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SYNTHESIS

Can we understand modern humans without considering pathogens?

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Abstract

Throughout our evolutionary history, humankind has always lived in contact with large numbers of pathogens. Some cultural traits, such as sedentarization and animal domestication, have considerably increased new parasitic contacts and epidemic transitions. Here, we review the various phenotypic traits that have been proposed to be affected by the highly parasitic human environment, including fertility, birth weight, fluctuating asymmetry, body odours, food recipes, sexual behaviour, pregnancy sickness, language, religion and intellectual quotient. We also discuss how such knowledge is important to understanding several aspects of the current problems faced by humanity in our changing world and to predicting the long-term consequences of parasite eradication policies on our health and well-being. The study of the evolutionary interactions between humans and parasites is a burgeoning and most promising field, as demonstrated by the recent increasing popularity of Darwinian medicine.

Introduction

There has probably never been a time in human's evolutionary history when we have not had contact with infectious life forms (viruses, bacteria, fungi, protozoa, arthropods and helminths) capable of causing us sickness, disease or death (Ashford 1991; Ewald 1994; Dobson and Carper 1996; Jackson 2000; Wolfe et al. 2007). The community composition of pathogens infecting humans has fluctuated greatly over time for several reasons (Barnes 2005). While the habitat of the first hominids was limited to tropical savannas, subsequent human migration and colonization of more temperate zones resulted in exposure to new pathogens (Armelagos et al. 1996). Group size and structure were among the primary factors influencing the dynamics and diversity of attendant parasites. Prior to the Neolithic, social groupings were more often than not composed of too few individuals for the maintenance of parasites that trigger protective immunity, have a high transmission coefficient and are infectious for

short periods of time (e.g. measles, mumps and influenza viruses). Conversely, pathogens that are persistently infectious and contagious (e.g. helminths, herpes viruses and *Helicobacter pylori*) could probably maintain themselves in these small human populations.

The Neolithic period witnessed several revolutions, including a parasitic one. An important change that occurred during this era was the organization of sedentary societies around centralized villages, making possible the gathering of a larger number of individuals than ever before. An almost immediate consequence of this was the appearance and persistence of several infectious diseases such as mumps, measles, influenza and smallpox. Still within the Neolithic, the proximity of humans and animals was accentuated by the domestication of livestock, a phenomenon linked to an upsurge of zoonoses (Polgar 1964; Ashford and Crewe 1998). It is hypothesized, for instance, that the paramyxovirus responsible for measles was introduced to humans through the domestication of poultry or ruminants and that its transmission to man

goes back as little as a few 1000 years (Gauthier-Clerc and Thomas 2010). Today, it is assumed that several contemporary diseases infectious to humans have an animal origin and that the beginning of pathogen transfers goes back to the Neolithic (Bennett and Begon 1997; Barrett et al. 1998; Wolfe et al. 2007).

The many environmental changes linked to the sedentarization of populations (roads, deforestation and mining) were also responsible for perturbations in the structure and functioning of ecosystems, sometimes leading to the proliferation of parasites (e.g. through the proliferation of rodents – the plague, for instance, was primarily a disease of small mammals and rodents in particular – through the creation of habitats favourable to insect vectors and through faecal pollution) (McNeill 1976, 1978; Risse 1988; Knapp 1989; Barrett et al. 1998). During their extensive travels, European explorers also transmitted infectious diseases (e.g. whooping cough, measles and smallpox), which decimated local indigenous populations within thousands of kilometres of their settlements (e.g. native Americans) (McNeill 1976; Black 1990; Dobyns 1993).

The world as we know it today is confronted with biological perturbations at scales and frequencies that are without precedent, including crises of health and hygiene that signal the emergence or re-emergence of pathogens (Gauthier-Clerc and Thomas 2010). Thus, humankind's constant modification of its habitat and customs throughout history has also effected profound changes within its pathogen community.

What roles did parasites play in human evolution?

In recent years, an increasing number of studies have demonstrated, or suggested, that multiple aspects of our biology – more specifically our life history traits, several of our behaviours and even our cultural diversity – are linked to our parasitic constraints. We easily forget (especially in the developed world) that a minor infection that is easily treated today with antibiotics could have been fatal only a few decades ago. This seemingly innocuous statement carries with it very serious implications, highlighting the major role played by parasitic constraints during human history. Even today, this phenomenon is far from being over, because parasites (in the largest sense) directly or indirectly kill millions of people each year. What are the strategies developed by humans to avoid the risks and/or consequences of infection for themselves or their descendants? Are humans themselves manipulated by parasites? Here, we review these roles of parasites, keeping in mind that explanations other than parasites can possibly apply in many cases.

Parasitism and human life history traits

Evolution of fertility and size dimorphism between males and females

Considerable variation in fertility (mean number of offspring per female) exists among different human populations. Guégan et al. (2001) proposed that this variation was at least partially attributable to the diversity of pathogen communities. In this comparative study encompassing 150 countries, the authors demonstrated that, all things being equal (in this case statistically correcting for bias associated with financial status, geography, culture and so on), fertility increases as the diversity of serious infectious diseases increases (e.g. malaria, yellow fever, dengue and cholera). The high level of infant mortality owing to diseases would be accompanied by a compensatory response to produce more offspring. This work not only illustrates a theoretically predictable adaptive response, but it also suggests that the global fight against parasitic diseases should paradoxically slow down human demographic growth because it would lead to a decrease in fertility (by halting the compensatory fertility response) in those countries that have the highest prevalence of diseases.

In another study, the same authors suggested that fertility variations between countries also influenced size dimorphism between males and females (males are on average taller than females, but the extent varies). In countries with the highest fertility, smaller females have been shown to be selected against because the risk of encountering a fatal obstetric problem is higher than for taller females (although caesareans reduce these risks today). In these countries, the sexual dimorphism is therefore less pronounced. Conversely, in countries with low fertility, the risks associated with childbirth are lower because there are fewer births, and therefore, there is not the same selective pressure favouring taller females. As a result, a more pronounced sexual dimorphism is observed (Guégan et al. 2000).

Evolution of birth weight

As is the case with fertility, average birth weight varies significantly among human populations (Kleinman and Kessel 1987; Vangen et al. 2002). The reasons for this are many; for instance, we know that the quantity of nutritional resources, stress, parental size, altitude and tobacco consumption can influence birth weight (see Abell et al. 1991; Brabin 1991; Emanuel et al. 1992; Zhang and Savitz 1992; Defo and Partin 1993; Koupilova et al. 2000; Wells 2002). While medical experts usually relate birth weight to current environmental constraints, evolutionary biologists have also proposed that some of the observed variation is because of the influence of natural selection.

Indeed, we expect that humans (like any other mammal) should maximize their fitness not only by producing more descendants, but also by producing offspring with an optimal birth weight considering local environmental constraints. Knowing that larger offspring are generally more resistant to infections or are better capable of tolerating their effects, Thomas et al. (2004) had predicted that (all things being equal) there should exist a positive relationship between the mean birth weight and the diversity of endemic infectious diseases. Their comparative study, encompassing 89 countries, supported the prediction: when the number of serious infectious diseases increases above a threshold, there was a concomitant increase in the average birth weight.

Lifespan

Although there is considerable variation between countries, men have, on average, shorter lifespans than women (5 years shorter on average; Møller et al. 2009). There are multiple causal factors for this phenomenon. For instance, men (like the males of many other species) experience an increase in fitness when monopolizing larger quantities of resources, because they are then more attractive to the opposite sex (Buss 1989, 1992). However, the costs associated with direct or indirect competition between males at the beginning of their reproductive life are reflected in an accelerated senescence as compared to females (Clutton-Brock and Isvaran 2007).

