# Chemical signals and parasite-mediated sexual selection

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Research into visual and acoustic signals has demonstrated that exaggerated sexual displays often provide an honest indicator of a male's resistance to parasites. Recent studies with rodents and humans now suggest that chemosensory signals also reveal a male's disease resistance and his genetic compatibility. Our understanding of sexual selection has been greatly enriched by considering the mechanisms underlying visual and acoustic displays, and recent advances in chemical communication will help to determine what kind of information is revealed by an individual's scent.

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Many species rely on chemical signals to attract mates[1] (Box 1). The scent glands, scent-marking behavior and pheromones that transmit chemical signals are often sexually dimorphic, even in species in which the males are visually drab or show no other conspicuous dimorphisms (Fig. 1). Darwin suggested that the exaggerated displays of males, including 'glands for emitting odours', evolved through sexual selection (cited in Ref. 2). Females direct their attention to male odors, which convey a surprising amount of information, such as a male's dominance status[3]. The chemical signals of a male might also advertise health or genetic quality to prospective mates[4] (Box 2). Hamilton and Zuk suggested that females prefer to mate with males with showy sexual displays because they are the healthiest and the most resistant to parasites[5]. By avoiding infected males, choosy females can reduce their risk of contracting contagious diseases, obtain more parental investment and increase the resistance of their progeny to parasites.

Numerous studies have found that a male's secondary sexual displays honestly reveal his parasite load[6]. Research on parasite-mediated sexual selection, however, has focused almost exclusively on visual and acoustic signals, ignoring chemical communication. Chemical signals could provide particularly effective indicators of an individual's health and infection status because they are direct and often more labile than morphological traits. Physicians and veterinarians have long used the taste and smell of their patient's body odor, breath, urine and flatulence to diagnose disease (Box 3 and Table 1). Furthermore, chemical signals provide information about an individual's genetic compatibility at loci that control immune recognition of parasites[7].

## Parasitic infection abolishes the attractiveness of male scent

Male house mice (*Mus musculus*) scent-mark with urine, and females are attracted to these marks. Recently, Kavaliers and Colwell found that female mice can discriminate the odors of parasitized from unparasitized males[8]. Additional odor-preference experiments have shown that females not only discriminate, but are also more attracted to the odor of uninfected males than those males experimentally infected with parasitic coccidian protozoans (*Eimeria vermiformis*)[9] or nematode worms (*Heligmosomoides polygyrus*)[10].

To test whether females were detecting infection from a male's urine odor (e.g. via metabolic by-products and scent glands) or simply from components of the parasites shed in the male's feces, we recently conducted an experiment using the urine from male mice collected before, during and after being experimentally infected with influenza, a respiratory virus[11]. We found that females were more attracted to a male's urine before and after infection than while he was combating the infection. Moreover, females were more likely to settle in nest boxes containing the scent of a male when he was uninfected than when he was infected. Our study supported Kavaliers and Colwell's[9] findings: females were more attracted to the urine of uninfected males than to a neutral control (water), but the urine of infected males was as attractive as the control. This suggests that rather than being aversive, the odor of infected males simply loses its attractiveness. Such indifference to infected individuals would not be a particularly effective mechanism for avoiding transmission of pathogens, although it would still enable females to avoid mating with infected males. Females might be more averse to infected males than they are to their scent marks, but this hypothesis has never been tested.

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### Box 1. Chemosensory sexual displays

Chemical communication between the sexes occurs in many species: bacteria, protists, fungi, plants and animals all use chemical signals to attract and select mates[1]. There is an enormous diversity of mechanisms mediating chemical communication, and these are often sexually dimorphic for both the sender and receiver.

