Special Issue on Avoidance, Resistance and Tolerance: Strategies in Host Defense

Infection-avoidance behaviour in humans and other animals

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Compared with living free, the parasitic way of life has many attractions. Parasites create problems for all animals. Potential hosts can respond by learning to live with parasites (tolerance), actively fighting them (resistance), or they can avoid becoming infected in the first place (avoidance). I propose here a new classification of avoidance behaviour according to the epidemiology of infection risk, where animals must avoid (i) conspecifics, (ii) parasites and their vectors, (iii) parasite-rich environments, and (iv) niche infestation. I further explore how the disgust adaptive system, which coordinates avoidance behaviour, may form a continuum with the immune system through the sharing of signalling pathways, sites of action, and evolutionary history.

Introduction

Compared with living free, the parasitic way of life has many attractions. A parasite that climbs onto or into a host can expect to find nutrition, warmth, and shelter, a lift to new habitats and reproductive opportunities [1]. Indeed, all living organisms are involved in parasitism in some way, either as hosts or as parasites, or both (Price 1980); there are more species of parasite than there are free-living animals on this planet [2]. Parasites, however, do not get it all their own way. Hosts resist being invaded, and some of the resources that parasites save by not being independent must be spent in evading host defences [1].

As this article series highlights, there are three types of host response to parasites. The host can learn to live with the parasites (tolerance), can actively fight them (resistance) or can avoid becoming infected with them in the first place (avoidance). This article concerns the behaviour that animals engage in to avoid becoming infected with parasites and pathogens.

We know more about the immunology, biochemistry, and genetics of infections than we do about the behaviours that prevent them. Nonetheless, behaviour (see Glossary) is the first line of defence against infection, preventing or reducing parasite encounter [2], and is likely the most cost-effective. If we are to understand how behaviour works in any species we need to be able to characterise it [3]. I propose here that there is a fundamental set of evolved behavioural strategies for the reduction of parasite infection risk. These include avoiding: (i) conspecifics, (ii) parasites themselves and their vectors, (iii) situations where encounter is likely, and (iv) constructing niches that are unconducive to parasites. I hypothesise that these four functional behavioural categories will be instantiated in behaviour production systems across Animalia including humans.

The system producing these behavioural responses to infection threat I label the disgust system. I further explore overlaps and synergies with the immune system that are suggesting of a common evolutionary origin for both resistance and avoidance. I explore the implications for disease control and propose avenues for future research

What is parasite avoidance?

Before we examine parasite-avoidance strategies it is important to be clear about the terms ‘parasites’, and ‘avoidance’. I adopt here the perspective of evolutionary biology and label all organisms with a parasitic way of life as ‘parasites’. Combes defines a parasitism as a durable relationship where one organism lives by eating one bigger than itself [1]. Hence, when I refer to parasites I include micro-parasites such as viruses, bacteria, fungi, and protozoa, as well as the worm and arthropod endo- and ecto- macro-parasites mostly studied by parasitologists. It follows that the terms ‘infection’ and ‘infestation’ are interchangeable in this context, and that ‘parasites’

Glossary

Behaviour: the fundamental adaptation of Animalia. Behaviour is a functional interaction between an animal body and its environment. Behaviour can be classed into ‘kinds’ according to distinct evolutionary function [3]. One type of function is parasite avoidance.
Conspecific: an animal of the same species
Disgust: a system based in neural tissue that evolved to detect reliable signals co-occurring with disease-causing infectious agents and which stimulates behaviours tending to reduce the risk of disease. Disgust and immunity are part of a defensive continuum: disgust acts before or immediately following contact, whereas immunity deals with infectious agents that evade evasion and penetrate the body boundary.
Epidemiology: the study of patterns, causes, and effects of health and disease conditions in populations. Infectious disease is still the main cause of death in humans in developing countries, whereas chronic and lifestyle diseases such as diabetes and cardiovascular conditions now predominate in the developed countries.
Niche: multidimensional space within which a species makes a living.
Parasite: animals that make a living by eating into animals larger than themselves. A parasite climbs onto or into a host to find nutrition, warmth, and shelter, and a lift to new habitats and reproductive opportunities [1]. There are parasitic species of viruses, bacteria, fungi, worms, and insects. Endoparasites live inside the host species whereas ectoparasites live on the surface of the host.

