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Evolutionary parasitology: the development of invasion, evasion, and survival mechanisms used by bacterial, viral, protozoan, and metazoan parasites

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11.1 Introduction

Evolutionary parasitology studies evolutionary processes at intraspecific and interspecific levels in both parasite and host species. At the intraspecific level, it focuses in particular on changes in virulence, resistance against the host's defense mechanisms and against human therapeutic interventions, changes in life-history parameters arising from coevolutionary struggle with the host species, development of host specificity and development of resistance, tolerance and life-history parameters in host species. At the interspecific level, it focuses on the origins of parasitism, cladogenesis of parasitic taxons and co-speciation of parasite and host species. The main practical objectives of evolutionary parasitology include the development of therapeutic and preventive measures to prevent increase in virulence and resistance in parasites or even help reduce them.

Parasitism is a form of symbiosis, i.e. a form of long-term coexistence of two organisms. A parasite is an organism that lives in a long-term close contact with another organism (the host), benefiting from this contact to the detriment of the other organism. If one organism benefits from the coexistence while the other organism suffers no harm, the relationship involved is not parasitism but commensalism. If coexistence is beneficial for both symbionts, it is mutualism. If the host suffers from the coexistence but the other organism neither benefits nor suffers from it, we speak of ammensalism. Both parasites and ammensals,

which have a negative effect on the viability and thus also the biological fitness of their hosts, are considered pathogens. The rate at which the parasite or ammensal (hereinafter referred to as the parasite) reduces the biological fitness of its host is called virulence (Combes, 2001). In medical terms, a parasite's degree of virulence largely coincides with the usual extent of pathogenic manifestations of the relevant infection. In epidemiological and evolutionary terms, however, a parasite that, for example, redirects all or part of the host's energy allocated for reproduction to the host's growth and protection against external influences (so-called castrator), basically enhances the host's viability, but shows higher evolutionary virulence than a parasite that causes infections associated with severe pathogenic symptoms, but does not limit its host's fertility in any major way.

The host's ability to resist the negative impact of a parasite and prevent it from entering the organism or multiplying afterwards is called resistance. Tolerance, on the other hand, means the ability of the host to resist a parasite's negative (pathogenic) activity without being able to prevent the infection or multiplication. Higher resistance or tolerance usually requires partial reallocation of resources from growth or reproduction to protection against the particular type of parasite. Therefore, if the given parasite disappears from the environment or if its abundance drops significantly, less resistant and less tolerant host lines will gradually prevail in the host's population. This creates favourable conditions for the parasite's return into the population and subsequently for a new rise in the frequency of genes for resistance or tolerance. As a result, resistance and tolerance of the members of a population may change in cycles. Genes for tolerance have more chance of becoming fixed in a population than genes for resistance (Roy and Kirchner, 2000). If the genes for resistance start spreading in the population, the size of the parasite population begins to diminish. As the size of the population diminishes, selection pressure of the parasite on the host population decreases proportionally, slowing in turn the spread of resistance genes in the genetic pool of the host population. A spread of the genes for tolerance, though, is not accompanied by a decline in parasite population. Thus, in this case, the intensity of the relevant selection pressure does not decrease and tolerance genes can become fixed in the population.

11.2 Microevolution in population of parasitic species

Microevolution is a set of evolutionary processes unfolding inside the populations of a particular species. Macroevolutionary novelties arise from mutations. At the level of the population, however, recombinants created in sexual reproduction as a consequence of genetic recombination and migrants introducing new alleles into the population from other populations represent a much more significant source of evolutionary novelties. While new mutations are mostly harmful, or neutral, for their bearer in terms of impact on biological fitness, migrants are much more likely to introduce potentially beneficial variants of

genes into the population. That is, only alleles that are useful to their bearers at least under certain conditions can be present in the population with a frequency so high that a randomly selected migrant is likely to carry their copies in its genome.

Most parasite species build highly structured populations (Poulin, 1998). In this respect, parasite species do not in fact differ too much from the host species. The sum of all continually appearing and disappearing populations created by the members of a particular species is called the metapopulation. In addition, and in contrast to host species populations, the individual populations show distinct internal structure. This is because they consist of separate infra-populations, i.e. groups of individuals parasitizing one member of the host species. While populations often persist at one place for a very long time, infrapopulations are by definition ephemeral and disappear with the death of the host organism. In a non-structured population, individual selection is the main driver of adaptive evolution. Such selection favours the fixation of 'selfish genes', i.e. alleles enhancing the biological fitness of their bearer, often to the detriment of the biological fitness of other members of the population. If members of a species can, within the population, distinguish individuals genealogically related and unrelated to them, kin selection can naturally also play a role (Hamilton, 1964). Kin selection produces the fixation of alleles whose manifestations enhance biological fitness of either their bearer or his or her relatives (who are highly likely to carry copies of the same alleles). In a structured population, moreover, group selection can also be at play (Alexander and Borgia, 1978). Group selection can, under certain circumstances, produce the fixation of 'altruistic genes', i.e. alleles whose manifestations enhance average fitness of the members of a population, often even to the detriment of biological fitness of the allele bearer.

