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SEX DETERMINATION, SEX RATIOS, AND GENETIC CONFLICT

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ABSTRACT

Genetic mechanisms of sex determination are unexpectedly diverse and change rapidly during evolution. We review the role of genetic conflict as the driving force behind this diversity and turnover. Genetic conflict occurs when different components of a genetic system are subject to selection in opposite directions. Conflict may occur between genomes (including paternal-maternal and parental-zygotic conflicts) or within genomes (between cytoplasmic and nuclear genes or sex chromosomes and autosomes). The sex-determining system consists of parental sex-ratio genes, parental-effect sex determiners, and zygotic sex determiners, which are subject to different selection pressures because of differences in their modes of inheritance and expression. Genetic conflict theory is used to explain the evolution of several sex-determining mechanisms, including sex chromosome drive, cytoplasmic sex-ratio distortion, and cytoplasmic male sterility in plants. Although still limited, there is growing evidence that genetic conflict could be important in the evolution of sex-determining mechanisms.

PERSPECTIVES AND OVERVIEW

Sex-determining mechanisms in plants and animals are remarkably diverse. A brief synopsis illustrates the point. In hermaphroditic species, both male (microgamete) and female (macrogamete) function reside within the same

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individual, whereas dioecious (or gonochoristic) species have separate sexes. Within these broad categories there is further diversity in the phenotypic and genetic mechanisms of sex determination. In dioecious species, various mechanisms exist, including haplodiploidy (males derived from haploid eggs, females from diploid eggs), paternal genome loss (sex determined by loss of paternal chromosomes after fertilization), male heterogamety (males with heteromorphic XY sex chromosomes and females with homomorphic XX), female heterogamety (ZW females and ZZ males), polygenic sex determination, environmental sex determination, and a variety of other mechanisms (reviewed in 17, 175). Sex determination can even differ markedly within a species and between closely related species. For example, platyfish (*Xiphophorus maculatus*) can have either male heterogamety or female heterogamety (104). In addition, mechanisms that appear to be the same can differ markedly in the underlying genetics. For example, male heterogametic systems can be based on dominant male determiners on the Y (e.g. in mammals) or on a genic balance between factors on the X and autosomes (e.g. in *Drosophila*). Molecular studies have shown that genes involved in primary sex determination evolve rapidly (48, 111, 166, 169, 170, 176) and that sex-determining genes in one species may not be involved in sex determination in related species (67, 100).

In this diversity lies a quandary. Although one would assume that such a basic aspect of development as sex determination would be highly stable in evolution, the opposite is the case. This observation leads to two important evolutionary questions: "Why are sex-determining mechanisms so diverse, and how do sex-determining mechanisms change, i.e. how do transitions occur from one sex-determining mechanism to another?" Presumably, sex-determining systems change when some factor (or factors) destabilizes an existing sex-determining mechanism, leading to the evolution of a new mechanism. Therefore, the focus should be on factors that potentially destabilize sex-determining mechanisms and whether some features of sex determination make it inherently unstable over evolutionary time.

In this review, we consider the role of genetic conflict in the evolution of sex-determining systems. Genetic conflict occurs when different genetic elements within a genome are selected to "push" a phenotype in different directions. There are two basic forms of genetic conflict. Intragenomic conflict involves conflicting selective pressures between different genetic elements within an individual organism (e.g. between cytoplasmic genes and autosomal genes). Intergenomic conflict occurs between genetic elements in different individuals that interact over a particular phenotype.

Genetic conflict is an inherent feature of sex-determining systems. For example, cytoplasmically inherited genetic elements (e.g. mitochondria, cytoplasmic microorganisms, plastids) are typically inherited through the egg cytoplasm

but not through sperm. As a result, these elements are selected to produce strongly female-biased sex ratios, which increases their transmission to future generations (42, 55). In contrast, autosomal genes (those residing on non-sex chromosomes) are generally selected to produce a balance in the sex ratio (57). As a result, cytoplasmic and autosomal genes are selected to push sex determination in different directions. There is considerable evidence that conflict between autosomal and cytoplasmic genes is widespread (86, 170). Genetic conflict over sex determination can also occur between sex chromosome and autosomal genes and between parental- and offspring-expressed genes. Coevolutionary interactions among these conflicting selective components may provide a "motor" for evolutionary change in sex determination.

We discuss various models for the evolution of sex determination, focusing on the potential role of genetic conflict. We argue that genetic conflict is the most likely general explanation for the diversity of sex-determining mechanisms. However, although the evidence for its role in sex determination is mounting, unequivocal examples of genetic conflict causing evolutionary transitions in sex determination have yet to be made. In light of this, possible directions for future research are discussed.

The reader is also referred to reviews on the diversity of sex-determining mechanisms (17, 175), sex-ratio evolution (3, 31, 171), the evolution of heteromorphic sex chromosomes (27, 142), and somatic and germline sex determination in fruitflies (35, 137, 156), vinegar worms (36, 80), mammals (64, 82, 100), and plants (66).

BRIEF HISTORICAL SKETCH

Genetic Conflict

The concept of genetic conflict is intimately associated with two closely related developments in evolutionary biology—the idea that selection operates on individual genetic elements rather than just on the individual organism (levels of selection) and the observation that some genetic elements can be selfish or parasitic (e.g. they gain a transmission advantage despite being detrimental to the organism in which they occur). Among the first publications on what is now known as intragenomic conflict were theoretical studies by Lewis (110), who considered the fate of cytoplasmic male sterility (CMS) genes in plants, and Howard (81), who investigated cytoplasmic factors causing all-female families in animals. Both showed that cytoplasmic factors producing female biases can spread through a population, even though they may potentially cause extremely female-biased sex ratios and population extinction. Thus, the idea of intragenomic conflict was associated with questions concerning sex determination from its very inception. However, the implications

of these models to the then-current views of natural selection were not widely recognized.

The botanist Östergen (135) was among the first to recognize that selection may operate in different directions on different parts of the genome. In his studies on B chromosomes [supernumerary chromosomes that occur in a wide range of species (102)], he realized that these genetic elements were parasitic, gaining a transmission advantage relative to the rest of the host's genome. Although long opposed (127), the idea that B chromosomes are selfish elements is now widely accepted (7, 102, 153, 173). The discovery of meiotic drive chromosomes (chromosomes that are transmitted to greater than 50% of gametes) (150) also stimulated consideration of the gene as the level of selection. Evolution of such systems can be understood by invoking conflicting selective pressures between the driving genes and unlinked repressors (56, 73, 94, 115, 180).