Single-celled organisms and the gametes of multicelled organisms use chemical signals to locate and recognize their mates. When male *Danaus* butterflies court females, they position themselves in front of the female and extrude a pair of elaborate structures called 'hairpencils' to display their chemical signals. When male blue crabs (*Callinectes sapidus)* perform their elaborate courtship display, they use their swimming legs to waft odors towards attentive females. Female lampreys (*Petromyzon marinus*) are attracted to testosterone and other odorants in a male's urine. The elaborate courtship behavior of salamanders, such as *Notophthalmus viridescens*, is centered around males rubbing or fanning odors secreted by various 'hedonic' glands onto a female's nostrils or body. Male lizards, such as *Iguana iguana,* release sexual odors through large, femoral glands, whose secretions reveal much information, including their androgen levels and dominance status. Male mammals display their scent for females using complex mixtures of odorants secreted by a diversity of androgen-dependent scent glands. A male's odor has remarkable effects on a female's reproductive physiology and behavior, such as accelerating puberty, activating ovulation, accelerating and synchronizing estrus, and inducing pregnancy block.

Despite these and numerous other examples, we still understand very little about the functions of chemical communication. Sensory biologists often assume these signals function only for species recognition or to coordinate mating between the sexes; they have largely been unaware of the advances in understanding the evolution of signal–receiver systems. At the same time, students of parasite-mediated sexual selection have focused on a small group of animals (mainly birds) and have ignored the chemical senses.
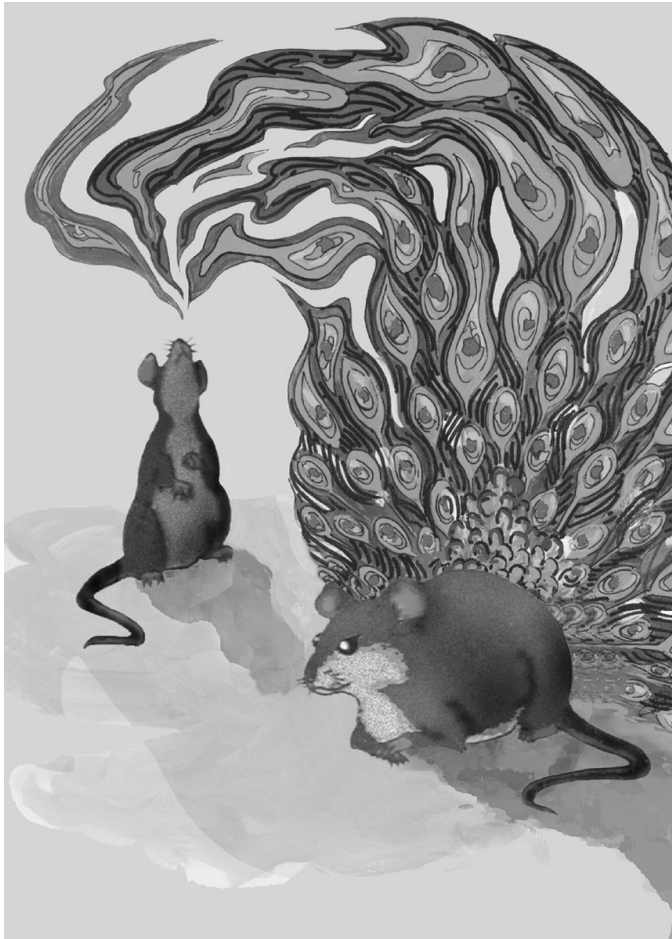
**Fig. 1.** The scent of a male mouse is the chemical equivalent of a peacock's plumage; they both function to attract females but are costly to produce.

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### Box 2. Honest signaling and the strategic-choice handicap model

Zahavi suggested that females use the elaborate sexual displays of males to assess their quality because such displays are costly and therefore cannot be easily faked[45]. Only males of high quality can afford to support such a handicap to survival (e.g. a peacock's elaborate train).

Initially, this counter-intuitive idea had little support among researchers because it seemed that choosy females would pass the male's handicap, as well as his good genes, to her progeny, so both females and males would be better off without exaggerated ornaments. Grafen showed that sexual handicaps can evolve to display a male's quality honestly if males have a mechanism that allows them to adjust their investment in sexual displays strategically, according to their condition[46]. (Previous attempts to model the handicap theory failed because they only allowed the presence or absence of a display; they did not allow males to choose from a continuous range of strategies.)

