of the leech to feed (Mumcuoglu et al. 2010). A leech is only used once in reconstructive surgery because of their potential to transmit diseases between patients. Consequently, the long-term survival of antibiotic-treated leeches is not a concern.

The nymphs and adults of the human body louse *Pediculus humanus humanus* (sub-order Anoplura) (Figure 7.11) have a symbiotic relationship with the gamma (γ) proteobacterium *Riesia pediculicola* – also referred to as *Candidatus Riesia pediculicola*. The term '*Candidatus*' is used in prokaryote taxonomy for an organism that may be well characterised from molecular and other studies but cannot be cultured in the laboratory. *Riesia pediculicola* are primary intracellular endosymbionts that provide their hosts with pantothenic acid (vitamin B5) and are essential to the survival of the lice. In nymphs and adult male lice, the symbionts live within a mycetome that some texts refer to as the 'stomach disc'. This is an unfortunate term because lice, like other insects, do not have a stomach in the mammalian sense of the word. Anyway, the mycetome is located on the ventral side of the mid-gut but unlike the leeches mentioned previously, there is no connection between the mycetome and the gut lumen (Perotti et al. 2008). In adult female lice, the bacteria re-locate to the oviducts and the developing eggs. Interestingly, molecular phylogenetic analysis cannot distinguish between the symbiotic bacteria of human head lice (*Pediculus humanus capitis*) and human body lice (*Pediculus humanus humanus*). This adds support to phylogenetic analysis of the lice themselves that indicates that although head lice and body lice occupy different ecological niches and body lice tend to lay their eggs on clothing whilst head lice attach their eggs to hair shafts, they are two morphotypes of the same species rather than two separate species. One suggestion is that body lice evolved from head lice relatively recently in human evolution once we started wearing clothing. The association between *Riesia* and *Pediculus* is between 12.95 and 25 million years old – which makes it one of the youngest host: primary endosymbiont relationships so far recorded (Allen et al. 2009). In common with other primary endosymbionts, *Riesia* has undergone a reduction in genome complexity and lost genes (Moran and Bennett 2014): this is because it has come to rely on its host for the provision of many nutrients and protection from the environment etc. In addition, because its transmission is via the eggs of its host, each louse symbiont population

is in reproductive isolation and unable to undergo recombination with other strains of *Riesia* in other lice. This has led to the suggestion that *Riesia* will lack the capacity to develop rapid resistance mechanisms to antibiotics – and because the *Riesia* is essential for the lice, killing the symbiont would result in host mortality.

1.2.2 Commensalism

The term 'commensalism' derives from the Latin *commensalis* and means 'at the same table together'. Most definitions state that one species benefits from the association and the other is unharmed (0+). Including the concept of 'harm' within any definition is seldom a good idea because harm is difficult to measure and varies with the circumstances. Similarly, a 'benefit' may not be immediately apparent, and some associations commonly cited as commensal might involve a degree of benefit to both parties (++) albeit they may not benefit to the same extent. A commensal association may be 'facultative', in which both species can live independently of one another or 'obligatory', in which one of the associates must live in association with its partner. For example, in many warmer parts of the world, the cattle egret (*Bubulcus ibis*) perches on the back of cattle and big game from which it swoops down periodically to capture lizards and insects that are disturbed as its ride moves through the undergrowth. The egret is perfectly capable of living apart from cattle, but it benefits from its mobile vantage point-cum-beater. The egrets probably do not remove many ectoparasites from the cattle and they get their Arabic name *Abu Qerdan* 'father of ticks' from the abundance of ticks associated with their nesting colonies. The cattle, therefore, appear to gain little from the relationship although the egret acts as an early warning system of the approach of predators. African Cape Buffalo (*Syncerus caffer*) have a good sense of smell but a notoriously poor eyesight: they are therefore vulnerable to predators approaching from downwind. The red-billed oxpecker (*Buphagus erythrorhynchus*) is sometimes said to have a similar commensal relationship with cattle, but this is almost certainly false. Unlike cattle egrets, the red-billed oxpecker has an obligatory relationship with cattle and big game and far from removing ticks it feeds primarily on scabs and wound tissue pecked from their host. Their feeding delays wound healing and thereby makes the affected animal vulnerable to infections and infestations with blowfly larvae.

The amoeba, *Entamoeba coli* (not to be confused with the gastro-intestinal bacterium *Escherichia coli,* which is also abbreviated to *E. coli*) is a common commensal that lives in our large intestine. Unlike its pathogenic cousin, *Entamoeba histolytica*, *E. coli* feeds on bacteria and gut contents and does not invade the gut mucosa or consume red blood cells. Therefore, *E. coli* is of little interest *per se*, although a study in Mexico suggested an association between moderate-heavy infestations and childhood obesity (Zavala et al. 2016). The most important feature of *E. coli* is that its morphological similarity to *E. histolytica* means that one must be careful to distinguish between the two species in microscope surveys of faecal samples.

1.2.3 Phoresis

The term 'phoresis' derives from the Greek verb φέρω ('*phero*') meaning to bear/carry. This association involves one species providing shelter, support, or transport for another organism of a different species and may be temporary or permanent. For example, apart from during their first instar, the larvae, and pupae of the blackfly *Simulium neavei* attach themselves to the outer surface of freshwater crabs. The larvae feed by filtering out phytoplankton and detritus from the water and the crabs act as a firm yet mobile substrate on which to attach. An appreciation of this association is important because adult *S. neavei* are vectors of the filarial nematode *Onchocerca volvulus* that causes 'River Blindness'.

1.2.4 Mutualism

Mutualistic (Latin, *mutuus* meaning 'reciprocal') relationships are those in which both species benefit from the association in terms of their growth and survival (++). Some authors further restrict the definition to one in which neither partner can live on its own, whilst others are less prescriptive. The association between *Wolbachia* bacteria and *O. volvulus* is clearly mutualistic. The bacteria live within the cells of the reproductive tissues and hypodermis in the adult female worms and provide them with essential metabolites. In the absence of the bacteria, the worms cannot establish themselves in their host and grow and adult females become infertile. The bacteria are therefore a potential target for the chemotherapy of filarial nematode infections (Jacobs et al. 2019; Taylor et al. 2019).

Whether the relationship between the Cnidarian *Hydra viridissima* and its algal partner *Chlorella* is mutualistic depends upon the strictness of one's definition. *Hydra viridissima* can grow and reproduce in the absence of their algal partner, but it is uncertain whether the strains/species of *Chlorella* associated with *H. viridissima* can survive independently. The algae live within vacuoles in the endodermal cells of the *Hydra* and thereby impart it with its characteristic green coloration. Whether this provides camouflage that is beneficial is uncertain. When the *Hydra* reproduces by budding, its algal partner is passed on to the offspring; the algae are not essential to the budding process, but *H. viridissima* seldom undergoes sexual reproduction if the algae are absent. Experiments in which the algae are removed from the *Hydra* by exposure to high light intensities (Habetha et al. 2003) indicate that the nature of the relationship depends upon the environmental conditions. Like other *Hydra* species, *H. viridissima* obtains its food by capturing prey on tentacles that are armed with nematocysts, whilst the alga carries out photosynthesis and releases the sugars maltose and glucose-6-phosphate that can potentially be used by *H. viridissima*. If there is suitable illumination and plenty of prey for the *Hydra*, the growth of *H. viridissima* with and without algae is similar. This indicates that, under these conditions, the sugars released by the algae have little importance for the *Hydra*. If, however, there is illumination but no food for the *Hydra,* then those lacking algae die after a few weeks, whilst those containing algae shrink but can survive for at least 3 months and commence feeding again if presented with food. Therefore, the symbiotic algae play an important role in the survival of *H. viridissima* whose normal food supply is low/absent. By contrast, if *H. viridissima* are kept in the dark but with plenty of prey available, those lacking algae grow much better than those containing them. Furthermore, the algal population declines by about 60% although they are not lost entirely and the *H. viridissima* remain pale green. This indicates that under these conditions, the algae receive nutrients from the *Hydra* to such an extent that the relationship changes from mutualism to one akin to parasitism.

1.2.5 Parasitism

Parasitism is a surprisingly difficult term to describe, and there are numerous definitions in the literature. We have adopted the definition that: 'parasitism is a close relationship in which one organism, the parasite, is dependent on another organism, the host, feeding at its expense during the whole or part of its life (− +)'. Parasitism is frequently a highly specific relationship that always involves a degree of metabolic dependence of the parasite upon its host and often, though not always, results in measurable harm to the host. The association is usually prolonged, and although it may ultimately result in the death of the host, this is not usually the case. It is therefore distinct from predation in which the predator usually quickly kills and consumes its prey. However, owing to the complexities of animal relationships, there are always 'grey areas' in which any definition starts to become unstuck. This is particularly apparent in the case of animals that feed on blood.