Dawkins (47) played an instrumental role in promoting the concept that selection operates at the level of the gene. Cosmides & Tooby (42) introduced the term intragenomic conflict and published a comprehensive paper on the possible role of intragenomic conflict in evolutionary processes including cytoplasmic inheritance, the evolution of anisogamy, the transition of hermaphroditism to dioecy, and the evolution of sex and sex determination. Several studies addressed the role of genetic conflict in evolution (1, 11, 55, 79). The idea that DNA could be selfish or parasitic started to receive attention through simultaneous publications by Doolittle & Sapienza (50) and Orgel & Crick (133), and an accumulating number of discoveries of selfish non-Mendelian elements such as transposons, B chromosomes, and cytoplasmic sex-ratio distorters. Werren et al (173) formally defined selfish genetic elements and reviewed existing evidence.

The concept of genetic conflict is now widely accepted in evolutionary biology (e.g. 89, 118; reviewed in 84, 91, 143). Recent theoretical and empirical work has focused on genetic conflict between cytoplasmic and autosomal sex-ratio factors (43, 59, 76, 145, 148, 160, 170), conflict between sex-chromosome–drive factors and repressors of drive (71, 72, 178), the potential importance of genetic conflict in the evolution of sex (78, 89), and paternal-maternal genome conflict over allocation of resources to progeny (70). Although the evidence of its importance is mounting, the role of genetic conflict in evolution remains to be established for many phenomena.

Sex Determination

An important early development in the study of sex determination was the discovery of sex chromosomes (77) and development of the theory of heterogametic sex determination (120). Subsequent research focused on the basic mechanisms of sex determination in a wide range of organisms (reviewed in 175) and

revealed considerable diversity. Detailed genetic studies of sex determination were limited to a few organisms, most notably *Drosophila melanogaster*, which has male heterogamety. In genic balance systems, sex depends on a balance between female-determining factors on the X chromosome and male-determining factors on the autosomes. This system was uncovered in early genetic experiments by Bridges (12), who varied the number of X chromosomes in *Drosophila* and suggested that sex in *Drosophila* is determined by the ratio between X chromosomes and autosomes. In dominant-Y systems (e.g. in some mammals), a dominant male determiner is present on the Y chromosome. Bull (17), in an important treatise of the evolution of sex-determining mechanisms, considered transitions between sex-determining systems and, among other forces, the possible role of genetic conflict. Evolution of sex chromosomes and heterogamety has also been widely considered (18, 20, 26, 27, 142).

Currently, the molecular regulation of sex determination is known in detail from only a few organisms, including the house mouse (*Mus*), the fruitfly (*D. melanogaster*), and a nematode (*Caenorhabditis elegans*) (reviews in 80, 156). These systems serve as a basis for comparisons with other systems. However, it is difficult to extrapolate on the evolutionary changes leading to the differences between these species, due to their phylogenetic distance.

There is an extensive theoretical and empirical literature on the evolution of sex ratios (31, 37, 63, 73, 171, 179), but most of these studies focus on how selection acts on the parent to manipulate sex ratio of offspring under various circumstances. There has been little consideration of the coevolutionary interactions between sex-ratio genes acting in the parent and sex-determination genes acting within the zygote (but see 19).

CONCEPTUAL FRAMEWORK

The Sex Determining System

As pointed out by Bull (17) sex-ratio selection is the underlying force shaping the evolution of sex-determining systems. Sex-ratio selection concerns the transmission success of genetic factors through male function (sperm or pollen) versus female function (eggs or ovules). When a particular genetic element has higher transmission through one sexual function than the other, selection will favor variants of that element that bias sex ratio (or sex determination) toward the transmitting sex.

To understand the evolution of sex determination, it is necessary to consider how selection acts on each of the components of the overall sex-determining system. This system consists not only of the genes acting within an individual to determine its sex but also of genes acting within the parents that influence either sex ratio or sex determination (Figure 1). Components of the sex-determining

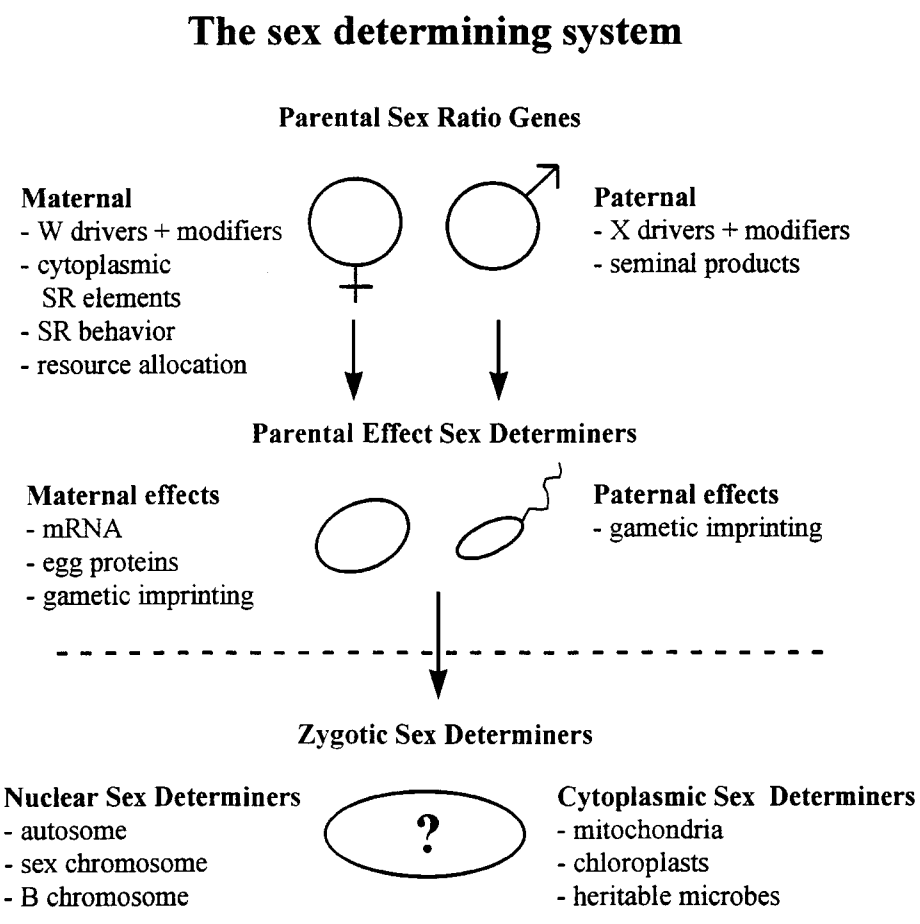

Figure 1 The sex-determining system, showing the different interacting components of the sex-determining system, including parental sex-ratio (SR) genes, maternal- and paternal-effect sex determiners, and zygotic sex determiners.

system can be further categorized based on their mode of inheritance. The mode of inheritance of a genetic element has a major influence on how sex-ratio selection acts on it.

