Reproductive Parasitism: Maternally Inherited Symbionts in a Biparental World

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Most species of insect, and many other plants and animals, carry maternally heritable microorganisms—viruses, bacteria, unicellular eukaryotes, and fungi that pass from a female host to her progeny. Maternal inheritance establishes a correlation between the fitness of symbiont and host female, which can select for the symbiont to contribute to host fitness. Nevertheless, its lack of transmission through male hosts places the symbiont in conflict with biparentally inherited nuclear genes. In this review, we first examine how this conflict is manifest in selection to promote the production and survival of infected female hosts and gametes. We then examine how the distorted population sex ratios that they produce may affect host reproductive ecology, and thus the intensity of other conflicts associated with sexual reproduction. Finally, we examine evolved host responses to symbiont manipulation. We argue that the unusual intensity of symbiont–host conflict generates extreme selection pressures that can drive changes in sex-determination systems, the basic pathway through which males and females are constructed.

Between 1909 and 1932, Hubert Simmonds bred individuals of the great eggfly, *Hypolimnas bolina*, seemingly as a pet project to distract him from his daily work as an agricultural entomologist in Fiji. What Simmonds discovered, by accident, was the presence of a trait in which female butterflies produced only daughters. He found that many females in his population had this trait, such that few males were present in the wild. He could maintain his all-female lines indefinitely, irrespective of the male used in the cross, and concluded that it was a trait acquired from the mother alone. Finally, he noted that half of the eggs laid by the female died during embryogenesis, and concluded that the

all-female trait was associated with the death of sons (Simmonds 1923a,b, 1926, 1927, 1928, 1930). He had, by accident and very careful observation, discovered the first maternally inherited male-killing agent.

Simmonds's observation was the first of a number of cases of unusual maternally inherited traits. In 1941, Lewis built the first model of evolution under cytoplasmic inheritance, which recognized that male sterility in plants spread into populations much more easily when the trait was maternally inherited (Lewis 1941). In the same year, maternally inherited feminization of woodlice hosts was observed by Vandel (1941). The next 20 years saw numerous

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G.D.D. Hurst and C.L. Frost

records of maternally inherited male lethality in ladybird beetles and flies (Lus 1947; Shull 1948; Magni 1953; Cavalcanti et al. 1957; Malogolowkin 1958). Further, unusual cross-incompatibilities between members of different populations of *Culex* mosquitoes were also noted as having a maternally inherited basis (Laven 1951). Collectively, these traits have been termed “reproductive parasitism”—because the impacts on reproduction are deleterious to host fitness.

Later work in the “molecular genetics age” examined the cause of these traits. “Reproductive parasitic” behaviors in plants are commonly associated with mutations in the mitochondrial genome, but have recently also been ascribed to heritable fungi (Gorischek et al. 2013). Reproductive parasitism in animals is associated with a wide variety of microbial symbionts: viruses, bacteria, unicellular eukaryotes, and fungi that pass from a female to her progeny either inside eggs or through smearing on the outside of eggs followed by trophic acquisition (Terry et al. 2004; Nakanishi et al. 2008; Duron and Hurst 2013; Gorischek et al. 2013). Although many heritable microbes are simply “beneficial symbionts,” reproductive parasitism of the type described above is widespread (and may be combined with beneficial impacts on the female host).

We first review the rationale underlying the selection for reproductive parasitic phenotypes, the mechanisms by which the manipulations are achieved, and the impact of the phenotypes on the symbiont’s population biology. We then examine the impacts of reproductive parasitism on host reproductive ecology and other conflicts associated with reproduction. We then examine nuclear responses to the presence of heritable parasites, first for sex-ratio/sex-allocation distorters and then for incompatibility-inducing symbionts. We argue that reproductive parasites can create the strongest selective pressures observed in nature, and these will likely be associated with changes in reproductive systems. We speculate that these strong forces may be important in driving “unusual” evolutionary events, such as those underlying the evolution of sex-determination systems.

MANIFESTATIONS OF CYTOPLASM–NUCLEAR CONFLICT; POPULATION BIOLOGY OF REPRODUCTIVE PARASITES

The selection for reproductive parasitic traits derives from the symbiont’s uniparental (maternal) inheritance (Cosmides and Tooby 1981). Maternally inherited symbiont fitness depends solely on the symbiont’s impact on the survival or production of female hosts. A symbiont that is purely maternally inherited will only spread if infected individuals on average produce more infected female offspring than uninfected hosts produce uninfected daughters. The “drive” that creates this increase in daughter production can simply be symbiont traits that increase the fitness of infected females over that of their uninfected counterparts. Indeed, many of these symbionts are beneficial in both sexes, providing “services” such as protection against natural enemies (Hamilton and Perlman 2013) or provision of anabolic capability (Moran et al. 2008). Notwithstanding this, drive can additionally (and not mutually exclusively [Himler et al. 2011]) be achieved through skewing sex allocation/sex ratio such that infected females produce more daughters. Alternately, the symbiont may leave males unharmed in terms of survival but modify male host gametogenesis, producing sperm that are modified to selectively eliminate uninfected zygotes. This phenomenon of cytoplasmic incompatibility promotes symbiont spread through selectively reducing the fitness of uninfected females. Altogether, these phenotypes represent cases of the wider phenomenon of intragenomic conflict, with the pattern of selection on uniparentally inherited elements differing from selection on nuclear genes with respect to sex allocation, sex ratio, and male fertility (Hurst et al. 1996).

The drive created by a symbiont must be sufficient to overcome any segregational loss—progeny that fail to inherit them—and any direct physiological/pathological costs of carrying a symbiont. Theory predicts that symbionts with perfect transmission (no segregational loss) that can invade populations will, in a panmictic population, become fixed (Hurst 1991). Indeed, reproductive parasitic symbionts are

known to infect all female individuals in some species (Stouthamer et al. 1990; Rigaud and Juchault 1992; Dyson and Hurst 2004). However, polymorphism of reproductive-parasite-carrying uninfected individuals is more common. Polymorphism is stabilized by three factors: (1) imperfect maternal inheritance, in which segregational loss prevents fixation of symbionts; (2) additional cost of symbiont carriage at high prevalence, for example, unmatedness of symbiont-carrying individuals (Groenenboom and Hogeweg 2002); and (3) evolution of host factors that affect the phenotype of the symbiont, for example, evolution of host suppressor genes.

