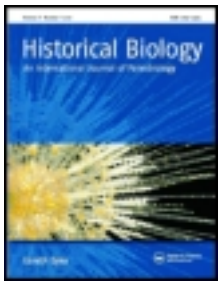

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Parasitism and evolution: opposing versus balancing strategies

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Parasitism and evolution: opposing versus balancing strategies

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Parasitism refers to a particular symbiosis (deBary 1879) of organisms that live at the cost of their hosts. Virulent microbes (*viruses* and *bacteria*) proliferate unlimited causing *toxic* infections that end either by the host's death or its protective immunity. By this *opposing* survival strategy, via the population density, i.e. the contact rate, finally results a sequence of epidemic and endemic periods. The host population is kept at a reasonable level to resources, but host and pathogenic agent are wasted in the evolutionary arms race. Sparing such losses, eukaryotic proto- and metazoan parasites induce in *natural* hosts a *delayed* infection course by self-controlled propagation and avoid *protective* immunity. Hosts are *'immunized but not immune'* and parasites propagate simultaneously with them. Metazoic and some protozoic parasitoses end with the *parasite's natural* death, pathogenic effects remain irrelevant. Nevertheless, the host's fitness becomes reduced by multiple re-infections and/or by increasing parasite loads. This *balancing* survival strategy controls host populations at lower costs. A network of parasitoses offers considerable selection advantages and explains the polyphyletic origin of eukaryotic parasites. Parasitism and other kinds of symbioses contribute to the stability of ecosystems and to stasis in long-term evolution but are invisible in the fossil record.

Keywords: coexistence; co-evolution; parasite immunology; malaria; filariasis

1. Introduction

In a joint paper with late Wolf-Ernst Reif (Seilacher et al. 2007), we have claimed that parasites play an important role in the evolution of their hosts. In the following, we show that this is achieved by, in principle, two different survival strategies. The present paper deals with the interpretation of *Plasmodium* sp. as an eukaryotic (sporozoan) parasite. As such, it differs from microbial pathogenic agents in the nature of its host–parasite interactions. As an example for metazoan parasites, a filarial nematode of small mammals *Litomosoides sigmodontis* is presented. Up to now, the evolution of eukaryotic parasites, such as that of microbial viruses and bacteria, has been characterised in terms of an arms race. However, severe general contradictions demand another hypothesis in proto- and metazoan parasites. For the sake of simplicity, pathogenic microbes are here termed *pathogenic agents* (shortend *'pathogens'*), as distinguished from eukaryotic proto- and metazoan *parasites*.

2. The coexistence of pathogenic agents and parasites with their hosts

2.1. The opposing survival strategy of pathogenic agents

Over generations, pathogenic agents and parasites can only survive within specific hosts, their *natural* hosts. In the case of directly transmitted highly virulent agents, e.g. myxomatosis in rabbits, the reproduction capacity of the agent and the potential of the host's immune defence compete with each other. In the race either the pathogenic agent kills the host or the host survives and becomes immune. Surviving hosts become resistant against re-infection in spite of being continuously exposed to the pathogenic agent. Immunity is memorised but, because it is acquired, it is not inherited and immune hosts can produce new generations of susceptible offspring (Figure 1).

Each host individual serves the pathogenic agent only once and only for a limited time. Hence, the agent must reach a new host before the host dies or becomes immune. In dense host populations with a high contact rate, the competition between individuals for food increases stress, so the lethality of the agent becomes high and the population density decreases. Thereafter, intraspecific competition as well as the contact rate of infected individuals diminish and the population density recovers. Over time, an alternating sequence of epidemic periods and endemic intervals maintains an equilibrium of pathogenic agent and host. Agent and host coexist over generations despite great losses of both partners during epidemic episodes. As a result of adaptations of some pathogenic agents, the amplitudes of both lethality during epidemics and fading away during endemics diminish so

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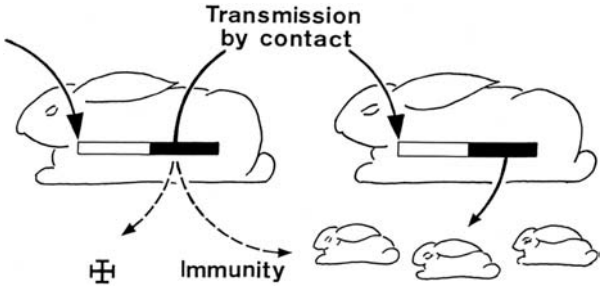

Figure 1. Opposing survival strategy of virulent microbial pathogenic agents. White bar: incubation period; black bar: manifestation period.

far that the infections become delayed (medically 'chronic') and the sequence of epidemic/endemic periods is replaced by a rather constant prevalence of the infection as observed in tuberculosis and leprosy. Nevertheless, pathogenicity and lethality are essential factors for the coexistence of microbial infective agents with their hosts. In other words, the long time survival of the pathogenic agent is based on an *opposing survival strategy* primarily based on death or survival of the host (Wenk and Renz 2003). The hypothesis of the evolutionary arms race is based on this 'opposing' aspect.