Mosquitoes and tsetse flies are not considered parasites because they only feed for a few seconds or minutes before departing. By contrast, hookworms and crab lice are parasites, because they live in permanent associated with their host. Blood-feeding leeches and lampreys, however, are free-living organisms that attach to their victim for several hours whilst taking a blood meal; some authors consider them parasites, whilst others define their feeding as a type of predation.

From Welcome Guest to Villain: The Derivation of the Term 'Parasite'

The word 'parasite' derives from the Greek παρά ('*para*') meaning 'beside' and σῖτος ('*sitos*') that means 'food'. In Ancient Greece, the term 'parasite' had religious connotations and nothing to do with infectious organisms. According to a stone tablet discovered in the temple of Heracles (Hercules) in Cynosarges, the priest was required to make monthly sacrifices in the presence of parasites who were to be drawn from men of mixed descent. Declining a request to act as a parasite was a punishable offence. (Cynosarges was an area near to the city walls of Athens. In addition to the temple there was also a gymnasium, and it was here that the Cynic philosophers taught.) Subsequently, the word came to mean someone who shared one's food in return for providing amusement and flattery. The '*parasitus ridiculosissimus*' was a popular character in Greek and early Roman comedies and they even had joke books to help them should they run out of witticisms. The greed of the parasite was a constant source of fun for dramatists, and he was often given crude nicknames such as 'little brush – because he swept the table clean'. Double entendres were as popular over 2000 years ago as they are today and the Latin for little brush '*peniculus*' is also a diminutive for a penis (Maltby 1999).

An obligate parasite is one that has no alternative but to develop as a parasite of its host. On the other hand, a facultative parasite can develop as a parasite or a free-living organism depending upon the circumstances. For example, the larvae of the warble fly *Hypoderma bovis* must develop as parasites of cattle and are therefore obligate parasites. By contrast, the larvae of the blowfly *Lucilia sericata* are facultative parasites. This is because if the female fly lays her eggs upon a live sheep, the larvae will feed on living tissue and therefore be parasites. Conversely, if she lays her eggs on a dead sheep, the larvae will feed as free-living detritivores. Similarly, the amoeba *Naegleria fowleri* can live as a free-living organism in ponds and lakes but if it enters the nostrils of someone swimming in the water, then it can become an opportunistic parasite and infect their brain.

As mentioned above, some organisms, such as the human body louse *Pediculus humanus*, are parasitic at all stages of their life cycle, whilst others are only parasitic at one or more stages. For example, the blood fluke *Schistosoma haematobium* parasitises us during its adult stage and snails during two of its larval stages but it also has two non-feeding free-living stages. The act of being a parasite is therefore stage specific. Some estimates suggest that as many as 50% of all known species are parasites at some point in their life cycle. However, this estimate is subject to the caveat that there is no consensus about what constitutes a species, especially among the prokaryotes. The number of known species is also a reflection of the interests of biologists in different groups of animals. For example, the fact that insects account for 72% of all known species is, at least partly, a consequence of them being studied intensively for over 200 years. In one insect order alone, the Hymenoptera (ants, bees, wasps), there are approximately 100,000 parasitoid species. By contrast, fewer people have studied mites and nematodes and the diversity of their parasitic species is probably vastly underestimated. Nevertheless, parasitism is a remarkably common lifestyle and parasites (and their hosts) exist in all the major groups of living organisms including the archaea, bacteria, fungi, plantae, protozoa, invertebrates, and vertebrates.

There is an endless debate as to whether viruses are parasitic organisms. At one level, this would appear to be self-evident since viruses are incapable of maintaining themselves or reproducing except when within their host cell. However, being composed of complex organic molecules and having the capacity to evolve is not necessarily synonymous with being a living entity, especially when those attributes are dependent upon existing within a host cell. We will discuss this topic further in Section 2.2.

1.2.5.1 Intra-specific Parasites

Although most parasitic relationships involve two different species, intra-specific parasitism also occurs. Brood parasitism is a common example of intra-specific parasitism among many birds (Tomás et al. 2017) and some social wasps (Oliveira et al. 2016). It involves a female laying her eggs in the nest of a conspecific (member of the same species) – this means that the costs of rearing, the young will be borne by another individual. Intra-specific parasitism sometimes occurs during sexual reproduction when the male attaches to the female and becomes dependent upon her for the provision of nutrients. For example, in certain deep-sea angler fish belonging to the suborder Ceratioidea, the larval fish develop in the upper 30 m of sea water and then gradually descend to deeper regions as they metamorphose into adults. The adolescent males have a very different morphology to the females: they are much smaller; they have larger eyes, and, in some species, they develop a large nasal organ that presumably helps in their search for females. Furthermore, the males cease feeding and rely upon reserves laid down in their liver during the larval period to fuel their swimming. Upon finding a suitable female, the male grasps onto her using special tooth-like bones that develop at the tips of his jaws (his actual teeth degenerate during metamorphosis). After attaching, the male grows (although he remains much smaller than his consort), and his testes mature. His skin and blood vessels fuse with hers at the site of attachment, and he remains attached for the rest of his life and draws all his nourishment from her. Some authors suggest that the male must find a virgin female. However, although most females carry only a single male, there are records of females with three or more males attached to them. This is presumably an adaptation to life in the deep-sea regions in which the opportunity to locate mates is limited. Nevertheless, this raises questions about how sexual selection occurs because it is unusual in nature for a female to mate with just one male for life, especially if that male is the first one to turn up. This type of relationship is not found in all ceratioid anglerfish; in some species, the males are facultative parasites rather than obligate ones as described in the above scenario, whilst in other species the males are free-living, capable of capturing their own food, and form only temporary attachments to females. Molecular evidence suggests that the development of the parasitic males is a relatively plastic phenomenon among anglerfish and has evolved and subsequently become lost on several occasions (Pietsch 2005).

1.2.6 Parasitoids

The term parasitoid is restricted to certain parasitic insects whose hosts are almost exclusively other insects – although a few species attack certain crustacea, spiders, millipedes, centipedes, and earthworms. Some parasites cause mortality and may even depend on the death of their host to effect transmission to the next stage of their life cycle, but host death is not inevitable. By contrast, parasitoids slowly consume their host's tissues so that the host remains alive until the parasitoid has completed its development. At this point, the host dies either through the loss of vital tissues or through the parasitoid physically eating its way out of its host. Parasitoids are all parasitic during their larval stage, and the adult insect is free living and feeds on nectar, pollen, dead organic matter, or is predatory, depending upon the species. Parasitoids can develop as endoparasites within their host or as ectoparasites attached to the outside but with their mouthparts buried deep within the host's body. The larva has only the one host in or on which it develops and those that are

endoparasites tend to exhibit the most host specificity. This lifestyle is therefore distinct from those insects such as warble flies (e.g., *Hypoderma bovis*) and bot flies (e.g., *Gasterophilus intestinalis*), which exhibit a more 'traditional' parasitic way of life that does not inevitably result in the death of the host. Many species of the order Hymenoptera (bees, ants, wasps) are parasitoids, and it is also a common lifestyle among the Diptera (true flies), but it is absent or very rare among the other orders. By contrast, most of the insect orders are hosts to parasitoids. Hyperparasitism is also common in which a parasitoid parasitizes another species of parasitoid. Parasitoids are effective for the control of agricultural pests, particularly within closed environments such as greenhouses. However, they have had limited success as control agents for parasites, their vectors, or intermediate hosts.

The parasitoid lifecycle typically begins with the adult female locating its host and either injecting one or more eggs or attaching them to the host's outer surface. Sometimes she also injects a toxin that temporarily or permanently disables her victim. The host is chosen based on its stage of development, which may be anywhere from the egg to the adult stage.

Parasitoid: Virus Interactions

Some endoparasitic wasps belonging to the families Ichneumonidae and Braconidae have a fascinating relationship with polydnaviruses. The polydnaviruses from these two wasp families are morphologically distinct, and they probably arose from the 'domestication' of two different viruses. However, through convergent evolution they exhibit many biological similarities (Drezen et al. 2017; Strand and Burke 2019).