The manipulation phenotypes above evolve because male hosts are a dead end for a maternally inherited symbiont. However, some symbionts can combine maternal transmission with infectious transmission, such that male hosts represent a viable source of onward infection. In a number of cases, female hosts are used exclusively for maternal transmission and male hosts for onward infectious transmission. Infectious transmission through sons often occurs relatively late in host development and is associated with the death of male hosts. This discrepancy in timing has led to these examples being termed “late male killing,” differentiating them from the more common embryonic male-killing interactions in which male death is not associated with infectious transmission (Hurst 1991).

Below we outline the three main manifestations of symbiont–host conflict (distortion of sex ratio/sex allocation, cytoplasmic incompatibility, and late male killing) in terms of mechanism, diversity, and population biology. For simplicity, we assume in our treatment of population biology that a symbiont has a single phenotypic impact on its host; the ramifications of contravening this assumption are discussed later.

Distortions of Sex Ratio/Sex Allocation

Maternally inherited symbionts in host species with separate sexes can spread either through biasing sex ratio to the production of daughters or, where there are antagonistic interactions be-

tween male and female siblings, through killing males and reducing the intensity of competition suffered by infected females. Within hermaphroditic host species, biasing sex allocation to female reproductive function is favored where there is a trade-off between male and female reproductive activity. Altogether, four different distortions of sex ratio/sex allocations have evolved to aid symbiont/organelle spread.

Feminization

Symbiont-induced feminization is commonly observed in amphipod and isopod Crustacea (Bouchon et al. 1998) and also in mites, leafhoppers, and butterflies. The phenotype is the conversion of genetic males into phenotypic females (Table 1). In the best-studied case of symbiont-induced feminization, *Wolbachia* infection of *Armidillidium vulgare*, *Wolbachia* infection inhibits the formation of the male-determining androgenic gland during early development, and in so doing results in female development of individuals that are karyotypically male (ZZ, the species being female heterogametic). Converted females (neofemales) are reproductively functional although with occasional intersex properties. In mate-choice experiments, males prefer true females to feminized neofemales (Moreau et al. 2001).

The dynamics of feminizers depends on the transmission efficiency of the symbiont, the efficiency of feminization, and the host sex–determination system. In *A. vulgare*, feminization is efficient, but 10% of the progeny of a female fail to inherit the infection and develop as male (Rigaud and Juchault 1992). Because the species is female heterogametic, spread of the *Wolbachia* may be associated with fixation of the Z chromosome (Taylor 1990; but see Kobayashi and Telschow 2010). Indeed, *A. vulgare* populations exist in which all females are ZZ and carry feminizing *Wolbachia*, and population sex ratio is determined by the proportion of zygotes that do not inherit the microbe and develop as males. In other feminization systems, some males escape feminization, which may also stabilize population sex ratio and persistence (Moret et al. 2001).

G.D.D. Hurst and C.L. Frost

Table 1. Incidence and mechanism of symbiont-induced feminization

Symbiont	Host	Suggested mechanism	References
<i>Wolbachia</i>	<i>Armadillidium vulgare</i> (Isopoda)	Inhibition of androgenic gland differentiation and/or inhibition of androgenic hormone reception	Bouchon et al. 1998
	<i>Zyginidia pullula</i> (Hemiptera)	Interference with male DNA methylation, resulting in female imprinting patterns across the genome	Negri et al. 2009
	<i>Eurema hecabe</i> (Lepidoptera)	Unknown; continuous during larval development	Hiroki et al. 2002; Narita et al. 2007
<i>Cardinium</i>	<i>Brevipalpus phoenicis</i> (Acari)	Feminization of haploid males	Weeks et al. 2001
<i>Microspora</i> sp.	<i>Gammarus duebeni</i> (Amphipoda)	Inhibition of androgenic gland differentiation	Jahnke et al. 2013
<i>Nosema granulosis</i>		Inhibition of androgenic gland differentiation and potential partial refractoriness to androgenic hormone	Jahnke et al. 2013

Parthenogenesis Induction

In haplodiploid arthropods, males develop from unfertilized embryos. In *Trichogramma* wasps, manipulation of ploidy by microbes (doubling of chromosome constitution) leads to development of a female host from these unfertilized eggs (Table 2). Various mechanisms of parthenogenesis induction are now recognized, and three microbes (*Wolbachia*, *Cardinium*, and *Rickettsia*) are recognized as able to induce asexuality. Negative consequences of these symbionts on the overall reproductive success of infected females have been shown in some laboratory comparisons (Stouthamer and Luck 1993; Huigens et al. 2004), but field studies have found either little impact or a beneficial impact of symbiont presence on host fecundity (Segoli et al. 2013). Whichever is the case, the number of females produced by symbiont-infected females is always greater than for uninfected hosts, and thus the drive for an increase in the number of “transmitters” over “nontransmitters” is achieved.

Outside of haplodiploid taxa, the involvement of microbes in parthenogenesis is uncertain. There are certainly many parthenogenetic species that harbor symbionts (Koivisto and Braig 2003), and in some of these there is also evidence that antibiotic treatment alters the capacity of the host to reproduce (e.g., Timmer-

mans and Ellers 2009). However, in nonhaplodiploid taxa, symbiont-free individuals do not produce males and antibiotic treatment may interfere with reproduction in other ways (e.g., because the symbionts are required for oogenesis as seen in *Asobara tabida* [Dedeine et al. 2001]) rather than being required for parthenogenesis, thus making definitively testing the role of symbionts in inducing parthenogenesis very difficult.

Embryonic Male Killing

Killing of zygotes that would develop as males is commonly observed, with multiple symbionts exhibiting this trait across a wide range of arthropods (Table 3). The mechanistic basis of male killing is also diverse, with male killing occurring via interference in male sex determination in some cases but as a result of host sex-specific symbiont responses in others.