However, virulence and transmission rate of pathogenic agents are permanent positively correlated only in host populations that are genetically homogeneous and in respect of susceptibility and density constant, i.e. under laboratory conditions as assumed for the models presented by Boots and Sasaki (2003). But the non-specific character of stress in the decision between death and survival by immunity and its dependence of population density by intraspecific competition makes the complex factor of virulence, comprising infectivity, toxicity and pathogenicity, highly variable.

2.2. *The balancing survival strategy of parasites*

Eukaryotic parasites, in contrast, have evolved a strategy of a *physiological* equilibrium for the coexistence with their hosts. Instead of death or survival, parasites and hosts propagate simultaneously and the resulting parasitosis is transmitted permanently sustaining a status of continuous endemicity. The physiological balance between both partners is characterised by the host becoming 'immunized, but not immune' (see below).

2.2.1. *Protozoan parasites*

The process will be illustrated by the example of *Plasmodium* species, to which belong the agents of malaria. Superficially, this parasitosis appears to be similar to a microbial pathogenic infection. The life cycle of the agent seems to be well known (Figure 2).

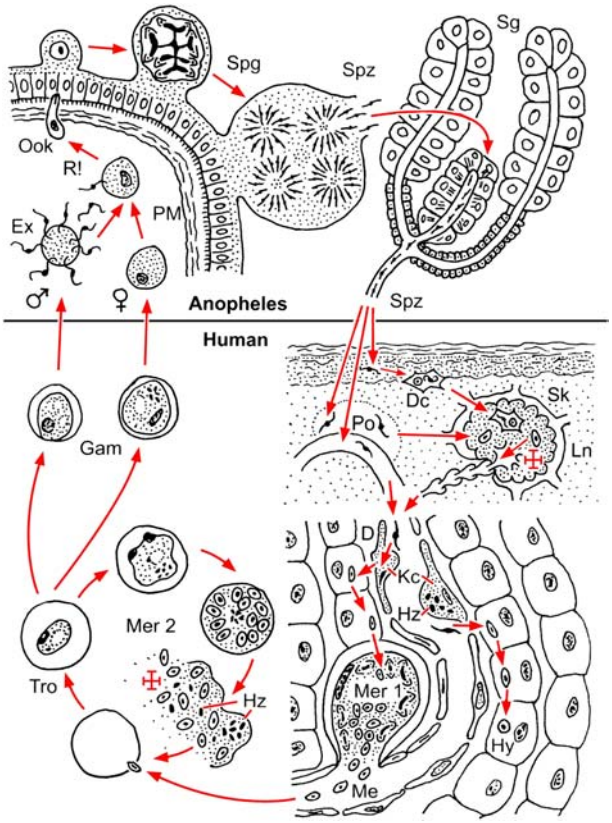

Figure 2. Life cycle of *Plasmodium vivax*. D: Dissé-space; DC: dendritic cell; Ex: exflagellation; Gam: gamonts; Hy: hypnozoite (precedent passage of two liver cells is speculative); Hz: haemozoin; Kc: Kupffer-cell; Ln: lymphnode; Me: merozoite; Mer 1: first merogonia in parenchymatic liver cell; Mer 2: second merogonia in red blood cells; Ook: ookinete; PM: peritrophic membrane; Po: haematoma pool; R!: reduction division; Sk: lingering merozoic skin stages; Sg: salivary gland; Spg: sporogonia; Spz: sporozoite; Tro: trophozoite; ✠: parasite stages partly degraded.

As might be expected in any protozoan parasitosis transmitted by a blood-feeding arthropod, after infective mosquito bites, the sporozoites transmitted by the saliva are deposited in the skin tissue. However, mosquitos are both capillary and pool feeders and sporozoites delivered simultaneously might reach the circulating blood immediately (as generally shown in figures). However, if deposited into the dermis during penetrating it or afterwards into the pool of blood around the tapped capillary, they will reach the lymph nodes draining the corresponding skin area at first.

> 'Migrating, skin-lingering and dead parasites release a spectrum of parasite and host products into the skin, from multifunctional proteins to peptides and glycolypid anchors. … This antigenic grapeshot' (Figure 2 ✠) 'is scattered at very low, sub-immunogenic (dominantly tolerogenic) doses throughout the local bite site tissue, and is immediately available to a broad range of antigen-presenting cells/pathways in the skin matrix, under a bite

> site microenvironment shown to strongly downregulate immune responses to local antigens. … Under natural conditions, the immune responses are primed in the skin-draining lymph nodes in which systemic adaptive responses are rapidly orchestrated inducing immunosuppressive (tolerance) mechanisms by regulatory T- and B-cells'. Since the *Plasmodium spec.* skin stages linger until the infection ends spontaneously (see below), the regulating immunological mechanisms continue as well. The consequence 'is that no current vaccination approach can be expected to work effectively in the long term in bite exposed populations'. (Guilbride et al. 2012).