Group selection and kin selection are often at work in parasitic organisms in particular. As we shall illustrate later, the basic growth constant R_0, or the average number of new hosts infected by each previously infected host in a naïve host population, is the fundamental parameter as regards biological fitness of members of a certain line of parasite species organisms. Consequently, alleles whose manifestations enhance biological fitness of all members of an infrapopulation have a high chance of becoming fixed, even if they essentially harm their bearer. While in a nonstructured population the chances of fixing an allele that reduces the speed of its bearer's multiplication are low, in the infrapopulation of a parasite species an allele that limits the pathogenic manifestations of parasitosis can significantly increase the number of the parasite's invasive stages that the whole infrapopulation will release into the environment during the host's lifetime. This means that in a parasite species kin selection can fix alleles that are detrimental to their bearer but enhance biological fitness of genetically related members of the infrapopulation. Group selection between infrapopulations can also fix alleles that are detrimental to their bearer but enhance biological fitness of genetically unrelated members of the infrapopulation.

11.2.1 Host–parasite coevolution: an evolutionary arms race

There is a constant coevolutionary struggle between the parasite and the host. The parasite develops evolutionary adaptations that help it overcome its host's defense mechanisms, infect the host successfully and produce new invasive stages. The host species, on the other hand, develops evolutionary adaptations that increase the organism's resistance to the attacks of the parasite. The parasite is usually a step ahead of the host in this never-ending struggle. This is because its evolutionary strategy gives it a number of advantages. During its lifetime, a parasite typically produces more offspring than a free-living species. For example, a tapeworm *Taenia saginata* can produce about 720 000 eggs per day. Only a fraction of the offspring survives until reproductive age. As a result, the processes of selection in a parasite species are much more effective than in a free-living species. Another factor facilitating a parasite's lead in the coevolutionary struggle with its host is aptly described by the so-called life–dinner principle (Dawkins and Krebs, 1979; Dawkins, 1982). A rabbit runs faster than the fox because in the race the rabbit is fighting for its life while the fox is only fighting for dinner. Similarly, a parasite defeated in the competition with its host loses the possibility to reproduce, while for the host the defeat usually means just a certain decrease in biological fitness. The last and probably the most important factor facilitating the parasite's lead in the coevolutionary struggle with its host lies in greater consistency of the relevant selection pressures. While all ancestors of any parasite have in the past met with the host, the same is not true for the host species, since in each generation only some individuals in a population are exposed to attacks by the parasite (Dawkins, 1982).

11.2.2 Maximization of basic reproduction rate (R_0) by optimization of virulence

The basic growth constant R_0, or the average number of hosts infected by one infected host in a naïve host population, is a critical parameter that determines biological fitness of members of a parasite species. This also largely determines the direction in which the microevolution of a parasite species will progress. In the course of microevolutionary processes, phenotypic properties increasing the R_0 under given circumstances become fixed, while properties decreasing the R_0 disappear. The idea that a parasite's virulence gradually decreases during the evolution of the parasite species has become an integral part of the scientific folklore. The parasite, which at the beginning caused severe harm to its host or even killed it, gradually adapts to the host, so that in the end it not only does not kill it but even minimizes the negative impact of its activities on the host's biological fitness. This notion is largely incorrect (Ewald, 1994). If it is useful for the parasite to reduce its virulence in order to increase the R_0, then it will indeed reduce it over time. However, if in a different situation it proves useful to increase the virulence in order to maximize the R_0, then an originally harmless commensal can gradually develop into a dangerous pathogen.

Observation of the natural environment and experience from the preparation

of attenuated vaccines by passaging human parasites in an animal host show that after so-called parasite capture (the transmission of a parasite to a new host species) the parasite is usually not able to multiply in the new host quite as efficiently, as a result of which it tends to show lower virulence. The parasite's virulence in the new host grows as it gradually adapts to it, until the pathological manifestations of parasitosis become so severe that they considerably shorten the life of the infected host and thus also the average duration of an infrapopulation. At that point the force of individual selection for the parasite's faster reproduction and hence for increased virulence becomes balanced by the force of kin and group selection operating in the opposite direction. A parasite's virulence is of course determined first and foremost by evolutionary constraints, for example, by which of the host's organs it parasitizes and which resources it takes from the host. Yet the resulting virulence of a parasite species or even a local parasitic population is determined by a whole range of external factors, some of which we are even able to affect by targeted (and naturally also non-targeted) interventions.

One important factor capable of affecting a parasite's virulence involves the genetic heterogeneity of the infrapopulation. An increase in the infrapopulation's genetic heterogeneity usually leads to an increase in virulence. It is known that parasites with a high mutation rate (e.g. the RNA viruses) or parasites with high-intensity recombination tend to be more virulent than parasites with lower mutation rate (DNA viruses) and with a low or zero recombination rate (e.g. clonal organisms) (Bonhoeffer and Nowak, 1994; Ewald, 1997). Superinfections, i.e. infections of an already infected host by a genetically unrelated line of the parasite, represent an extremely significant source of genetic heterogeneity in a population. If superinfections are very frequent, or even regular, it is not worthwhile for the parasite to make its host last, but it is much more useful to multiply as fast as possible and thus produce the highest number of invasive stages before the host is killed by another strain of the parasite, faster in multiplying and hence also more virulent. A high likelihood of superinfection is one of the main causes of increased virulence of many different parasitoses during wartime, and it also seems to be the cause of the unusually high virulence of parasites causing nosocomial infections (infections in hospitals) (Bonhoeffer and Nowak, 1994; Ewald, 1994).