The evolutionary advantage for male-killing behavior derives from the impact that death of males may have on the survival/reproduction of their sisters, who will share the symbiont infection through descent. In ladybird beetles, female larvae consume the eggs containing their dead male brothers, which increases their chance of survival (Elnagdy et al. 2011). In other cases, male and female siblings compete for re-

Table 2. The diversity and mechanism of parthenogenesis induction by heritable symbionts

Symbiont	Host	Suggested mechanism	References
<i>Wolbachia</i>	<i>Trichogramma</i> spp. and <i>Leptopilina clavipes</i> (Hymenoptera)	Doubling of chromosome number (haploid males) by failure of chromosomes to segregate at the first mitotic division	Stouthamer and Kazmer 1994; Pannebakker et al. 2004
	<i>Muscidifurax uniraptor</i> (Hymenoptera)	Doubling of haploid male chromosome number via the fusion of two cell nuclei following the initial mitosis	Gottlieb et al. 2002
	<i>Frankliniopsis vespiformis</i> (thrips)	Not known	Arakaki et al. 2001
	<i>Bryobia praetiosa</i> and <i>Bryobia</i> sp. (Acari)	Apomictic parthenogenesis suggested, whereby a lack of meiosis in eggs means that doubling of chromosome number is not required or else automictic parthenogenesis with central fusion	Weeks and Breeuwer 2001
<i>Cardinium</i>	<i>Encarsia hispida</i> (Hymenoptera)	Both automictic parthenogenesis (chromosome doubling) and feminization is required for a female phenotype, but the mechanism for these is unknown	Giorgini et al. 2009
<i>Rickettsia</i> —transitional group	<i>Neochrysocharis formosa</i>	Occurs via achiasmatic apomictic parthenogenesis, whereby a lack of the creation of chiasma during egg meiosis means that doubling of chromosome number is not required	Adachi-Hagimori et al. 2008
<i>Rickettsia</i> —bellii group	<i>Pnigalio soemius</i> (Hymenoptera)	Not known	Giorgini et al. 2010

This list is exemplars, and many other examples exist.

sources, and the death of males reduces the intensity of competition suffered by female hosts (Koop et al. 2009). Finally, where females in a species suffer from inbreeding, male killing may be advantageous to the symbiont as a mechanism of promoting outbreeding (Werren 1987; but see Dannowski et al. 2009).

The magnitude of “drive” provided by male killing to the symbiont is inevitably less than that achieved through conversion of individuals from one sex to another. Under the most compliant biology, the viviparous harlequin pseudoscorpion *Cordylocheres scorpoides*, male killing reduces the intensity of resource competition in utero and infected females produce 26% more daughters, with these daughters also being larger in size than those from uninfected mothers (Koop et al. 2009). However, the drive achieved by male killers is likely to be

commonly much lower than this. This low level of drive makes the frequency of male killers quite variable and sensitive to vertical transmission efficiency (Fig. 1). Although male killers with perfect maternal inheritance do obtain very high prevalence (>80% of females infected) (Jiggins et al. 2002; Dyson and Hurst 2004), imperfect maternal inheritance combined with modest benefits of male killing (and a lack of other benefits to female hosts) is associated with low prevalence. In many cases, male killers exist in <20% of female hosts (Williamson and Poulson 1979; Hurst et al. 1993, 2000). At this prevalence, they may still create strong selection against their action, but ecological impacts are more limited.

In some host species, male killing has no obvious adaptive benefits. Examples of symbionts that appear to “accidentally” impact male

G.D.D. Hurst and C.L. Frost

Table 3. The diversity and mechanism of male-killing symbionts in arthropods

Symbiont	Host taxa	Suggested mechanism	References
<i>Wolbachia</i>	<i>Ostrinia scapularis</i> (Lepidoptera)	Interference with the sex-specific splicing of <i>doublesex</i> , with mismatch between the phenotypic and genetic sex resulting in the death of males	Sugimoto and Ishikawa 2012; Sugimoto et al. 2012
	<i>Drosophila bifasciata</i> (Diptera)	Modulation of male chromatin remodeling followed by disruption of normal mitotic spindle formation	Riparbelli et al. 2012
	Various Lepidoptera, Diptera, Coleoptera, and harlequin pseudoscorpions	Unknown	Hurst et al. 1999a; Zeh et al. 2005
<i>Rickettsia</i>	Ladybird and buprestid beetles	Unknown	Werren et al. 1994; Lawson et al. 2001
<i>Arsenophonus nasoniae</i>	<i>Nasonia vitripennis</i> (Hymenoptera)	Inhibition of formation of maternal centrosomes required for early male development in haplodiploids	Ferree et al. 2008
Hamiltonella related	<i>Cheilomenes sexmaculata</i> (ladybird beetle)	Unknown	Majerus and Majerus 2010
<i>Spiroplasma poulsoni</i>	<i>Drosophila melanogaster</i> / <i>Drosophila nebulosa</i>	Widespread apoptosis in male-killed embryos; neural tissue is inhibited from properly packing into the neural chord and from forming axons; male killing requires the male form of the dosage compensation complex	Veneti et al. 2005; Bentley et al. 2007; Martin et al. 2013
<i>Spiroplasma ixodetis</i> group	Various ladybird beetles, Lepidoptera, and Hemiptera	Unknown	Hurst et al. 1999b; Jiggins et al. 2000a; Sanada-Morimura et al. 2013

This list is exemplars, and many other examples exist.

fitness include protective *Spiroplasma* in aphids, which causes lethality in sexual males only (Simon et al. 2011), and *Spiroplasma* embryonic male killing in *Danaus chrysippus*, in which females lay solitary eggs, such that sibling–sibling interference is limited (Jiggins et al. 2000a). There are two possible logics underlying male lethality in these cases. First, male killing may be a relict following switch of a symbiont from a host in which male killing is adaptive into a novel host species in which it is not, but is nevertheless not disadvantageous. Second, it may derive from lack of selection against deleterious impacts observed in male hosts only (the “mother’s curse” as discussed in Wade [2014]).