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include all potentially infective stages, even dormant ones. The discussion here is confined to the evolved relationship where it is adaptive for hosts to avoid parasites, and excludes the cases where parasite encounter can be beneficial, such as when ants apparently immunise themselves [4–6], and when humans reduce their risk of autoimmune conditions in dirty environments [7], presumably via complex immune interactions with microorganisms present in these environments, or through therapeutic worm infection [8].

I use the term 'avoidance' here to refer to behaviour, and take behaviour to be a phenomenon exhibited only by animals. Although, technically, any animal or plant can avoid infection via an impermeable or tough external layer or via cytotoxic secretions, I class such physiological defences as types of resistance. Avoidance thus concerns actions taken by an animal (or group of animals) to reduce its (or their) chances of becoming infected with pathogens or parasites.

Infection-avoidance strategies

To what extent do animals, including humans, manifest infection-avoidance behaviour? Answering this question is surprisingly difficult. Few systematic studies of disease-avoidance behaviour have been carried out in any species, let alone across Animalia. Published papers tend to contain examples of animals performing the behaviour in question, but not of animals failing to perform it, hence conclusions will inevitably be coloured by publication bias. Further, behaviour in the wild responds to many adaptive needs, and needs must be traded off against one another [9]. Infection-avoidance behaviour may be hard to identify because it can be suppressed by a more pressing need for nutrition, sociality, or sex. Suspected disease-avoidance behaviour should ideally be tested for in controlled experiments that manipulate behaviour and examine the impact on infection. However, this is hard to do except in the lab or with domesticated species, and few such studies exist. Hence, much of the evidence collected here is of the less rigorous natural experiment or anecdotal type.

Despite these difficulties, there are two reasons why it is important to understand infection avoidance. First, the biology of behaviour and the systems that produce it is still poorly understood across species, and infection-avoidance behaviour provides an excellent model system for relating function to production. Secondly, understanding the production of avoidance behaviours should help us to create the conditions that can help to reduce the economic and social costs of infection.

What behavioural strategies, then, can potential hosts employ to avoid becoming prey to a parasite? Parasites vary hugely in lifestyle, mode of transport, and route of entry into their targets, but an epidemiological perspective (Box 1) would suggest that control strategies should mirror the main sources of infection risk. The first, and potentially the greatest, source of risk is contact with conspecifics who are likely to harbour the parasites and pathogens that are adapted to infect the target host. Hence, conspecifics should be avoided, especially if they show signs of infection. The second source of risk is the parasites themselves, as well as their vector species, and hence these should be avoided. The third type of risk to avoid is objects and environments that might harbour parasites, pathogens or their progeny. Finally, animals can modify their environments to make them less likely to support parasites, a form of niche construction [10]. I will examine these four parasite-avoidance strategies in turn.

Box 1. The Psychology of disgust

Disgust has long puzzled psychologists and philosophers. Early accounts made disgust part of the psychodynamics of repression [86], or a cultural construct that helped to keep order in social categorisation [87]. More recently the standard account of disgust has followed the school of Paul Rozin and Jon Haidt [88]. These psychologists propose that disgust is purely human, has its origins in distaste, and has mechanisms that include protecting the body and soul from pollution, particularly from thoughts that one is an animal and may therefore die. In 2001 we set out a more parsimonious theory of disgust as an adaptive system for infection avoidance. We showed how almost all disgust elicitors could be mapped onto agents of infectious disease [47] and that stimuli with greater infection risk were found more disgusting in a global sample [27]. This implied that disgust mechanisms would be found across Animalia and would respond to other parasitic threats than those that enter via the oral route (distaste). Further work from various authors supports the account that disgust is an adaptive system for infection avoidance that is, to a limited extent, modifiable according to individual learning and local culture [27,46,48,49,89]. Schaller uses a similar concept to our disgust adaptive system that he labels the 'behavioural immune system' [90].