The way in which a parasite is transmitted from host to host represents another factor significantly affecting its virulence. Parasites borne by a vector (be it insects or running water) tend to be more virulent than parasites transmitted by direct contact of the infected hosts; (Ewald, 1983, 1991). This is because it is in the interest of a parasite transferred in direct contact (e.g. the influenza virus) not to harm its host too much, allowing the host to contact and thus also infect as many members of the host species as possible. High virulence is also typical for so-called sit-and-wait parasites, i.e. parasites producing persistent spores which remain in infectious stage on the site of the host's death for a long time and wait for the arrival of a new uninfected host (e.g. anthrax) (Ewald, 1995). Foodborne parasitoses tend to show high virulence. Parasites

whose life cycle involves transmission from prey to predator, in particular, often cause significant harm to their host, thus increasing the chances of the infected host becoming prey of the predator (e.g. tapeworm echinococcus) (Ewald, 1995). The lowest virulence is shown in parasitoses of mostly vertical transmission within the population from parents to offspring, since in this case it is in the interest of the parasite that the host should have as many offspring as possible (Bouma and Lenski, 1988; Bull *et al*., 1991; Clayton and Tompkins, 1994). If the parasite's transmission is exclusively vertical through the host's gametes, biological interests of the parasite and the host become so closely interlinked that the parasite apparently dissolves in its host (Law and Dieckmann, 1998). This, for example, has been the fate of the predecessors of today's mitochondria and plastids. Low virulence also tends to be typical of sexually transmitted parasitoses, where the parasite benefits from the host having as many sexual partners as possible.

Host population characteristics also have a big impact on the virulence of parasites. Short-lived hosts (e.g. rodents) tend to have more virulent parasites, which have to use their host's resources before he dies a natural death (Ebert and Herre, 1996; Restif *et al*., 2002). Similarly, if mortality in the population of any species increases for any reason (for example, because of the appearance of a new parasite or in a human population during war), this mostly benefits the fast-reproducing lines of parasites whose infrapopulations can produce a maximum number of infectious stages before their host dies for other reasons. Parasites in a growing host population show higher virulence than parasites in a population stagnating in numbers, since in a growing population the number of immunologically naïve hosts increases, offering the parasites a big chance to establish new infrapopulations (Knolle, 1989; Ebert, 2000). For similar reasons, higher virulence is also characteristic of parasites in dense populations, populations with frequent contacts of a high number of individuals, and populations with individuals migrating over long distances (Haraguchi and Sasaki, 2000).

11.2.3 Evolution of host specificity

Evolution of a parasite species often leads to the narrowing of the host spectrum, i.e. to specialization in one or a few, mostly phylogenetically related, host species. A considerable similarity between the phylogenetic trees of the parasite and the host taxon suggests that parasites remain fairly loyal to their hosts even on large time scales and that parasite capture by an unrelated host remains more of an exception (Brooks, 1993). Similarity between the trees also suggests that cospeciation, i.e. speciation of the host species (split into two daughter species) accompanied by speciation of its parasites, is a very frequent event in the course of evolution.

Specialization in a particular host species or a particular small circle of host species develops with different intensity in different groups of parasites, depending on the form of the parasite's coexistence with the host (endoparasite, ectoparasite, social parasite), as well as on other ecological and physiological

characteristics of the parasite and host species. Generally speaking, the parasite's host-specificity increases over time as the consequence of evolutionary trade-offs, evolutionary fixation of a mutation enhancing the parasite's ability to infect members of one host species, which at the same time reduces its ability to infect (survive, reproduce in) members of another species (Poulin, 1998). The constraints of successful infection of other species can be divided into two groups. On the one hand, there are ecological constraints, consisting in the parasite's inability to meet representatives of the relevant species with sufficient frequency. On the other hand, there are physiological constraints, consisting in the parasite's inability to multiply in the members of the new species quite as efficiently (Combes, 2001). Experimental studies suggest that ecological constraints seem to be more important and that if, in particular, there is repeated contact between the parasite and a new, initially unsuitable species, the parasite will mostly manage to adapt to the new species successfully. Characteristically, humans acquired a large part of their parasites, around 260 species are usually mentioned, not from their phylogenetically related ancestors but from the phylogenetically unrelated farm animals with which they have lived in a long-term close physical contact for centuries (Ashford, 2000). In some cases, parasite capture simply broadens the parasite's host spectrum, while in other cases the subpopulation of parasites that adapts to the new species loses ability to parasitize the original species efficiently, thus giving rise to a new species of parasite.