Furthermore, as is the case for many other species (e.g. fish, birds and mammals; see Poulin 1996), men have shorter lifespans than women because they are also more susceptible to infections or to their consequences (Teriokhin et al. 2004). This marked difference in susceptibility to pathogens between men and women is also observed very early in life, a fact that has been well acknowledged by medical epidemiologists (see for example Read et al. 1997; MacDorman and Atkinson 1998) and for which an extension of the Trivers–Willard hypothesis might provide an evolutionary explanation (Trivers and Willard 1973). Let us begin by reviewing this hypothesis. Because the variance in reproductive success is higher for men than for women, it is theoretically predicted that, in a scenario where resources were optimal, it would be advantageous for females (in evolutionary terms) to produce male offspring: when males are of high quality, they generally have high reproductive success. On the other hand, in conditions of low resource availability, it would be more advantageous for mothers to produce females, as the variance associated with their reproductive success is less dependent on resources. The fact that gender is genetically determined does not hinder this reasoning because multiple mechanisms exist for biasing the pri-

mary or secondary sex ratios (e.g. physiological preferential selection or not of sperm carrying Y chromosomes and spontaneous differential abortion). Several mammalian studies have provided support for the Trivers–Willard hypothesis (see for example Cameron 2004; Roche et al. 2006). Although still hotly debated, this theory also appears to be applicable to humans. For example, as predicted by the theory, billionaires have significantly more male offspring compared with the rest of the population (Cameron and Dalerum 2009). Within the polygamous Mormons of the 19th century, women who were married to higher-status men produced significantly more male offspring than those married to lower-status men (Mealey and Mackey 1990; see also Bereczkei and Dunbar 1997; Gibson and Mace 2003; Mathews et al. 2008).

Within the framework of this theory, natural selection would have, according to Wells (2000), favoured all mechanisms that would enhance the vulnerability of young males compared with females, and not only from conception until birth but also until weaning. From an evolutionary perspective, this phenomenon would in essence (for the mother) limit the occurrence of the most unfavourable scenario: investing time and energy into parental care of a male offspring whose eventual reproductive success is limited, and this without being able to reproduce again until the latter is weaned. In this case, the evolutionary cost is certainly not negligible if we consider the fact that nursing can take up to 4 years (Blurton-Jones 1986) and, in situations of low resource availability, prevents the mothers from procreating again. Thus, the nature of the post-natal disease spectrum could partially be attributed to natural selection of physiological traits that maximize maternal reproductive fitness. This model suggests that regardless of improvements in medical care, any environmental stress – especially malnutrition – that interacts with infection after birth will always affect males more severely than females in early life (Wells 2000). Furthermore, reductions in mortality that translate into increases in early morbidity may directly increase the sex difference in disease prevalence.

Menstruation

The end of the ovarian cycle in many primates, including humans, is characterized by a loss of blood and the shedding of the uterine lining (endometrium); this phenomenon is termed menstruation. Although the proximate causes of this biological phenomenon are clearly understood, the evolutionary significance remains more enigmatic. Certain authors, such as Profet (1993), have postulated that menstruation evolved to prevent the colonization of the uterus and oviducts by pathogens transmitted by sperm. Although interesting, this hypothesis

has been greatly criticized (see for example Martin 2007), especially given the fact that some of the predictions made by Profet (1993) have not been demonstrated. For instance, at the interspecies level, there is no link between the abundance of menstruation and the degree of sexual promiscuity (Strassman 1996). There is still no consensus on the evolutionary significance of menstruation; certain authors even argue that it could be a nonadaptive trait (Finn 1998).

Many 'nonparasitic' diseases have a parasitic origin!

When humans do not die of old age, by an accident or by parasitic diseases, they die of somatic diseases (e.g. cancers, cardiovascular diseases and mental illness). When not fatal, these illnesses can still be exceedingly disabling or incur devastating consequences (e.g. schizophrenia). While it has been customary to distinguish parasitic from somatic diseases, an increasing number of studies have confirmed that many of the diseases classically thought to be 'nonparasitic' in origin do indeed have an infectious origin (Cochran and Ewald 2000). These discoveries are of profound significance because infections are often avoidable (through vaccinations for example) or treatable; the associated somatic illnesses could then be avoidable.

Cancers

In the early 1970s, 1% of cancers were estimated to be of parasitic or viral origin. Today, the World Health Organization states that 20% of cancers are caused by infectious agents, with special emphasis on RNA and DNA viruses and bacteria. For instance, hepatocellular carcinomas (the most common liver cancer), stomach cancers and cervical cancers are largely attributable to hepatitis B and C viruses, *H. pylori* bacteria and to human papillomavirus, respectively (De Martel and Franceschi 2009). Ewald (2009) suggested that by 2050, scientists may have demonstrated that most cancers have an infectious origin. What are the characteristics of oncogenic pathogens and how do they cause/trigger normal healthy cells to become cancerous? Ewald (2009) highlighted the fact that the vast majority of pathogens capable of causing cancers are those that are transmitted through intimate contact (sexual relations or intimate kissing) and have a relatively low transmission rate (as compared to the flu virus for instance) but persistent and often permanent infections (e.g. herpes virus). This aspect is crucial to the understanding of why and how these viruses lead to the derailment of cellular processes causing cancer.

Normal healthy cells have at least four fail-safes that prevent them from falling into the unicellular self-

centeredness of cancerous cells: they only divide when having been told to do so, they commit suicide (apoptosis) when they have accumulated too many genetic anomalies, they have a limited number of cell divisions (unlike cancerous cells, which are immortal thanks to an activated telomerase) and finally they adhere to one another, thus preventing them from metastasizing, which cancer cells do during the generalization phase of the disease. It is interesting to note that, although oncogenic pathogens are phylogenetically diverse, they are all capable of sabotaging these four barriers; this is indeed favourable to their preservation and transmission over long periods of time during which they must reside in the host and escape the host's immune system. The major problem associated with this sabotage is that it allows mutations to accumulate within cells and prevents these modified cells from being eliminated through apoptosis (Ewald 2009). The number of mutations will also increase with exposure to mutagens (tobacco, alcohol, etc.). When mutations begin to affect the zones responsible for one of the four anticancer fail-safes, the cells are no longer simply sabotaged or 'manipulated' by a pathogen within the context of its replication strategy, they are considered genetically cancerous: neither the host nor the pathogen have control over the cells' anarchic replication. There are several other proximate mechanisms by which pathogens can transform healthy cells into cancerous ones, for example, through the induction of chromosomal instability and translocations as well as inflammatory responses (see zur Hausen 2009 for a review). The infectious origin of cancer is currently a hot topic in research.

Mental illnesses

Since the 1930s, we have known that many mental illnesses do not always have a neurological or psychological origin; in certain cases, they may be caused by bacterial, viral and even parasitic infections incurred *in utero*, through childhood and even as adults (McSweegan 1998; Boksa 2010). For example, pre- or post-natal exposure to the herpes simplex 2 virus (the causative agent of genital herpes) could lead to cerebral anomalies resulting in psychosis or schizophrenia (Buka et al. 2001; Babulas et al. 2006). When not treated, the causative agent of syphilis (*Treponema*) has also been shown to induce psychiatric troubles such as hallucinations and dementia (Henry et al. 1978).