Classically, genetic studies of sex determination have focused on genes that act within the developing zygote to influence its sex. However, the evolution of sex determination is influenced by selection acting on three broad categories of genes—(*a*) sex-ratio genes, which are genes that act within the parent to influence the sex ratio among its progeny, (*b*) sex-determination genes, which are genes that act within the developing zygote to influence its sex, and (*c*) parental-effect sex determiners, genes that are expressed in the parent (i.e. they depend on parental genotype) but that act in the developing zygote to influence sex. Examples of the latter category are maternal-effect sex-determining genes in *D. melanogaster* (34, 156), in the housefly (*Musca domestica*) (51, 93), in species demonstrating monogeny-production of all-male or all-female famies (e.g. *Chrysomya*, 167), and in coccids that show paternal genome loss early in development (17, 130). These three categories of sex-determination genes are briefly discussed below, and examples are given in Table 1.

PARENTAL SEX-RATIO GENES Parental influences over sex ratio occur in a broad range of species. One category of parental sex-ratio genes are those causing sex-chromosome meiotic drive. Sex-chromosome drive is a parental phenotype that alters the ratio of gametes bearing X and Y (or Z and W) genes but does not directly affect the zygotic sex-determining mechanism. X-chromosome drive has been documented in a wide range of species with male heterogamety, including fruitflies, mosquitoes, and lemmings (see below). Parental influences on sex ratio are common in haplodiploid insects, in which females manipulate the sex ratio among progeny by altering the probabilities that an egg is fertilized (63). Unfertilized eggs develop into males, and fertilized eggs develop into females. Genetic variation for fertilization proportion has been documented in some species (135) and is inferred in many others (63). Another mechanism of parental effects on sex-ratio selection is differential allocation of resources to male and female progeny. By allocating more resources to offspring of one sex, parental phenotypes could alter selection acting on zygotic sex determiners. In species with environmental sex determination, the parent can influence sex among progeny by selectivity in oviposition sites, as shown in terrapins (146) and western painted turtles (96). This, in turn, will affect how selection operates on environmental sex-determining genes expressed in the zygote. Some birds [e.g. the Seychelles warbler (108)] alter sex ratio among progeny based on available resources. This is due to either preferential segregation of Z or W chromosomes during meiosis (a parental sex-ratio effect) or to maternal modification of zygotic sex determination (see below).

Table 1 Categories of genetic elements involved in sex determination

Category	Expression	Action	Examples	Reference
Sex-ratio genes				
Maternal	Maternal	Maternal	Sex-ratio control in parasitic wasps	63
			Oviposition site selection (ESD systems)	96
			Sex ratio meiotic drive (ZW females)	17
			msr cytoplasmic factor in *Nasonia vitripennis*	154
Paternal	Paternal	Paternal	X-chromosome drive in many species	92, 1
			Suppressors of sex chromosome drive	122
Parental-effect genes				
Maternal effect	Maternal	Zygotic	Maternal-effect SD in coccids	128
			da in *Drosophila melanogaster*	156
			f factor in *Musca domestica*	44, 9
			Monogeny in *Chrysomia rufifacies*	167
			Cytoplasmic sex-ratio distorters	86
Paternal effect	Paternal	Zygotic	Paternal imprinting of *sd* genes (hypothetical)	8
			psr chromosome in *N. vitripennis*	131
Zygotic sex-determining genes	Zygotic	Zygotic	*D. melanogaster sd* cascade (X:A balance genes, *Sxl*, *tra*, *dsx*)	156
			Caenorhabditis elegans sd cascade (*sdc*, *her*, *tra*, *fem*)	80
			SrY in humans, housemice	100
Other (social) interactions				
Sex ratio	Individual 1	Individual 2	Worker sex-ratio manipulation in social insects	164
Social effect	Individual 1	Individual 2	Social influences in ESD species (*Heterodera* nematodes, *Mytilicola* copepods)	17

ESD, Environmental sex determination; SD, segregation distorter; *da*, daughterless; *f* factor, feminizing factor of unknown etiology; CMS, cytoplasmic male sterility; *psr*, paternal sex-ratio chromosome; *Sxl*, *Sex lethal* gene; *SrY*, dominant male determiner.

PARENTAL-EFFECT SEX DETERMINERS Functionally, parental-effect sex-determining genes are similar to zygotic sex determiners because their products act within the developing zygote. However, they are subject to the same selection pressures as sex-ratio genes because they are expressed in the parent and depend on parental genotype. Both maternal- and paternal-effect sex determiners exist (Table 1).

Most maternal effects are due to maternal products (e.g. mRNA or proteins) placed in the developing egg. Maternal effects are typically important in early development because in most organisms the zygotic genotype is not expressed during early mitotic divisions, and early development is therefore dependent on products placed in the egg. Thus, gene products placed in the egg by the mother could have major effects on sex determination in the developing zygote. Molecular genetic studies of sex determination have revealed several interesting maternal effects. In *D. melanogaster*, daughterless (*da*) is a maternal-effect nuclear gene that produces a transcription factor involved in sex determination (34, 156). Similar maternal effects on zygotic sex determination have been detected in *M. domestica* (51, 93) and *Chrysomya rufifacies* (167). Nur (128) modeled maternal control of sex determination.

One example of a paternal-effect sex determiner appears to be the paternal sex-ratio chromosome (psr), a supernumerary (B) chromosome, that occurs in the parasitic wasp *Nasonia vitripennis* (131). Normally these wasps control sex among their progeny by either fertilizing eggs (diploid female progeny) or withholding fertilization (haploid male progeny). After fertilization of the egg by psr-bearing sperm, the paternal chromosomes (except psr) fail to condense properly in the first mitotic division and are eventually lost. Thus, the fertilized egg is hapliod and develops into a male. Indirect evidence suggests that psr acts during spermatogenesis to modify the developing sperm, although its expression occurs in the fertilized egg (10). Despite few current examples of paternal-effect sex determiners, they may be more common than appreciated. One mechanism could be paternal imprinting of sex-determining genes, thus influencing their expression in the developing zygote (8, 125).