11.3 Mechanisms of invasion, evasion, and survival

Biological interests of the parasite and its host are in many respects antagonistic. Anything that enhances the biological fitness of the parasite usually reduces the biological fitness of its host. Most parasite adaptations take the form of arms that allow the parasite to overcome its host's defense mechanisms, while many adaptations of the host take the form of counter-arms designed to defend against specific and non-specific parasites. A parasite's most important defenses include various mechanisms allowing the propagules to seek members of suitable host species and penetrate their bodies (on their bodies in the case of ectoparasites), to remain, mechanically, inside or on their bodies, to draw the necessary amount of suitable resources from their bodies in an efficient way, to resist the host's defense (e.g. immune) systems, put them out of operation or re-direct their activity in a way that renders them harmless to the parasite. The most important defenses of the host include the individual components of the immune system, designed to kill parasitic organisms or reduce their vitality and fertility, together with various patterns of behaviour that reduce the risk of contact with the parasite's infectious stages (Moore, 2002). These include, for example, avoiding places contaminated with feces or avoiding cannibalism. Some defense mechanisms operate at the population level and have probably developed in the course of evolution through some form of group selection. These are, for

example, the removal of feces (many species of birds), avoiding contact with other members of the population that are in bad health, and migration of sick individuals (birds, rodents, and possibly even humans) over larger distances (thus protecting the related individuals from infection) (Poulin, 1994; Rozsa, 2000). In some cases infected individuals even seem to commit active or passive suicide. The parasitized individuals are in such cases sometimes killed by an apparently non-adaptive overreaction of their own immune system, at other times, in the case of butterfly caterpillars for example, they move to places where they are easily spotted by insectivorous birds (Trail, 1980).

Characteristics preserved within a population by group selection from the part of parasites are often considered to include sexuality. Many believe that the reason why asexual individuals (who can reproduce twice as fast because they do not have to produce males) do not prevail in the population of a sexually reproducing species is that sexual reproduction offers a more effective defense against parasites (Bell, 1982). The Red Queen model assumes that the disadvantage of asexual reproduction lies in the fact that biological fitness often shows negative heritability owing to the existence of parasites. Parasites are indeed fast in adapting to individuals with the most abundant genotype, that is, individuals that are currently most biologically fit. In the next stage, their offspring are exposed to the hardest attack by the parasites and thus, in turn, become the least biologically fit. In sexually reproducing organisms, the genotype is not inherited from generation to generation but is created *de novo* every time by a random mixing of genes coming from two parent individuals. The parasites therefore cannot adapt to the most successful individuals and thanks to that the sexual line of the host will in the medium-term defeat the asexual lines.

Obviously, group selection is also at play in the evolution of parasites. As has been mentioned earlier, competition among infrapopulations leads to optimization of the growth rate and thus also to optimization of the parasite's virulence. However, group selection or species selection can also be responsible for investment of a large part of the reproductive potential in the production of long-distance migrants (who will not compete with their relatives in the local host population) and possibly also for introducing vectors in the life cycle of the given parasite species.

11.3.1 Parasite invasion strategies

In the course of their evolution, parasite species have developed a whole series of extremely varied invasion mechanisms that allow them to invade host organisms successfully and overcome their defense systems. The best-known invasion mechanisms include the development of indirect life cycles, avoidance of immune system surveillance, molecular mimicry, immunosuppression, immunomodulation, and manipulation with the host's endocrine and neural systems.

One of the most successful and widespread ways of invading host organisms consists of the introduction of intermediary hosts into the parasite's life cycle (Poulin, 1998; Combes, 2001). Life cycles of parasites are divided into direct

and indirect. Parasites with direct life cycle will make do with one host species and can only switch between two stages during their life cycle the parasite stage and the free-living stage, designed solely to facilitate transfer from one individual of the host species to another by getting across open environment. Depending on parasite species, the two stages can, but do not have to, differ morphologically and physiologically. It may not be easy for the free-living parasite stages to find a new host and a large part of them may die in the open environment. That is why in the course of their evolution a considerable number of parasite species developed indirect life cycles of varying complexity, involving a higher number of successive host species in different roles. The parasites often use an ecological, mostly trophic, relationship between different species for effective transfer from host to host. The intermediary host would in this case be a species eaten by the final host species. The final host becomes infected by hunting down and eating an infected intermediary host. Or, the intermediary host can be a micropredator, such as a mosquito or flea, which repeatedly suck on a large number of members of the host population and can thus transfer parasites from host to host.

Very often the parasite does not just passively wait in its host for the trophic event to occur but actively promotes it, often in a very sophisticated way (Fig. 11.1). A number of trophically transmitted parasites can influence the behaviour of their host in ways that increase the likelihood of the host being hunted down by the corresponding predator. For example, the *Toxoplasma gondii* protozoan, whose final hosts are felines, reduces the fear of cats in parasitized rats (Berdoy *et al*., 2000), while in parasitized mice and humans (the incidence of *Toxoplasma* in humans reaches a global average of around 30%) it decreases psychomotor performance of hosts and lengthens the reaction time of infected mice and human (Webster, 2001; Havlicek *et al*., 2001). In humans (as opposed to other primates or mice), a longer reaction time (observed in computerized simple reaction time tests) does not increase the chances of *Toxoplasma's* transfer into the intestine of a feline (i.e. infection does not increase the likelihood that people with toxoplasmosis will be eaten by cats) but it can, for example, increase the risk of car accidents, and the higher prevalence of toxoplasmosis in victims of car accidents suggests that it could be increasing that risk up to 2.6-fold (Box 11.1). The *Leishmania* protozoan, for its part, can damage the suction system of its vector (the sandfly) so the micropredator cannot suck enough blood, is always hungry, and moves from member to member of the host population in attempts to satisfy its appetite (Schlein, 1993).