Deviations in Sex Allocation in Hermaphrodite Plants

Cytoplasmic male sterility (CMS), in which male reproductive function is selectively destroyed, is widespread in flowering plants. It is commonly associated with particular mitochondrial types, often associated with unusual open reading frames. Plant mitochondrial genomes commonly exist as minicircles that recombine. This intragenomic recombination creates new open reading frames, which are chimeric fusions, a fraction of which induces male sterility. The mechanism of CMS is known in a number of cases (Kubo et al. 2011). Typically,

Figure 1. Equilibrium prevalence of a cost-free maternally inherited male-killing bacterium that is transmitted to a fraction $1 - \mu$ of daughters, and whose daughters have increased chance of survival $1 + b$ associated with the death of their brothers. Calculated from $p^* = [(1 - \mu)(1 + b) - 1]/b$, following Hurst (1991). Lines represent, from left to right, $b = 0.25$, $b = 0.2$, $b = 0.15$, $b = 0.1$, $b = 0.05$, and $b = 0.01$.

CMS involves mitochondrial genes that encode hydrophobic proteins, and commonly derives from genes encoding ATPase subunit. Interestingly, CMS mitochondria do not appear to have strongly deleterious effects outside of anther tissue. Notwithstanding major patterns like these, mechanisms are variable. In rice, CMS is associated with a novel mitochondrial gene whose product accumulates in anther tapetum, where it interferes with the function of a nuclear-encoded factor causing anther death (Luo et al. 2013).

The spread of CMS mitochondria relies on a compensation process, in which energy that would be dedicated to production of pollen instead is allocated to ovules (Poot 1997). Unlike heritable microbes, mitochondria have perfect vertical transmission, which can allow very high frequency of CMS types if CMS plants do not suffer from pollen limitation (McCauley and Brock 1998). The dynamics of CMS thus depend in part on pollen availability, which varies with the spatial setting of the plant (Olson et al. 2005) and whether hermaphrodite plants can self-fertilize. Stabilization of polymorphism for CMS mitochondria will be seen in a metapopu-

lation, as female individuals cannot found new populations (owing to lack of pollen) and can only invade existing ones (McCauley and Taylor 1997). As CMS spreads through a local population, pollen availability becomes more and more limiting, such that local patches may go extinct through CMS, again creating the conditions for CMS and wild-type mitotypes to coexist. Finally, selfing may provide a means for non-CMS individuals to avoid pollen limitation when CMS is common, and can produce a polymorphic equilibrium for CMS/wild-type mitochondria.

More recently, a shift in sex allocation from male to female function has been observed to be associated with maternally inherited fungal endophytes in *Elymus virginicus* grass. Although fungal endophytes are commonly considered defensive mutualists, Gorischek et al. (2013) observed that hermaphrodites infected with fungal symbionts had female-biased sex allocation; this is in contrast to the male-biased allocation pattern observed in non-endophyte-infected conspecific individuals obtained through segregation (imperfect maternal inheritance). They also showed greater vegetative propagation, again permitting symbiont maintenance.

G.D.D. Hurst and C.L. Frost

Incompatibility Associated with Symbiosis

In the reproductive phenotypes discussed thus far, the symbiont/organelle spreads by compromising the rate at which male hosts are produced or survive, or in hermaphrodites, investment into male gametes. However, in the most common reproductive phenotype, cytoplasmic incompatibility (CI), males are produced in normal numbers and develop to reproductive maturity in normal numbers. The symbiont has its impact in male gametogenesis, whereby it modifies sperm so that when they fuse with uninfected or differentially infected eggs, the offspring are not viable (Fig. 2). This trait is known for two symbionts, *Wolbachia* and *Cardinium* (Yen and Barr 1971; Hunter et al. 2003).

In diploids the CI phenotype is typified by mortality of both sexes. The mechanism of CI involves condensation of paternally derived chromatin in uninfected zygotes, through unknown microbial effectors (Callaini et al. 1997; Tram and Sullivan 2002; Tram et al. 2006; Landmann et al. 2009). In haplodiploid species, such as the Hymenoptera, CI results in male-biased sex ratios. Here male individuals are haploid and not the product of fertilization. Two types of CI are observed—ones in which diploid individuals are returned to full haploid status and develop as functional males (all male broods of normal size), and ones in which diploid individuals that are the product of incompatible crosses are characterized by widespread aneuploidy and death (all male broods corresponding in size to the number of males produced

normally) (Breeuwer and Werren 1990; Vavre et al. 2000).

In causing cytoplasmic incompatibility, the symbiont selectively decreases the fitness of uninfected females. The degree of decrease in fitness of uninfected lineages is positively frequency-dependent—where infected males are common, uninfected females suffer more commonly. Where the symbiont is not perfectly transmitted or imposes a cost on its female bearer, there is a threshold frequency of infection that must be attained before deterministic spread of the symbiont (Fine 1978; Turelli et al. 1992). Below this frequency the CI drive phenotype is too rare to compensate for segregational loss/cost of carriage. Above this frequency it has a positive drive and will invade. The threshold frequency may be achieved through stochastic processes or through alternative drive mechanisms such as direct benefit (Fenton et al. 2011). Indeed, strains of *Wolbachia* that induce CI are also commonly known to make the host tolerant to viral attack (Hedges et al. 2008; Teixeira et al. 2008; Osborne et al. 2009), suggesting that both direct benefit and reproductive parasitism may contribute to invasion/dynamics.

Following invasion, CI strains can spread to very high prevalence. Spatial waves of advance of CI symbionts have been observed on multiple occasions (Turelli and Hoffmann 1991; Hoshizaki and Shimada 1995; Kriesner et al. 2013), indicating that there are ongoing and repeated waves of symbiont spread in insects. The ability to drive rapidly to high prevalence is useful in that it potentiates *Wolbachia*-mediated control-

A

♂

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U

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U

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Figure 2. Cross-compatibility relationships in the presence of *Wolbachia*/*Cardinium* inducing CI. (A) Compatibility (viable zygotes) for the case of unidirectional incompatibility (one symbiont)—crosses are compatible save between infected male and uninfected female. (B) Compatibility for bidirectional incompatibility, with two symbionts, W₁ and W₂, alongside uninfected individuals. *Wolbachia*-infected males are incompatible with both uninfected females and females carrying the alternate strain.

of-vector competence following introduction (Walker et al. 2011; Yeap et al. 2011). This is currently being trialed in *Aedes aegypti*, into which the *Wolbachia* strain wMel has been transinfected (Hoffmann et al. 2011). Mosquitoes carrying wMel are refractory to onward transmission of dengue, and the *Wolbachia* also induces incompatibility, allowing its spread into populations following release. High-prevalence infections have been established in natural populations through release and CI-mediated spread, raising the possibility of interrupting dengue transmission in nature.