Disgust-mediated avoidance behaviour is both innate and learnt. Thus, for example, infants respond reflexively to sour tastes that could betray that food is contaminated, whereas adults may carry learnt aversions to foods eaten at an earlier date that accompanied nausea (the Garcia effect). Although the repertoire of stimuli that cause disgust in humans is similar across the globe, there are local cultural variations. See [46] for a full description of the disgust adaptive system.

Avoid conspecifics, especially if they show signs of infection

Because parasites tend to target specific hosts [2], for one host the most likely source of infection is another animal of the same species. Animals should therefore avoid close contact with conspecifics, and be particularly cautious of contact with conspecifics manifesting signs of infection.

An obvious behavioural defence against parasites is therefore to adopt a solitary way of life [11], as most animals do, for most of their lives. Animals that are social can reduce infection risk by restricting the size of their group. Altizer *et al.* found lower levels of parasite prevalence, intensity, and diversity in smaller, compared to larger, groups of vertebrates including prairie dogs, mangabeys, cliff swallows, bobwhites, and feral horses [12]. However, other studies have shown mixed or contrary effects; for example, solitary rodents have fewer ectoparasite species, but not endoparasites, than social species [13]. Grouping together may also have the opposite effect, for example, in helping some fish to avoid parasites [14].

Freeland has hypothesised that parasite pressure limits group size in primates – in a habitat rich in pathogens, such as the warm, humid rainforest, typical primate troop size for the colobus monkey is low, whereas in the hot dry savannah of highland Ethiopia, with much lower pathogen loads, gelada groups number several hundred [15]. Group size in primates is controlled by individual young males and females choosing to leave a large group, likely harbouring many parasites, to join a smaller, presumably healthier group, and by the males that stay, fighting to keep their group size low. Membership candidates showing signs of sickness remain marginalized. Freeland points out that primate troupes actively avoid each other; smaller groups give way when encountering larger ones, vocal displays are carried out at a distance, and physical confrontations are avoided [15]. This helps to avoid conflict, but probably also reduces exposure to novel pathogens. A comparative phylogenetic study found higher rates of attack from malarial mosquitoes in primates with higher group size [16]. Sexual reproduction requires social contact, even for solitary animals. It is important for a female, in particular, not to acquire an infection during copulation. Like a male, she could fall ill directly and her offspring could suffer from congenital malformations or low birthweight, but, unlike a male, she could become sterile, be unable to carry a pregnancy, or she could infect her young during pregnancy, birth or lactation. Female housemice *Mus musculus domesticus* investigate potential partners by sniffing them, and they prefer the odour of unparasitised males to those carrying the protozoan parasite *Eimeria vermiformis* [17]. The 'bright birds' hypothesis holds that healthy-looking individuals, such as a peacock with a fine tail, are preferred as mates because this demonstrates their quality as potential parents [18]; however, such behaviour also serves to avoid the transmission of infections. When researchers painted red lumps on the wattles of the males of half of a flock of Sage grouse *Centrocercus urophasianus*, the apparently lousy males had less success attracting female grouse [19], hence protecting both current and future generations.

Another strategy to avoid the risks associated with sociality is to avoid conspecifics that show signs of infection. The Caribbean spiny lobster *Panulirus argus* is highly sociable, but refuses to share dens with other lobsters who are infected with the lethal PaV1 virus [20]. About 7% of the tadpoles of the bullfrog, *Rana catesbeiana*, have a debilitating yeast infection. Given the choice, healthy tadpoles avoid approaching those that have the infection [21]. Similarly, Killifish, *Fundulus diaphanous*, prefer not to shoal with conspecifics that have been painted to appear parasitized [22].