Let us focus our discussion on a parasite that has received much attention lately: the protozoan *Toxoplasma gondii*. This parasite is extremely common worldwide, with 30–40% of the world's population estimated to be infected. In recent years, an increasing number of studies have suggested that this parasite is associated

with mild-to-serious neurological disorders in humans (Webster 2001; Henriquez et al. 2009; Flegr 2010; Lagrue and Poulin 2010; review in Poulin and Levri in press). The life cycle of this parasite can be either complex or simple. The parasite develops in the intestinal cells of felines (e.g. cats), and the oocytes are expelled along with the faecal matter. It is therefore possible for the parasite to complete its life cycle directly by re-infecting a feline host or indirectly by infecting another warm-blooded vertebrate (usually rodents), which serves as intermediate host. Within the intermediate host, the parasite reproduces asexually and forms permanent cysts, which are primarily found in the brain. Humans are typically exposed to *T. gondii* through contaminated kitty litter or contaminated meat that is not properly cooked. According to conventional medicine, *T. gondii* infections are only problematic for pregnant or immunosuppressed individuals acquiring the parasite for the first time. In all other cases, infection results in flu-like symptoms that dissipate rapidly. Studies have demonstrated that *T. gondii* in infected rodents induced behavioural modifications that facilitate parasite transmission, including slower reaction times. The most striking of these modified behaviours is the apparent disappearance of the innate aversion to cat urine in infected rodents; indeed, they have even been shown to be attracted to these predators (Berdoy et al. 2000; House et al. 2011). As in rodents, infection in humans is associated with significantly slower reaction times. In the past, this phenomenon could have been adaptive because it could eventually lead to increased predation by felines; today, this decrease in vigilance is predominately linked to higher levels of car accidents in infected individuals (Flegr et al. 2002; Yerehi et al. 2006; Kocazeybek et al. 2009). Although not necessarily systematic, *T. gondii* infection can also be linked with serious psychiatric disorders, such as bipolarity (Hinze-Selch 2002), dementia (Freidel et al. 2002; Habek et al. 2009), obsessive-compulsive disorders (Miman et al. 2010a), Parkinson's (Miman et al. 2010b), hyperactivity, epilepsy (Prandota 2010), depression (Miman et al. 2010a) and, last but not least (with over 40 studies demonstrating it), schizophrenia (Ledgerwood et al. 2003; Torrey et al. 2007; see Poulin and Levri in press for a review).

In addition to serious neurological disorders, *T. gondii* infection is also linked to personality changes. Even though an increased sense of guilt in infected individuals is common in both sexes, males and females otherwise respond differently to infection. Infected males tend to have lower self-esteem, to be more suspicious and jealous and less likely to obey rules. In females, these tendencies appear to be reversed: infected females are friendlier, more conscientious and perseverant. According

to Lafferty (2006), as the prevalence of infection varies from 0% to 100% depending on the country, the behaviour of entire nations could be influenced by this parasite. In a comparative study encompassing 38 nations, he detected a positive correlation between aggregate neuroticism and seroprevalence of *T. gondii*, suggesting a higher overall obsessiveness and anxiousness in countries where the parasite is frequent. For Western nations, there were also positive correlations between *T. gondii* seroprevalence, masculine sex roles and uncertainty avoidance. There could be significant cultural implications from these parasitic effects. For instance, nations rated as having stronger masculine sex roles are more likely to have more gender-specific roles in family and work, to be more materialistic, more ego-driven and to focus more on individual achievement than on life quality and interpersonal relationships (Lafferty 2006; see also Poulin and Levri in press). Nations with greater uncertainty avoidance are also expected to develop more rule-oriented societies because this limits exposure to uncertain situations. Lastly, although this pathogen is not viral, Thomas et al. (2011) showed that incidences of brain cancers are significantly higher in countries with high *T. gondii* infection rates. Given how common toxoplasmosis is in the global human population, it appears crucial to determine whether its biology is indeed associated with tumour formation.

The level of fluctuating asymmetry

The majority of our features have a left-right type of symmetry (eyes, arms, etc.). However, this symmetry is imperfect because of a phenomenon known as fluctuating asymmetry; essentially, normally developing individuals are unable to allocate identical resources to both the left and the right parts of the body. The implications of fluctuating asymmetry in evolutionary ecology are considerable, especially in the context of mate selection where preference is biased towards highly symmetrical individuals (Scheib et al. 1999). There are at least two reasons for which there can exist a positive relationship between the level of fluctuating asymmetry and parasitic infections (see Møller 1996, 2006 for reviews). Firstly, the most asymmetrical individuals could also be those with the weakest immune systems. Here, asymmetry reflects the overall poor condition of the individuals, and it is therefore not surprising that they are more sensitive to parasitic infection. Secondly, parasites can also be directly involved in causing asymmetry when the energy that is supposed to be allocated to developmental homeostasis is too often transferred to the immune system because of repeated parasitic infections.

Body odours

A large number of parasitic diseases as well as cancers are accompanied by changes in body odour (see Prugnolle et al. 2009 for a review). Although this phenomenon has been known for some time, it is surprisingly seldom used in diagnosis. Few studies have explored the underlying causes of this phenomenon and its evolutionary consequences on interpersonal relationships. When dealing with diseases that are caused by pathogens transmitted by insect vectors (e.g. malaria and dengue), it is tempting to think that the modifications to body odour could be parasitic manipulations aimed at increasing the transmission of the parasite towards its vector. Interestingly, this idea has been confirmed in animal models (e.g. Mahon and Gibbs 1982; Baylis and Nambiro 1993; O'Shea et al. 2002). In humans, the demonstration that these changes in body odour are adaptive is still debated. To date, the most promising work supporting the theory is that of Lacroix et al. (2005), which demonstrated that the causative agent of malaria *Plasmodium falciparum* renders the male carriers of the stage infective to the vector more attractive (by way of body odour) to the mosquito vector in search of a blood meal.

The diversity of the MHC

The genetic polymorphism of populations can also be directly influenced by parasitism. The human leucocyte antigen [HLA, also known as the major histocompatibility complex (MHC)] system is a gene complex that plays a central role in the recognition of self and nonself and is involved in presenting nonself to the effector cells of the immune system. MHC molecules function to present foreign antigens. A person's MHC make-up is therefore very likely to influence their particular vulnerabilities to infection. Interestingly, the genes coding for HLA are among the most polymorphic genes in humans: the single HLA B gene has had close to 400 alleles identified so far in the world population. Why are these genes so polymorphic? It seems clear that these genes were exposed to strong balanced selective pressures, meaning that they were submitted to a type of selection favouring the maintenance of polymorphism within populations. Many causal mechanisms have been put forward, from the avoidance of crossbreeding between kin (with HLA playing a role as a marker of relatedness between individuals) to the selection imposed by the diversity of pathogens encountered by populations. This latter type of selection is expected if each allele is maintained within the population because of its capacity to confer protection against one or several particular pathogens. Many studies are in agreement with the concept of balancing selective pressure imposed by

pathogens, most notably that of Prugnolle et al. (2005). These authors analysed the genetic diversity of the HLA genes in 61 human populations from significantly different parasitic environments. Once the portion of the genetic diversity that is attributed to the demography of the population (and not selection) is corrected for, the authors were able to demonstrate that the residual portion of the genetic diversity of HLA genes – explained solely by selection – was positively correlated with the pathogen diversity to which the populations were exposed. Populations residing in zones where parasite diversity was highest are in effect subjected to stronger balancing selective pressures from pathogens and therefore have the highest level of polymorphism in the HLA genes. The work of Prugnolle et al. (2005) strongly demonstrates how pathogens (and their diversity) could have shaped the diversity of certain genes in humans. In the same context, Barnes et al. (2010) demonstrated that the frequency of the SLCA1 1729 + 55del4 allele that confers a resistance to several intracellular pathogens (e.g. the causative agents of tuberculosis and leprosy) increases with the age of the city. These results are in accordance with the hypothesis that the regrouping of human societies into large urban bodies was accompanied with an upsurge of deadly infectious diseases, simultaneously leading to a selection for resistant individuals.