Another strategy that helps the parasites to colonize host organisms successfully consists of avoiding the immune system surveillance. Bodies of organisms contain certain so-called immunoprivileged organs and tissues in which the common immune mechanisms do not operate or operate to only a limited degree. These organs include, for example, the nervous system, in which a strong immune reaction would result in death or cause severe damage to the individual, and the eye lens, in which a similar reaction could easily lead to blindness. To a certain degree, it also is true in mammalian red blood cells

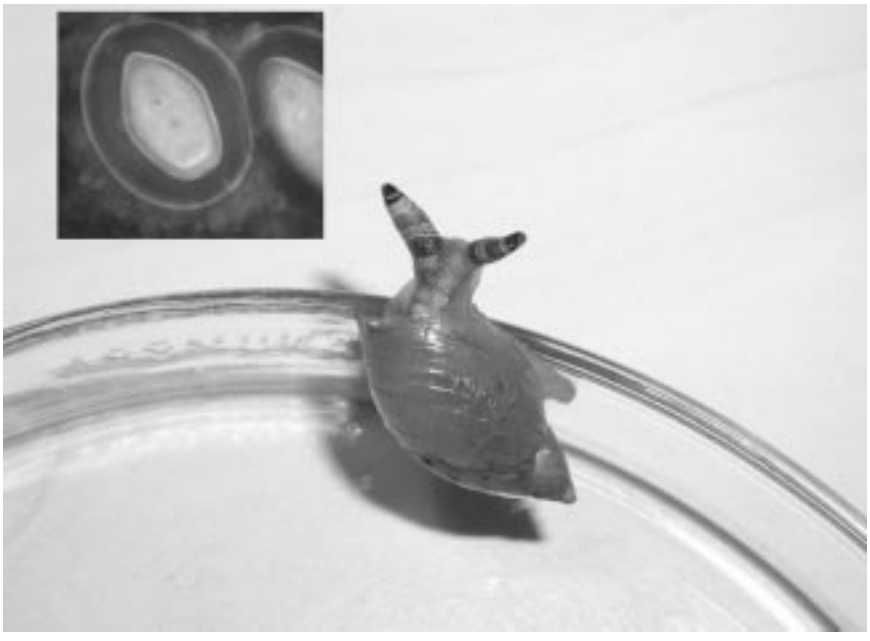

Fig. 11.1 Increased probability of the parasite's transmission by manipulation of the intermediate host morphology and behavior. Trematodes of the genus *Leucochloridium* must get from their intermediate host (land snail, here the amber snail *Succinea putris*) to the definitive host, an insectivorous bird. Their large elongated sporocysts with brightly pigmented brown, green, and white bands move into the snails's tentacles and transform the tentacles into large pulsating caterpillar-like organs. Inside the sporocysts, hundreds of infective metacercariae (inset) wait for their opportunity to infect the bird definitive host. (Photo author).

which, owing to the absence of nucleus and proteosynthesis, do not express class I MHC antigens on their surface so they cannot signal the presence of intracellular parasites to T lymphocytes. Many parasite species, including viruses (human cytomegalovirus – brain), bacteria (meningococcus – brain), protozoa (*Toxoplasma* and *Frenkelia* – brain, *Thaileria* and plasmodium – erythrocytes), and helminthes (schistosomes, cysticerci of some tapeworms – brain), specialize in the use of these immunoprivileged tissues and organs.

Another strategy used by a whole range of parasite species involves molecular mimicry (Damian, 1964; Moloo *et al*., 1980). The parasite tries to mimic the molecular set up of the host species with its own molecular set-up as much as possible. In some cases it achieves this by synthesizing the relevant proteins directly from its own genes, which it had either directly stolen from its host in the past, e.g. the tapeworm *Spirometra mansonoides* (Phares and Cox, 1987), or created from its own genes through a series of mutations, e.g. schistosomes (Dissous and Capron, 1995). In other cases it simply steals molecules from the cells of the host organism and attaches them to its own surface.