A further strategy to avoid parasitisation is not to eat conspecifics, even when severely food-stressed. Few animals feed on their own species. Unusually, Tiger Salamander larvae *Ambystoma tigrinum nebulosum* have cannibal and non-cannibal varieties, but the cannibals carry higher numbers of intestinal nematodes and bacteria [23].

As a hyper-social species, humans should be in particular need of infection-avoidance strategies. Do humans behave as in the other animal examples above: restricting group size, minimising contact, quarantining and avoiding the sick, testing the health of others, and refusing cannibalism?

Although there has been no comprehensive survey of human parasite-avoidance strategies, it does seem likely that we do. Hyper-sociality has conferred huge adaptive benefits [24–26], but we nevertheless restrict our social proclivities. The occasions on which we willingly risk close contact with strangers are rare and serve special bonding needs (temple, party, cultural event). We find forced proximity with strangers unpleasant, for example, seeking the least crowded carriage on the train or the far corner of the lift. In workplaces we seek the greatest distance from others as possible commensurate with social interaction. It is considered bad manners to sit too close to someone or to breathe in their face. An international web-recruited sample found that a photo of a full underground train was reported as significantly more disgusting than an empty one [27]. In the same study we also showed that an individual made up to look sick was found twice as disgusting as his healthy counterpart. Aversion for those who show signs of disability, disfigurement, sickness or odd behaviour that might betray the presence of parasites is well established [28,29], and such contact requires special effort [30]. Those who have psycho-social conditions that cause them to fail to observe norms of personal hygiene find themselves socially excluded. Quarantining behaviour is ancient in humans, *cf* this biblical example:

> If the shiny spot on the skin is white but does not appear to be more than skin deep and the hair in it has not turned white, the priest is to isolate the affected person for seven days. On the seventh day the priest is to examine them, and if he sees that the sore is unchanged and has not spread in the skin, he is to isolate them for another seven days. *Leviticus 15/4-5*.

Do humans also avoid mating with those who show signs of sickness? I could find no studies addressing this question. However, in an examination of emotional decision-making Ariely showed that sex acts that involved urination, anal sex, or sex with old or obese partners were found to be unattractive, but became less so when the student subjects were placed in a 'high lust condition' [31]. Do humans also test the health of potential mates by provoking them to fight? Experimental evidence is lacking, but it is known that young men take more risks in competition when potential mates are watching, so advertising their fitness and lack of infectious disease [32].

Humans also tend to avoid cannibalising conspecifics. There are few examples of humans eating humans for food, other than in exceptional conditions of starvation, war, or bonding rituals (Curtis, 2013b).

Humans then, like other social animals, balance the trade-off between the need for sociality and the need to avoid the associated infection risks, for example, measles, diarrhoeal diseases, respiratory infections, malaria, smallpox, cholera, plague, as well as ectoparasites that vector numerous infections [33]. Humans only accept sharing bodily fluids with others in specific circumstances, for example, when mating or when kin or sick others need tending. Handshaking and kissing deliberately violate this no-contact rule. Such actions may serve as a costly and hard to fake signal of social commitment, implying that one is willing to make an investment in the other, despite the disease risk.

Avoid species that are parasitic or which vector parasites

The second type of animal infection-avoidance behaviour is to keep away from other species that might be, or might vector, a parasite. Such behaviour is common across taxa. *Caenorhabditis elegans*, for example flees parasitic *Bacillus thuringiensis* placed in its petri dish [34]. Rainbow trout (*Oncorhynchus mykiss*) swim away from parasitic eye flukes that cause blindness, and, as a result, suffer fewer infections [35]. Multiple species of lice, fleas, ticks, mites, blood-sucking flies, mosquitoes, leeches, as well as bacteria and fungi, exploit the epidermis of vertebrates. Avoidance behaviour includes cattle swishing their tails to drive away tsetse flies, fish and elephants scraping themselves, vampire bats (*Desmodus rotundus*) scratching to remove batflies [36], and impala using their teeth as tick combs [37]. Elephants use tree branches to switch flies [38].