In contrast to microbes, the parasite *Plasmodium* sp. limits its first replication genetically, e.g. the merogonia in the liver cell of man, to 13 (*P. vivax)*, 14 (*P. ovale, P. malariae)* and 15 (*P. falciparum*) divisions, which are followed by a (still hypothetical but logical) feedback of the merogonia in the red blood cells of the circulating blood (Figure 3). This keeps the parasitaemia (percent parasitised blood cells) at a low level of about 1%. Simultaneous rupture of parasitised blood cells delivers periodically another grapeshot of antigens (Figure 2 ✠) and causes the well-known periodic fever attacks. The host indeed suffers but the feedback mechanism prevents a fatal flooding of the red blood cells with parasites. Obviously, the *Plasmodium* sp. survives not in spite of, but with the aid of the immune response.

The propagation of *Plasmodium* sp. is restricted to sexually determined gamonts ('gametocytes') in red blood cells; these gamonts finally become gametes, however, only when they arrive in the intestine of a blood-sucking mosquito, where they fuse (mate) and propagate in the subsequently produced sporogonia, a process that again is limited to 12 divisions (*P. falciparum*).

The gamonts appear in the circulating blood in small numbers (a few percent of the 1% parasitised erythrocytes), and the prevalence (rate of gamont-carrying persons in endemic region) and individual density (rate of gamont-carrying erythrocytes in circulating blood) of the latter even decreases drastically with the age of the human host. However, prevalence and individual density of gamonts periodically increase during the rainy season, when vector-biting rates are high. Additionally, in the uppermost age classes, the gamonts' prevalence increases during the rainy season by a factor of 4 and its individual density by a factor of 15. Both factors increase the transmission reservoir of *P. falciparum* seasonally by 60-fold (Molineaux and Gramiccia 1980). The seasonal gradually increasing transmission rates in increasing human age classes (which decrease in size) compensate the age drift, which all repeatedly transmitted parasites suffer themselves. In addition, the susceptibility of human hosts increases during the dry season, compensating for the low chance of becoming infected by the rare vectors (Figure 4).

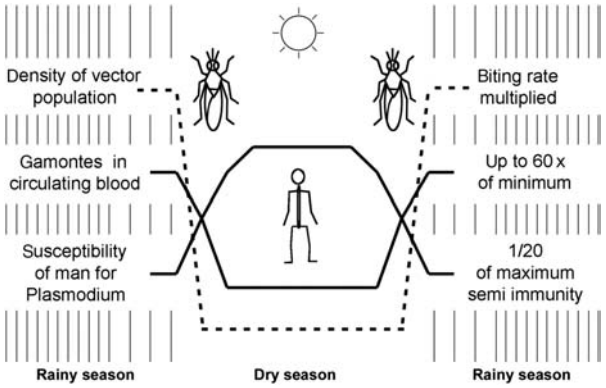

Figure 4. Seasonal compensation of gamogonia in *P. falciparum* and susceptibility in human hosts during rainy and dry season. Data from Molyneaux and Gramiccia 1980.

In short, *Plasmodia* 'know' the age of their actual human host, can sense whether the host lives under a permanent risk of infection and whether the rainy or dry season is underway. Its pathogenic effects are counter-productive or at least not relevant for the persistence of the *Plasmodium infection*. Re-infection happens as a rule (Figure 5). The costly up and down of repeated epidemics is replaced by a constant endemic. Peaceful coexistence

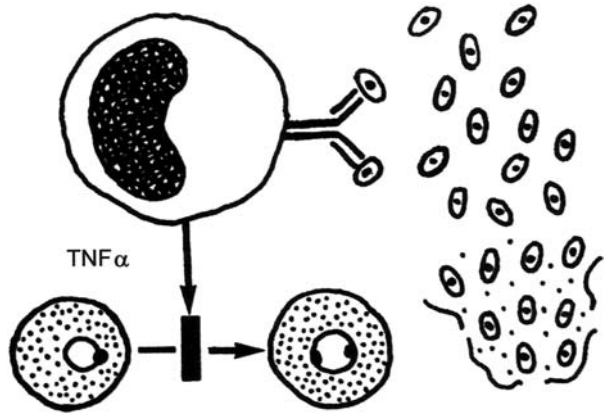

Figure 3. Regulation of parasitaemia (*P. falciparum*) by TNFα stimulated by sessile antibodies against merozoites (from Druilhé and Pérignon 1997).