ZYGOTIC SEX DETERMINERS Studies of sex determination classically consider genes acting in the zygote to determine its sex. Examples of zygotic sex determiners include *SrY* in mice and humans (64), *Sex lethal* in *D. melanogaster* (156), and the *xol* and *sdc* genes in *C. elegans* (80). In both *D. melanogaster* and *C. elegans*, the primary sex-determining signal is the X:A ratio. Multiple X numerator elements are present on the X chromosome, and a regulatory cascade involving several genes determines somatic sex (80). The evolution of X:A systems appears to be associated with the evolution of dosage compensation. An unresolved evolutionary question is how X:A sex determination evolved from

an ancestral state presumably involving a major sex determiner on a nascent sex chromosome. In other words, why did the system evolve from a major-effect gene to multiple female-determining elements on the X chromosome and male determiners on the autosomes? Wilkins (177) proposed, based on the molecular genetic structure of these systems, that *C. elegans* and *D. melanogaster* sex determination evolved by a sequential addition of genetic switches, each reversing sex determination of the previous. He further proposed that the process was driven by frequency-dependent sex-ratio selection. The model is consistent with strong sex-ratio selection induced by genetic conflict or other mechanisms (see below). A dominant male determiner exists in mice and humans (*SrY*), although it is still unclear whether *SrY* is the primary signal or whether other signals induce the *SrY* testis-determining cascade (100).

Genetic Conflict Over Sex Determination

Genetic conflict will occur when the various components of the sex-determining system are selected to push zygotic sex determination or parental sex ratios in different directions. Given the divergent selective pressures acting on genes with different inheritance patterns (cytoplasmic, autosomal, and sex chromosomal) and different sites of expression (maternal, paternal, and zygotic), genetic conflict is an inherent feature of sex-determining systems. Here we list the general arenas of conflict over sex determination and sex ratios.

CYTO-NUCLEAR CONFLICT Conflict between cytoplasmic and nuclear genes over sex determination and sex ratios is obvious and appears to be common and widespread. Many cytoplasmic sex-ratio distorters are microorganisms that are transmitted through the egg cytoplasm but not through sperm (reviewed in 86). In plants, cyto-nuclear conflict has been documented between maternally inherited organelles inducing CMS and autosomal suppressors of cytoplasmic male sterility (CMS) (reviewed in 39, 148). In the absence of suppression or other counterbalancing forces, cytoplasmic sex-ratio distorters can spread near or to fixation, potentially driving the population (and species) to extinction (81, 160). Cyto-nuclear conflict is discussed in more detail below.

SEX-CHROMOSOME DRIVE AND B-CHROMOSOME DRIVE CONFLICT Sex-chromosome drive is just one manifestation of selection favoring meiotic drive loci, which also occur on autosomes (reviewed in 114). However, the sex-ratio distortion resulting from it can create intense sex-ratio selection. There is considerable evidence that X-chromosome drive selects for repressors on the Y chromosome and autosomes (see below). In species with recombination on the sex chromosomes, selection on linked genes can favor either enhancement of drive or suppression of drive, depending on how tightly linked the gene is and whether linkage disequilibria are maintained (180). However, the

possibility that sex-ratio distortion induced by X-drive favors compensatory shifts in zygotic sex determination (or maternal-effect sex determiners) has not been extensively explored. Sex-chromosome drive can also potentially cause population extinction (73, 112, 113).

Many B chromosomes are parasitic genetic elements that have an increased transmission in gametes (transmission drive), by which the chromosomes are maintained within populations despite the fitness costs they impose on the host (127, 129). In many cases, transmission of Bs through males and females (or male and female function in hermaphrodites) is asymmetric. Under this circumstance, selection is expected to lead to the accumulation of sex ratio and sex-determining genes that bias sex toward the transmitting sex. However, detailed studies in a few coccid species with biased transmission of B chromosomes have failed to show an effect of B on sex determination (U Nur, personal communication). One striking example of a sex-ratio distorting B chromosome is the *psr* chromosome in *N. vitripennis* described previously (131).

PARENT-OFFSPRING CONFLICT Trivers (163) originally formulated the idea that parents and offspring can have divergent genetic interests due to the fact that they are genetically related but not genetically identical. Studies of parent-offspring conflict usually concern conflict over the amount of resources allocated to offspring. However, Trivers & Hare (164) proposed that conflict should exist between a queen social insect and her worker progeny over sex ratios in social insects. Empirical studies provide strong support that such conflict exists (159).

Given the growing evidence for maternal-effect sex-determining genes, the possibility of conflict over sex determination needs to be considered more thoroughly. There are two situations in which such conflict is likely: (*a*) when fitness costs to a parent of a son and daughter differs, and (*b*) under partial inbreeding or local mate competition. When one sex is more costly to the parent to produce than the other, natural selection will favor the parent overproducing the less-costly sex (57). However, selection acting on the zygote will generally favor a more-balanced sex ratio. This is particularly true when the cost to the mother is in terms of future survival and reproduction. For example, in red deer (*Cervus elaphus*), producing a male is more reproductively costly to the mother than producing a daughter, and the mother often fails to reproduce in the year following a male birth (38). The dynamics of this interaction have not been explored theoretically. Depending on the mating system, paternal-effect sex determiners will have genetic interests more concordant with either zygotic or maternal genes.

Under partial inbreeding or local mate competition, maternal-effect genes will be selected to produce a more female-biased sex ratio. Zygotic-effect sex

determiners will also be selected to produce a female bias, but the equilibrium ratio should be less biased because of asymmetries in genetic relatedness. The result will be conflicting selective pressures. A possible outcome would be the accumulation of maternal modifiers and zygotic modifiers pushing in opposite directions. Again, the interacting system has not been explored theoretically. Conflict also clearly occurs between parental sex-chromosome drivers and zygotic sex-determining genes. In principle, the sex-ratio distortion resulting from driving sex chromosomes should lead to compensatory shifts in sex determination to the underrepresented sex (113).

MATERNAL-PATERNAL CONFLICT Interest has focused primarily on intragenomic conflict between maternally derived and paternally derived genes over resource allocation to developing zygotes and on intergenomic male-female conflict over female reproductive effort (70). Nevertheless, there are some interesting applications to sex determination evolution. Brown (13) and Bull (15, 17) have shown that maternal gene/paternal gene conflict can lead to the evolution of paternal genome loss and haplodiploid sex determination. Basically, there is a selective advantage to maternal genes that "eliminate" the paternal genome. This advantage (termed the automatic frequency response by Brown) results from a higher maternal genome transmission in the next generation in haploid males relative to diploid males (i.e. no reduction due to meiosis). The advantage accrues as long as haploid males have a fitness greater than one half that of diploid males.