Animals face a trade-off dilemma about what to eat. Prey species may provide good nutrition but may also harbour parasites. Oystercatchers (*Haematopus ostralegus*) feed, not on the biggest cockles (*Cerastoderma edule*) because these have the most parasites, nor on the smallest, because these are too costly to feed from, but from middle-sized cockles, thus balancing the need for a cheap and a safe feed [39]. Predators may find it easier to prey on the sicker, weaker members of a prey troupe, but if they do they run a high risk of infection. Prey killed by predators are consistently infected with more trematodes, nematodes, and ectoparasites than randomly collected individuals [40]. However, adaptive trade-offs are complicated by the fact that it is in the interest of the parasite to manipulate the behaviour of the host to make it more attractive and easier prey to predators, and is therefore not clear whether predators do avoid parasitized individuals [41]. The omnivorous rat has the ability to learn to avoid foods that are associated with parasite infection [42].

Humans display many behaviours that serve to avoid parasites, or the species that vector them. Humans groom themselves and each other to remove ectoparasites such as lice, scabies mites, and ticks. They avoid consuming helminth or nematode worms or worm eggs in foods. Like rats we avoid foodstuffs that are paired with an episode of infection [43]. There are always trade-offs; humans may be attracted to domestic companion animals, but few will choose to pet a mange-infested dog or a cat with weeping sores. A satiated person is more likely to avoid parasite-infested meat than a hungry one [44]. In some cultures pork is prized for its flavour, despite it being likely to harbour pathogens and parasites adapted to humans [45]. Parasites in all of their visible forms as well as most parasite vectors (rats, bats, snails, cockroaches, flies, pigs and sick animals) occasion emotional disgust responses and behavioural avoidance [46–49].

Avoid objects and situations of infection risk

The third behavioural means of avoiding becoming prey to a parasite is to keep away from objects and environments where there is an elevated risk of parasite encounter. Ants of the species *Temnothorax albipennis* avoid building nests in sites where they find dead ants, presumably because dead conspecifics are a cue to local parasite risk [50]. If *Acromyrmex striatus* ants encounter a patch of fungal spores close to their nest they close off the nearest entrance, presumably to help prevent nestmates importing contamination [51]. The water flea (*Daphnia magna*) must balance the dual risks of predatory fish near the surface and parasitic bacteria in the mud at the bottom of the water column. When extracts of predatory fish were added to the top of a tank they swam nearer the bottom, and ended up with an increased load of microbial parasites [52]. Birds have also been documented to avoid parasite-rich environments. Opplinger and colleagues offered great tits (*Parus major*) two types of used nest boxes to choose from. One half were infested with blood-sucking hen fleas (*Ceratophyllus gallinae*), whereas the others had been microwaved to kill the parasites. Of the 23 pairs of great tits that started breeding, three quarters chose the parasite-free nests [53].

Herbivores face another trade-off dilemma. Soils that have been fertilized with dung produce more nutritious grass, but also contain more parasite larvae. In feeding tests, sheep avoided grass laced with gastrointestinal nematode-containing faeces [54]. Reindeer and caribou may migrate each year because they are looking for clean, dung-free pasture on which to feed, calve, and bring up their young [55].

Humans manifest similar avoidance responses to environments and objects with elevated parasite risk. We avoid the body products of other humans such as shed blood, urine, and faeces, as well as items contaminated with them such as medical wastes, used tissues, menstrual items, and soiled linen. Given the choice, we prefer clean, dry environments in which to live, avoiding slums with poor drainage, wastes, and lack of toilets. A hotel with a reputation for bedbugs will lose custom [56]. Graveyards are unlikely picnic sites. Anthropologists relate that one of the reasons that nomadic pastoralists in Mongolia and the Kalahari choose to migrate is the build-up of wastes around campsites.