Grafen's 'strategic-choice handicap' model is consistent with the hypothesis that males adaptively allocate energy and resources between sexual displays and immunological defenses (the adaptive reallocation hypothesis)[18]. Although a male's odoriferous secretions might be a handicap to survival, they do not necessarily have to be costly to reflect health honestly. Metabolic wastes must be excreted, and it might be physiologically impossible (or too costly) for a sick animal to fake a healthy odor.

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### How does a male's odor reveal his infection status?

There are many ways that an individual's odor might signal infection. First, infection might change the composition of commensal microbes that play an important role in shaping an individual's odor.

Second, infection might also trigger immunological responses that alter an individual's odor. For example, the highly polymorphic genes of the major histocompatibility complex (MHC) control immunological self/nonself-recognition and also influence individual odor and mating preferences in mice[7]. Because the expression of MHC genes is increased during infection, the MHC might play a role in honestly signaling the activation of immune defenses[9,10]. Although it is still unclear how MHC genes alter odor, a recent study found that they influence the concentrations of various volatile acids that serve as sexual odorants ('copulins') in mammals[12]. The composition of these volatile acids appears to be altered during the course of infection[13], although it is unknown how this occurs.

Third, activation of the immune system probably alters the excretion of other metabolic by-products from the endocrine system. For example, infected individuals have high concentrations of plasma corticosterone[14] and low concentrations of androgens, hormones suspected to control the production of 'alarm odors' and 'sex pheromones', respectively.

If females are detecting chemical cues from the immune system or stress responses, then why does the odor of infected males simply lose its attractiveness, rather than being aversive? One explanation is that a normally attractive odorant is absent in the urine of infected males. Androgen metabolites and secretions from androgen-dependent glands might provide such an odorant because increased androgen levels increase the attractiveness of a male rodent's urine odor to females[15], and androgen levels generally decline during infection[16]. Infected males might lower their androgen levels to ameliorate the immunosuppressive effects of these steroid hormones[17] or to act as a signal to reallocate energy and resources into immune responses[18] – better to be a dull-smelling male than a dead male! Decreased androgen levels can also result from manipulation by parasites[19] that benefit by diverting their host's reproductive efforts into their own reproduction. If a male's androgen levels generally decrease during infection for any reason, then his parasite load will be revealed honestly by his androgen-dependent odor.

### Androgens and the immunocompetence handicap hypotheses

Androgens, such as testosterone, control the development of many secondary sexual characters, but why would sex hormones suppress the immune system? Folstad and Karter proposed that androgen-dependent signals provide honest indicators of a male's health because of the immunosuppressive effects of androgens[17]. However, they assumed that the adverse effects of androgens were an unwelcome by-product or unmodifiable constraint[17]. Androgens are simply chemical messengers, with one of their functions being to trigger the development of secondary sexual traits. If androgens are actually immunosuppressive *per se*, then it is difficult to understand why males cannot evolve a nonimmunosuppressive sex hormone, convert androgens into a nonimmunosuppressive form, or abolish the sensitivity of immune effectors to androgens. None of these possibilities would seem to be insurmountable evolutionary steps.

Recently, it has been suggested that testosterone is immunosuppressive because it prevents autoimmune attacks on developing sperm in the testes that express novel antigens[20,21], implying that the immunosuppressive effects of androgens on systemic immunity is a tradeoff to protect sperm from the immune system. However, this hypothesis assumes that testosterone 'overflow' into the rest of the

## Box 3. Odor and diagnosis of diseases

Physicians have long used odor to diagnose various diseases (Table 1), as illustrated in this woodcut. Nearly two centuries ago, one of the originators of Hindu medicine, Susruta Smhita, claimed that 'by the sense of smell we can recognize the peculiar perspiration of many diseases, which has an important bearing on their identification'[43]. One thousand years ago, the Arabian physician Avicenna observed that an individual's urine odor changed during sickness. Physicians once tasted a patient's urine to diagnose disease. For example, diabetes mellitus (which means 'passing through sweet') was once diagnosed by a patient's sweet urine and for centuries the disease was called 'pissing evil'. Veterinarians often use halitosis and other odor cues to diagnose diseases, such as bovine ketosis. Technological devices are currently being developed to diagnose disease from breath and other odor samples. Fisher long ago pointed out that bad breath may be sexually unattractive because halitosis is associated with various diseases[47]. Hamilton and Zuk suggested that when females are inspecting potential mates they should, like physicians, 'unclothe the subject, weigh, listen, observe vital capacity, and take blood, urine and fecal samples'[5]. Thus, it is surprising that chemical signals have not received more attention as potential disease indicators by students of sexual selection.