In addition, intergenomic maternal-paternal conflict clearly occurs in species with haplodiploid and paternal genome–loss sex determination (71). In haplodiploids, males are under selection to increase the proportion of fertilized eggs (proportion of females) produced by their mates. However, it is unclear what opportunities are available to males for affecting female sex ratios. In paternal genome–loss systems [e.g. coccids (130)], paternal genes will be selected to escape or suppress paternal genome loss. Some supernumerary chromosomes have evolved escape mechanisms from paternal genome loss, such as in the mealy bug (127) and the flatworm *Polycelis nigra* (9).

Alternative Models for Sex-Determination Evolution

Genetic conflict is an inherent feature of sex-determining systems. However, a number of models have been proposed for the evolution of sex determination besides that of genetic conflict. We briefly review some models currently in the literature, focusing on factors that destabilize sex-determining systems and cause evolutionary transitions in the sex-determining mechanism.

TRANSIENT COVARIANCE OF FITNESS AND SEX (HITCHIKING) Bull (17) has proposed that transient linkage disequilibrium between sex-determining alleles

and genes under strong positive selection could destabilize sex determination by causing distorted population sex ratios. These distorted sex ratios would create counter-selection for sex-determining loci producing the opposite sex. Such an affect may explain the diversity of sex determination found in *M. domestica*, in which some sex-determination variants appear to be linked to pesticide-resistance alleles (106, 124, 147). In the platyfish, several body-color genes are tightly linked to sex-determining loci (104).

ACCUMULATION-ATTRITION Graves (67) proposed an "addition-attrition" model to explain the evolution of mammalian sex determination. According to the model, mammalian sex determination evolves by a series of autosomal additions (translocations) to the Y chromosome followed by degeneration of these pseudo-autosomal regions. Only genes that evolve functions in male sex determination escape mutational degradation that results when crossing over is suppressed between X and Y chromosomes. A series of translocation events could result in turnover of sex-determining genes on the Y. The model is consistent with the view that sexually antagonistic genes can accumulate on the sex chromosomes (e.g. Y-linked genes that enhance male fitness and diminish female fitness) (141, 142) and the idea that male growth enhancers will accumulate on the Y (87, 88).

POPULATION STRUCTURE AND INBREEDING Hamilton (73) pointed out that subdivided populations with local mating (and inbreeding) select for parents that have female-biased sex ratios. There is considerable empirical evidence that local mate competition does lead to female-biased sex ratios (reviewed in 3, 74). However, there has been little consideration of how inbreeding and local mate competition shape the zygotic sex-determining mechanism in species without parental sex-ratio control.

Two other population-structure effects relevant to sex-determination evolution are local resource competition (33) and local resource enhancement (152). Whenever fitness returns differ through males and females (or male and female function for hermaphrodites) as a function of amount of investment in that sex (e.g. because of differential dispersal), biased sex ratios will be selected (58, 59). However, most models of these effects implicitly assume parental sex-ratio control. The same selective force should also select for biases in the zygotic sex-determining genes, although less strongly than for parental sex ratio and parental-effect sex-determining genes. Such effects have not been investigated theoretically.

VARIABLE FITNESS OF MALES AND FEMALES Facultative adjustments in sex ratio and sex determination are expected when male and female fitness are differentially affected by some environmental factors. For example, Trivers &

Willard (165) pointed out that when maternal condition varies, and this variation translates into a greater fitness effect on sons versus daughters, then selection will favor mothers in good condition overproducing sons and mothers in bad condition overproducing daughters. Variable fitness affects are also invoked to explain age-specific sex change in sequential hermaphrodites and host-size effects on sex in parasitic wasps (31).

Variable fitness effects almost certainly are important in the evolution of environmental sex determination (16, 32). Environmental sex determination is observed in some marine worms and molluscs, in parasitic nematodes such as mermithids, in some plants (136), in a few fish, and in some lizards, turtles, and crocodillians (reviewed in 17, 97). In invertebrates, crowding or poor nutrition is typically associated with increased male determination. Sex determination is temperature sensitive in a variety of reptiles, although the selective factors favoring such sex determination are still unclear.

Locked-In Sex Determination?

Some sex-determining systems may be more rigid than others, reducing or precluding further evolution of the system. Heteromorphic sex chromosomes are believed to evolve primarily by mutational degeneration of chromosomes in the heterozygous state (the Y in XY males and W in ZW females) following suppression of recombination between homomorphic sex chromosomes (27, 142). Once heteromorphic sex chromosomes have evolved, further changes in sex determination may be constrained by sterility or inviability of XX males, XY females, and/or YY individuals of either sex (21). For instance, in mice and humans, male fertility factors are present on the Y chromosome, restricting the potential fitness of XX males (67). Phylogenetic patterns support the view that evolution of sex chromosome heteromorphisms increases conservation of sex-determining mechanisms (17, 133).

Pleiotropic effects of sex-determining genes can constrain sex determination evolution. For example, complicated interactions between sex determination and dosage compensation likely restrict the ability of heteromorphic XX/XY and ZW/ZZ sex-determining systems to change. Because dosage compensation and primary sex determination are intimately entangled in the X:A balance system of *D. melanogaster*, mutants in the central sex-determining gene, *Sex lethal* (*Sxl*), are typically lethal for one sex (hence the name) due to disruptions in dosage compensation (149). In humans, *SrY* and related sex-determining genes (*DAX1, SF1*) have pleiotropic effects on other developmental processes, such as skeletal, nervous, and adrenal development (105, 140).

Arguing against the notion that sex-determination mechanisms can become locked in is the mounting evidence that superficially similar sex-determination mechanisms can differ in underlying genetic structure (41, 111, 126). For

example, murine rodent species differ in the number of *SrY* genes (111) and *SrY* can differ in potency even between different geographic strains of *Mus musculus*, resulting in the production of hermaphroditic and XY females in interstrain crosses (126). Furthermore, it is clear that even groups believed to be conserved by heteromorphic sex chromosomes (e.g. mammals) show variation in this feature. Some vertebrates previously believed to have genetic sex-determining systems actually have a mixture of genetic and environmental sex determination (44), and transitions between these mechanisms may be relatively easy (40, 45, 101).