The viruses replicate within the calyx cells of the wasps' ovaries and are then secreted into the oviducts. Therefore, when a wasp injects her eggs into a suitable host, usually a lepidopteran caterpillar, she also injects the virus. The viruses cannot replicate within the caterpillar, but they do invade several of its cell types. Within these cells, the viruses integrate into the caterpillar's genome and cause the expression of substances that facilitate the establishment of the parasitoid. For example, one of the main immune responses that insects express in response to an invader is encapsulation. Encapsulation depends upon recognition of the invader and then a co-ordinated physiological response: amoeboid-like cells present in the haemolymph surround the invader and then either kill it through the production of toxic chemicals and/or lack of oxygen or physically isolate it and thereby prevent it damaging the host.

If one implants wasp eggs without the virus into a host, then these are rapidly encapsulated and killed. The protective effect of the virus probably results from it causing the caterpillar to express protein tyrosine phosphatase enzymes and thereby interfering with the encapsulation process. Protein tyrosine phosphatases dephosphorylate the tyrosine residues of several regulatory proteins and are therefore closely involved in the regulation of signal transduction. Altering the levels of regulatory proteins makes it impossible for the host to express an effective immune response and therefore the parasitoid egg develops unmolested. The viruses also have other effects on the caterpillar including preventing its further development once it reaches the stage at which the parasitoid is to emerge. Consequently, the polydnaviruses have a mutualist-like relationship with the parasitoid within which they replicate. They are transmitted vertically as an endogenous provirus that integrates into the wasp genome but have a pathogenic relationship with the parasitoid's host, within which it cannot replicate.

It is probable that there are many other examples of symbiotic virus-parasitoid/parasite relationships awaiting discovery. However, not all wasp parasitoids have relationships with viruses and these inject toxins that cause similar disruptions to the host immune response and host development.

1.2.7 The Concept of Harm

The term 'harm' is often employed when describing interactions between organisms but is particularly pertinent to any discussion of host: parasite relationships. Unfortunately, harm is a difficult term to define and is not always easy to measure. For example, parasites are usually much smaller than their host and a single parasite may have such a minor impact that its effect on the physiology and well-being of the host is too trivial to measure. By contrast, a large number of the same parasite could cause serious illness or even death. Similarly, a low parasite burden may have little impact upon a healthy, well-nourished adult host, but the same number of parasites infecting an unhealthy, starving young host may prove fatal. Consequently, harbouring a pathogen (being infected) and expressing the signs and symptoms of being infected (suffering from a disease) are not necessarily synonymous. A common analogy is that a single glass of water will not harm you and may even do you good, but the rapid consumption of a thousand glasses of water would kill you. Does that mean that water is beneficial or poisonous? Clearly, it can be both and, likewise, harm is dependent upon the context in which it is being considered. For human parasites, one should also consider the context and psychological consequences. Among some poor communities, being infected by lice and parasitic worms may be considered an unremarkable fact of everyday life. By contrast, in affluent communities, the very thought of harbouring worms inside the body or being bitten by fleas may cause mental torment far above any physical harm caused. It is therefore not a good idea to make the ability to record measurable harm as a prerequisite for the classification of the relationship between two organisms. Indeed, in certain instances, low levels of parasitic infection may benefit the well-being of the host (Maizels 2020). Nevertheless, many parasite species have the capacity to cause morbidity, that is, a diseased state, and some may cause mortality (death). We discuss the possible beneficial consequences of low parasite burdens in more detail in Chapter 12.

The morbidity that parasite infections induce is often reflected in a reduction in the host's fitness as measured in terms of its growth or reproductive output. This is often attributed to the direct pathogenic effect of the parasite, such as through the loss of blood and the destruction of tissues or competition for resources. For example, many gut helminths act as so-called kleptoparasites (literally, thieving parasites) and compete with their host for nutrients within the gut lumen. However, the situation is far more complicated than this. Although a functional immune system is crucial for an organism to protect itself against pathogens, immune systems are energetically costly and when nutrients are limiting, it must trade these costs against other physiological processes. Ilmonen et al. (2000) demonstrated this by injecting one group of breeding female pied flycatchers (*Ficedula hypoleuca*) with a diphtheria-tetanus vaccine and a control group with a saline solution. The vaccine was not pathogenic and did not induce an infection, but it activated the birds' immune system. They found that birds injected with the vaccine exhibited a lower feeding effort, invested less in self-maintenance and had a lower reproductive output, as determined by fledgling quality and number. The authors therefore concluded that the energetic consequences of activating the immune system can be sufficient to reduce the host's breeding success.

1.3 Parasite Hosts

A parasite host is an organism on or in which the parasite lives and from which it derives its nutrition. The host is usually not related taxonomically to the parasite although this is not always the case (see intra-specific parasites). Most parasites are highly host specific and only infect one host

species or a group of closely related species. This is because all hosts represent a unique challenge in terms of the complex adaptations the parasite requires to evolve to identify, invade, and survive within/upon them. Nevertheless, a few parasite species, exploit a wide range of hosts. For example, the protozoan parasite *Toxoplasma gondii* infects, grows, and asexually reproduces in virtually all warm-blooded vertebrates although sexual reproduction only takes place within the small intestine of cats.

Hosts can be divided into classes, depending upon the role they play in the parasite's life cycle. The 'definitive' (or final) host is the one in, or on, which the parasite reaches maturity and undergoes sexual reproduction, whilst the 'intermediate' host is the one in which the parasite undergoes its developmental stage(s). There may be just one or several intermediate hosts and the parasite may or may not undergo asexual reproduction during this time, but it cannot develop into an adult or reproduce sexually. In this way, some parasites exploit their hosts to maximum effect by combining the reproductive power of asexual reproduction in the larval stage with the advantages of sexual reproduction during the adult stage.

Parasites devote more of their energies to reproduction than free-living animals because they do not have to worry about food, shelter, and fluctuations in environmental conditions. This is important because the chances of any offspring locating and establishing themselves within a suitable host are very low. The completion of a parasite's life cycle sometimes depends upon the death of the intermediate host and the subsequent consumption of the larval form by the definitive host. In this situation, the parasite is often very pathogenic in its intermediate host but has relatively minor effects on the definitive host. The intermediate host is not always killed or consumed by the definitive host. For example, after undergoing asexual reproduction in the snail intermediate host, the cercariae of the liver fluke *Fasciola hepatica* physically and chemically bore their way out and swim off to transform into metacercariae attached to aquatic vegetation. The snail survives the damage to its tissues, and the lifecycle is completed when the metacercaria are consumed by the sheep definitive host (see Section 5.2.1.1.1 for more details).

Parasites of Parasites

Viruses infect several parasitic protozoa such as *Leishmania* spp. (Rossi and Fasel 2018) and *Giardia lamblia* (Janssen et al. 2015) but, at the time of writing, there was surprisingly little evidence of their presence in helminths – though this is probably because few scientists have looked for them. Some workers suggest that viruses could be used to combat parasite infections (Hyman et al. 2013), but there is increasing evidence that many of the viruses found in parasitic protozoa contribute to their pathogenicity (Gómez-Arreaza et al. 2017).

Parasites are also infected by prokaryotic (e.g., bacteria) and eukaryotic (e.g., fungi and protozoa) parasites. Those parasites that infect other parasites are known as hyperparasites. For example, the microsporidian *Nosema helminthorum* is parasitic on the tapeworm *Moniezia expansa* that lives within the small intestine of sheep and goats (Canning and Gunn 1984). Sheep become infected by the tapeworm when they accidentally ingest oribatid mites containing the cysticercoids of *M. expansa*. Subsequently, the sheep must consume the infective cysts of *N. helminthorum* and these must then penetrate the tegument (tapeworms lack a gut of their own) of the tapeworm. Within the tapeworm, *N. helminthorum* reproduces and causes numerous raised opaque bleb-like patches but is not especially pathogenic. Related microsporidia affect various other platyhelminth parasites (Canning 1975; Sokolova and Overstreet 2020), but there are remarkably few reports of them infecting parasitic nematodes

(e.g., Kudo and Hetherington 1922). The discovery of microsporidia infecting the free-living nematode *Caenorhabditis elegans* has opened the potential of developing a laboratory model for studying both nematode immunity and the biology of microsporidia (Zhang et al. 2016). This is because *C. elegans* is a commonly used model organism whose full genome is known. Several species of microsporidia cause pathogenic infections in humans and domestic animals and a simple laboratory model would prove extremely useful in the development of drug treatments etc.