Sleep and afternoon naps

The significance of sleep remains a complete enigma to evolutionists. It is relatively easy to identify the many costs associated with sleep (vulnerability to predators and/or insect vectors, no foraging or mating opportunities during this state, etc.), but the benefits are more difficult to determine. Paradoxically, sleep appears to be a strict necessity in a great number of species (deprivation of sleep is usually rapidly accompanied by negative effects). Several works have suggested that sleep has evolved to allow organisms to allocate more energy to the immune system. It is well known that sleep deprivation is linked to increased vulnerability to infections (Everson and Toth 2000; Spiegel et al. 2002) and that we sleep more when we are ill (Toth and Krueger 1989), which significantly accelerates recovery (Toth et al. 1993; Lange et al. 2003). To function properly, the immune system requires a significant proportion of our daily energy budget (Lochmiller and Deerenberg 2000). Within this context, an elegant way of allocating more energy to the immune system is to place all the other functions in 'rest mode', in other words, put them to sleep. A recent interspecific study on mammals supports this prediction: more the species sleep, the better their immune system functions and the fewer parasites they have (Preston et al.

2009). This immunity hypothesis for the role of sleep still needs to be explored, especially in humans.

Spices in cooking

Although spices have been used in cooking for several 1000 years, there exists great variability in this practice among nations. Several authors have proposed that the use of spices has evolved in response to risks of infections as a great number of spices have antimicrobial properties (Nakatani 1994; Billing and Sherman 1998; Sherman and Billing 1999). Following this hypothesis, we would expect that (i) all things being equal, the use of spices would be more pronounced in warmer countries, where the diversity and developmental rates of pathogens are higher and that (ii) recipes involving meats would be more associated with spices than those with vegetables because meats spoil more rapidly. Sherman and Hash (2001) tested these hypotheses by examining some 2129 cooking recipes taken from 107 traditional cooking books from 36 countries. They demonstrated, in accordance with the hypotheses, that the use of spices increases with the average temperature of the countries and that their use is more pronounced in recipes involving meats.

Selection and sexual behaviour

In many species, a way of increasing one's fitness is by selecting a sexual partner that will endow your progeny with higher levels of resistance to infection. Is there any remnant of this process in the modern human? The works of Wedekind et al. (1995) and Wedekind and Furi (1997) seem to indicate that there is. Their experimental protocol was elegant; it consisted of having young mature males wear a t-shirt for a given period of time, and the t-shirts were then given to women who had to rank them in order of preference based on smell. The results of the study indicated that females selected males whose MHCs were the most genotypically distinct from their own, which would give rise to descendants with high heterozygosity within the MHC region and therefore would be better equipped to face infections. In the same line of thought, Milinski and Wedekind (2001) demonstrated that individuals having portions of their MHC genotype in common tend to prefer the same perfumes. The authors suggest that the extensive use of perfumes for the last 1000 years could be explained by the fact that they somehow enhance body odour.

The avoidance of partners who are more susceptible to infection can also be done through the basis of fluctuating asymmetry (Thornhill and Gangestad 1993). Many environmental factors, most notably parasites, can induce a dissymmetry in traits that are normally symmetrical

(e.g. size or height of the eyes) (see above and Møller 2006 for review). Furthermore, several studies have also demonstrated that in sexual selection, symmetrical faces are more often preferred over nonsymmetrical ones (Thornhill and Gangestad 1993; Gangestad and Thornhill 1997, 1998; Thornhill et al. 2003).

Lastly, other than influencing the choice of sexual partners, infectious diseases can also modify sexual behaviours, favouring more 'prudent' attitudes when infection risks are high (Schaller and Murray 2008). This phenomenon is more pronounced in females than in males, as the former have more to lose than to gain (in terms of fitness) by having multiple sexual partners in areas of high risks of infections.

The evolution of disgust and nausea

Long before being able to visualize pathogenic microorganisms under the microscope, humans (as well as other species) developed a plethora of hygienic behaviours that probably limit the risks of infection (such as quarantine practice). The evolution of such behaviours is not surprising, especially when we consider that an act as simple as the washing of one's hands efficiently reduces the risks of acquiring pathogens responsible for diarrhoea and currently saves millions of lives in certain areas of the world (Curtis 2003). General attitudes of disgust towards potential sources or carriers of pathogens are also considered to be psychological adaptations that evolved to avoid infection. These behaviours are present in all societies, although their innate or cultural characters are still debated (see Curtis and Biran 2001; Curtis et al. 2011 for reviews).

The nausea and vomiting of pregnant women have been at the centre of many controversies. This interesting phenomenon is found in almost all human cultures, from the Jivaros to Europeans and even among Romans some two millennia ago. Essentially, it is manifested during the period when the embryo's organs are developing, within the first 3 months of the pregnancy. Here, nausea and vomiting are triggered in pregnant women by foods that would have no effect when consumed by other individuals. In fact, nausea and vomiting are usually triggered even before the food is ingested. We are therefore dealing with a very specific manifestation, involving more than 60% of pregnant women, which demands an explanation (Flaxman and Sherman 2000). To avoid rejecting the precious foreign body within her womb, the immune system of the pregnant woman is attenuated (immunosuppression). The lowered activity of the immune system is compensated for by pathogen avoidance behaviours, and it is within this framework that the nausea and vomiting of pregnant woman are currently interpreted. According to

several studies, the strongest and most common aversions, in the majority of the populations studied, are those towards meat, the food item that is the most susceptible to pathogen contamination (Flaxman and Sherman 2000; Fessler 2002). The metabolic cost of meat aversion is most likely not elevated, as the metabolic demands of the embryo during the first trimester are relatively modest. However, the gain achieved from avoiding contact with parasites is of great importance during this period of immunosuppression. As expected for an adaptive trait, there is a positive correlation between the presence of nausea and a decrease in stillbirths and a negative correlation between nausea and mean birth weight (Ronald et al. 1989). Nausea is sometimes so great that it could lead to lethal dehydration. This paradox can be resolved by considering the tendency for the bacteria *H. pylori* to exaggerate nausea, apparently to facilitate its transmission (Doyle et al. 2007). A profound understanding of the natural mechanisms through which humans are able to avoid infection could be of great importance and use to the implementation of preventative strategies in public health.

What of our IQ?

The intellectual quotient (IQ) is a measure of certain cognitive abilities that do not hold the same level of importance among different ethnic groups. Since the publication of the average IQ values of different nations (Lynn and Vanhanen 2001, 2002, 2006), six studies have attempted to identify the causes of the observed variations. The last of these studies deals with parasitic pressures (Eppig et al. 2010). The brain is the most complex and energy-hungry organ in the human body: in newborns, for example, the brain consumes 87% of the energy budget (Holliday 1986). According to Eppig et al. (2010), parasitic infections can have an impact on the proper development/functioning of the brain because they deprive the brain of a portion of the energy that it requires. For example, certain parasites (flukes) feed directly on host tissues. The energy necessary to compensate for this is energy that is no longer available for other functions, such as optimal brain function. Several parasites inhabit the host's digestive tract where they can cause diarrhoea; this in turn reduces the host's energy intake. Viruses utilize the host's cellular machinery – and therefore host's energy to work the machinery – to replicate. Lastly, immune responses are not without energetic costs for the host: the energy utilized to fight the infection is energy that is not available for the brain. The study, which sampled over 113 countries, demonstrated that infectious diseases are strongly negatively correlated with IQ, and this result remains significant even with the

addition of several correcting factors to the model (Eppig et al. 2010).