### Table 1. Body odor is a diagnostic indicator for many diseases[a]

| Disease | Description of odor |
| --- | --- |
| **Infectious** | |
| Smallpox | Stench |
| Typhoid | Freshly baked brown bread |
| Diphtheria | Sweetish |
| Yellow fever | Butcher shop |
| Scrofula (tuberculosis) | Stale beer |
| Gingivitis | Significant |
| Herpes labialis | Unpleasant |
| Syphilis | Characteristic |
| Gangrene | Obnoxious |
| Hyperhidrosis | Offensive |
| Infected eczema | Unpleasant |
| Bacterial vaginosis | Malodor |
| Pediculosis (lice) | Odor from matting of hair with pus and exudate |
| Infected ulcers | Unpleasant |
| Abscesses | Unpleasant |
| **Noninfectious** | |
| Scurvy | Sweat has putrid odor |
| Diabetic ketosis | Breath and sweat has the fruity aroma of decomposing apples |
| Gout | Sweat has a characteristic odor |
| Schizophrenia | Pungent body odor from increased trans-3-methyl-2-hexanoic acid in the sweat |
| Phenylketonuria | A musty odor, resembling stale, sweaty locker-room towels |
| Defective metabolism of amino acids (valine, leucine and isoleucine) | Maple syrup or caramelized sugar in sweat, ear wax and urine |
| Inability to metabolize methionine | Breath, sweat and urine smells like boiled cabbage |
| Hyperaminoaciduria | Dried malt or hops (oast house syndrome) |
| Inability to metabolize butyric and hexanoic acids | The odor of sweaty feet syndrome |

[a]Odor descriptions are from Refs 43 and 44.

body is unpreventable or that testosterone cannot be converted into a nonimmunosuppressive form when it enters the body. Testosterone might protect sperm, along with the blood–testes barrier and peripheral immunological tolerance mechanisms, but it is unclear that testosterone is unconfinable or unconvertible. This hypothesis seems to substitute one unlikely, unexplained constraint for another.

It is likely that androgens allocate energy and resources between reproductive functions and immunological defenses (the adaptive reallocation hypothesis)[18]. There is an inescapable tradeoff between survival and reproduction. To allocate energy into immunological defenses, infected males may be forced to reduce the costs of sexual displays by lowering their androgen levels. The costs of both sexual displays and immunological defenses seem metabolically expensive; however, more work is needed to determine if they create tradeoffs, such as competing energetic demands[22]. Women postpone reproduction if they have insufficient fat reserves, which indicates that they have 'metabolic detectors' that assess the availability of metabolic fuels and make allocations between survival and reproductive functions. Interestingly, many studies find that male rodents housed in social conditions in which dominance interactions occur have reduced immune responsiveness compared with males housed in isolation[23]. These and other studies support the idea that males faced with aggressive competitors or mating opportunities divert energy and resources away from immunological defenses[24]. The main challenge in determining how males allocate between reproductive and immune functions is finding more accurate methods for assessing immunocompetence (Box 4).

## Receiver psychology: detecting and responding to chemical signals

In addition to determining how infection alters a male's odor, we must also determine how females detect, process and respond to olfactory information, because communication involves a signaler and a receiver ('receiver psychology')[25]. Understanding the design features of olfactory mechanisms will help to determine their function. Olfactory mechanisms, like chemical signals, are often sexually dimorphic[26]. Why is this? Sexual selection theory predicts that male chemosensory systems should be designed to locate females, whereas females, when they are the choosier sex, should be designed to discriminate the quality of males. Our understanding of chemosensory systems has lagged behind the visual and acoustic senses. However, recent advances using molecular tools are helping to determine how olfactory discrimination occurs. Progress on olfaction promises to have important implications for sexual selection, such as helping to determine how females discriminate the odor of infected and uninfected males.