Male Lethality/Virulence Associated with Infectious Transmission

Selective killing of male hosts during larval phases is commonly associated with symbionts that can be both maternally and infectiously transmitted. It was first described in mosquitoes, associated with pathogenic activity of microsporidian symbionts. These symbionts are commonly vertically transmitted through females, and a subset of these are also pathological to male hosts during the fourth larval instar (Kellen et al. 1965; Hurst 1991). Spore transmission occurs through the aquatic phase and commonly requires a secondary host (e.g., copepod) (Andreadis 1991). “Late” male killing of this type has also recently been observed in a terrestrial insect, the Oriental tea tortrix, *Homona magna*. Here an infectious RNA virus exhibits vertical transmission in female hosts and male-specific lethality in late instar caterpillars (Morimoto et al. 2001; Nakanishi et al. 2008). Parallel limitation of virulence associated with female hosts is observed in helminth parasites of mammals. Shoop (1991) described how helminths show sex-specific tropism and pathogenesis, achieving vertical transmission through milk/accumulation in mammary tissue in females and infectious transmission through the gut in males.

Male death (in contrast to cases of embryonic male-killing) is associated with liberation of infectious spores into the environment and onward infectious transmission. Intuitively, efficient infectious transmission would select for killing of both sexes, and late male killing will be

thus favored where infectious transmission rates are low. It is notable in this context that symbionts can be plastic, exhibiting vertical transmission in a growing population in which opportunities for heritable transmission are good, and infectious transmission in one at carrying capacity in which opportunities are rare (Agnew and Koella 1999; Kaltz and Koella 2003). They may also evolve to be benign where vertical transmission opportunities are common (Magalon et al. 2010).

IMPACT OF CYTOPLASMIC SEX-RATIO DISTORTERS ON HOST REPRODUCTIVE ECOLOGY AND PATTERNS OF INTRAGENOMIC AND SEXUAL CONFLICT

The spread of a symbiont that affects host sex ratio, sex allocation, or sexuality has obvious impacts on the host mating system. These include obligate loss of sex, alteration of host mating system from one of dioecy to gynodioecy, and alteration in operational sex ratio. These alterations may then impact on other conflicts associated with sexual reproduction, such as those exhibited between selfish genetic elements and their hosts, and between male and female.

Symbionts and the Evolution of Obligate Asexuality

Species and populations of haplodiploid arthropods that are obligate asexuals as a result of symbiont activity are common. Indeed, the only male specimens ever obtained in many of these species are those produced following treatment of the host with antibiotics (Stouthamer et al. 1990). However, for a symbiont alone to produce loss of sexual reproduction, it would be required to be transmitted with near perfect fidelity and to be completely accurate in inducing female development in unfertilized males. Given that symbionts commonly show some segregational loss/imperfect manipulation abilities, the transition into obligate asexuality is more commonly a complex process that involves host evolution in addition to symbiont spread.

Stouthamer et al. (2010) propose a scenario in which symbiont spread promotes the loss of

G.D.D. Hurst and C.L. Frost

sexual function in females. In haplodiploid species, symbiont induction of asexuality commonly involves diploidization of unfertilized male embryos. Where the symbiont becomes common and males are rare, selection can promote the production of sons through “virginity” mutations, which inhibit females from mating (Stouthamer et al. 2010). Uninfected females then produce male offspring exclusively, and infected females produce more sons if there is inefficient transmission of the symbiont or if some haploid individuals escape diploidization. The spread of virginity mutations will drive up the frequency of the asexuality-inducing symbiont, as uninfected females produce fewer daughters. The process can thus lead to the fixation of the symbiont and the loss of all sexual reproduction.

Empirical studies bear out the observation that sexual function degrades rapidly and, as predicted by the virginity hypothesis, female reproductive function is lost first. In three species (*Leptopilina clavipes*, *Asobara japonica*, and *Apoanagyrus diversicornis*), interpopulation variation in the presence of a symbiont that induces asexuality has allowed the functionality of males and females derived from asexual lineages to be tested. In all three cases this revealed female function to have deteriorated before male, with infected females unable to use sperm from males, while derived males were partially fertile (Pijls et al. 1996; Pannebakker et al. 2005; Kremer et al. 2009). In a variety of cases the loss of sexual traits has been shown to have a simple genetic basis (Jeong and Stouthamer 2005; Russell and Stouthamer 2011).

Alteration in Mating System/Reproductive Ecology

Symbiont-induced sex-ratio biases have been observed to alter the pattern of reproductive competition in a number of arthropod species. In *Acraea encedon* butterflies, 95% of females in some populations carry a *Wolbachia* male killer. These populations are sex role reversed, with female reproduction limited by access to males and female–female competition for mates in evidence (Jiggins et al. 2000b). In *H. bolina* but-

terflies, male killer prevalence across islands varies from absence (1:1 population sex ratio) to 100 females per male. Interestingly, comparison of reproductive systems between islands suggests that the impacts on host reproduction are nonlinear (Charlat et al. 2007b). Female mating rate is highest in populations in which males are moderately (but not very) scarce, with polyandry most profound at 50%–75% male-killer prevalence. It is believed that increases in polyandry where males are quite scarce are associated with an increased desire to remate for females that receive small spermatophores. The size of spermatophore transferred by a male declines with increasing male mating rate. Strongly female-biased sex ratios are thus associated with the transfer of small spermatophores and elevated female mating rate.