GENETIC CONFLICT SYSTEMS

Sex-Chromosome Drive

Meiotic-drive chromosomes are inherited in a non-Mendelian fashion, typically ending up in 70–100% of gametes (150). The best known examples are Segregation Distorter in *Drosophila* (46, 162) and the *t*-locus in *Mus* (112). Meiotic-drive sex chromosomes are easily recognized because they have an immediate effect on the progeny sex ratio. They are known from several mammals and insect groups, including fruitflies, mosquitoes, and butterflies (reviewed in 92). Most examples are driving X chromosomes typically referred to as Sex-Ratio (SR) chromosomes. Driving Y chromosomes are rare, probably because of their stronger drive capacity leading to fast extinction in the absence of counter-selection (73).

Recent evidence (5, 94, 122) accords with predictions by Frank (60) and Hurst & Pomiankowsky (92) that driving sex chromosomes are much more common than was previously thought. Without countering selection, meiotic drive of sex chromosomes would quickly lead to extinction of carrier populations (73). Counter-selection can occur at the gene, individual, and group levels (see 94). At the individual level, driving sex chromosomes often reduce male fertility (115), the result of their mode of action that typically involves dysfunction of gametes carrying the nondriving sex chromosome homolog (138). If driver genes are associated with chromosomal inversions, females may have reduced fitness as well (see 95). Wilkinson et al (178) found that the frequency of Y drive increased as a correlated response in populations selected for increased stalk-eye size, which suggests that genes involved in this male character are Y linked.

Selection generally favors alleles on the autosomes and the nondriving sex chromosome that suppress the meiotic drive of the SR chromosome. Theoretical models have shown that a system of sex chromosome drive is most likely to evolve into a two-locus polymorphism with linkage disequilibrium (114, 180). The drive allele is expected to show coupling with enhancer alleles

and repulsion with suppressor alleles, which might be further promoted by chromosome inversions (115). The evolution of autosomal suppressors to drive is not inevitable and depends on the specific fitness effects of driver chromosomes in males and females (180). Jaenike (94) has invoked frequency-dependent selection in the absence of linkage. Modifiers of SR chromosomes occur in a number of organisms (5, 23, 24, 114, 122, 139, 155). For example, Cazemajor et al (25) showed that in *Drosophila simulans* drive results from the action of several X-linked loci and the modification of drive from drive suppressors on each major autosome as well as on the Y chromosome. Similarly, in the plant *Silene alba*, restorer loci on the Y chromosome balance the sex-ratio bias caused by a postulated driving X (161). Hurst (85, 90) has argued that the Stellate locus in *D. melanogaster* is a relict driver gene on the X chromosome that has been silenced by modifier genes on the Y chromosome.

Driving sex chromosomes clearly illustrate intragenomic conflict. However, does sex-chromosome drive select for compensatory changes in the zygotic sex-determining mechanism? There is not strong evidence for this in nature. All known modifier genes appear to counteract the action of the driver within the parent. In contrast, Lyttle (113) constructed laboratory populations of driving Y chromosomes containing segregation distorter (SD) genes in *D. melanogaster*. In most populations, suppressors of drive evolved, but in one population, the sex-ratio distortion was counterbalanced by the accumulation of sex chromosome aneuploids (XXY females and XYY males). This example shows that a new sex-determining system (although the X:A ratio is maintained) may evolve in response to a driving sex chromosome. More such experimental studies are needed to explore the possible evolutionary outcomes of sex-chromosome drive. Whether sex-chromosome drive selects for changes in the zygotic sex-determining system will likely depend on the severity of sex-ratio distortion in the population and on the nature of standing genetic variation for the relevant traits.

Cytoplasmic Sex-Ratio Distorters in Animals

Cytoplasmically inherited sex-ratio distorters are widespread in animals (reviewed in 54, 83, 86). In most cases, cytoplasmic sex-ratio distortion is caused by maternally inherited microorganisms that distort sex ratio toward females. Cytoplasmic sex-ratio distorters include male-killers, primary sex-ratio distorters, feminizers, and parthenogenesis inducers. Examples of male-killing microbes include spiroplasms in *Drosophila willistoni* (69), gamma proteobacteria in *Nasonia* wasps (174), rickettsia, spiroplasms and flavobacteria in ladybird beetles (83, 172), and microsporidia in mosquitoes (2). Feminization of genetic males is caused by *Wolbachia* rickettsia in isopods (144) and microsporidia in amphipods (52). *Wolbachia*-induced parthenogenesis is found in an array

of hymenoptera (158; reviewed in 157) and is implicated in other organisms. Primary sex-ratio distortion toward females is caused by the msr element in *Nasonia* (154); although the causative agent is unknown, it is possibly due to a mitochondrial variant.

Coevolutionary interactions between cytoplasmic sex-ratio distorters and nuclear genes can be complex. When transmission of the sex-ratio distorter is incomplete, selection for compensatory shifts in the parental sex ratio can lead to a positive feedback that results in monogeny—some females producing all-female progeny (cytoplasmic control) and some producing all-male progeny (nuclear control following compensation) (17, 170). This effect does not occur when transmission of the distorter is near 100% (170). A similar effect was shown for cytoplasmic sex determiners (53). Autosomal repressors of cytoplasmic distorters are generally favored, both in the parent and in the zygote (168) because of sex-ratio selection. Theoretical studies indicate there is no selection for compensatory sex-ratio alleles in response to male-killing microorganisms, at least in panmictic populations (170), although repressors to male-killers are expected to evolve.

Taylor (160) investigated the coevolution of nuclear zygotic sex determiners (compensatory genes), zygotic suppressors, and cytoplasmic feminizing elements. He found that compensatory nuclear male determiners will increase. However, in the presence of nuclear restorers, sex ratios will often evolve back to 1:1, with suppression of the cytoplasmic element. If this process is common in nature, interspecies crosses may reveal cytoplasmic sex-ratio distorters due to their release from suppressing genotypes. It has been proposed that hybrid lethality and sterility can result (60, 92). One interesting feature of cytoplasmic sex-ratio distorters is hitchhiking by associated mitochondria. If transmission of the distorter is incomplete or restorer genes are present, the mitochondrial variant associated with the cytoplasmic distorter can become fixed in the population. Similar arguments apply to cytoplasmic sterility in plants (see below). Features that can limit the spread of cytoplasmic distorters include reduced fitness of YY individuals (in male heterogametic systems) (160) and interdemic selection against local populations with male scarcity (17).