Recently, Bonds et al. (2010) built a mathematical model illustrating the complex and reciprocal relationships that exist between poverty and parasitic pressures worldwide. Their analyses concluded that pathogens (through their negative effects on the cognitive and physical capabilities of individuals) exert a negative influence on national economies. To make matters worse, the poverty that is a direct result of this is also an element that is favourable to the development of parasites. This interactive phenomenon would explain why the poorer countries of the planet are also those that are the most frequently exposed to infections. Aside from the description of this dynamic, the model also predicted that the fight against diseases (malaria, AIDS, tuberculosis, etc.) should indirectly improve the economies of these poorer countries. Depending on the nature of the relationship between the different variables (e.g. linear, exponential) subtle effects on health could have strong consequences on the economics of those countries and *vice versa*.

Diversity of religions and languages

It has recently been argued that parasitic pressures may have indirectly favoured the emergence of multiple religions and languages within the tropics, where parasitic diversity is very high. What processes would be involved here? Because parasitic pressures in humans (as well as in many other animals) favour the emergence of behaviours aimed at avoiding contagion, for example, xenophobia or a limited propensity for dispersion (Faulkner 2004), they eventually lead to the fractioning of populations into smaller functional groups. This in turn would have favoured cultural differentiation to particular religions (Fincher and Thornhill 2008a) and languages (Fincher and Thornhill 2008b). Although it is evident that these correlative studies could not possibly explain all the variability in languages and religions through the presence of pathogens, they are interesting in that they show that we undoubtedly underestimate the roles that parasites played on the evolution of human culture (see also Hays 1998; McNeill 2006; Fincher et al. 2008).

Concluding remarks

Throughout our evolutionary history, humans have always lived in contact with a large number of parasites. In certain regions of the world, these contacts have recently been strongly diminished owing to large environmental or sociological changes. For example, the widespread access to running water, drainage of soiled water into sewers, desiccation of marshes, evolution of agricultural practices

and the 19th and 20th century ways of life are all major factors that explain the disappearance of malaria in Western Europe (Bruce-Chwatt and de Zulueta 1980). In more general terms, changes in hygiene and large-scale vaccinations during the 20th century as well as the increasing use of antibiotics in the mid-1940s have contributed to an unprecedented drop in the level of parasitism.

This has had some important positive consequences – for example, an increase in the mean life expectancy – that are usually attributed solely to medical progress but are essentially because of a lowering of contact with parasites (Armstrong et al. 1999), to which medical science has obviously contributed greatly. What has yet to be explored, and is of great interest, is an evaluation of the degree to which this drop in parasitism has contributed to other secular changes such as the increase in mean birth weight, the drop in fertility and the increase in IQ.

The reduction in parasitic contact has also had certain negative consequences stemming from the fact that we have indeed coevolved with these organisms and in doing so created complex interactions that are not easily terminated. Determining how these phenomena create a mismatch with our evolutionary heritage is becoming an increasing necessity in medicine to correctly assess modern health problems. For example, intestinal parasites such as flukes evolved the capacity of attenuating the type II immune response to increase their survival (Melendez et al. 2007). As a consequence of this, the human immune response also evolved a way of re-establishing normal immune expression in the presence of flukes. By suddenly eliminating all the intestinal worms, we are essentially favouring immune dysfunction; by removing the flukes, we are also removing an immune regulator leading to inappropriate immune (autoimmune) response. It is within this context that the recent major increase in allergies, Crohn's disease, type 1 diabetes and asthma, to name a few, might be better understood. The fact that Crohn's disease can be ameliorated by the ingestion of eggs of a parasite species that hatch but does not develop in humans, as demonstrated by Summers et al. (2005), opens the door to the possible application of parasites in the treatment of these autoimmune disorders (Falcone and Pritchard 2005). Contemporary human populations are composed of individuals responding to the recent absolute improvement of their lifestyle.

Most of the studies cited in this review does not provide definitive conclusions and therefore need to be confirmed by additional works. Nevertheless, the study of evolutionary interactions between humans and parasites is a burgeoning and most promising field, as demonstrated by the recent increasing popularity of Darwinian medicine (Nesse and Stearns 2008).

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Literature cited

- Abell, T. D., L. C. Baker, and Ch. N. Ramsey. 1991. The effects of maternal smoking on infant birth weight. *Family Medicine* **23**:103–107.
- Armelaos, G. C., K. C. Barnes, and J. Lin. 1996. Disease in human evolution: the re-emergence of infectious disease in the third epidemiological transition. *National Museum of Natural History Bulletin for Teachers* **18**:1–6.
- Armstrong, G. L., L. A. Conn, and R. W. Pinner. 1999. Trends in infectious disease mortality in the United States during the 20th century. *Journal of the American Medical Association* **281**:61–66.
- Ashford, R. W. 1991. The human parasite fauna: towards an analysis and interpretation. *Annals of Tropical Medicine and Parasitology* **85**:189–198.
- Ashford, R. W., and W. Crewe. 1998. *The Parasites of Homo sapiens: An Annotated Checklist of the Protozoa, Helminths and Arthropods for Which we are Home*. Liverpool School of Tropical Medicine, Liverpool.
- Babulas, V., P. Factor-litvak, R. Goetz, C. A. Schaefer, and A. S. Brown. 2006. Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. *American Journal of Psychiatry* **163**:927–929.
- Barnes, E. 2005. *Diseases and Human Evolution*. University of New Mexico Press, Albuquerque, New Mexico.
- Barnes, I., A. Duda, O. G. Pybus, and M. G. Thomas. 2010. Ancient urbanization predicts genetic resistance to tuberculosis. *Evolution* **65**:842–848.
- Barrett, R., C. W. Kuzawa, T. McDade, and G. Armelaos. 1998. Emerging and re-emerging infectious diseases: the third epidemiologic transition. *Annual Review of Anthropology* **27**:247–271.
- Baylis, M., and C. O. Nambiro. 1993. The effect of cattle infection by *Trypanosoma congolense* on the attraction, and feeding success, of the tsetse fly *Glossina pallidipes*. *Parasitology* **106**:357–361.
- Bennett, M., and M. Begon. 1997. Virus zoonoses – a long-term overview. *Comparative Immunology, Microbiology and Infectious Diseases* **20**:101–109.
- Berdoy, M., J. P. Webster, and D. W. Macdonald. 2000. Fatal attraction in rats infected with *Toxoplasma gondii*. *Proceedings of the Royal Society of London B* **267**:1591–1594.
- Bereczkei, T., and R. I. M. Dunbar. 1997. Female-biased reproductive strategies in a Hungarian gypsy population. *Proceedings of the Royal Society of London B* **364**:17–22.
- Billing, J., and P. W. Sherman. 1998. Antimicrobial function of spices: why some like it hot. *Quarterly Review of Biology* **73**:3–49.
- Black, F. L. 1990. Infectious disease and the evolution of human populations: the examples of South American forest tribes. In A. C. Swedlund, and G. J. Armelaos, eds. *Diseases in Population in Transition: Anthropological and Epidemiological Perspectives*, pp. 55–74. Bergin & Garvey, New York.
- Blurton-Jones, N. 1986. Bushman birth spacing: a test for optimum birth intervals. *Ethology and Sociobiology* **7**:91–105.