The mating system changes observed to date in the butterfly sex-ratio distorter systems are plastic—in *Hypolimnna* the reproductive investment patterns of males do not vary between island populations when the males are maintained in a common garden environment (Charlat et al. 2007b). This may be partly explained by the weak efficacy of selection where male killers are common (see above). However, there is evidence in feminizer–host systems for evolution of male reproductive behavior. In a comparative analysis, the male ability to fertilize multiple females was higher in two species carrying a feminizer than in five other species in which there was no feminizer present (Moreau and Rigaud 2003). This is consistent with the action of selection to partition ejaculates to enable a greater mating rate in males. Further, in *Gammarus duebeni*, males are sperm-limited and allocate larger ejaculates to females that do not carry feminizing symbionts (Dunn et al. 2006). Although this may be the expression of a historic preference for high-quality females, it is also consistent with adaptive preferences evolved to counter the problem of feminization.

Consequences for Other Conflicts Associated with Reproduction

Changes in mating system are very likely to alter the intensity of other conflicts. Selfish genetic

elements, for instance, possess the highest drive in outbreeding populations. In plants the spread of cytoplasmic male sterility alters the host mating system from one of dioecy (all individuals hermaphrodite) to gynodioecy (a mix of female plants and hermaphrodites). CMS mitochondria enforce outbreeding and will reduce the rate of selfing within the population. Selfing both creates homozygosity for particular elements (preventing drive) and exposes selfish genetic elements to the damage they cause (Burt and Trivers 1998). Thus, the spread of CMS, and consequent reduction in frequency of dioecious individuals and inbreeding, may facilitate the spread of other selfish genetic elements. An expectation is that in species where selfing is possible, the presence of CMS mitochondria at high frequency would be associated with a higher load of B chromosomes and transposable elements.

The intensity of sexual conflict is likely to be affected by sex-ratio distortion. In biasing population sex ratio toward females, the conflict between male and female is likely to change in both intensity and direction. Further, the intensity of male–male precopulatory conflict will diminish. Although not examined for any particular natural case, the impact of sex-ratio manipulation on the intensity of these conflicts is well-known from experimental evolution studies (Wigby and Chapman 2004; Linklater et al. 2007). Where insects are maintained in female-biased sex ratios, selection results in a reduction in the intensity with which males manipulate female physiology, and females are less selected to resist harm and are more susceptible to damage. Further, males are selected to partition ejaculates in the “expectation” of future mating opportunities.

HOST RESPONSES TO SEX-RATIO DISTORTER ACTIVITY, AND THE EVOLUTION OF CORE FEATURES OF MALE/FEMALE BIOLOGY

Both sex ratio–distorting microbes and mitotypes that alter sex allocation via CMS can generate unusually strong selective forces. Where they become common, males/male gametes be-

come very rare. This places them in conflict with selection on biparentally inherited nuclear genes. The nature of Fisherian selection on the sex ratio is such that modifiers of the host nuclear genome that restore male production are very strongly selected as the male host/function they rescue has very high fitness. Thus, the impact of the parasite on sex ratio makes the conflict between the parties potentially the most intense in nature.

The evolution of restoration of male function is established widely for cases of cytoplasmic male sterility induced by mitochondrial variants, in which nuclear genes are commonly termed *Rf* genes, or “restorers of fertility.” Restorer genes in these systems often encode proteins with pentatricopeptide motifs, which bind RNA and function through posttranscriptional suppression of the mitochondrial transcript that would create CMS. However, alternate mechanisms of restoration exist (Luo et al. 2013). Restoration of male host survival is also known in five cases for male killing induced by heritable microbes, in which the genes are commonly termed “suppressors” (Table 4). However, the mechanisms of restoration are not known in any case. Nuclear genes that reduce the vertical transmission of feminizing microbes are also known (Rigaud and Juchault 1992).

The evolutionary dynamics of suppressor/restorer genes are quite variable. The strength of selection will depend on the initial frequency of the distorting element, the effectiveness with which the symbionts eliminate male hosts/function (e.g., all infected males die or are feminized vs. some), and the degree to which the nuclear gene restores phenotype (e.g., partial vs. complete restoration of male fertility). Following invasion, the equilibrium prevalence of the microbe/mitochondria and frequency of the suppressor gene depend on whether the microbe has an alternate source of “drive,” as well as the “cost” of carrying a suppressor.

Where the symbionts have no alternate form of drive, a cost-free suppressor will eliminate the symbiont, whereas suppressor and male killer are expected to remain polymorphic when suppressors are costly (Randerson et al. 2000), as

G.D.D. Hurst and C.L. Frost

Table 4. Nuclear-encoded factors that prevent the action or transmission of sex ratio–distorting symbionts

Natural host	Symbiont	Nature of suppression	Notes	References
<i>Hypolimnasthe bolina</i>	<i>Wolbachia</i> wBol1	Dominant zygotic suppression of male killing	Spatially variable; evidence of recent rapid spread in some populations	Hornett et al. 2006, 2009; Charlat et al. 2007a
<i>Cheilomenes sexmaculata</i>	<i>Hamiltonella</i> relative	Dominant zygotic suppression of male killing	Suppressor polymorphic within populations	Majerus and Majerus 2010
<i>Drosophila recens</i>	<i>Wolbachia</i>	Suppression suggested by emergence of male killing in some lines of <i>Drosophila subquinaria</i> following transfer from <i>D. recens</i>		Jaenike 2007
<i>Ephesthia cautella</i>	<i>Wolbachia</i>	Suppression suggested by emergence of male killing following transfer into <i>Ephesthia kuehniella</i>		Sasaki et al. 2002
<i>Drosophila prosaltans</i>	Unknown	Polymorphic recessive factor affecting male killing		Cavalcanti et al. 1957
<i>Armadillidium vulgare</i>	<i>Wolbachia</i> wVul1	Nuclear-mediated resistance to transmission of feminizing symbiont	Sex jointly determined by <i>Wolbachia</i> presence and nuclear factor influencing its transmission	Rigaud and Juchault 1992

observed in the ladybird *Cheilomenes sexmaculata* (Majerus and Majerus 2010). However, many symbionts have alternate drive mechanisms such that they may be retained even when suppression is complete. For instance, in *H. bolina* the suppressed male killer induces cytoplasmic incompatibility in rescued males (Hornett et al. 2008), which drives the symbiont to fixation following spread of the suppressor (Hornett et al. 2010). At this point, the suppressor becomes required for male host survival in the population and can become a fixed aspect of the host biology—albeit one whose evolutionary origins are in maintaining survival against heritable parasites alone.