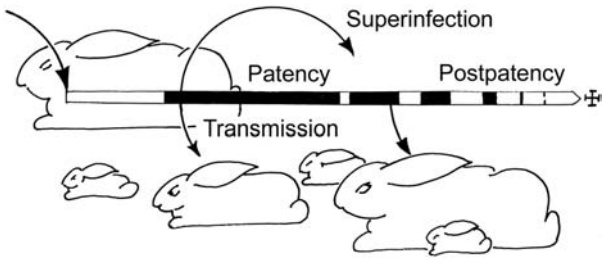

Figure 5. Balancing survival strategy of eukaryotic protozoan parasites, e.g. *Plasmodium* sp. White bar: periods without symptoms.

regulates the potential surplus of both parasite and vertebrate host. In the long run, fatality thresholds by either overpopulation or extinction are avoided for both partners (Seilacher et al. 2007).

People suffering from repeated re-infections acquire over time a partial protection against malaria. Frequent infectious mosquito bites generate weaker or no fever attacks, a clinical state called 'semi-immunity'. In contrast to the complete protective immunity of microbial infections, this partial protection is lost again if not challenged permanently. People who come from endemic areas but who have left these areas for at least five years, e.g. Africans returning home after having studied in Europe, can suffer a life-threatening malaria attack when challenged.

In biological terms, this status of semi-immunity should be understood as a *habitat defence* of the parasite. Additional super-infections with severe symptoms will threaten the patient's life and thereby impair the survival and further transmission of the established *Plasmodium* population. Contradictory to what might be expected, persistent repeated infections do not synergistically threaten the patient's life in spite of weakening its fitness. In the course of multiple re-infections, the parasite obviously cause praemunition and, with increasing age, the frequency of re-infections causing severe symptoms diminishes as measured as the ratio of life expectancy parasite to host, i.e. malaria re-infection rates in children and adults (Table 1). The apparent reduced susceptibility can even change every year quite rapidly: during the rainy season, 100 infectious mosquito bites are necessary for a patent infection, whereas in the dry season, only 5 are needed, i.e. 1/20 of the dose (Figure 4). This change is more pronounced in older age groups than in children up to five years (Molineaux and Gramiccia 1980).

The remarkably complex reaction potential is reflected by the complex organised genome of *Plasmodium* sp. as eukaryotic protists (Cavalier-Smith 1985). In *P. falciparum*, there are 23.3 Mbp (megabasepairs) organised in 14 chromosomes comprising $5-6 \times 10^3$ genes. In addition, there is extrachromosomal DNA of two organelles, the mitochondrium (ca. 6 kbp) and of the apicoplast (35 kbp coding for 30 proteins). Additionally, 551 genes of the mitochondrium are localised in the nucleus. Moreover, the genome of *P. falciparum* is rather variable: in one generation, about 2% of the plasmodia in red blood cells change their genome. The *Plasmodium*-induced surface protein PfEMP1 belongs to a variable *var*-gen-family of adherence proteins (MG 200–300 kilodalton), a clone of which changes its sequences during the course of an individual infection every several weeks, and in each single patient several clones are present simultaneously (Gardner et al. 2002; Kyes et al. 2007; Lucius and Loos-Frank 2008).

The implications of the complex composed metazoan genome are specifically relevant for an endoparasite living in an endothermic host such as mammals or birds that present a rather constant but highly specific and

Table 1. Synoptic quantification and qualification of the life cycle of *Plasmodium falciparum*; inf. infection.

Factors controlling parasite population dynamics (*P. falcip*arum)	**Vector**  **r-strategist**	**Definitive host**  **K-strategist**
Individuals per area	**Large**	**Small**
Density during seasons	**variable**	**constant**
Potential prevalence	**low (<1%):**	**high (up to 90%):**
Susceptibility	genetically determined individually graduated	seasonally variable individually generalised
Life expectancy	2 months/2 months **= 1**	**Children** 16 inf./5 years **= 3.2**
Parasite: host		**Adults** 1.4 inf./5 years = **0.3**
Type of affection	**Single infection**	**Multiple infections**
Regulation of parasite multiplication	Time window for developing ookinetes, limited sporogony	Limited merogony in liver, regulated merogony inclusive gamogonia in circulating blood
Influence on host	**Physiological modification** of feeding behaviour	**Praemunition**: defence of occupied host by parasite ('semi-immunity')
Defence mechanism	**Internal defence system**	**Immune response**
Type of resistance	**Inherited, but not memorised reversible** (short term)	**Not inherited, but memorised irreversible** (long term)

particularly immunologically reactive biotope. In contrast to microbial organisms, eukaryotes exhibit different inheritance systems. Genetic inheritance is an *information*-based system and its characteristics are ancient, almost universal and highly evolvable. Extrachromosomal inheritance by plasmatic DNA and symbiotic microorganisms, such as mitochondria and apicoplasts (as in *Plasmodium*), is a *sample*-based inheritance system. It has less variance, but is more robust and more modular than information-based inheritance. It supports evolutionary innovation, is highly evolvable, 'essentially because samples generate their phenotypic effects in ways that are relatively independent of other developmental resources'. (Sterelny 2004). Symbiogenesis, the stable integration of symbionts into the genome is an important mechanism of evolutionary innovation (Margulis and Cohen 1994).