A paratenic host, also sometimes referred to as a transport host, is one that a parasite enters but within which it cannot undergo further development. Paratenic hosts are not usually essential for a parasite to complete its life cycle although they may provide a useful bridge between the infective stage/intermediate host and definitive host. For example, the definitive hosts of the nematode *Capillaria hepatica* are primarily rodents although it infects several other species of mammals including dogs, cats, and pigs. Human infections are rare but potentially serious. The adult worms reside in the definitive host's liver and their unembryonated eggs remain there until the host dies/is killed and a scavenger/ predator consumes them (Figure 1.2). The unembryonated eggs pass through the gut of the scavenger/predator and then out with the faeces. This helps disperse the

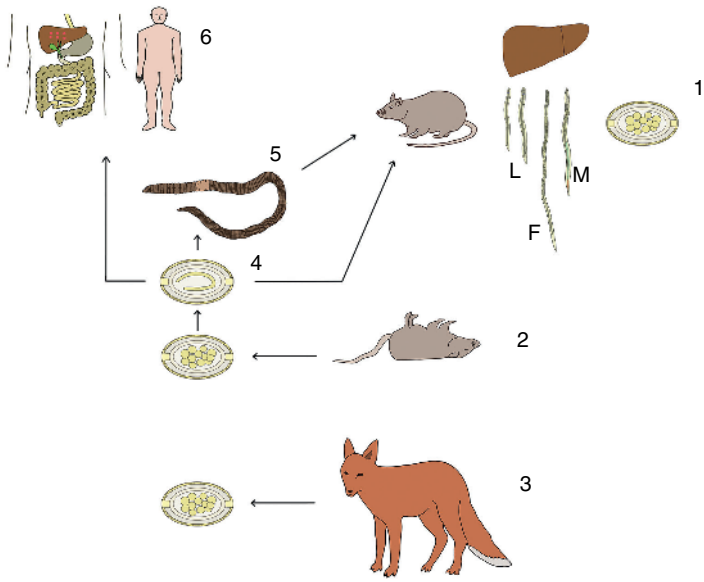

Figure 1.2 Life cycle of the nematode *Capillaria hepatica* illustrating the role of paratenic hosts in the transmission cycle. Drawings not to scale. 1 = A rodent becomes infected when it consumes embryonated eggs. These hatch in the small intestine, the larvae penetrate the gut, enter the circulation, and reach the liver. The larvae (L) moult become adult male (M) and female (F) worms and commence laying eggs. The unembryonated eggs remain in the liver. 2 = When the rodent dies its body decays and the unembryonated eggs enter the soil. If a scavenger eats the body, the unembryonated eggs pass through the gut and are dispersed. 3 = If a fox or other predator eats a live infected rodent, the unembryonated eggs are passed in its faeces. Scavengers and predators therefore act as dispersal hosts. 4 = The eggs embryonate to the infective stage in the soil. A rodent, human, or other susceptible mammal becomes infected when it consumes the infective eggs. 5 = Earthworms that consume infective eggs act as paratenic hosts if they are subsequently eaten by a rodent (or other susceptible mammal such as a pig). 6 = Humans are accidental, dead-end hosts within whose liver the parasites can develop to adulthood and produce eggs.

eggs in the environment. Development of the eggs to the infective stage occurs within the soil and takes several weeks or even months. If the definitive host's body is not consumed, the eggs embryonate to the infective stage, but there will be little dispersal. Earthworms ingest infective embryonated eggs of *C. hepatica* whilst feeding on soil and detritus. Because many rodents consume earthworms, these probably facilitate the transfer of the nematode to its definitive host.

1.4 Zoonotic Infections

A zoonotic infection (zoonosis) is one that is freely transmissible between humans and other vertebrate animals. The transfer of *Plasmodium falciparum* malaria between two people by a mosquito is therefore not zoonosis because a mosquito is not a vertebrate and *P. falciparum* only infects humans. By contrast, a mosquito transmitting *Plasmodium knowlesi* from a monkey to a human would be an example of a zoonosis because the *P. knowlesi* infects both monkeys and humans and we are both vertebrates. A disease that is only transmitted between humans is called an anthroponosis and a good example would be *P. falciparum*.

Many of the most important parasites in human and veterinary medicine are zoonotic infections. For example, pigs are the normal intermediate host of the pork tapeworm *Taenia solium,* and we are its definitive host. Therefore, pigs infect humans, and we infect pigs. Sometimes, humans are just one additional host within a parasite's life cycle. For example, the blood fluke *Schistosoma japonicum* has many definitive hosts apart from humans, including dogs, cattle, pigs, and rats. Consequently, all these definitive hosts can shed eggs that will infect the snail intermediate hosts, and the resultant cercariae can infect all of them.

The transmission of zoonotic parasites is usually heavily influenced by the nature of human: animal relationships. Therefore, they can be both simultaneously theoretically simple and recalcitrant to control. This is because their control often depends upon changing human behaviour, and this depends upon a complex mix of culture, religion, tradition, economics, personality, and politics. For example, theoretically, many zoonotic infections might be halted by simple acts of basic hygiene or the cooking of food. However, people are often unable or unwilling to change the way they live their life for all sorts of reasons. Zoonotic infections should not always be considered from the risks that they pose to us. Sometimes, wild animal populations can be threatened by the diseases that we transmit to them. We will consider specific instances of this throughout the book.

1.5 The Co-evolution of Parasites and Their Hosts

Evolution can be defined as a change in gene frequency between generations, but for this to occur three criteria need to be met. First, there must be genetic variation within the population. If the population is genetically homogeneous, then variation can only occur sporadically through random mutation. The second criterion is that the variation must be heritable: if the variation cannot be passed on to offspring, then it will be lost regardless of the benefits it imparts. The third and final criterion is that the variation must influence the probability of leaving reproductively viable offspring. If the variation is beneficial, then the organism possessing it will leave more offspring; however, unless these are reproductively viable, the variation would be quickly lost from the gene pool. Parasites live in close association with their hosts and the two organisms will co-evolve. The nature of the host: parasite relationship may therefore change with time. For example, provided

the three criteria are met, the host will evolve resistance/susceptibility factors depending upon the pressure exerted by the parasite. Although ever greater resistance to infection may appear to be 'ideal', this is unlikely to arise if the energetic cost impacts on the ability to leave viable offspring. At the same time, the parasite will evolve virulence/avirulence factors that promote its own survival.

It is often stated that long-standing parasite: host relationships are less pathogenic than those that have established more recently. This is based on the reasoning that if the parasite kills its host, then it will effectively 'commit suicide' because it will have destroyed its food supply. Consequently, over time, it is to be expected that the parasite will become less harmful to its host – that is, it becomes less virulent. However, this assumption is questionable because a pathogen's virulence often reflects its reproductive success. For example, let us consider two hypothetical strains, A and B, of the same nematode species that lives in the gut of sheep. Strain A is highly virulent and causes the death of the sheep whilst strain B is relatively benign and seldom causes any mortality. At first glance, one might expect that strain B would leave more offspring because its host lives for longer. However, if virulence was linked to the nematode's reproductive output and the eggs were released at a time when they were likely to infect new hosts, then strain A would bequeath more of its genes to subsequent generations. Consequently, the proportion of strain A in the nematode population would increase with time and there would be constant selection for increasing virulence. The sheep and the parasites may eventually be driven to extinction by these changes, but individual animals (and humans) are almost always driven by their own immediate self-interest rather than hypothetical future prospects.

1.5.1 The Red Queen's Race Hypothesis

The scenario described above naturally begs the question of, if this is true, why does life still exist today. This is because, on this basis, parasites and other pathogens should have killed everything off many millions of years ago. The answer is that the scenario is too simplistic and all host: parasite/pathogen relationships involve a complex array of competing factors. Consequently, the evolutionary endpoint of any relationship is case-dependent. Sometimes the parasite becomes more virulent, and sometimes its virulence attenuates to an intermediate level, but one cannot assume that the natural endpoint is a mutually beneficial form of mutualism. Indeed, the relationship between a parasite and its host is often likened to a 'co-evolutionary arms race' in which the parasites attempt to acquire more resources from the host to produce their offspring whilst the host evolves mechanisms for reducing its losses and eliminating the parasite. This has given rise to the ecological theory known as the Red Queen's Race. The name derives the Red Queen in Lewis Carroll's *Alice Through the Looking Glass* who says, "Now, here, you see, it takes all the running you can do, to keep in the same place" (Ladle 1992). One should also bear in mind that a parasite and its host are not co-evolving in isolation. Hosts usually harbour various parasites and other pathogens, and these may influence its response to an infection. Similarly, the parasite may be competing with other infectious agents for the host's resources. For example, experiments using bacteria infected with phage viruses suggest that the presence of numerous pathogens can speed up host evolution (Betts et al. 2018).