The spread of suppression of male killing has been observed in natural populations of the butterfly *H. bolina*. As discussed previously, the male-killing *Wolbachia* in this species can attain very high prevalence. This is most obvious on Samoa, where four records over a 100-year period up to 2001 reported population sex ratios of 100 females per male. This extreme sex ratio had disappeared completely by 2006

(Charlat et al. 2007a). The heritable microbe was still present in the population, but the spread of a nuclear gene that rescued male embryos (a suppressor of male killing) had restored individual and population sex ratios to parity. The spread was observed in real time over Savai'i, one of the two large islands in Independent Samoa, with population sex ratios of 100 females per male in 2005 and parity of sex ratio in 2006, 8–10 generations later.

In this system, the strength of selection at the point of origin of the suppressor is extreme. Where the sex ratio is 100 females per male, essentially all surviving male hosts will carry the suppressor in the generation after its introduction (male survival without the suppressor is negligible). Where the suppressor activity is dominant (the case in *H. bolina*), all males in the population are heterozygous for the suppressor element after one generation. Thus, the frequency of the suppressor increases to 25% in a single generation.

The strength of selection that suppression can engender is important for two reasons.

First, it determines the pace of change in reproductive systems of its host—in the case of *H. bolina*, a switch from a reproductive system in which males are the “in-demand” sex to a female-limited one in potentially a single generation. Second, it determines what type of mutation can spread. Where selection is intense, mutations that would otherwise be very deleterious can actually spread. For the case of a 100:1 female/male sex ratio, a suppressor that rescued males could spread even if it reduced female host fitness by 99%.

The ability to drive the spread of mutations that would otherwise be highly deleterious is perhaps one of the most interesting features of sex ratio–distorting symbionts. The intensity of conflict is such that it may drive unusual, and otherwise forbidden, alterations in the way in which male and female individuals are constructed (their sex-determination system). Although we do not know the molecular nature of suppressor mutations in any system, sex-ratio distorters interact with host sex–determination systems in multiple ways (Table 3), and thus an obvious avenue for selection is change in these systems. Our thesis is that the evolution of suppression of sex ratio–distorting activity will frequently involve loci associated with sex determination. Theory has proposed that the evolution of haplodiploidy and paternal genome elimination may be driven by sex ratio–distorting activity (Engelstadter and Hurst 2006; Ubeda and Normark 2006). More widely, more subtle changes in the construction of sex-determination systems are likely. We would argue that although extreme prevalence of sex-ratio distorters may be rare, they create the circumstances that can drive change in genetic systems that otherwise are rarely selected because mutations within them are otherwise deleterious. Thus, they may be a rare force that drives revolutionary changes of the type classic theory finds hard to explain.

There is already some evidence for the involvement of sex-ratio distorters in the evolution of sex-determination systems. Trivially, microbes that feminize are novel sex-determining loci. In the female heterogametic pill woodlouse, *A. vulgare*, spread of the feminizing agent

is also associated with loss of the female-determining chromosome, such that sex becomes primarily determined by the presence/absence of *Wolbachia*-induced feminization. Nuclear factors that affect *Wolbachia* transmission are then, de facto, novel sex-determination factors, as all progeny that do not inherit *Wolbachia* develop as males.

Evolution of sex-determination systems has also been implied in recent study of the moth *Ostrinia scapulalis*. In this species *wSca Wolbachia* induces male killing. Male killing is associated with alteration of the splicing of the gene *doublesex*, such that all individuals have the female splice form of *dsx* and those that are ZZ (destined to be males) die, presumably from an imbalance between sex chromosome karyotype and developmental sex (Sugimoto and Ishikawa 2012). Interestingly, when ZW individuals with *Wolbachia* (destined to be female) are cured using antibiotics, all male sex ratios are observed associated with male-form splicing of *dsx* in all progeny, and the death of ZW progeny (Kageyama and Traut 2004). The investigators conclude that the *Wolbachia* kills through feminization and that female sex–determining factors on the W chromosome have degraded in the presence of the male killer, as their expression was made redundant by the *Wolbachia* feminization.

CONFLICTS ASSOCIATED WITH CYTOPLASMIC INCOMPATIBILITY—INDUCING SYMBIONTS MAY DRIVE THE EVOLUTION OF SPERMATOGENESIS AND MATE-CHOICE PATTERNS

The spread of cytoplasmic incompatibility–inducing symbionts produces different selection on male and female hosts. Because possession of a CI-inducing symbiont confers protection against CI, female hosts are selected to maintain and transmit the symbiont. In contrast, the incompatibility produced by the symbiont imposes a cost on the male host. There may also be additional costs associated with the presence of a symbiont in developing sperm bundles (e.g., Snook et al. 2000). Thus, selection favors modifiers that restrict the proliferation of the

G.D.D. Hurst and C.L. Frost

symbiont in males and prevent entry to, and modification of, the germline (Koehncke et al. 2009). Importantly, selection on the symbiont to maintain the CI phenotype is very weak when the symbiont is common (Orr 1996), such that an antagonistic arms race is unlikely and symbiont loss thus probable. This logic creates an evolutionary trajectory where the spread of a CI symbiont is followed by host selection to prevent incompatibility, leading to the loss of the symbiont over time.

Two observations support this evolutionary trajectory. First, there is considerable variation between host species in the expression of CI by given symbiont strains (Veneti et al. 2003). Second, cytoplasmic incompatibility-inducing symbionts do not persist within a host species over long periods of evolutionary time—sibling species pairs commonly either have different infection status (infected vs. uninfected) or carry different symbiont strains that do not share a common ancestor within the host matriline in which they are currently found (Raychoudhury et al. 2009). Although there are alternate explanations for this pattern (e.g., Turelli 1994), we believe they are most likely a manifestation of selection on male hosts to prevent entry into testes/germline modification.