Understanding how females respond physiologically to the odor of infected males could help explain why they lose their attraction for such odors. Kavaliers and Colwell's studies on parasite-mediated odors in mice were prompted by a curious discovery they made while investigating how chemical signals trigger neuroendocrinological responses in mice[8]. They found that when females are exposed to the odor of parasitized males they activate analgesic mechanisms that increase pain tolerance [via elevations in opioid (β-endorphins and enkephalins) and nonopioid (serotonergic) levels]. Why do female mice increase their levels of endogenous opioids when they are exposed to the odor of infected males? There are several possible explanations.

First, Kavaliers and Colwell suggested that because opioid levels also increase during stressful situations, such as exposing mice to the odor of restrained mice, odor-mediated analgesia is a part of a general stress response (proximate hypothesis) that functions to avoid disease transmission and mating with infected individuals (ultimate hypotheses)[9,10]. Their hypotheses are consistent with the observation that maximum analgesia occurs when females are exposed to odors collected from parasitized males during the infective stages[8]; but it is inconsistent with the observations that females do not treat the odor of infected males as aversive.

Second, odor-mediated analgesia might reflect a preparatory, defensive response against possible infections. Opiates are used to treat diarrhea (the intestine is rich with opioid receptors) – increasing opioid levels might, therefore, be a useful defense against gut parasites (e.g. coccidia) that trigger debilitating diarrhea as a way to spread their infective stages. Analgesia might also reflect immunological preparation, because opioids can enhance immune responsiveness[27]. The preparatory-defense hypothesis is not as far fetched as it might seem, because plants use chemical cues from infected conspecifics to activate preparatory defenses against infectious agents[28].

Third, increasing endogenous opioids might inhibit sexual receptivity (proximate hypothesis) to avoid mating with infected males (ultimate hypothesis). The use of opiate drugs in humans is well known to reduce sexual libido, and experiments indicate that increasing opioid levels can inhibit sexual receptivity (lordosis and estrus) in females[29]. If odor-induced analgesia is part of a stress response or inhibits sexual receptivity, then either mechanism would support the sexual inhibition hypothesis. All of these hypotheses can be tested with the appropriate physiological and behavioral experiments.

Finally, Zuk et al. recently suggested that '…induced analgesia is one of a limited number of physiological pathways available for responses to stressors, and therefore not a specific adaptation to detect and avoid parasitism'[30]. This implies that odor-induced analgesia arose originally as a mechanism for avoiding stressed individuals, and then the mechanism was evolutionarily coopted for avoiding parasitized individuals. Although an interesting hypothesis about the evolutionary origins of odor-induced analgesia, they unfortunately presented their historical hypothesis as an alternative to the functional (adaptive) hypotheses presented by Kavaliers and Colwell. Historical explanations are not alternatives to functional explanations. If odor-induced opioid-mediated analgesia was coopted from a pre-existing stress mechanism to detect infected individuals, then it is probably being modified or adapted to detect infected individuals better and respond appropriately. The main problem is that Zuk et al. assumed that the analgesic response triggered by the odor of infected males is a general purpose stress mechanism (i.e. it is the same mechanism triggered by stress) – this hypothesis has not been tested.

## What is the function of MHC-dependent mating preferences?

Females might be able to use a male's odor to obtain disease-resistance genes for their offspring by mating with males carrying dissimilar MHC genes. Studies of house mice under laboratory and seminatural conditions have shown that house mice prefer to mate with individuals expressing dissimilar MHC genes, and these preferences can be experimentally reversed through cross-fostering[31]. How do mice recognize the MHC-identity of potential mates? Numerous studies by Kunio Yamazaki et al. have shown that laboratory mice can be trained to detect odors of mice that differed genetically only at single MHC loci (reviewed in Ref. 7). We have recently found that wild-derived mice can discriminate MHC-determined odors without training[32]. Richard Brown et al. have shown that rats can also discriminate the odors influenced by genes in the MHC region[7]. These studies indicate that rodents can recognize the MHC-identity of potential mates through specific odor cues.