Parasites and other pathogens are generally smaller than their hosts are and reproduce faster. Consequently, one might expect them to win any arms race because, potentially, they could evolve adaptations to overcome their host's defences faster than the host could generate new ones. However, hosts that are comparatively long-lived usually have sophisticated immune systems that identify and kill or neutralize new parasite variants. The host is therefore not a constant

environment for the parasite. Parasite virulence is also affected by the mode of transmission. Horizontally transmitted parasites, especially those with a wide host range, can 'afford' to be highly virulent because there are lots of potential hosts and if one or more of them dies it has no direct consequences. However, when the parasite is vertically transmitted (e.g., via the eggs of its host or across the placenta) there is a direct link between the effect of the parasite on its host and its own reproductive success. For example, a virulent parasite's genes will not be transmitted; if the parasite is so pathogenic, it kills the host before it can reproduce. Similarly, if it kills the host's eggs while they are *in utero* or reduces the number of host eggs that are produced or survive to become adults and reproduce themselves, then the parasite is compromising its own reproduction. It is therefore to be expected that, as a rule (there will always be exceptions), vertically transmitted parasites should be less pathogenic than those that are transmitted horizontally. There is some support for this hypothesis. For example, two ectoparasites of swifts – a louse and fly – that are vertically transmitted have no effect on nestling growth or fledgling success even when the numbers of these parasites are artificially increased or the birds are stressed (Tompkins et al. 1996). Similarly, in feral pigeons, a vertically transmitted louse has little impact on the birds' health but horizontally transmitted ectoparasitic mites cause so much distress that the birds' reproductive success drops to zero (Clayton and Tompkins 1995).

1.5.2 Parasites in the Fossil Record

Most parasites are soft-bodied organisms, and they lack the hard structural features that facilitate preservation in the fossil record. It is therefore impossible to ascertain whether parasitism has always been a common 'lifestyle' – although this is highly likely. Conway Morris (1981) suggested surveying the commensals, symbionts and parasites of those organisms that have remained apparently unchanged for millions of years (the so-called living fossils) might reveal unusual organisms and provide insights into animal associations. For example, horseshoe crabs (Phylum Chelicerata, Subclass Merostomata) have existed almost unchanged for hundreds of millions of years. There is little published information on their parasites although flatworms of the family Bdellouridae only form associations with them (Riesgo et al. 2017). Despite the paucity of the fossil record, studies to date suggest that many parasite–host relationships persist for millions of years, and that parasite life cycles and morphology remain remarkably constant (Leung 2017)

Copepod ectoparasites that were morphologically similar to those in existence today have been identified attached to fossil teleost fish dating to the Lower Cretaceous Period (145–100.5 million years ago) (Cressey and Boxshall 1989). Evidence of nematode parasites is largely restricted to those infecting insects that became trapped in amber (Poinar 1984). Helminth eggs can be identified in coprolites (fossilised faeces), but while there have been extensive studies on animal and human faeces found in archaeological sites (Camacho et al. 2018), there is less data on coprolites dating back millions of years. As with any faecal analysis, one must not assume that presence indicates parasitism. An organism's presence may result from passage through the gut following accidental consumption (e.g., eggs of a parasite of another animal) or invasion of faeces after its deposition (e.g., eggs of a detritivore). Preservation of animals following rapid mummification under desiccating conditions or freezing in tundra enables the identification of soft-bodied parasites with greater accuracy. For example, nematodes and botfly larvae can be identified from woolly mammoths that died thousands of years ago on the Siberian tundra (Grunin 1973; Kosintsev et al. 2010).

Sometimes one can infer the presence of parasites in fossilised remains from the pathology they cause (Donovan 2015). For example, the pearls found in mussels and oysters often form

because of infection by trematode parasites. Pearls thought have been caused by trematode parasites have been identified in fossil mussels dating back to the Triassic era (250–200 million years ago) (Newton 1908). Dinosaurs almost certainly had their full complement of parasites although their evidence is sadly lacking from the fossil record. However, marks found on the bones of the dinosaur *Tyrannosaurus rex* are thought to resemble the pathology caused by the protozoan parasite of birds *Trichomonas gallinae* (Wolff et al. 2009). Similarly, Tweet et al. (2016) found sufficient evidence in the fossilised gut contents of a hadrosaurid dinosaur to describe a vermiform organism that they called *Parvitubilites striatus* that may have been parasitic. Poinar and Poinar (2008) have even suggested that parasites were a major factor in the ultimate extinction of the dinosaurs – although this is not a widely accepted view amongst palaeontologists.

1.5.3 Parasites and the Evolution of Sexual Reproduction

Sex has fascinated biologists (amongst others) for generations. From a logical point of view, sexual reproduction does not make sense because of what is referred to as the two-fold cost of sex. Firstly, the males, who usually constitute in the region of 50% of a population, serve only to inseminate the females and do not reproduce themselves. Furthermore, a lot of time and effort is often employed in searching for a mate and mating can itself be an energetically expensive and potentially dangerous process. By contrast, in an asexually reproducing organism 100% of the population can reproduce. Consequently, an asexually reproducing population is theoretically able to grow faster and respond to changes in the environment (e.g., increased food supply) faster than one that reproduces sexually. The other 'cost' of sexual reproduction is that the gametes are haploid and the process of recombination at meiosis means that an individual can only pass on 50% of its genes to each of its offspring. Consequently, useful genes and gene combinations could be lost in the process of generating new genetic variants. Despite these problems, and several others, most organisms undertake sexual reproduction and therefore it must have some major advantage(s)

There are several theories why so many organisms reproduce sexually (Burke and Bonduriansky 2017). One of the most popular is that of Hamilton et al. (1990) who suggest that sexual reproduction arose as a mechanism by which organisms can limit the problems of parasitic infections. Parasites can potentially reproduce faster than their hosts, and therefore, they will evolve to overcome the most common combination of host resistance alleles. Therefore, hosts with rarer resistance alleles will then be at a competitive advantage and ultimately one of these will become the most common resistance allele combination in the host population. The arms race will continue *ad infinitum* with the parasites adapting to the most common resistance allele combination and the host generating new allele combinations. The process of recombination ensures that (provided the initial gene pool is sufficiently diverse) there will be a constant supply of novel resistance alleles. Furthermore, a resistance allele combination to which parasites have adapted need not be lost from the population because it may prove useful again in the future. By contrast, in an asexually reproducing organism the offspring will have the same resistance allele combinations as their parents, and once parasites have overcome these, then the whole population is vulnerable to infection.

If sexual reproduction arose as means of reducing the depredations of parasites, then one would expect it to be common where parasites are abundant and challenge frequent. By contrast, asexual reproduction should be favoured where parasites are absent, or the level of challenge is low. Although there are several instances of exactly this in the literature, they remain remarkably few. The best-known example is that of the snail *Potamopyrgus antipodarum* that originated in New Zealand and has since spread to many parts of the world. It exists as sexually reproducing

populations, asexually reproducing populations, and mixed sexually and asexually reproducing populations. Positive correlations have been described between the extent of parasitism by parasitic flatworms and the frequency of sexual reproduction. Sexual reproduction is rare where flatworm parasite challenge is low, and conversely, it is common where the parasite challenge is high (Lively and Jokela 2002). Another commonly cited example is that of certain minnow populations living in Mexico (Lively 1996). These minnows exist as both asexually reproducing and sexually reproducing populations, but those reproducing sexually tend to have lower parasite burdens (except where inbreeding has resulted in reduced genetic diversity). Most multicellular parasites reproduce sexually themselves, although some combine it with asexually reproducing larval stages, such as schistosomes and the tapeworm *Echinococcus granulosus*. Even some parasitic protozoa, such as the trypanosomes, exhibit something akin to sexual reproduction. This suggests that even endoparasites living in protected environments such as the gut or bloodstream of another animal remain vulnerable to infections. However, although there is experimental evidence that parasitism influences the evolution and maintenance of sexual reproduction (Auld et al. 2016), there are almost certainly many other factors involved. For example, sexual reproduction may help protect against transmissible cancer cells (Thomas et al. 2019).

1.6 Parasitism as a 'Lifestyle': Advantages and Limitations

Provided one can get away with it, stealing something is easier than making it oneself or earning money to purchase it. Therefore, it is unsurprising that so many organisms have adopted a parasitic lifestyle to some extent. If one takes the view that the main purpose of an organism's existence is to transfer as many of its genes as possible into the next generation, then all organisms should maximise their reproductive output. However, an organism must trade the costs of reproduction against other activities such as finding food and then digesting and absorbing it, finding a mate, and protecting itself against competitors, predators, and the environment. By living upon or within a host, a parasite can reduce many of these 'other costs' and thereby devote more of its time and energy to reproduction. Most parasites stay in association with their host for the duration of a life cycle stage, and therefore, having located and infected their host, the need for sensory apparatus and locomotion are reduced because the parasite has access to a guaranteed food source. This guarantee also means that the parasite does not have to extract as much energy as possible from each 'unit of resource'. Instead, it can afford to be wasteful, and many parasites have reduced metabolic pathways. Furthermore, there is no need to lay down metabolic reserves beyond those required for the next life cycle stage. Parasites rarely need well-developed food gathering apparatus and, in some cases, such as the tapeworms, they have dispensed with a mouth and gut altogether, relying on nutrients being absorbed across the body wall.