2.2.2. *Metazoan parasites*

Parasitic nematodes, trematodes and cestodes enter their vertebrate hosts via the mouth by ingestion with food and/or through the skin and are transported or migrate to their definitive location in the host's tissues. On their way, infective larvae develop into adults, which mate and deliver propagation stages (embryonated eggs and infective larvae) until they naturally die. Propagation stages leave the host (evasion) either passively by the faeces or mediated by a blood-feeding arthropod as a vector. The time between entry into the host and onset of transmission, the period of prepatency lasts weeks or months, whereas the subsequent delivery of propagation stages (patency) may continue for years. After the natural death of the parasite, the remaining memory of the host's immune response, e.g. allergic reactions, determines the phase of postpatency.

The immune response is stimulated by the invasion stages immediately and humoral and cellular antibodies appear after some days. Nevertheless, the period of prepatency lasts several times longer than any latency of the immune reactions. Furthermore, the immune response is boosted permanently during patency and thereafter is memorised for months if not years. However, this does not protect the host against re-infection. The host is once again *'immunized, but not immune'*.

The cellular and molecular mechanisms of this remarkable state are still a matter of intensive research. They are usually interpreted as 'manipulation' or 'circumvention' or 'evasion of the immune response' by the parasite. However, any effectory part of an immune response has to be switched off *finely*, otherwise the host would be killed by a tumour caused by its own immunreactive, e.g. antibody-producing, cells. The advantage of being 'immunized, but not immune' should be seen at the level of ecology, because it allows the survival and *simultaneous* propagation of host and parasite and its continuously released propagation stages or, in other words, their coexistence.

In biological terms, as explained above for *Plasmodium* sp., semi-immunity should also be understood as a (more or less effective) *habitat defence* of the metazoan parasite. Continuous super-infections increase the parasite load excessively and its excretions and the deteriorating adult and propagation stages damage the host's tissues. These crowding effects finally threaten the host's life and thereby impair the survival and further transmission of the established parasite.

The self-control of propagation has been experimentally investigated for a filarial nematode, *L. sigmodontis*, which is propagated by larvae (microfilariae) circulating in the peripheral blood of the cotton rat *Sigmodon hispidus* (Figure 6). The viviparous females continuously release microfilariae into the pleural cavity. However, before entering the peripheral circulation, they accumulate in the lung capillary system at extremely high densities (several thousand microfilariae per microlitre of blood). Thereafter, 1/10 of the density is observed in the peripheral circulating

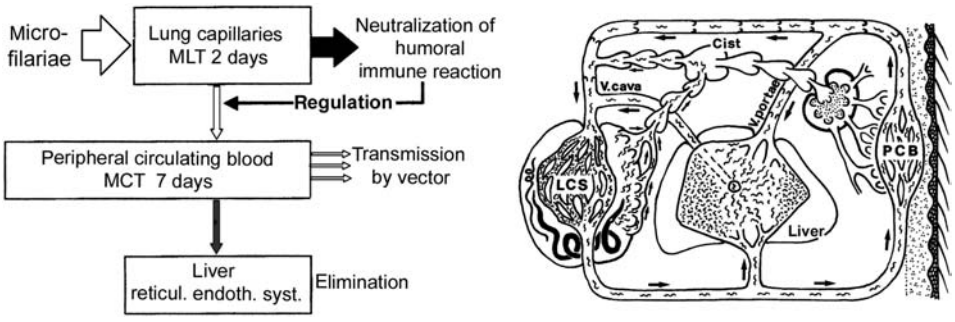

Figure 6. Output regulation of microfilariae (mf) of *Litomosoides sigmodontis* in the cotton rat. Left: White arrows – young mf, black arrows – old or dead mf; MLT: median mf lifetime in lung capillaries; MCT: median mf circulation time; Right: adults in pleural cavity deliver mf which migrate across the diaphragm into lymphatic vessels to the cisterna chyli (Cist) and into the lung capillary system (LCS). Here, mf accumulate and absorb anti-mf antibodies (neutralisation of the humoral immune reaction). Surplus mf move into the peripheral circulating blood (PCB). After natural death, mf are eliminated in the liver (Wenk et al. 1993; Wenk and Renz 2003).

blood (corresponding to the blood volume of about 4/5 of the total amount of microfilariae simultaneously present) for a median of seven days and will subsequently be eliminated (Wenk et al. 1993). Accordingly, the turnover in the peripheral blood is regulated by feedback via the output (elimination) neutralising the humoral immune reaction (Figure 7). In *Acanthocheilonema viteae*, living subcutaneously in the gerbil *Meriones unguiculatus*, feedback occurs via the input (production) by using metabolites of the microfilariae (Wenk et al. 1994). In general, both mechanisms can act side by side or alternatively depending on where the adult worms settle. A more detailed description is found in Wenk and Renz (2003).