Although it is expected, there is not extensive empirical evidence for nucleocytoplasmic conflict over sex determination in animals. However, few systems have been investigated in detail. The best example occurs in the isopod *Armadillidium vulgare*, populations of which can harbor a feminizing *Wolbachia*, a second feminizing factor of unknown etiology (*f*), masculinizing autosomal genes, and suppressors of the feminizing factors (145; reviewed in 144). The *f* factor shows a complex inheritance pattern, with primarily cytoplasmic transmission but also some paternal transmission. An apparent association between *Wolbachia* and *f* led Legrand & Juchault (109) to propose that *f* was a bacterial

phage carrying feminizing elements from the *Wolbachia* that occasionally incorporated into the isopod genome. It is unclear whether this is the case or whether *f* is actually a nuclear gene showing variable penetrance and expression. A dominant masculinizing gene has been characterized that can restore males in the presence of *f* but only weakly so in the presence of the feminizing *Wolbachia* (mostly resulting in functional intersexes). Populations differ considerably in frequencies of these elements, although the presence of feminizing factors is associated with the masculinizing autosomal gene.

A. vulgare normally has female heterogamety (ZZ males:ZW females). However, in populations harboring the feminizing factors, the female-determining chromosome (W) can be driven from the population because of sex-ratio selection. Juchault & Mocquard (103) proposed a cycle where presence of the *Wolbachia* with incomplete transmission causes loss of the W chromosome, leading to ZZ males and ZZ+WO females followed by integration of the *f* factor onto an autosome, which results in a neo-W (female determining) chromosome. This process would effectively prevent the evolution of degenerate (heteromorphic) sex chromosomes. What is less clear, is whether nucleo-cytoplasmic conflict could result in a shift of sex determination from female heterogamety to male heterogamety (i.e. due to the spread of an autosomal masculinizer and repressors of feminizing elements). The sequence of events is likely to strongly influence the outcome of this genetic conflict, although the full spectrum of possibilities has not been explored theoretically. Rigaud (144) pointed out that the physiological mechanism of sex determination (production of an androgenic gland) may make isopods particularly vulnerable to "hijacking" of sex determination by cytoplasmic elements.

Cytoplasmic Male Sterility in Plants

CMS is the failure of anther or pollen development caused by a cytoplasmically inherited factor. CMS is widespread (e.g. in maize, *Petunia*, rice, the common bean, and sunflower), occurring as a polymorphism in species with a mixture of hermaphroditic and male-sterile individuals (referred to as gynodioecy). Lewis (110) first pointed out that male sterility is much more readily selected for when caused by a cytoplasmic rather than a nuclear gene. CMS will be selectively favored as long as a male-sterile plant produces more effective ovules than does a hermaphroditic plant. This can occur, for example, when there is resource allocation to ovule production or (even slight) outbreeding advantage to ovules in male steriles. In contrast, a dominant nuclear male sterility gene is favored only when more than twice as many effective ovules are produced. The result is nucleo-cytoplasmic conflict, and there is now overwhelming evidence that such conflict occurs in plants (43, 49).

This conflict is manifested by complex interactions between CMS genes and nuclear repressors of CMS. Because many plant species showing CMS are of economic importance, extensive molecular genetic analyses of CMS have been conducted (reviewed in 148). In all cases examined, CMS genes occur within the mitochondria and are chimeras resulting from genetic rearrangements. Nuclear restorers of male fertility have been shown to function by elimination of CMS sequences (in *Phaseolus vulgaris*) and modification of CMS transcripts (in maize) or transcript abundance (in *Petunia*).

Genetic studies indicate a specificity between CMS genes and nuclear restorers in many systems (107). Most gynodioecious species harbor more than one CMS cytotype and multiple interacting nuclear restorers segregating within populations. For example, there are three different CMS types in *Plantago lanceolata*, each with a set of specific nuclear restorer loci (49). These range from dominant to recessive to epistatically interacting restorers. It is likely that the occurrence of restorers restrains the spread of CMS cytotypes in many species, although other processes such as deme level selection may also be involved (59, 119). Under some circumstances, CMS cytotypes can go to fixation within a species but be repressed by restorer alleles and therefore be cryptic. Such situations can subsequently be detected in interspecies crosses, in which the CMS cytotype escapes its nuclear suppression. Consistent with this scenario, CMS is a common source of hybrid sterility in plants (110).

There is an extensive theoretical literature on the coevolutionary dynamics of CMS and nuclear genes (e.g. 28–30, 59, 65, 116, 119, 151). Among the interesting questions is whether gynodioecy is a transitional stage to the evolution of dioecy, i.e. whether nucleo-cytoplasmic conflict promotes the evolution of dioecy. Consistent with this view, Maurice et al (116) documented a taxonomic association of gynodioecy and dioecy. One modeling approach involves investigating the fate of a nuclear female-sterile allele in a gynodioecious population (an extreme form of a compensatory gene). Results generally show that evolution of dioecy is restrictive but possible (28, 30, 116, 151). More models are needed to determine if dioecy can evolve by sequential shifts of sex allocation to male function in gynodioecious populations rather than by large-effect female sterile alleles. Consistent with the view that sex allocation shifts toward male function can be favored, Atlan (4) observed such sex allocation shifts in gynodioecious populations of *Thymus vulgaris*. Explicit genetic models (e.g. 30) are necessary for investigating these complex processes because phenotypic models do not capture the nonrandom association of alleles (gametic phase disequilibria) that can be crucial to the ultimate fate of different genotypes. Nevertheless the clearest and most compelling examples of genetic conflict causing turnover in sex-determining alleles occur within these plant systems.

Other Systems

Genetic conflict has been invoked as a driving force in the evolution of sex-determining systems in the cases described below. These systems show that the role of genetic conflict (*a*) is still hypothetical in most cases, (*b*) cannot be fully interpreted because of lack of information in some cases, and (*c*) is worth considering because it could help to explain the genetic structure of the sex determination system.

LEMMINGS The evolution of aberrant sex-chromosome systems of lemmings has been extensively considered (61, 62, 68). The wood lemming (*Myopys schisticolor*) has three types of individuals: XX are normal females, XY are normal males, and X*Y are females. The variant X chromosome [X* (considered to suppress the male determining effect of the Y so that X*Y individuals are female)] shows drive in X*Y females, which results in a strongly biased sex ratio toward females in carrier populations. X*Y females have X*X* oocytes through nondisjunction (YY cells die) and produce nearly all daughters. A somewhat similar system has been described from various lemmings (*Dicrostonyx groenlandicus* and *D. torquatus*) (62). In these species, X*Y females also occur but have sons and daughters, presumably through production of both X* and Y eggs. The X* is considered to suppress the male sex determiner on the Y chromosome.