Box 11.1

About 30–60% of the population in both developed and developing countries is infected with the parasitic protozoon *Toxoplasma gondii*. Definitive hosts of *Toxoplasma* are various species of felids and the intermediate host can be virtually any mammal or bird species, including humans. The human hosts usually acquire infection by consumption of raw or undercooked meat containing tissue cysts of *Toxoplasma* or by ingestion of food contaminated by cat feces containing *Toxoplasma* oocysts. In an immunocompetent human the acquired toxoplasmosis, characterized by rapid reproduction of tachyzoites in cells of different tissues, is a relatively mild disease. Usually, it is unrecorded or is misdiagnosed as a common viral or bacterial disease. Within weeks or months the tachyzoites disappear and tissue cysts form in various tissues, mainly in the brain and muscles. The latent toxoplasmosis, i.e. life-long presence of these cysts and presence of anamnestic concentrations of anti-*Toxoplasma* antibodies in immunocompetent subjects, is considered asymptomatic and harmless. However, a recent study of blood donors showed that subjects with latent toxoplasmosis have significantly impaired psychomotor performance (prolonged simple reaction times) in comparison with *Toxoplasma*-negative subjects (Havliček *et al*., 2001). It is also known that subjects with latent toxoplasmosis express specific changes in some personality factors measured with 16PF questionnaire (Flegr and Hrdý, 1994; Flegr *et al*., 1996, 2000). The differences in psychomotor performance and personality factors increase with duration of infection (Havlíček *et al*., 2001; Flegr *et al*., 2002). A retrospective case-control study showed that people infected with parasitic protozoon *Toxoplasma gondii* have about 2.6 higher risk of traffic accidents than uninfected subjects. The underlying basis of the increased risk cannot be determined on the basis of these results; however, both the decrease in psychomotor performance and the personality changes observed in the infected persons could play an important role. Infected men have decreased superego strength, i.e. they have tendency to disregard rules, and infected women have higher affectothymia, i.e. they are more outgoing and easygoing. Because of extremely high prevalence of life-long latent toxoplasmosis (about 30% of people worldwide are probably infected with the *Toxoplasma*) and high incidence of traffic accidents (according to WHO data about 3.5 million people are killed in traffic accidents/year), latent toxoplasmosis, which is mostly considered to be more or less harmless, could be indirectly responsible for more then 150 000 fatalities/year. If this is correct, then latent toxoplasmosis, a common foodborne disease, could be the second most important protozoan killer (after malaria).

Probably the most common strategies of parasite's protection against the host's immune system consist in immunosuppression and immunomodulation (Chandra, 1982; Binaghi, 1993). In the former the parasite directly switches off immune mechanisms of the host's immune system, for example by killing a specific subpopulation of immunocytes (e.g. HIV and CD4 T lymphocytes) or by damaging an immune organ. Given that an immunosuppressed host can easily die of infection by another parasite species, this parasitic strategy is not particularly convenient for the infrapopulation. That is why many parasite species have developed much more sophisticated mechanisms that allow the parasite to re-direct the activity of the immune system to areas where it does not pose any danger to the particular parasite, without limiting the host's overall capacity of defense in any major way.

Adaptive immunity consists of two basic defense components – humoral immunity and cellular immunity. Humoral immunity provides defense mainly against parasites that live freely in the host's tissues and against their toxins, using antibodies as its principal effector. Cellular immunity, on the other hand, is mainly aimed against intracellular parasites and also against multicellular parasites. In some situations, both components of the immune system cooperate closely. It is also true, however, that activation of the humoral component usually leads to a suppression in the cellular component activity and vice versa. A number of parasites, including an intestinal nematode *Trichuris* (Grencis and Entwistle, 1997) can produce molecules of specific immunomodulators to switch the functions of the immune system in a way that suits them suppressing the component that is dangerous for them and enhancing the component that does them no harm (Wilson, 1993). Until historically recent times, people lived in a certain form of permanent symbiosis with intestinal helminths. Only since around the middle of the last century have people living in developed countries become free of these parasites as a result of better hygiene and public health infrastructure. It has been postulated that the absence of helminth intervention in the operation of our immune system has produced shifts in the activity of the immune system components and that this shift is responsible for the surge in the incidence of allergies seen in the developed countries in recent decades (Bell, 1996).

Another weapon used by parasites in the fight with their host consists of purposeful interventions in their endocrine system. A number of parasites can produce substances with hormonal activity through which they are able to alter the physiology, immunity, and behaviour of the host organism for their own benefit. A partial or complete parasitic castration represents a frequent type of parasite's hormonal intervention into its host's physiological condition. By hormonally castrating the host organism the parasite achieves a reallocation of resources from reproduction to growth and maintenance, which are, from the point of view of horizontally transmitted parasites, functions substantially more usefully than the host's reproduction (Wilson and Denison, 1980). Through these interventions, the parasite (for example, larvae of some species of flukes) significantly enhances its host's vitality to the detriment of its fertility (hence to the detriment of its biological fitness) (Box 11.2). A parasite's hormonal interventions in the

Box 11.2

The phenomenon of parasitic castration was studied on various parasite–host systems. For example, the ant *Allomerus demerarae* living in symbiosis with the tree *Cordia nodosa* castrates its host plant by bittion of all flowers. *Allomerus* workers protect new leaves and their associated domatia (specialized plant organs inhabited by an ant colony) from herbivory, but destroy flowers, reducing fruit production to zero in most host plants. Castrated plants occupied by *Allomerus* provide more domatia for their associated ants than plants occupied by three species of Azteca ants that do not castrate their hosts. *Allomerus* colonies in larger plants have higher fecundity. As a consequence, *Allomerus* appears to benefit from its castration behavior, to the detriment of *C. nodosa* (Yu and Pierce, 1998). Parasitic castration and gigantism is extensively studied on trematode parasites of snails. It was observed in *Schistosoma–Biomphilaria*, *Trichobilharzia–Lymnea* and *Diplostomum–Lymnea* systems. It is widely believed that the host-derived factor called schistosomin, which appears in the snail hemolymph at the time trematode cercaria develop, influences the parts of the neuroendocrine system that regulate reproduction and growth (de Jong-Bring, 1999). However, it must be admitted that some parasitologists consider the gigantism to be a host strategy that was more consistent with the snail making the best of a bad situation, and some suggest that certain cases of gigantism were artifacts of abundant nutrients provided during the laboratory studies.

physiology of its host can also aim to change the function of the immune system indirectly through sex change. It is, for example, known that female mice are much more susceptible to infection by *Taenia crassiceps* tapeworm than males. However, when a male becomes infected, he experiences a 200-fold increase in estrogens and a 10-fold decrease in testosterone, which brings the defense capacity of this feminized male close to the defense capacity of a female (Larralde *et al.,* 1995). Bacteria of the genus *Wolbachia*, which can only be transmitted to the next generation in eggs, not sperm, can even change the sex of their host, a land crustacean for example, from male to female. The crustacean's population then consists almost exclusively of females, but a more detailed analysis will show that a large part of the females are, in fact, genetic males (Knight, 2001).