Because parasites live within or upon their host, they have less need to maintain body surfaces and behaviours that protect them from desiccation, heat, cold because this is done by the host. Similarly, the parasite is to a large extent protected from predators and pathogens, because these must overcome the host's immune system before locating the parasite. Even ectoparasites receive protection to some extent because hosts cannot always distinguish between a predator attempting to take a bite out of them from an animal solely interested in removing a flea or louse.

A parasite will be transported wherever the host goes and therefore the limits of its dispersal depend upon the dispersal powers of its host, coupled with whatever other special needs the parasite must complete its life cycle (e.g., the presence of a suitable vector or environmental conditions). Consequently, a parasite does not have to devote energy to dispersal.

Table 1.1 Summary of advantages and disadvantages associated with the parasite lifestyle.

Advantages	Disadvantages
Once host located, no need for further searching	Extreme host specificity can increase vulnerability to extinction
Food permanently available	
Limited requirement for complicated food capturing mechanisms	Must locate at optimal site on/in host to ensure food/survival
Reduced need for food processing	
Protection from environmental extremes	Must adapt to host's internal physiological environment (internal parasites only)
Protection from predators and diseases	Must overcome host's immune defences
Reduced need for dispersal because host (+ vector) carries the parasite.	Spread limited by host's geographic range
Can devote larger proportion of energy intake to reproductive output than a free-living organism	Transmission can be extremely risky and most offspring die before establishing in a new host

If the benefits of parasitism are so enormous, this therefore begs the question why there are not more highly specialized parasites and why parasitism tends to be extremely common among some groups of organisms but rare among others. For example, there are comparatively few parasitic higher plants, Lepidoptera, or vertebrates.

Any would-be parasite must first overcome the putative host's immune defences and adapt to its internal physiological environment: this involves many physiological modifications, and therefore most parasites are host specific. However, host-specificity places the parasite in a difficult situation because its existence then becomes dependent upon that of its host. Should the host become extinct, then its parasites will follow suit unless they are able to infect other organisms. Furthermore, for the individual parasite, finding hosts is seldom easy. Although many parasites produce huge numbers of offspring, the chances of any one of them managing to locate a suitable host, establishing an infection, and reproducing successfully are extremely small. The advantages and disadvantages of the parasite lifestyle are summarised in Table 1.1.

1.7 The Economic Cost of Parasitic Diseases

The morbidity (illness) and mortality (death) associated with parasitic diseases causes financial losses to both an individual, their family, and to the wider society. These losses divide into the direct costs and indirect costs, and these are used in 'cost-of-illness' studies to prioritise healthcare funding decisions (Onukwugha et al. 2016). The direct costs include factors such as the costs of diagnosis and treatment. They are therefore relatively easy to identify and calculate because they consist of purchase costs and wages. By contrast, the indirect costs are much more wide-ranging and nebulous. For example, they include the costs associated with the infected individual's inability to work or reduced efficiency/productivity. They also include wider and often unappreciated costs that are borne by the family and/or the community. For example, the death of someone results in their family incurring the funeral costs (which can be considerable), as well as debilitating psychological stress that may impair their ability to work. Because most parasites cause chronic infections that persist for months or even years, the indirect costs associated with them often

exceed the direct costs. For example, a study in China found that one case of malaria cost $US 239 (1,691.23 Chinese Yuan) of which the direct costs constituted 43% and the indirect costs 57% (Xia et al. 2016). Furthermore, the costs were equivalent to 11% of a household's income. Similarly, in southern India, lymphatic filariasis costs in the region of US$ 811 million per year and cause productivity losses as high as 27% in the weaving sector (Ramaiah et al. 2000). Parasitic diseases that cause disfigurement often results in social exclusion that further traps the sufferer in poverty and mental ill health. People suffering from lymphatic filariasis can become so isolated that they will not venture out to seek freely available treatment at government clinics, let alone to look for paid employment (Wijesinghe et al. 2007). Although it is not a financial calculation, experimental studies indicate that for wild animals living communally, it is also the indirect costs of parasitism that impact most upon the group (Granroth-Wilding et al. 2015).

For domestic animals, there are the direct costs of diagnosis and treatment along with mortalities but the losses that result from lost productivity (e.g., milk yield, live weight gain) and/ or work capacity (e.g., draught oxen, camels, donkeys) are much greater. Unfortunately, the calculation of losses associated with parasites in the agricultural industry is problematic, and there is a lot of variation between individual farms. In addition, published figures can rapidly become out of date through currency fluctuations, changes in farming practices and the value of stock (amongst many other factors). Therefore, we provide just a few figures to illustrate the potential of parasites to cause financial losses. In the United Kingdom, gastrointestinal parasitic infections in lambs are estimated to cost the British sheep industry ~£84 million per year (~USD$ 102.4 million); the costs associated with infections in breeding ewes are not known but the combined figure would obviously be much higher (http://beefandlamb.ahdb.org.uk/wp-content/uploads/2013/04/Economic-Impact-of-Health-Welfare-Final-Rpt-170413.pdf). Brazil is a much larger country with a huge cattle industry, and the financial impact of parasitic diseases is correspondingly massive. They are estimated to cause losses of approximately US$13.96 billion per year; gastrointestinal nematodes are responsible for ~51% of these losses and the tick *Rhipicephalus microplus* a further 23% through direct effects and as a vector of other parasites (Lopes et al. 2015a). In the United States, the protozoan parasite *Neospora caninum* is estimated to cause in the region of US$ 546 million per annum in the dairy industry alone. The losses it causes in agriculture on a worldwide basis could be as high as US$ 2.38 billion per annum (Reichel et al. 2013). There are no figures for the economic cost of *N. caninum* infection in dogs, but many dog owners will spend large sums of money on the welfare of their pets and pedigree dogs can sell for hundreds or even thousands of pounds. Consequently, control of the disease in dogs is of concern to owners, as well as a means of preventing its transmission to cattle.

In developing countries, the economic costs of parasitic diseases of livestock can have consequences for the expansion of agriculture and the ability of populations to feed and clothe themselves. For example, in Pakistan, the increasing demand for milk and milk products has seen the import of high-yielding Holstein-Friesian breeds. Unfortunately, these are particularly susceptible to the tick-borne protozoan parasite *Theileria annulata* (causative agent of Tropical Theileriosis) and the losses it causes can account for 13.8% of a total farm's costs (Rashid et al. 2018). Similarly, in east, central, and southern Africa, East Coast Fever in cattle caused by *Theileria parva* results in annual losses of hundreds of millions of pounds/dollars and is one of the reasons many people in the region remain subsistence farmers (Muhanguzi et al. 2014). Although vaccines against both *T. annulata* and *T. parva* have been available for many years, there are practical problems associated with their use. Consequently, preventing the transmission of infections is mostly through acaricides that kill the tick vectors. However, because tick populations are increasingly resistant to these, there is a fear that the ticks will spread and consequently so will the diseases.

1.7.1 DALYs: Disability-Adjusted Life Years

A common means of measuring the consequences of human disease and other causes of morbidity is to calculate disability-adjusted life years (DALYs). These are derived by summing an estimate of a disease or condition's potential for reducing lifespan and an estimate of the amount of time a person suffering from the disease/cause is disabled (www.who.int/evidence/bod). One DALY is the equivalent of the person losing a year of healthy life.

DALY = Number of years of life lost through premature mortality + Years of life lived with disability

For example, a person committing suicide or dying in a traffic accident would suffer premature death, but there would be little or no disability (assuming they died instantly), whilst a person with malaria may suffer prolonged ill health and ultimately die prematurely years later. DALYs facilitate the comparison of morbidity and mortality factors and thereby help prioritize funding and policy decisions and determine the effectiveness of health initiatives. In some studies, the DALY model is refined to place greater value on the life of a young adult than of a child or older person. This version considers young adults more economically beneficial to society and with a longer productive life in front of them than a child or older person. However, the use of age weighting is contentious and the WHO ceased using this approach in 2010.