The balancing survival strategy of metazoan and protozoan parasites is considerably more 'economic' than epidemic waves and therefore provides a considerable selective advantage for the parasite: measured by the number of secondary cases following a primary case, eukaryotic parasites are generally much more successful as measured by the considerably higher case reproduction rate than microbial agents and do not risk their own survival. By means of an extended transmission phase, balance strategists achieve maximum frequencies of cases (prevalence) combined with tolerable levels of pathogenicity and lethality.

3. Discussion and conclusions

As they evolved later, metazoans were probably never free from protozoan parasites but, as they left no traces in the fossil record, this side of co-evolution is mostly overlooked. Because of their complex organised genome in comparison with that of microbes, metazoan parasites were able to evolve the ingenious adaptations that have been summarised as the *balancing* survival strategy in contrast to the *opposing* strategy of microbial pathogenic agents.

The apicomplexa (*syn.* sporozoa) are a class of exclusively parasitic protozoa, including *Plasmodium* sp., which depended on other eukaryotic organisms from their very beginning. However, the vertebrate hosts of the hundreds of species of *Plasmodium* sp. present today in reptiles, birds and mammals appeared last of all. Primarily, the ancestors of *Plasmodia* were most probably intestinal commensals of insects that mated inside the host's intestine. Offspring were excreted with the faeces and became transmitted by contamination of the insects' environment. Preference for particular intestinal conditions then led to the diversification of the *monoxenic* life cycle.

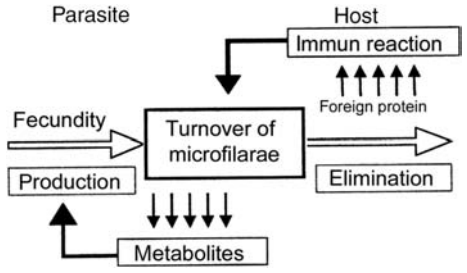

Figure 7. Possible turnover regulation of circulating microfilariae. Left: Restriction of fecundity (production) mediated by the metabolites of microfilariae. Right: Amplification of immune reaction (elimination) mediated by foreign protein (from Wenk and Renz 2003).

As soon as the descendants of these parasites colonised and later penetrated the insect intestine epithelium, i.e. making accessible new host tissues for an increased food resource, they had to pass the haemocoel and were then confronted with free cells of the internal defence system (IDS, Van der Knaap and Loker 1990). These cells normally initiate the encapsulation of *foreign* bodies. Instead of being recognised as foreign, we can postulate that a rare variation of the presumptive invader's molecular surface pattern proved to be compatible with these defence cell recognition patterns. This compatibility upgraded and avoided the activation of the internal defence reactions. Notably, invertebrates do not differentiate between individual 'self' and 'not-self' characteristics, a feature that, in endotherms, is acquired prenatally. In exotherms, experimentally transplanted organs are tolerated between individuals, species or even systematically more distant categories.

The seasonal waves of the insect population compensated the parasite's selection losses by compatible but deleterious invaders. A few non-fatal mutations guaranteed enduring coexistence to allow the parasite's evolution. Numerous sporozoan parasites demonstrate that the invertebrate host can survive, even if it is full of sporozoites and finally dies. In this case, the carcass contaminates the habitat.

When the insect host changed from being a vegetarian sap-feeder to being a blood-feeder on mammals or birds, the parasite could establish a *heteroxenic* life cycle. Instead of creating a carcass filled with parasite stages, the insect's repeated blood feeding became the prerequisite for the parasite's transmission to the next vertebrate host, which could most easily be reached via the insect's saliva in order to arrive immediately within the circulating blood.

Plasmodium sp. of mammals are transmitted exclusively by a limited number of species of the genus *Anopheles* (Diptera: Nematocera), *Plasmodium* sp. of birds, instead, by distinct species of *Culex*, a separation determined by genetically based structural and physiological differences. Taking in view the four human *Plasmodium* sp., in each continent a geographic and regional patchwork of species–species parasite–host relations may be observed. However, *P. falciparum* is, e.g. restricted to tropical regions because in northern temperate zones the digestion of blood followed by the development of eggs did

not run synchronised with the penetration of the rapid hardening of the peritrophic membrane necessarily to be passed by the ookinete for the sporogonia of the *Plasmodium* in the intestinal cells. Nevertheless, a rapid switching onto different *Anopheles* species with a suitable hardening process of the peritrophic membrane could establish *P. falciparum* in a temperate region, given repeated manifold contacts to infected people. The general conditions for such 'ecological fitting' are presented by Agosta et al. (2010).