11.3.2 Parasite evasion strategies

Several basic evasion strategies can in general be distinguished, used by different parasite groups to a varying extent and in different specific forms.

Hit and run strategy

The principle of this strategy consists of the parasite's multiplying as fast as possible after having penetrated the host organism, to produce the maximum

number of propagules and infect the maximum number of other host population members before the host builds a sufficiently effective immune response to eliminate the parasite. If the immunity against a particular parasite species lasts for a longer time or even for the lifetime of a previously infected individual, the disease tends to behave in an epidemic fashion, returning to the population in waves at regular or irregular intervals. This strategy (rare in macroparasites) is used by a large group of viruses and bacteria.

Good guy strategy

Parasites using this strategy try to behave as inconspicuously as possible in the host organism. The host's immune system detects the presence of a dangerous foreign agent through, among other, the presence of molecules from damaged tissues and also through the dynamics of a growing concentration of foreign molecules in the population. If the parasite does not damage host tissues and cells, and does not multiply within the host but only produces propagules that are released into the outer environment, the host's immune system may not detect the parasite's presence at all. A number of parasites behave in the host organism in such a restrained way that from the ecological point of view they can rather be considered neutralists or even mutualists. This strategy is used by a number of macroparasites and other parasites, causing chronic or latent (more-or-less symptom-free) diseases. However, many of these parasites have a back-up strategy should the condition, and thus also the life expectancy, of their host deteriorate. A good guy can then very often turn into a bad boy and by using the hit and run strategy quickly use up all the host's remaining resources.

Moving target strategy

This is a relatively sophisticated and effective strategy used by a number of bacterial and single-celled eukaryotic microparasites (Seifert and So, 1988; Michael and Turner, 1999). In a more primitive form, though, the strategy is even used by some viruses. It is in principle a variation on the hit and run strategy. The parasite multiplies in the host organism and gradually induces the host's immune response. After some time this response is so strong that the rate at which parasites are killed exceeds the rate of their multiplication, making the numbers in parasite populations drop fast. At that time, however, the parasite population already contains a limited number of immunologically distinct variants that are not affected by the host's immune response. Their populations start to multiply and in time again provoke an immune response against themselves. Thus, waves of different peaking antigenic variants of the parasite replace one another until the parasite uses up its repertory of antigenic variants or until the host succumbs to total exhaustion. In eukaryotic parasites, such as trypanosomes causing sleeping sickness, the parasite's genome contains a ready-made reserve of as many as hundreds of genes for the immunodominant surface coat antigen, while in viruses antigenic variants are usually generated through mutations.

Smokescreen strategy

This strategy is based on the fact that the host's immune system usually cannot chase a large number of 'rabbits' (i.e. antigens) at the same time. If the parasite can induce an immune reaction against other antigens present at that moment in the host's body, it can itself escape the surveillance of the immune system. A number of parasites, including a number of viruses with a relatively small genome, include genes for the so-called superantigens such as, for example, molecules that bind to the constant regions of antigen receptors on T lymphocytes, thus activating the T lymphocytes (Llewelyn and Cohen, 2002). As a result, a high percentage of T lymphocytes are activated simultaneously in the body of the infected organism and the immune system may start to build an immune response against antigens inherent to the body. Such a situation can of course be deadly to the host, but from the parasite's perspective it is beneficial because behind the smokescreen of general activation the parasite can easily escape the surveillance of the immune system. The parasites sometimes bring live helpers to the host to create a smokescreen, such as viruses or bacteria of other species. For example, helminths of the genera Steinernema and *Heterorhabditis* inject the body of the parasitized host with bacteria of the genus Xenorhabdus which quickly multiply and put the defense system of the invertebrate host perfectly out of action (Forst *et al.*, 1997). Given that the life span of activated immunocytes (in both invertebrates and vertebrates) is limited, it is sometimes difficult to decide whether the objective of the strategy is to create a smokescreen or to eventually suppress the activity of the immune system.

Mafia strategy

In most cases this strategy seems to have developed from a strategy of starting as a good guy and switching to hit and run if things go wrong. Under normal circumstances, the parasite tries not to damage the host organism too much and uses the resources in a moderate way. However, as soon as the organism starts attacking it through the immune system or in any other way, its behaviour changes and it starts to harm the host actively (Zahavi, 1979). This strategy was first described in a nest parasite, the great spotted cuckoo. The cuckoo lays an egg in another bird's nest and regularly checks to see how the involuntary foster parents treat it. If the involuntary hosts throw the egg out of the nest, the cuckoo will destroy their whole clutch during the next check.