The use of DALYs began in 1994 and although the WHO and many other organisations employ them, they have always been controversial. For a detailed consideration of the limitations of DALY calculations, see Parks (2014). The use of DALYs to assess the importance of parasitic diseases is particularly difficult because the estimation of the years of life with disability includes a weighting factor that supposedly accounts for the severity of the disease. This can result in wildly different estimations. For example, although some studies suggest that the global burden of human schistosomiasis is ~3 million DALYs, others have put it as high as 70 million (Hotez et al. 2010). Furthermore, coinfections with several parasite species and parasite–pathogen interactions (e.g., *Leishmania*-HIV) are common and can have major implications for disease progression and outcome.

A comprehensive study of global health metrics by Hay et al. (2017) provides an insight into the relative importance of various causes of mortality and morbidity. Table 1.2 shows a selection of their data. Except for malaria, many parasitic diseases have comparatively small DALYs compared with other sources of morbidity/mortality – this is because they operate within restricted distributions. For example, car accidents are a common source of morbidity and mortality in all countries, and therefore, it is not surprising that they have high DALY values. Similarly, diarrhoeal diseases, sexually transmitted infections, and measles are serious diseases throughout the world – though many people do not realise that in addition to causing morbidity, many can also be fatal. The accuracy of all statistics depends upon the accuracy with which the data are recorded. For developing countries with few resources and those in the grip of armed conflict, this is extremely difficult. Consequently, the literature often includes huge discrepancies about how many people suffer from a disease and how many people die from it. For example, according to Wang et al. (2016), the nematode *Ascaris lumbricoides* was responsible for 2,700 deaths in 2015, but a WHO website suggested that around 60,000 people die of the disease every year (https://www.who.int/water_sanitation_health/diseases-risks/diseases/ascariasis/en/).

Although some workers have attempted to use economic costings for wildlife diseases, it is a controversial approach: how much is a blackbird worth? Indeed, there has been a tendency for parasitologists to view wildlife mainly from the perspective of their potential as reservoirs of disease for human infections or those of our domestic animals (Thompson et al. 2010). This has

Table 1.2 A comparison of global disability adjusted life years (DALYs) and mortality for selected parasites and other factors.

Factor	All-age DALY (million) (year = 2016]	DALY range (year = 2016]	Mortality per annum (year)	Reference for mortality data
Malaria	56.2	45.8–67.9	435,000 (2017)	https://www.who.int/news-room/fact-sheets/detail/malaria
Visceral leishmaniasis	0.71	0.40–1.21	24,200 (2015)	Wang et al. (2016)
Cutaneous/mucocutaneous leishmaniasis	0.27	0.18–0.40	Rarely fatal	
African trypanosomiasis	0.13	0.06–0.22	3,510 (2015)	Wang et al. (2016)
Schistosomiasis	1.86	1.12–3.18	4,400 (2015)	Wang et al. (2016)
Lymphatic filariasis	1.19	0.59–2.11	Rarely fatal	
Ascariasis	1.31	0.88–1.94	2,700 (2015) 60,000 (date not stated, website accessed 2019)	Wang et al. (2016) https://www.who.int/water_sanitation_health/diseases-risks/diseases/ascariasis/en/
Hookworm	1.69	1.00–2.65	Rarely fatal	
HIV/AIDS	57.6	54.6–61.0	570,000–1.1 million (2018)	https://www.unaids.org/en/resources/fact-sheet
Measles	5.72	2.15–12.26	73,400 (2015)	Wang et al. (2016)
Ebola	0.0003	0.0002–0.001	5,500 (2015) 33 (2018)	Wang et al. (2016) https://www.afro.who.int/health-topics/ebola-virus-disease
Diarrhoeal diseases	74.41	63.4–93.4	1.65 million (2016)	Troeger et al. (2018)
Syphilis	9.42	5.47–14.60	107,000 (2015)	Wang et al. (2016)
Road injuries	71.40	67.52–76.13	1.35 million (2018)	https://www.who.int/violence_injury_prevention/road_safety_status/2018/en/

DALY and DALY range data were derived from Hay et al. (2017). The mortality data were derived from the most recent year available at the time of writing and from various sources.

sometimes led to widespread culling of wildlife. For example, in parts of Africa it was once common practice to kill antelopes and other large game animals to prevent them acting as a reservoir of *Trypanosoma brucei* infection. Similarly, at the time of writing, the practice of culling badgers in the United Kingdom to prevent the spread of TB in cattle is proving hugely controversial and expensive. Its effectiveness is also debateable.

The rate of extinctions amongst animals and plants is proceeding at an alarming rate and with it the realisation that we need to do more to conserve them. This is not just an ethical issue, but it also has economic implications since wildlife tourism is big business in some countries. Any attempt at conserving an organism must consider the diseases it suffers from. In addition to natural infections, wild animals are also afflicted by parasites introduced to their habitat by humans. It would be wrong to consider natural infections as invariably benign and those introduced by humans as invariably malign. For example, until the introduction of the New World screwworm fly (*Cochliomyia hominivorax*) eradication campaign in the USA, one estimate suggested that it killed up to 80% of white-tailed deer fawns in the southern states every year (Fuller 1962). The screwworm fly was present naturally and the eradication campaign was solely to prevent infections in cattle and other domestic animals, but the result was beneficial to wildlife too. More commonly, a parasite colonises a new area through contamination (e.g., in soil or ship ballast water) or through infections of us and our domestic animals. The consequences then depend upon whether the invading species finds other suitable hosts and, if it needs one, a suitable vector or intermediate host. The exposure of any naïve animal (or human) to an agent capable of establishing an infection in them often ends badly and if that agent can complete its life cycle in the area, then the consequences for the local population of new hosts is equally dire. For example, on the Galapagos Islands, the populations of several of the species of Darwin's finches have been devastated following the arrival of the fly *Philornis downsi*. It probably came to the islands in the 1960s among imported fruit and vegetables. The adult flies are free living, but their blood-feeding larvae are ectoparasitic on nestling birds and cause high mortalities (McNew and Clayton 2018). Wildlife tourism brings in hundreds of millions of dollars per year to the Galapagos Islands (https://www.galapagos.org/wp-content/uploads/2012/01/TourismReport2.pdf). Although most people do not visit the Galapagos Islands to spot Darwin's finches, the loss of iconic species such as the Giant Tortoises to introduced parasitic infections would undoubtedly have serious implications for the tourist industry.

1.8 Why Parasitic Diseases Remain a Problem

Whenever a seemingly simple but intractable problem arises, a commonly heard refrain is 'if we can put a man on the moon, why can't we do X, Y, or Z'. As we have seen, parasitic diseases cause suffering to us and to our domestic animals, and the economic costs are enormous. Furthermore, many diseases could be controlled by simple measures such as providing safe drinking water and appropriate waste disposal facilities. So, one might ask, why do parasitic diseases continue to afflict so many people and impact so heavily on agriculture?

As with so many apparently simple questions, the reason parasitic diseases remain a problem does not have a single simple answer and is also tied up with the most exasperating factor of all – human behaviour (Table 1.3). To begin with, human parasitic diseases are predominantly (although not entirely) a problem of poor people who live in insanitary conditions and who do not have a healthy diet. The diseases are therefore most prevalent in developing countries where neither the government nor individual people have money to spare. For example, in 2016 the total healthcare

Table 1.3 Summary of factors contributing to the problems of parasitic diseases.

Poverty
Lack of sanitation
Complacency
Poor nutrition
Lack of health infrastructure
Lack of government interest
Corruption
Urbanization
Social conflict/wars
Movement of non-immune people to regions where they become infected from the resident population.
Movement of infected people to regions where they infect non-immune resident population
Man-made environmental damage
Natural disasters
Lack of effective drugs/ parasite resistance
Increasing resistance of vectors/ intermediate hosts

expenditure in Zimbabwe as a percentage of the gross domestic product (GDP) was similar to that of the United Kingdom (9.41% cf 9.76%) and considerably more than that of oil-rich Saudi Arabia (5.74%) (https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS). However, in terms of total health expenditure per capita, the United Kingdom spent US$4192, Saudi Arabia US$1147, and Zimbabwe US $94 (https://knoema.com/atlas/Zimbabwe/Health-expenditure-per-capita). Needless to say, US $94 does not buy many medicines.