Several authors have modeled the evolutionary dynamics of these systems and considered how selection might lead to modifications of the reproductive biology (6, 19, 22, 117). Most work deals with how effects of inbreeding and reduced fertility under subdivided population structure may influence the spread of the driving X* chromosome and its potential suppressors (see 19 for a comprehensive treatment). To what extent can X*Y females select for changes in the sex-determining system? One of the most straightforward means of eliminating XY females would be evolution of a Y-linked suppressor gene of X*, but invasion of a suppressor Y appears restricted under inbreeding. This is consistent with the fact that there is little empirical evidence for the existence of resistant Ys in lemming populations. Models based on structured populations further show that selection for autosomal restorer genes is even weaker than for Y-linked suppression. The actual path that evolution has taken in the wood lemming seems to have involved evolution of an X* that feminized X*Y males followed by evolution of a modifier of the segregation ratio so that X*Y females produce exclusively X* oocytes, which overcame their reduced fertility (half of the Y oocytes die when they are fertilized by Y sperm). As an alternative scenario, McVean & Hurst (121) suggested that the current situation is a response to a driving Y chromosome, i.e. X*Y females counteract the spread of the driving Y by suppressing its male-determining gene and producing only

X* oocytes. There is, however, no empirical evidence for the existence of a driving Y. In conclusion, the evolution of aberrant sex-chromosome systems in lemmings may be interpreted from a genetic conflict perspective, but its exact role is unclear.

SCIARA COPROPHILA In the fungal gnat *Sciara coprophila*, sex determination is associated with paternal genome loss (14, 123). All zygotes are initially XXX, and sex is determined by maternal factor causing somatic loss of X chromosomes. In addition, certain chromosomes (so-called limited, or L, chromosomes) are present in the germline but not in the somatic line. During spermatogenesis, all paternally derived chromosomes (i.e. both X and all autosomes) are eliminated except for the L chromosomes and the maternal X, which is doubled. Thus, males transmit only maternally derived chromosomes (i.e. two Xs and all autosomes). Females transmit all paternally and maternally derived chromosomes except for one paternal X that is eliminated during early development. Haig (72) suggested an evolutionary scenario based on genomic conflict to explain this unusual sex-determining mechanism. He envisaged the following steps: (*a*) origin of a driving X chromosome causing female-biased sex ratios, counteracted by (*b*) conversion of XX daughters into sons by elimination of one paternal X, and (*c*) origin of dispensable L chromosomes derived from X chromosomes that favor male-biased sex ratios, followed by (*d*) origin of an X′ chromosome that suppresses the effect of L chromosomes. The conflicting parties are the driving X chromosome and L chromosomes that gain a transmission advantage by biasing the sex ratio toward females and the maternal autosomes and variant (doubling) X′ that counteract their effects. A weak test of this scenario is the prediction that the L chromosomes are derived from X chromosomes.

COCCIDS The evolution of unusual chromosome systems of scale insects (Cocoidea) (130) has been described in the context of genetic conflict (13, 15, 71, 75). Using similar reasoning as for *Sciara*, Haig (71) attempted to explain the origin of paternal genome loss from heterogamety through a number of evolutionary transitions. Several of these transitory stages are found in the scale insects, many species of which exhibit paternal genome loss [paternally derived chromosomes are not transmitted by males because they are eliminated from their germ lines at different developmental stages (see 14, 130 for details and references)]. Haig's model involves three steps: (*a*) meiotic drive by the X chromosome in XO males causing female-biased sex ratios; (*b*) linkage of the maternal set of autosomes in males to exploit X-drive; and (*c*) conversion of XX daughters into sons by autosomal genes expressed in mothers. One outcome could be mothers that determine the sex of their offspring by controlling the

elimination of X chromosomes during embryogenesis, as observed in *Sciara*. Conflict between sex chromosome drive and autosomal suppressors is considered the driving force. Haig's model illustrates how genetic conflict may lead to novel sex-determining mechanisms, but although evolutionarily plausible, there is currently no supportive empirical evidence that the observed system is indeed the outcome of conflict between sex-determining genes.

MOLES Using genetic conflict theory, McVean & Hurst (121) proposed three evolutionary pathways to explain the high frequency of intersexes in moles (*Talpa europaea* and *T. occidentalis*) (98, 99). Males are XY and have only testes, but females are XX and have ovotestes, i.e. functional ovaries and a variable amount of nonfunctional testicular tissue. In their first model, McVean & Hurst (121) consider the evolution of a Y-linked factor (in our terminology, a paternal-effect sex-determining gene) that masculinizes XX embryos and that is counteracted by a modifier on the autosomal or X-chromosome. In their second model, they considered intersex XX individuals as the outcome of a balance between a driving X chromosome with a masculinization effect in females and an autosomal modifier that restores functional femaleness. Their third alternative is a driving Y chromosome in males that is counteracted by an X-linked suppressor that causes partial sterility when present in the homozygous state, followed by invasion of an autosomal modifier that restores fertility in XX intersexes. We agree with McVean & Hurst (121) that there is currently little empirical evidence for any of these models.

CONCLUSIONS

Evidence for the role of genetic conflict in the evolution of sex-determining systems is growing but still circumstantial. Genetic conflict theory is consistent with much of the observed diversity, including sex-chromosome drive systems, cytoplasmic sex-ratio distorters in animals, and CMS in plants. Plausible scenarios have been developed for specific systems. However, more convincing evidence for the role of genetic conflict exists in only a few cases, notably the genetic diversity in sex determination of *A. vulgare* and CMS in plants. In many systems, the invoked role of genetic conflict is speculative and future empirical research is needed. There is also ample scope for further theoretical investigation.

Interesting issues concerning genetic conflict and the evolution of sex-determining systems include (*a*) how X:A balance systems evolve from major sex-determining gene systems and whether genetic conflict is involved, (*b*) whether sex-chromosome drive and cytoplasmic sex ratio distortion cause compensatory changes in zygotic sex-determination mechanisms, and (*c*) whether parental

gene/zygotic gene conflict plays a role in sex-determination evolution. We believe that genetic conflict will eventually be shown to be an important force shaping sex-determining mechanisms, but this has yet to be demonstrated.

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