Why do mice prefer to mate with MHC-dissimilar individuals? There are several ways that MHC-disassortative mating preferences might enable mice to increase the resistance of their offspring to pathogens and parasites:
• They will increase the MHC-heterozygosity of an individual's progeny. MHC heterozygotes recognize a wider array of foreign antigens than homozygotes and therefore could be resistant to infections of multiple parasites[33].
• They might provide a moving target to rapidly evolving pathogens. Because pathogens evolve ways to evade MHC-dependent immunity, such as molecular mimicry, MHC-dependent mating preferences might enable hosts to alter the immune systems of their progeny, shifting the targets of pathogen evolution.
• They might reduce inbreeding by increasing overall genetic heterozygosity, which is likely to increase disease resistance.

These mechanisms are not mutually exclusive. MHC-dependent mating preferences might enable individuals to obtain all of these benefits, although none of these potential functions has been adequately tested. Determining the benefits of these preferences should help to predict which species have evolved this behavior.

## Pheromones and mate choice in humans

Although humans are not known for their olfactory prowess, we can discriminate a wide array of scents and we have a functional vomeronasal organ (VNO)[34] – the chemosensory organ that is used for detecting sexual pheromones in other mammals. Unlike the main olfactory system, information from the VNO bypasses the conscious centers of the brain and travels directly to the amygdala and hypothalamus, which control sexual behavior. Humans have more scent glands than any other primate[35] and human pheromones have potent effects on the female reproductive cycle[36]. We use chemical senses, both taste and scent, during courtship and sex (in some languages kiss means smell). A recent survey suggested that women attend to odor cues to assess prospective mates more often than is assumed[37].

It is unknown if women use odor cues to assess a male's infection status – however, the results of several studies are consistent with this hypothesis. Humans universally find signs of disease and infection sexually unattractive, and people living in geographical regions with the highest risk of parasitic infection value a mate's physical attractiveness more than in other areas[38]. Women prefer the scent of men with symmetrical features, and body symmetry is often correlated with resistance to parasites[39]. A recent study found that both men and women prefer the odor of MHC-dissimilar individuals[40], and another found that couples tend to marry individuals expressing dissimilar MHC genes[41]. Our aim is not to exaggerate the importance of pheromones in human sexual behavior but simply to point out that chemical signals potentially transmit more information than had previously been considered.

## Future directions

Chemical signals are used during mate choice in a wide diversity of species and have been shown to honestly reflect an individual's health[9–11] (Box 3). However, it is unknown if females use a male's chemical signals to avoid disease transmission or to increase the resistance of their progeny. Future work on chemical signals and sexual selection should consider several important points.

First, females might attend to chemical cues that reveal a male's previous, as well as his current, infection status. Females might avoid infected males to avoid contracting diseases through transmission, but females seeking good genes for their progeny should examine a male's 'medical history', assessing cues that reflect a male's health integrated over his lifetime. For example, genetically susceptible males might have poorly developed scent glands as a result of having more infections during their lifetime.

Second, to understand the function of chemical signals, future studies should consider the costs, as well as the benefits, of displays. Although an individual's odor does not need to be costly to be honest (Box 2), odoriferous displays probably have energetic costs and attract predators.

Third, if females do not use a male's odor directly to assess his current or past health, they might still use odor cues indirectly to reveal this information. For example, females might prefer the odor of dominant males – who have demonstrated that they can pass an arduous physical fitness test – because this may be the most effective way to obtain a male that can cope with parasites[42] (Box 4).

Fourth, females might use a male's chemical signals to increase the resistance of their progeny via good parental investment, rather than good genes. For example, females of certain lepidopterans use a male's pheromones to assess his stores of toxic alkaloids. During copulation, males transfer the toxins to the female as a nuptial gift that females incorporate into their eggs, which protects the eggs from predators and parasitoids[1].

Finally, more work is needed to determine how chemical signals influence our own sexual behavior. Chemical signals clearly affect human reproductive behavior and physiology, although we are not consciously aware of their effects. For example, women synchronize their menstrual cycles through odor cues[36], although they are not aware of the mechanism. It is unclear why we are oblivious to our own chemosensory communication, but perhaps our lack of awareness explains why chemical signals have been neglected by students of parasite-mediated sexual selection.

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