We humans are extremely adaptable creatures. Consequently, we can survive harsh environments, oppressive regimes, and cruel exploitation. Unfortunately, this adaptability can degenerate into acceptance and complacency on the parts of both individuals and governments. Because parasitic diseases are so prevalent in developing countries, there is a tendency not to prioritise them: fevers and diarrhoea become an accepted part of everyday life. Furthermore, parasitic diseases tend to cause chronic disease and although the patient may ultimately die, the condition does not capture the attention of the local or world media. For example, Ebola virus is well known in the developed world because of its appalling pathology and images of patients being treated by nurses and doctors dressed in spacesuit-like protective clothing. However, although Ebola virus causes about 70% mortality, the numbers of people who have died of the infection are relatively few. By comparison, Human African Trypanosomiasis (HAT, often referred to as 'sleeping sickness') causes almost 100% mortality if untreated and kills many more people than Ebola (Table 1.2), but it seldom receives a mention in the media. The reason is simple, HAT kills slowly by comparison. Furthermore, the transmission of HAT depends upon tsetse flies, and these have demanding environmental requirements that limit their distribution. Consequently, HAT is only a threat to people living in certain parts of Africa. By contrast, Ebola spreads through close human contact and therefore the virus could conceivably spread anywhere in the world. Consequently, people in distant countries feel threatened even though their risk is incredibly small. The fact that Ebola virus has been touted as a possible biological warfare agent also helps to engender interest in the disease and funds to study and control it.

In addition to being poor, the countries in which parasitic diseases are most problematic are often unstable and suffer high levels of corruption. Consequently, those in control often devote much of their revenue into the trappings of power and military spending: many developing countries spend

less than 4% of their GDP on healthcare. This means that even less of not very much is available for the treatment and control of parasitic diseases. The instability of the regimes and conflicts, which can last for decades makes it difficult to provide health services and co-ordinate control strategies. They also lead to the destruction of basic infrastructure and the decline in agricultural and commercial activity – and this contributes to poverty and malnutrition. At its worst, conflicts lead to large numbers of refugees who are frequently housed in squalid campsites, which lack proper sanitation. These displaced people are often in poor health and malnourished, they take their parasites with them wherever they go, and they are highly vulnerable to the local strains of parasites at wherever they arrive. For example, the civil wars in the Central Asian states such as Tajikistan, which occurred after the breakup of the Soviet Union in the early 1990s, displaced people to neighbouring countries including Afghanistan. The most common type of malaria in Tajikistan at that time was caused by *Plasmodium vivax,* whereas in Afghanistan, the more virulent *Plasmodium falciparum* was found, and drug-resistant strains were circulating. Some of the refugees who returned home in the late 1990s were infected with drug-resistant *P. falciparum* and since there was a suitable mosquito vector, this form of malaria was subsequently transmitted among people who had never left Tajikistan (Pitt et al. 1998). Similarly, at the time of writing, the wars in Syria and Yemen had resulted in an almost complete collapse of their health infrastructure. In both Syria and Yemen, leishmaniasis was becoming a serious problem, and the disease was being transmitted to refugee camps in surrounding countries (Al-Salem et al. 2016; Du et al. 2016). Syria also saw a rise of almost 100,000 cases of malaria between 2015 and 2016 (https://www.globalcitizen.org/en/content/malaria-yemen-crisis-increasing-cases/) whilst in the Yemen, control programmes that aimed to eliminate onchocerciasis and lymphatic filariasis by 2015 foundered with no prospect of them resuming (Abdul-Ghani 2016).

Natural disasters, such as cyclones and earthquakes, can lead to similar destruction of infrastructure and refugee problems to those of war. Widespread flooding also provides extensive breeding conditions for mosquitoes and thereby increases the spread of mosquito-borne diseases such as malaria. The destruction of sewage systems and facilities for waste disposal, in conjunction with a warm wet environment, also facilitates the spread of faecal-oral transmitted protozoa and helminths. It is therefore not surprising that widespread flooding in tropical countries usually results in an increase in malaria and water-borne diseases (Boyce et al. 2016; Okaka and Odhiambo 2018).

The damage we cause to the environment can encourage the spread of disease by making conditions more suitable for vectors and intermediate hosts and/or the survival of parasite eggs and cysts. For example, clearance of the rainforests in the Amazon produces open sunlit pools that are ideal breeding grounds for the mosquito vector of malaria *Anopheles darlingi* (Harris et al. 2006). Also, as people move into these clearings to live or work, they come into contact with zoonotic infectious agents that may not be perfectly adapted to living in us but can still cause disease.

The way we live and organise our societies is a major contributor to the spread of parasitic diseases. Throughout the world, there is an increase in urbanization. This means that more people are living close together and the potential for disease transmission between them is therefore high (McMichael 2000). Vector species that can live in an urban environment, such as *Anopheles stephensi* and certain other mosquitoes, therefore pose a particular risk (Takken and Lindsay 2019).

If a high population density combines with inadequate sanitation, then widespread transmission of contaminative diseases is inevitable. In some slums, over 50 households may share a single toilet. Furthermore, this toilet may be 50 m or more from the dwellings. Consequently, urinating and defecating on the bare ground by both children and adults are common in some of these communities. In a study of slum dwellers in Gujarat (western India), 71% of the participants were infected with parasitic protozoa and 26% with helminth infections (Shobha et al. 2013). Not surprisingly, many

claimed to suffer from diarrhoea. Similarly, a study of slum children (1–5 years old) in Karachi (Pakistan) found that the prevalence rate of intestinal parasites was 53 and 10% of the children harboured two or more parasite species (Mehraj et al. 2008). Many of these children suffered from stunted growth.

Sometimes, parasites and their vectors spread by less obvious means. For example, the increased use of cars and motorised transport has resulted in large numbers of used tyres entering the ecosystem. Used tyres retain water after it has rained, and they make excellent breeding grounds for some mosquito species. There is a huge international market in used tyres that are loaded onto lorries and ships and moved within and between countries. In the process, mosquitoes are also moved around the world and notorious vectors of disease such as the Asian tiger mosquito *Aedes albopictus* are now established in countries such as Spain where they were formerly absent. *Aedes albopictus* does not transmit parasitic diseases but is an important vector of viruses such as Dengue virus, yellow fever virus, and Zika virus. The adults are not capable of dispersing far by flight, but it has colonized many countries through the transport of its larvae in used tyres. The adult mosquitoes also disperse by unintentionally hitching a ride inside a car or other vehicle (Eritja et al. 2017). It is likely that many other mosquitoes and other vectors disperse in similar fashions. For example, there are several reports of 'airport malaria' in which a person contracts the disease from a mosquito that has been carried from one country to another within a plane (Isaäcson and Frean 2001).

Before the COVID-19 pandemic that began in 2019, people were increasingly mobile and cheap air travel meant that millions of people rapidly moved between countries for leisure and business. In addition, large numbers of people moved long distances as economic migrants and political refugees. The COVID-19 pandemic brought much of this movement to a sudden halt, and at the time of writing, it was uncertain when and to what extent mass movements will return. Anyone who moves to a new environment becomes exposed to diseases to which they have no previous experience, and hence immunity. They are therefore vulnerable to infection. Similarly, those who are already infected (but may not be aware of the fact) carry their diseases with them and could potentially transmit their infections to a non-immune population on arrival. Obviously, when many people are moving there are many opportunities for disease transmission. For domestic animals, it is possible to instigate legislation that governs their movement. For example, a passport scheme can ensure that they have received appropriate vaccinations and/or drugs to remove infections. Similarly, a period of quarantine upon arrival at their destination can be imposed. Except in very authoritarian regimes, this is seldom feasible as a long-term solution for human populations. Although some countries closed their borders and/or imposed strict quarantines on people during the COVID-19 pandemic, this approach cannot be sustained for any length of time because of the economic consequences. Some countries insist that all persons entering their borders have documentation proving they have received certain vaccinations, such as for yellow fever. However, there are few anti-parasite vaccines and even where effective prophylactic medicines are available to treat parasites, such as anti-malarial drugs, it is notoriously difficult to persuade people to take them as prescribed.

Another of the major reasons why parasites remain a problem is the lack of suitable drugs and vaccines to treat them. The development of drugs for use in human medicine takes many years and is extremely expensive. Consequently, the drug companies need to be sure that they will obtain a good rate of return for their investments. See Chapter 14 for more information on the treatment of parasitic diseases. Unfortunately, those who suffer most severely from parasitic diseases are usually poor and cannot afford expensive drugs. Similarly, the development of anti-parasite vaccines is hampered by a combination of cost and the difficulty of generating protective immunity against parasitic infections. These issues are dealt with in detail in Chapter 15.

The control of parasites by targeting their vectors/intermediate hosts is also becoming more problematic. For many years, this approach proved highly effective, and in the 1950s, it was even believed possible that malaria might be eradicated by killing the anopheline mosquito vectors. However, some vectors are exhibiting increasing resistance against a wide range of insecticides and new chemicals are not being developed to replace those in current use. Furthermore, there are mounting concerns for the environmental damage that can result from inappropriate use of insecticides and fears over risks they pose to our health.