- Boksa, P. 2010. Effects of prenatal infection on brain development and behaviour: a review of findings from animal models. *Brain, Behaviour and Immunity* **24**:881–897.
- Bonds, M. H., D. C. Keenan, P. Rohani, and J. D. Sachs. 2010. Poverty trap formed by the ecology of infectious diseases. *Proceedings of the Royal Society of London B* **277**:1185–1192.
- Brabin, B. 1991. An assessment of low birthweight risk in primiparae as an indicator of malaria control in pregnancy. *International Journal of Epidemiology* **20**:276–283.
- Bruce-Chwatt, L. J., and J. de Zulueta. 1980. *The Rise and Fall of Malaria in Europe. A Historico-Epidemiological Study*. Oxford University Press, London, 240 pp.
- Buka, S. L., M. T. Tsuang, E. F. Torrey, M. A. Klebanoff, D. Bernstein, and R. H. Yolken. 2001. Maternal infections and subsequent psychosis among offspring. *Archives of General Psychiatry* **58**:1032–1037.
- Buss, D. M. 1989. Sex differences in human mate preferences: evolutionary hypotheses tested in 37 cultures. *Behavioral and Brain Sciences* **12**:1–49.
- Buss, D. M. 1992. Mate Preference Mechanisms: Consequences for Partner Choice and Intrasexual Competition. In J. H. Barkow, L. Cosmides, and J. Tooby, eds. *The Adapted Mind. Evolutionary Psychology and the Generation of Culture*, pp. 249–266. Oxford University Press, New York.
- Cameron, E. Z. 2004. Facultative adjustment of mammalian sex ratios in support of the Trivers-Willard hypothesis: evidence for a mechanism. *Proceedings of the Royal Society of London B* **271**:1723–1728.
- Cameron, E. Z., and F. Dalerum. 2009. A Trivers-Willard Effect in contemporary humans: male-biased sex ratios among billionaires. *PLoS ONE* **4**:e4195.
- Clutton-Brock, T. H., and K. Isvaran. 2007. Sex differences in ageing in natural populations of vertebrates. *Proceedings of the Royal Society of London B* **274**:3097–3104.
- Cochran, G. M., and P. W. Ewald. 2000. Infectious causation of disease: an evolutionary perspective. *Perspectives in Biology and Medicine* **43**:406–448.
- Curtis, H. 2003. Talking dirty: how to save a million lives. *International Journal of Environmental Health Research* **13**:S73–S79.
- Curtis, V. A., and A. Biran. 2001. Dirt, disgust and disease: is hygiene in our genes? *Perspectives in Biology and Medicine* **44**:17–31.
- Curtis, V., M. de Barra, and R. Aunger. 2011. Disgust as an adaptive system for disease avoidance behaviour. *Philosophical Transactions of the Royal Society of London B* **366**:389–401.
- De Martel, C., and S. Franceschi. 2009. Infections and cancer: established associations and new hypotheses. *Critical Reviews in Oncology and Haematology* **70**:183–194.
- Defo, B. K., and M. Partin. 1993. Determinants of low birthweight: a comparative study. *Journal of Biosocial Sciences* **25**:87–100.
- Dobson, A. P., and E. R. Carper. 1996. Infectious diseases and human population history. *BioScience* **46**:115–126.
- Dobyns, H. F. 1993. Disease transfer at contact. *Annual Review of Anthropology* **22**:273–91.
- Doyle, C., H. A. S. Ewald, and P. W. Ewald. 2007. Premenstrual syndrome - an evolutionary perspective on its causes and treatment. *Perspectives in Biology and Medicine* **50**(2):181–202.
- Emanuel, I., H. Filakti, E. Alberman, and S. J. W. Evans. 1992. Inter-generational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect. *British Journal of Obstetrics and Gynecology* **99**:67–74.
- Eppig, C., C. L. Fincher, and R. Thornhill. 2010. Parasite prevalence and the worldwide distribution of cognitive ability. *Proceedings of the Royal Society of London B* **6**:1–8.
- Everson, C. A., and L. A. Toth. 2000. Systemic bacterial invasion induced by sleep deprivation. *American Journal of Physiology – Regulatory Integrative and Comparative Physiology* **278**:R905–R916.
- Ewald, P. W. 1994. *Evolution of Infectious Disease*. Oxford University Press, New York, NY.
- Ewald, P. W. 2009. An evolutionary perspective on parasitism as a cause of cancer? *Advances in Parasitology* **68**:21–43.
- Falcone, F. H., and D. I. Pritchard. 2005. Parasite role reversal: worms on trial. *Trends in Parasitology* **21**:157–160.
- Faulkner, J. 2004. Evolved disease-avoidance mechanisms and contemporary xenophobic attitudes. *Group Processes and Inter-group Relations* **7**:333–353.
- Fessler, D. M. T. 2002. Reproductive immunosuppression and diet. An evolutionary perspective on pregnancy sickness and meat consumption. *Current Anthropology* **43**:19–61.
- Fincher, C. L., and R. Thornhill. 2008a. Assortative sociality, limited dispersal, infectious disease and the genesis of the global pattern of religion diversity. *Proceedings of the Royal Society of London B* **275**:2587–2594.
- Fincher, C. L., and R. Thornhill. 2008b. Parasite-driven wedge: infectious diseases may explain language and other biodiversity. *Oikos* **117**:1289–1297.
- Fincher, C. L., R. Thornhill, D. R. Murray, and M. Schaller. 2008. Pathogen prevalence predicts human cross-cultural variability in individualism/collectivism. *Proceedings of the Royal Society of London B* **275**:1279–1285.
- Finn, C. A. 1998. Menstruation: a non-adaptive consequence of uterine evolution. *Quarterly Review of Biology* **73**:163–173.
- Flaxman, S. M., and P. W. Sherman. 2000. Morning sickness: a mechanism for protecting mother and embryo. *Quarterly Review of Biology* **75**:113–148.
- Flegr, J. 2010. Influence of latent toxoplasmosis on the phenotype of intermediate hosts. *Folia Parasitologica* **57**:81–87.
- Flegr, J., J. Havlicek, P. Kodym, M. Maly, and Z. Smahel. 2002. Increased risk of traffic accidents in subjects with latent toxoplasmosis: a retrospective case-control study. *BMC Infectious Diseases* **2**:11.
- Freidel, S., C. Martin-Solch, and U. Schreiber-Gasser. 2002. Alzheimer's dementia or cerebral toxoplasmosis? Case study of dementia following toxoplasmosis infection. *Nervenarzt*, **73**:874–878.
- Gangestad, S. W., and R. Thornhill. 1997. Human sexual selection and developmental stability. In J. A. Simpson, and D. T. Kenrick, eds. *Evolutionary Social Psychology*, pp. 169–195. Erlbaum Associates, Hillsdale, New Jersey.
- Gangestad, S. W., and R. Thornhill. 1998. Menstrual cycle variation in women's preference for the scent of symmetrical men. *Proceedings of the Royal Society of London B* **265B**:927–933.
- Gauthier-Clerc, M., and F. Thomas. 2010. *Ecologie de la santé et Biodiversité*. De Boeck, Bruxelles, Belgium, 538 pp.
- Gibson, M. A., and R. Mace. 2003. Strong mothers bear more sons in rural Ethiopia. *Proceedings of the Royal Society of London B* **270**:S108–S109.
- Guégan, J. F., A. Teriokhin, and F. Thomas. 2000. Human fertility variation, size-related obstetrical performance and the evolution of sexual stature dimorphism. *Proceedings of the Royal Society of London B* **267**:2529–2536.
- Guégan, J. F., F. Thomas, M. E. Hochberg, and F. Renaud. 2001. Disease diversity and human fertility. *Evolution* **55**:1308–1314.