Alter the niche to discourage parasites

The fourth means that animals use to avoid parasitic infection is to modify their niches so as to discourage parasites. Wood ants (*Formica paralugubris*) build resin from pine trees into the fabric of their nests to inhibit the growth of bacteria and fungi [57]. The nests of most social insects comprise many separate chambers instead of a single large hall. Mathematical models show that dividing nests into a series of rooms can help to reduce the severity of epidemics of disease [58]. Ventilation systems are often built into the nests of social insects, keeping them dry and therefore unconducive to fungal and microbial pathogens.

Animal wastes are not merely a source of parasites, they are a nuisance; they build up in the environment, they can attract predators, and they provide a substrate for fungal and bacterial growth. Sedentary species, in particular, need strategies to remove wastes; insects fling their frass, tent moths build latrines, birds and badgers defecate away from their nests [59]. However, the greatest parasite threat comes not from one's own wastes but from the wastes of conspecifics. Hence it is the social species that specialise in niche modification to prevent parasite infection.

Most ants remove faecal material as well as sick and dead colony members from their nests [60]. The social crickets (*Anurogryllus muticus*) share a special latrine chamber [61] and social spider mites (*Schizotetranychus* *miscanthi*) always use the same spot within their nest for defecation [62].

Insects can also do another sort of niche engineering – modifying their social environments to induce others to do their dirty work. Many species of ant have castes of cleaning workers, who collect the faeces, the sick, the dying, and the dead and carry them off to refuse piles a safe distance from the nest [63]. There are subdivisions of labour, with the ants that do the dirtiest work – on the midden – being segregated from those that collect the wastes. Any attempt by midden workers to socialise with others is met with aggression [63]. Older workers are more likely to be coerced into doing this dirty work [4].

Animals also modify their nests, their most immediate environments, and their external coverings as prophylaxis against pathogens. Blue tits in Corsica bring aromatic herbs to their nests, thus reducing bacterial infection in nestlings [64] and northern California dusky-footed wood rats bring flea-repelling bay leaves into their sleeping nests [65].

Over 250 species of bird are known to 'ant'; rubbing crushed insects such as millipedes over their plumage. This distributes compounds that protect them from bacteria, fungi, and arthropods. Grey squirrels and colobus, owl, and capuchin monkeys also rub their fur with leaves and fruit juices, probably for similar reasons [66].

As with other animals, humans also modify their personal, domestic, and social environments to reduce the threat of parasitisation. We use phytotoxic compounds such as lavandula, citrus, tea tree oil, and pine extracts on our bodies and hair, and in cleaning products (as well as synthetic antibacterials such as bleach and triclosan). Traditional purification rituals make use of many similar substances (astringents, bitter herbs, fire) [67]. We maintain our immediate environments by removing wastes that can harbour or nurture parasitic organisms. We defecate selectively, change bedding, launder clothes, clean utensils, remove food wastes, preserve foodstuffs, and use heat to kill spoilage agents and pathogens. Collectively as a social species we have invented many technologies to help us in these tasks, such as cleaning products, soaps, combs, hard surfaces in kitchens and bathrooms, solid floors and walls, and roofs and windows that prevent insect access and colonisation, fridges, cookers, kettles and microwaves. We have also built large-scale collective infrastructure which delivers safe food and water, removes sewage, and wastes and drains our habitat, keeping it low in parasites and pathogens.

Like ants, we also engineer our social niches to reduce the threat of pathogens. Those who behave unhygienically are found to be disgusting, and people who know they disgust others feel shame, which encourages them to improve their hygiene, in turn reducing the parasite threat [59]. Hence we use disgust to manipulate our conspecifics into lessening the threat they pose to us. Further, many human societies are stratified into those who do the dirty work (often immigrants or castes that are kept apart) and those with the means to keep themselves pure and above the dirt of daily life, hiring others to deal with wastes and dirt, hence protecting themselves from infection. Hygiene manners are inculcated into children at an early age, and this helps to protect all members of the social group from disease, representing a powerful type of social niche construction (Curtis, 2013b).