However, parasites that successfully invade an endotherm host and persist inside its tissues or even cells, as does *Plasmodium* sp. in erythrocytes, are typically restricted to susceptible hosts. These might comprise single species or even families as demonstrated by felids, all of them being the final hosts of *Toxoplasma gondii*. For the development of the susceptibility of endotherms to infection as detected by microbial pathogenic agents, Matzinger (2002) has proposed a convincing concept: the increasingly complex organisation of vertebrates and finally endotherms led to the development of surface receptors adapted to recognise degenerated proteins produced by their own bodies, e.g. from dead cells or by injury. Microbes in contact with these vertebrates constantly variegated their own surface antigen patterns haphazardly. If these patterns coincided by chance with the surface receptors of the vertebrate, the microbe was then able to invade it and could consider the endotherm as susceptible. The endotherm is now called 'the host', and the host's receptors are called pathogen recognition receptors. The microbe's compatible surface pattern is termed the pathogen associated molecular pattern. This concept is valid, particularly for parasites. A stay within the relatively short-lived erythrocytes in order to consume their limited haemoglobin content also required the exploitation of the immune response for feedback regulation, as has been postulated by Druilhe and Pérignon (1997).

All these steps must have been advantageous for the parasite. For heteroxenic species, the longer time needed for sexual propagation (in contrast to microbes, which propagate in hours) and the separation of replication and propagation in sporozoa also had to be adjusted to the life expectancy of the endothermic final hosts. The possibility of repeated infections increased the disposable host population by additional parasite-experienced but still susceptible members. It also avoided the extended period of memorised *protecting* immunity by the antibody-based feedback of *immunised, but not immune* mechanisms (the box in which the key for a vaccine is hidden). For the short-living intermediate hosts (insects, ticks), the surplus in seasonal variation of the population density and the minute investment in transmission, in which only a small proportion takes part, made memorised protective immunity unnecessary. The selective advantage of the complicated heteroxenix life cycle is based on the combination of (1) a host living over several seasons and (2) another short-living but abundant host. The opposing factors of vertebrate and invertebrate hosts are summarised in Table 1.

Molecular compatibility was a prerequisite for the coevolution of parasite *and* host and provided selective advantages for *both partners* from the beginning. We have, however, also to seek the hosts' selective advantages. No free-living metazoan organism exists without a multitude of mono- and heteroxenic endoparasites. Both live often simultaneously inside their hosts without creating protective immunity. Nevertheless, the parasites regulate the population density of their hosts by reduced fitness (Figure 8), in addition to predator–prey relationships in heteroxenic life cycles. In effect, parasites are the true distance holders to the fatality thresholds of their hosts (Seilacher et al. 2007).

Pathogenic agents as well as parasites live a life resembling that of a bird living on hemp seeds. However, the specificity of the host makes them live in a golden cage, a cage that they have to leave for propagation. Opposing strategists destroy the cage by protecting immunity or death of the host, whereas balancing strategists stay within the cage until their *natural* death as a rule. Only their propagation stages leave the host via its excretions or, in the case of tissue and cell parasitism, by the vector.

Balancing parasites should not be called 'pathogens' but parasites. They are transmitted repeatedly by trickle inoculations of mostly small doses. The first few adults (i.e. the very first ones) are harmless but nevertheless propagate sufficiently for existence in their local host population. Pathogenic effects do only appear later because of an accumulation of the parasite's load by repeated re-infections. Such parasites compete with each other: their reproduction (fecundity) is reduced (advantageous for the host's survival) but the host tissues are damaged by their excretions and deteriorating remains. All these phenomena are summarised as crowding effects.

The consideration of pathogenicity as *irrelevant* for the coexistence of *Plasmodium* sp. in its human host might be difficult to believe in the light of *P. falciparum* being the most dangerous malaria infective agent. The rate of infected people, the prevalence, can reach over 90% in children up to five years, whereas the lethality of malaria remains at 1%. This leads to about two million death cases annually in Africa, mostly in children. However, these numbers are attained because of high prevalences and many other collateral events. From a biological aspect, the 99% surviving children that have passed through five dangerous years reflect the optimal adaptation of the parasite. Any pathogenic effects, at least fatal ones, now are a superfluous waste and counterproductive for the survival of the *Plasmodium* sp. However, they carry no weight in view of the regular re-infections in children and