- Habek, M., D. Ozretic, K. Zarkovic, V. Djakovic, and Z. Mubrin. 2009. Unusual cause of dementia in an immunocompetent host: toxoplasmic encephalitis. *Neurological Sciences* **30**:45–49.
- zur Hausen, H. Z. 2009. The search for infectious causes of human cancers: where and why (Nobel lecture). *Angewandte Chemie International Edition* **48**:5798–5808.
- Hays, J. N. 1998. *The Burdens of Disease: Epidemics and Human Response in Western History*. Rutgers University Press, Rutgers.
- Henriquez, S. A., R. Brett, J. Alexander, J. Pratt, and C. W. Roberts. 2009. Neuropsychiatric disease and *Toxoplasma gondii* infection. *Neuroimmunomodulation* **16**:122–133.
- Henry, E. Y., P. Bernard, and C. Brisset. 1978. Les troubles mentaux de la syphilis. In E. Y. Henry, P. Bernard, and C. H. Brisset, eds. *Manuel de psychiatrie*, pp. 844–861. Masson, Paris.
- Hinze-Selch, D. 2002. Infection, treatment and immune response in patients with bipolar disorder versus patients with major depression, schizophrenia or healthy controls. *Bipolar Disorders* **4**:81–83.
- Holliday, M. A. 1986. Body composition and energy needs during growth. In F. Falkner, and J. M. Tanner, eds. *Human Growth: A Comprehensive Treatise*, Vol. 2, pp. 101–117. Plenum, New York.
- House, P. K., A. Vyas, and R. Sapolsky. 2011. Predator cat odors activate sexual arousal pathways in brains of *Toxoplasma gondii* infected rats. *PLoS ONE* **6**:e23277. doi:10.1371/journal.pone.0023277
- Jackson, F. L. C. 2000. Human adaptation to infectious disease, Chapter 8. In S. Stinson, B., Bogin, R. Huss-Shmore, and D. O'Rourke. *Human Biology: An Evolutionary and Biocultural Perspective*, pp. 273–293. Wiley-Liss, Inc, USA, New York.
- Kleinman, J., and S. Kessel. 1987. Racial differences in low birth weight: trends and risk factors. *New England Journal of Medicine* **317**:749–753.
- Knapp, V. J. 1989. *Disease and its Impact on Modern European History*, Vol. 10. Mellen, Lewiston, NY.
- Kocazeybek, B., Y. A. Oner, R. Turkooy, C. Babur, H. Cakan, N. Sahip, A. Unal *et al.* 2009. Higher prevalence of toxoplasmosis in victims of traffic accidents suggest increased risk of traffic accident in *Toxoplasma*-infected inhabitants of Istanbul and its suburbs. *Forensic Science International* **187**:103–108.
- Koupilova, I., K. Rahu, M. Rahu, H. Karro, and D. A. Leon. 2000. Social determinants of birthweight and length of gestation in Estonia during the transition to democracy. *International Journal of Epidemiology* **28**:1088–1095.
- Lacroix, R., W. R. Mukabana, L. C. Gouagna, and J. C. Koella. 2005. Malaria infection increases attractiveness of human to mosquitoes. *PLoS Biology* **3**:e298.
- Lafferty, K. D. 2006. Can the common brain parasite, *Toxoplasma gondii*, influence human culture? *Proceedings of the Royal Society of London B* **273**:2749–2755.
- Laguerre, C., and R. Poulin. 2010. Manipulative parasites in the world of veterinary science: implications for epidemiology and pathology. *Veterinary Journal* **184**:9–13.
- Lange, T., B. Perras, H. L. Fehm, and J. Born. 2003. Sleep enhances the human antibody response to Hepatitis A vaccination. *Psychosomatic Medicine* **65**:831–835.
- Ledgerwood, L. G., P. W. Ewald, and G. M. Cochran. 2003. Genes, germs, and schizophrenia: an evolutionary perspective. *Perspective in Biology and Medicine* **46**:317–348.
- Lochmiller, R. L., and C. Deerenberg. 2000. Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos* **88**:87–98.
- Lynn, R., and T. Vanhanen. 2001. National IQ and economic development: a study of eighty-one nations. *Mankind Quarterly* **41**:415–435.
- Lynn, R., and T. Vanhanen. 2002. *IQ and the Wealth of Nations*. Praeger, Westport, 196 pp.
- Lynn, R., and T. Vanhanen. 2006. *IQ and Global Inequality*. Washington Summit Publishers, Augusta, GA. ISBN: 13:978-1-59368-025-1.
- MacDorman, M. F., and J. O. Atkinson. 1998. Infant mortality statistics from the linked birth/infant death data set – 1995 period data. *Monthly Vital Statistics* **46**:22.
- Mahon, R., and A. Gibbs. 1982. Arbovirus-infected hens attract more mosquitoes. In J. D. Mackenzie, ed. *Viral Diseases in Southeast Asia and the Western Pacific*, pp. 502–504. Academic Press, Sydney.
- Martin, R. D. 2007. The evolution of human reproduction: a primatological perspective. *Yearbook of Physical Anthropology* **50**:59–84.
- Mathews, F., P. J. Johnson, and A. Neil. 2008. You are what your mother eats: evidence for maternal preconception diet influencing fetal sex in humans. *Proceedings of the Royal Society of London B* **275**:1661–1668.
- McNeill, W. H. 1976. *Plagues and People*. Anchor/Doubleday, Garden City, NY.
- McNeill, W. H. 1978. Disease in history. *Social Science and Medicine* **12**:79.81.
- McNeill, J. R. 2006. Yellow Fever, empire and revolution: the political impacts of infectious disease in the Caribbean region, 1640–1900. In P. Hämmäläinen, ed. *When Disease Makes History: Epidemics and Great Historical Turning Points*, pp. 81–111, University Press, Helsinki.
- McSweeney, E. 1998. Infectious diseases and mental illness: is there a link? *Emerging Infectious Diseases* **4**:123–124.
- Mealey, L., and W. C. Mackey. 1990. Variation in offspring sex ratio in women of differing social status. *Ethology and Sociobiology* **11**:83–95.
- Melendez, A. J., M. M. Harnett, P. N. Pushparaj, W. S. F. Wong, H. K. Tay, C. P. McSharry, and W. Harnett. 2007. Inhibition of FcεRI-mediated mast cell responses by ES-62, a product of parasitic filarial nematodes. *Nature Medicine* **13**:1375–1381.
- Milinski, M., and C. Wedekind. 2001. Evidence for MHC-correlated perfume preferences in humans. *Behavioural Ecology* **12**:140–149.
- Miman, O., E. A. Mutlu, O. Ozcan, M. Atambay, R. Karlidag, and S. Unal. 2010a. Is there any role of *Toxoplasma gondii* in the etiology of obsessive-compulsive disorder? *Psychiatry Research* **177**:263–265.
- Miman, O., O. Y. Kusbeci, O. C. Aktepe, and Z. Cetinkaya. 2010b. The probable relation between *Toxoplasma gondii* and Parkinson's disease. *Neuroscience Letters* **475**:129–131.
- Møller, A. P. 1996. Parasitism and developmental instability of hosts: a review. *Oikos* **77**:189–196.
- Møller, A. P. 2006. A review of developmental instability, parasitism and disease: Infection, genetics and evolution. *Infection, Genetics and Evolution* **6**:133–140.
- Møller, A. P., C. L. Fincher, and R. Thornhill. 2009. Why men have shorter lives than women: effects of resource availability, infectious disease, and senescence. *American Journal of Human Biology* **21**:357–364.
- Nakatani, N. 1994. Antioxidative and antimicrobial constituents of herbs and spices. In G. Charalambous, ed. *Spices, Herbs, and Edible Fungi*, pp. 251–272. Elsevier, Amsterdam.
- Nesse, R. M., and S. C. Stearns. 2008. The great opportunity: evolutionary applications to medicine and public health. *Evolutionary Applications* **1**:28–48.