Therefore, as we have seen, animals including humans display behaviours that minimise their risk of becoming prey to pathogens. They use four strategies that mirror the epidemiology of infection risk: avoiding conspecifics, avoiding parasites and their vectors, avoiding parasite-rich environments, and constructing niches unconducive to parasites. What do we know about the production of these behaviours, how does this relate to immune function, and what are the implications for public health and for basic research?

Disease avoidance and immunity

We have described the neural system that drives parasite-avoidance behaviour across Animalia as the 'disgust adaptive system' [46]. This system is analogous to the fear adaptive system that organises flight, fight, or freeze behaviours in response to the perception of predation risk [68]. Pathogens, however, are hard to perceive, hence disgust responds to signals that reliably co-occur with infection risk, for example, to individuals manifesting olfactory or visible cues of infection. The disgust system, however, is not failsafe and the pathogens that do gain entry must be combated by the immune system. Disgust and immunity can thus be considered part of a continuum, with some molecular, cellular and mechanistic overlap that would suggest a probable shared evolutionary history [69]. The point of overlap for the two systems is the epithelium, including the skin and the gastrointestinal, respiratory, and genitourinary tracts. Here immune, sensory and behavioural responses to parasitic attack combine, for example, where penetration by an insect such as a jigger flea (*Tunger penetrans*) causes inflammation, which causes itching and then scratching, potentially serving to eject the parasite. There is a similar overlap of immune and behavioural response in sneezing, diarrhoea, and emesis.

What are the molecular signals that translate the sensing of a pathogen or an infected conspecific into a behavioural response? In general interactions between the immune, sensory, and behaviour control circuits are not well understood. We have hypothesised that the monoamine neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) provides a signalling pathway mediating both avoidance behaviour and immune systems [70]. In humans most 5-HT is found in the gastrointestinal tract, and is implicated in triggering emetic and peristaltic responses to pathogenic processes in the gut. It may also be implicated in the Garcia effect where humans and rats learn to avoid foodstuff previously been paired with an episode of nausea [71].

Serotonin is present in peripheral tissues as well as in many of the constituents of the immune system in humans [72]. In *C. elegans* serotonin functions as a negative reinforcing signal whereby the worm learns to avoid pathogenic bacteria previously paired with sickness [73]. The TIR-1–NSY-1–SEK-1–MAPK pathway, homologous to the p38 pathway in mammalian cells, is required for immunity against pathogenic microbes and is associated with the production of antimicrobial factors; this pathway has also been shown to involved in pathogen-avoidance behaviour [74] and is associated with serotonin production. Further the Gaq–RhoGEF Trio–Rho signalling cascade has been shown to trigger both an innate immune and a behavioural response to infection in the worm [75]

Much less is known about mechanisms bridging immune and behavioural-avoidance (disgust) responses in humans; however, studies suggest that these are in place. For example, Schaller showed that white blood cells from participants exposed to photographs of symptoms of infectious disease produced more interleukin-6 than those in the control condition (depicting guns) [76]. Miller and Maner showed that participants with a recent history of illness manifested stronger avoidance responses to signs of disfigurement [77] and Fessler has shown that the progesterone-induced downregulation of immunity during the luteal phase of the menstrual cycle is accompanied by a heightened compensatory prophylactic disgust response [78]. The molecular pathways that connect and regulate these responses, and the cellular systems (epithelial, immune and neuronal) involved, are fertile ground for further investigation.