The same strategy seems to be used by a whole range of microparasites (Soler *et al.*, 1998). For example, the *Corynebacterium diphtheriae* bacterium, which causes diphtheria, behaves in a rather orderly way in the host until the host withholds all reserve iron, which most parasite species need for growth, in response to their multiplication. At that point the bacteria start to produce their diphtheria toxin that kills the surrounding cells, making them release, among other substances, the iron. The original objective of this strategy is, of course, to obtain the otherwise unavailable iron. A long-term use of the strategy produces the side effect of selection for hosts that will not withhold iron if infected by this species of bacteria.

Drug dealer strategy
A whole number of symbionts, formally classified as mutualists, are in fact parasites using the drug dealer strategy. The strategy consists in making the host addicted in some way to the parasite's presence. The addiction sometimes emerges spontaneously when the host starts using a resource produced by the parasite and, as a result of parasite's long-term presence in the host's populations, eventually loses the ability to obtain the resource in any other way. For example, beetles of the genus *Sitobius* lose their ability to fly if purged of their bacterial symbionts with the help of antibiotics. In other cases, however, the parasite actively helps to induce the addiction by putting an organ of the host organism out of operation and then replacing its function. A parasitic crustacean, *Cymothoa exigua*, can be used as an illustrative although not typical example (Brusca and Gilligan, 1983). It bites out the tongue of its fish host and then holds to the stub permanently with its hind claws, using the front claws when the fish 'sticks it out' from the mouth to collect pieces of food for the fish (and for itself).

11.4 Future trends

For the food processors, evolutionary parasitology has two pieces of news. As such things go, one is good and the other is bad. The good news is, without question, that as a result of the rising sanitary and veterinary standards applied to both the agricultural and industrial parts of food production, not only is the risk of foodborne infections becoming lower but, in addition, a gradual microevolutionary decrease in virulence of the parasitic infections is under way. This is due to the fact that if the average success rate of parasite transmission from host to host decreases, the situation by definition favours those parasite lines within the species that are able to treat their host with consideration if possible and make him last longer. The good guy strategy, for example, gains significant competitive edge over the hit and run strategy. Obviously, in developed countries the same phenomenon is also effectively enhanced by the overall increase in life expectancy owing to better nutrition, better health care and a lower risk of war conflicts. Here again, it is convenient for the parasites to make their long-living hosts last and avoid damaging the host organism unnecessarily so as not to shorten the time during which they enjoy the host's resources. It must also be recalled, however, that microevolution of the parasite species populations is not irreversible and that any deterioration in the living conditions of human populations (even if only occurring at a local scale) can turn this trend around.

And this brings us to the bad news. Many processes taking place ever faster in the human population lead, in contrast, to an increase in the virulence of parasitoses and to a general increase in parasitic risks. In the first place I would like to mention the growing connectivity of human populations in general, as well as the increasing mobility of individuals. An outbreak of the most virulent

Ebola-type parasitoses would be practically impossible without modern means of transport. Before the infected individual could reach the next village, he or she most likely succumbed to a disease of such virulence, which prevented the infection from spreading to a larger number of people. Today, however, even a highly virulent infection can quickly reach any international airport and a sufficiently infectious disease can easily persist in the dense populations of the present-day urban agglomerations despite its high virulence. Another risk of emergence of new pathogens and increase in the virulence of known pathogens is linked with the globalization of the world trade. This makes it possible for people in any part of the world to come in contact with parasites and pathogens to which their populations are not adapted at all and which they cannot fight. Globalization comes hand in hand with the trend of decreasing natural global genetic diversity in farm animals and cultural plants. Reduced genetic diversity renders any species much more vulnerable to parasites, which can quickly adapt to the most abundant genotypes thanks to their greater speed of microevolution. Globalization and increased mobility of individuals, in contrast, result in higher local genetic diversity of parasite species. As has been mentioned above, increased genetic diversity in parasitic populations spurs their evolution towards higher virulence. More virulent lines begin to prevail at the population level and more virulent species at the level of community.

Globalization, together with other trends currently under way in our environment, also significantly increases the risk of new parasite capture, i.e. the risk that a parasite until now adapted to another species would jump to humans. This risk is enhanced by the global trade in exotic pets, as well as exotic foods. Last but not least, new parasite capture can be facilitated by the growing proportion of old or immunosuppressed individuals in general population. The latter include both the 'naturally' immunosuppressed persons, such as those with HIV who live ever longer thanks to advances in medicine, and persons whose immune system has been switched off artificially, for the purpose or in consequence of medical interventions (transplants, radio or chemotherapy, treatment of allergies).

The last risk that must not be omitted, especially in connection with food processing, consists of the emergence of parasite lines resistant to chemotherapeutics as a result of the frequent and extremely intensive use of these substances in farming. Resistance to chemotherapeutics develops very easily and very fast in the parasites, often with a cross-over effect, meaning that resistance to antibiotics used to boost meat production in animal farming can also equip the parasites with partial or total resistance to antibiotics used in human medicine. It may be useful to recall that different species of parasites are quick and willing to exchange the genes for resistance, making it possible for resistance developed in one species to spread very easily to many other (even unrelated) parasite species.

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