In the above models, males are selected not to express CI, to avoid the cost of incompatible matings. Where cross-incompatibility exists, there may also be selection on females to avoid incompatible matings (Telschow et al. 2005). An example of this process can be seen in *Drosophila subquinaria*, *Drosophila recens* and *D. subquinaria* are sympatric in part of their range. *D. recens* carries a *Wolbachia* that causes incompatibility in crosses to *D. subquinaria* males. *D. subquinaria* females show behavioral avoidance of mating with *D. recens* males, but only where the two species are sympatric (Jaenike et al. 2006). The thesis is that *Wolbachia*-induced cross-incompatibility selects for “reinforcement” through females’ refusing incompatible matings in the zone where hybridization is possible. Indeed, the evolution of premating barriers in *D. subquinaria* in sympatry with *D. recens* also creates behavioral isolation against allopatric males of the same species.

AREAS FOR FUTURE RESEARCH

We currently understand the rationale underlying reproductive parasitism and have a good working knowledge of the population biology of these symbionts when they exhibit a single phenotype (e.g., male killing). However, the impact of these agents in natural populations is not well established. Further, there are good reasons, based on the strength of selection they produce, to believe they will drive rapid evolution in the host, but the systems under selection remain unclear. Finally, our comprehension of the biology of these symbionts has been impeded by the historical tendency to separate symbionts into “beneficial” and “reproductive parasite,” whereas it is now clear that a particular symbiont can have multiple impacts, directly benefiting their host in terms of providing “function” and manipulating host reproduction to enhance their spread. Below we outline how these areas of research may be approached in future studies.

The Mechanisms of Reproductive Parasite Action

Outside of cytoplasmic male sterility, our knowledge of the mode of action of reproductive parasites is weak. There is currently little functional knowledge of the microbial effectors important in inducing phenotype, with research limited to candidate genes expressed at appropriate phases of host development (Sinkins et al. 2005). There is more (but still limited) knowledge of the host pathways with which these effectors interact (see Tables 1–3), but in no case have the host genes affecting reproductive parasite action been defined.

Study of microbial effectors has been limited by the fastidious nature of most heritable symbionts, which have generally proven recalcitrant to transgenic manipulation (despite having been shown to have recombining genomes). Study of host systems that alter symbiont action has been limited by the nonmodel nature of the species. However, it is now straightforward and cheap to obtain genome sequences for arthropods, and we expect this to allow at least the genes involved in evolved host responses to be

identified. Further, transgenic manipulation of nonmodel species is becoming more routine and may allow more-defined functional testing.

Mechanistic work of this kind has a high priority because it will both potentiate the use of symbionts in control and also uncover the foci for selection in host species that are subject to a reproductive parasite. Currently, the nature of host responses to reproductive parasites is at the level of high-level phenotypic description: “modifies CI strength,” “rescues males from death,” and “prevents symbiont transmission.” We should be able to establish the extent to which suppression of phenotype is associated with changes in sex determination, which genes involved in testes biology are altered to reduce symbiont impact in testes, and whether processes of oogenesis/egg formation alter to prevent symbiont transmission. This will require a mix of functional and genetic analysis.

The Importance of Multiple Phenotypes

The population and evolutionary ecology of heritable symbionts has traditionally been viewed through a single-phenotype prism—a symbiont has one impact on a host. It is clear that this is not generally true. Symbionts may combine nonprotective benefit with sex-ratio distortion (Himler et al. 2011), combine protection and reproductive manipulation (Osborne et al. 2009), and may also combine reproductive manipulation with increased susceptibility to natural enemies (Graham et al. 2012).

Symbionts that have more than one phenotypic effect will be expected to have different dynamics to our current understanding under the single-phenotype models, and the intensity of the conflict with the nuclear genome will also differ. For symbionts that produce both natural enemy resistance and reproductive parasitism, two consequences seem likely:

1. A reproductive manipulation phenotype would allow a symbiont to persist even in the absence of an ecologically contingent benefit. The advantage gained from many symbiont phenotypes is ecologically contingent—they provide benefit only in the pres-

ence of a particular parasite or in a particular abiotic environment. This renders them susceptible to loss when the pressure that produces the benefit is relaxed (Oliver et al. 2008). A symbiont with additional reproductive parasitism may be maintained indefinitely, as it additionally possesses a drive mechanism that does not rely on ecological circumstance.

2. Symbiont frequency, and thus population sex ratio, may be altered by natural enemy pressure. The link between natural enemy pressure and population sex ratio is likely to create unusual dynamics, as population sex ratio can affect population growth/density, which will have an impact on the success of the natural enemy.

The multiphenotype model also changes the intensity, and potentially the direction, of cytoplasm–nuclear conflict. First, it alters whether the host is selected to remove or retain the symbiont. Beneficial symbionts do not engender selection to remove them and may produce selection for active maintenance. Fixation and maintenance is best recognized for symbionts that make an anabolic contribution to the host (Moran et al. 1993), but is also observed for some cases of natural enemy protection (Nakabachi et al. 2013). Combining beneficial impacts with sex-ratio distortion will alter the direction of selection when a symbiont is common; the nature of Fisherian selection on the host’s sex ratio is such that a symbiont that alters host sex ratio will promote the spread of modifiers that prevent sex-ratio distortion/symbiont presence when the symbiont is at high frequency, notwithstanding any benefits of symbiont presence.

At longer evolutionary timescales, protective symbionts will clearly be vulnerable to mutation that leads to the acquisition of reproductive manipulation phenotypes. It is notable that even where “dual phenotypes” are not known, related symbiont microbes are parasitic or protective. Given the ease of movement of traits between bacteria, it is likely that it will be “easy” for symbionts to acquire additional phenotypes.

G.D.D. Hurst and C.L. Frost

The acquisition of parasitic traits may change the direction of selection on the host from maintenance to removal, and may in part explain why protective symbionts, despite being beneficial, commonly do not have long evolutionary histories with their host. One prediction from this is that protection is likely to be maintained for longer periods of evolutionary time in host taxa in which common reproductive manipulations (e.g., male killing) are not beneficial. Conversely, protective symbiosis should be less common in groups in which reproductive parasitic phenotypes are common, as here protection does not contribute to long-term maintenance.

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