Box 2. Important areas for future research

- Characterise infection-avoidance behaviour in multiple species
- Establish the genetic and neuroanatomical basis of the disgust adaptive system for disease-avoidance behaviour across species.
- From this characterise the workings of the disgust system in humans. Benefits could include: reducing the toll of infectious diseases through the promotion of safer hygiene [91], finding therapies for disgust pathologies (e.g., obsessive–compulsive disorder), better support those who have to deal with wastes and infectious processes, and countering social processes of stigmatisation and xenophobia [92].
- Establish the evolutionary history of the mechanisms shared by the disgust and the immune systems, in particular the role of serotonin.
- Investigate interactions between the disgust adaptive system and the immune system in a variety of animals, including the 'compensatory prophylaxis hypothesis' [78].
- Disgust is an adaptive system for disease-avoidance behaviour. We have proposed that there are multiple similar dissociable adaptive systems such as fear, nurture, love, status, play, and justice with evolutionary origins in animals antecedent to ourselves. Elucidating the evolutionary history of such motives and determining their discrete functions and mechanisms of behaviour production is a fundamental research agenda for psychology [93].

Concluding remarks

This paper has postulated a new classification of animal disease-avoidance behaviour according to the epidemiology of parasite infection risk: (i) conspecifics, (ii) parasites and their vectors, (iii) places and objects likely to harbour parasites – which can be avoided or, (iv) modified to avoid parasite risk arising. Other schemas such as that or Hart and Schmidt-Hempel overlap but are not as inclusive or systematic [2,79]. This fundamental classification of four infection-avoidance challenges predicts four types of behavioural response mechanisms. Each should have its own independent evolutionary history traceable in the phylogeny of brain tissue, neurochemistry and genetics. The human disgust system should carry out each of these four separate infection-avoidance tasks somewhat differently and these should be dissociable through factor analysis and brain imaging [30]. One system in particular deserves more attention: aversion to conspecifics has rarely been mentioned as a parasite-avoidance strategy, but illuminates much about animal and human behaviour [4]. Conspecific avoidance should have arisen separately each time sociality evolved, for example in social mammals and in insects, and hence should not share common mechanisms.

Avoidance behaviour is the first line of defence employed by free-living animals in their struggle to maintain fitness in the face of parasite threat, is likely the most cost-effective strategy as compared to resistance and tolerance, yet it is little researched. Understanding it better could lead to gains for animal and human health. Indeed, much about the biology of behaviour remains to be discovered; unpicking its discrete evolved disease-avoidance functions provides one excellent starting point for studies of the genetic, neurological, and neurochemical basis of behaviour in general [70,80]. Avoidance behaviour is the first part of a continuum of avoidance, resistance, and tolerance. These responses to the strong selection pressure applied by parasitic organisms throughout the evolutionary history of Animalia overlap, interact, and share an evolutionary history in ways that still remain to be elucidated. I discuss some important areas of inquiry in Box 2.

Although we have here sketched out the infection-avoidance behaviour of Animalia in general, humans have some special abilities with respect to disease avoidance. We can imagine a disgusting mess if foods are not stored safely. We can plan on a grand scale; for example to build a sewerage network to protect a whole town from pathogens. We can use microscopes, culture techniques, and gene amplification to detect and characterise pathogens, and the tools of epidemiology allow us to model and quantify infection risk. We use this body of knowledge to find new ways to avoid parasites.

Yet, despite all this knowledge, 2.5 billion humans do not have a safe toilet, and one billion have to defecate in the open [81]. Less than 17% of the world population wash their hands with soap after the toilet [82]. Inequalities in rates of infection show that avoidance behaviour has failed in the places that need it most. This favours the parasites. Poor environmental sanitation and hygiene lead to new variants of pathogens such as those that cause global cholera pandemics [83], poor animal husbandry favours new strains of influenza [84], and poor hospital hygiene is breeding strains of pathogens that we can no longer control with antibiotics [85]. *Homo sapiens* is a special animal because we understand the behaviour of parasites; however, we have still failed to understand our own behaviour well enough to extend the benefits of disease avoidance to the whole of our species.

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