- O'Shea, B., R. D. Rebolgar-Tellez, J. G. C. Hamilton, D. El Naiem, and A. Polwart. 2002. Enhanced sandfly attraction to *Leishmania*-infected hosts. *Transactions of Royal Society of Tropical Medicine and Hygiene* **96**:117–118.
- Polgar, S. 1964. Evolution and the ills of mankind. In S. Tax, ed. *Horizons of Anthropology*, pp. 200–211. Aldine Publishing Co, Chicago.
- Poulin, R. 1996. Sexual inequalities in helminth infections: a cost of being male? *American Naturalist* **147**:287–295.
- Poulin, R., and E. P. Levri. 2012. Applied aspects of host manipulation by parasites. In D. Hughes, J. Brodeur, and F. Thomas, eds. *Host Manipulation by Parasites*. Oxford University Press, Oxford.
- Prandota, J. 2010. Neuropathological changes and clinical features of autism spectrum disorder participants are similar to that reported in congenital and chronic cerebral toxoplasmosis in humans and mice. *Research in Autism Spectrum Disorders* **4**:103–118.
- Preston, B. T., I. Caprellini, P. McNamara, R. A. Barton, and C. L. Nunn. 2009. Parasite resistance and the adaptive significance of sleep. *BMC Evolutionary Biology* **9**:7.
- Profet, M. 1993. Menstruation as a defence against pathogens transported by sperm. *Quarterly Review of Biology* **68**:335–386.
- Prugnolle, F., A. Manica, M. Charpentier, J. Guégan, V. Guernier, and F. Balloux. 2005. Pathogen-driven selection and worldwide HLA class I diversity. *Current Biology* **15**:1022–1027.
- Prugnolle, F., T. Lefèvre, F. Renaud, A. P. Møller, D. Missé, and F. Thomas. 2009. Parasite and body odours: evolutionary and medical perspective. *Infection, Genetics and Evolution* **9**:1006–1009.
- Read, J. S., J. F. Troendle, and M. A. Klebanoff. 1997. Infectious disease mortality among infants in the United States, 1983 through 1987. *American Journal of Public Health* **87**:192–198.
- Risse, G. B. 1988. Epidemics and history: ecological perspectives and social responses. In E. Fee, and D. M. Fox, eds. *AIDS: The Burdens of History*, p. 33.66. Univ. Calif. Press, Berkeley.
- Roche, J. R., J. M. Lee, and D. P. Berry. 2006. Pre-conception energy balance and secondary sex ratio – partial support for the Trivers-Willard hypothesis in dairy cows. *Journal of Dairy Science* **89**:2119–2125.
- Ronald, M., M. Weigel, and M. Weigel. 1989. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review. *British Journal of Obstetrics and Gynaecology* **96**:1312–1318.
- Schaller, M., and D. R. Murray. 2008. Pathogens, personality and culture: disease prevalence predicts worldwide variability in sociosexuality, extraversion, and openness to experience. *Journal of Personality and Social Psychology* **95**:212–221.
- Scheib, J., S. Gangestad, and R. Thornhill. 1999. Facial attractiveness, symmetry and cues of good genes. *Proceedings of the Royal Society Biological Sciences Series B* **266**:1913–1919.
- Sherman, P. W., and J. Billing. 1999. Darwinian gastronomy: why we use spices. *Biosciences* **49**:453–463.
- Sherman, P. W., and G. A. Hash. 2001. Why vegetable recipes are not spicy. *Evolution and Human Behaviour* **22**:147–163.
- Spiegel, K., J. F. Sheridan, and E. Van Cauter. 2002. Effect of sleep deprivation on response to immunization. *Journal of the American Medical Association* **288**:1471–1472.
- Strassman, B. I. 1996. The evolution of endometrial cycles and menstruation. *Quarterly Review of Biology* **71**:181–220.
- Summers, R. W., D. E. Elliott, J. F. Urban Jr, R. Thompson, and J. V. Weinstock. 2005. *Trichuris suis* therapy in Crohn's disease. *Gut* **54**:87–90.
- Teriokhin, A. T., E. V. Budilova, F. Thomas, and J.-F. Guégan. 2004. Worldwide variation in life-span sexual dimorphism and sex-specific environmental mortality rates. *Human Biology* **76**:623–641.
- Thomas, F., A. T. Teriokhin, E. V. Budilova, S. P. Brown, F. Renaud, and J.-F. Guégan. 2004. Human birth weight evolution across contrasting environments. *Journal of Evolutionary Biology* **17**:542–553.
- Thomas, F., J. Lafferty, E. Brodeur, and M. Elguero. 2011. Incidence of adult brain cancers is higher in countries where the protozoan parasite *Toxoplasma gondii* is common. *Biology Letters* 2011, doi:10.1098/rsbl.2011.0588 *Biol. Lett.* [Epub ahead of print].
- Thornhill, R., and S. W. Gangestad. 1993. Human facial beauty: averageness, symmetry and parasite resistance. *Human Nature* **4**:237–269.
- Thornhill, R., S. W. Gangestad, R. Miller, G. Scheyd, J. K. McCollough, and M. Franklin. 2003. Major histocompatibility complex genes, symmetry, and body scent attractiveness in men and women. *Behavioural Ecology* **14**:668–678.
- Torrey, E. F., J. J. Bartko, Z. R. Lun, and R. H. Yolken. 2007. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin* **33**:729–736.
- Toth, L. A., and J. M. Krueger. 1989. Effects of microbial challenge on sleep in rabbits. *Federation of American Societies for Experimental Biology* **3**:2062–2066.
- Toth, L. A., E. A. Tolley, and J. M. Krueger. 1993. Sleep as a prognostic indicator during infectious disease in rabbits. *Proceedings of the Society for Experimental Biology and Medicine* **203**:179–192.
- Trivers, R. L., and D. Willard. 1973. Natural selection of parental ability to vary the sex ratio of offspring. *Science* **179**:90–92.
- Vangen, S., C. Stoltenberg, R. Skjaerven, P. Magnus, J. R. Harris, and B. Stray-Pedersen. 2002. The heavier the better? Birth weight and perinatal mortality in different ethnic groups. *International Journal of Epidemiology* **31**:654–660.
- Webster, J. 2001. Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour. *Microbes and Infection* **3**:1037–1045.
- Wedekind, C., and S. Furi. 1997. Body odour preferences in men and women: do they aim for specific MHC combinations or simply heterozygosity? *Proceedings of the Society of London B* **264**:1471–1479.
- Wedekind, C., T. Seebeck, F. Bettens, and A. J. Paepke. 1995. MHC-dependent mate preferences in humans. *Proceedings of the Royal Society of London B* **260**:245–249.
- Wells, J. K. C. 2000. Natural selection and sex differences in morbidity and mortality in early life. *Journal of Theoretical Biology* **202**:65–76.
- Wells, J. K. C. 2002. Thermal environment and human birth weight. *Journal of Theoretical Biology* **214**:413–425.
- Wolfe, N. D., C. P. Dunavan, and J. Diamond. 2007. Origins of major human infectious diseases. *Nature* **447**:279–283.
- Yereli, K., I. C. Balcioglu, and A. Ozbilgin. 2006. Is *Toxoplasma gondii* a potential risk for traffic accidents in Turkey? *Forensic Science International* **163**:34–37.
- Zhang, J., and D. A. Savitz. 1992. Preterm birth subtypes among blacks and whites. *Epidemiology* **3**:428–433.