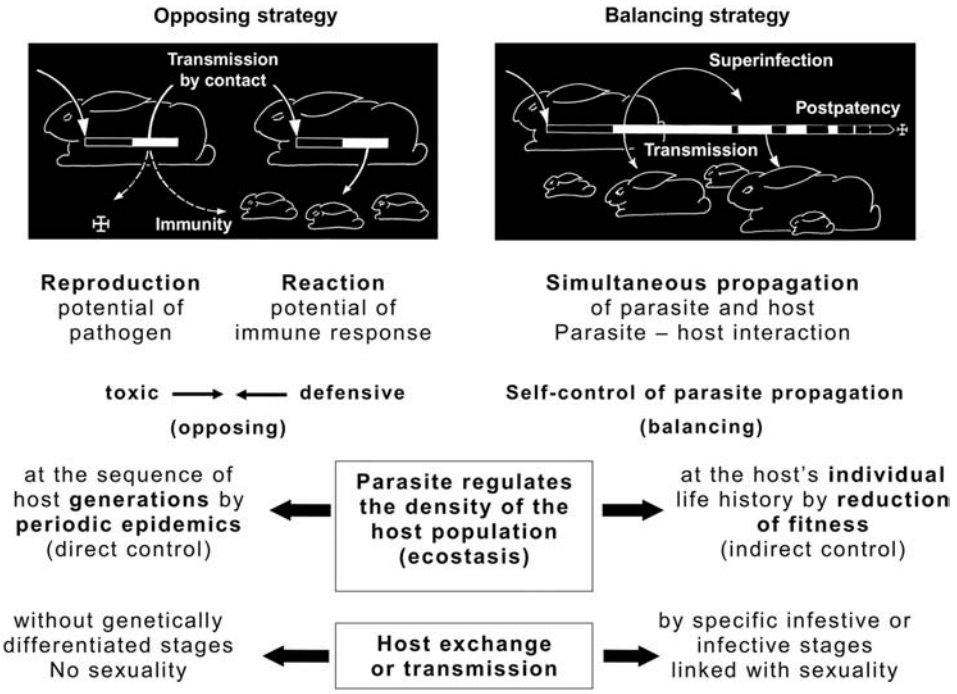

Figure 8. Comparison of opposing and balancing survival strategies of prokaryotic pathogenic agents and eukaryotic proto- and metazoan parasites (from Wenk and Renz 2003).

adults (see Table 1). We should, however, not forget that each *Plasmodium sp*. infection ends spontaneously after a genetically again limited number of fever attacks letting behind an again susceptible host.

Recent studies of numerous captive and wild-living Gorillas and Bonobos (*Gorilla gorilla, G. beringeri*) and five species of chimpanzees (*Pan troglodytes* ssp.) in Western and Central Africa have detected new *Plasmodium* sp. closely related to *P. falciparum* (subgenus *Laverania*) and more distant species (non-*Laverania* species). The results reflect the biological aspect also emphasised here: 'It is now apparent that *Plasmodium* parasites are widely distributed in wild-living great apes, with multiple *Laverania* and non-*Laverania* species present, often at the same location and in the same individual, with prevalence approaching 100% at some sites' (Rayner et al. 2011).

The presented concept of opposing versus balancing survival strategies of pathogenic agents and parasites, respectively, is based on biology, not medicine. It applies only to pathogenic agents and parasites in their *adequate* or *natural* hosts; in inadequate hosts, they may cause severe, often lethal effects leading to an evolutionary dead end, such as zoonoses generated by parasites of animals accidentally transferred to man. The specific pathogenic agents and parasites and their *adequate* hosts are defined by their evolutionary success. As with any functional argument in biology, this can be regarded as a circular *but essential* argument (Kant 1799).The merit of the biological aspect is its significance at the population level; this is relevant for the evolution of diversity (predator–prey relationships, food pyramids in savannah and offshore habitats) and because of calamities in artificial monocultures.

Concerning the medical aspect, we should keep in mind that the types of parasite–host interplay of opposing and balancing strategies differ in principle: on the one hand, temporary competition between toxicity and immunological defence making pathogenicity essential and, on the other hand, sustained cooperation by self-controlled propagation and immunological tolerance, making pathogenicity irrelevant. The considerable difference in complexity might be metaphorically expressed like Nine Men's Morris (Cowboy Checkers) and Chess. In the case of an opposing strategist, a vaccine is simply an information advance. Against two pathogenic agents, a bivalent vaccine acts like a double bind. However, to try by an information advance to protect against a balancing strategist is like playing Chess by the rules of Nine Men's Morris.

Evolution theory has proceeded from the observed diversification of species, based primarily on the genetics of individuals and secondarily on populations, and includes the arms race operating in the opposing strategy of pathogenic microbes. The concept of the balancing strategy in eukaryotic parasites, however, transgresses the species limit by an *inter*specific coevolution. Parasite and host in partnership are each still species but belong to far-distant

systematic categories. Evidently, evolution is an ecological process (Seilacher et al. 2007, present contribution). The major three factors of evolution, namely mutation, selection and abiotic factors (climate, geographical isolation up to continental drift, global catastrophes), should be complemented by symbiosis in its broadest sense.

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