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SEX DETERMINATION, SEX RATIOS AND GENETIC CONFLICT

John H. Werren[1] *and Leo W. Beukeboom*[2]

[1]Biology Department, University of Rochester, Rochester, N.Y. 14627
[2]Institute of Evolutionary and Ecological Sciences, University of Leiden,
NL-2300 RA Leiden, The Netherlands

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 due to 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 distorters and cytoplasmic male sterility in plants. Although the evidence is still limited, the role of genetic conflict in sex determination evolution is gaining support.

PERSPECTIVES AND OVERVIEW

Sex determining mechanisms are incredibly diverse in plants and animals. A brief summary of the diversity will illustrate the point. In hermaphroditic species both male (microgamete) and female (macrogamete) function reside within the same individual, whereas dioecious (or gonochoristic) species have separate sexes. Within these broad categories there is considerable 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 20,228). 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 (129). In addition, mechanisms that appear to be the same can differ markedly in the underlying genetics. For example, male heterogametic systems can be based upon dominant male determiners on the Y (e.g. in Mammals) or upon a genic balance between factors on the X and autosomes (e.g. *Drosophila*). Recent molecular studies have shown that genes involved in primary sex determination evolve rapidly (58, 141, 217) and that sex determining genes in one species may not be involved in sex determination in related species (82, 124).

In this diversity there 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. Sex determining mechanisms appear to be one of the most rapidly evolving developmental processes, and some genes involved in sex determination (e.g. *SrY* in mammals) show unusually fast sequence evolution (214, 229). The 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) destabilize an existing sex determining mechanism, leading to the evolution of a new mechanism. Therefore, the question can be reformed to focus on factors that potentially

destabilize sex determining mechanisms and whether some features of sex determination make it inherently unstable over evolutionary time.

Genetic conflict

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 who interact over a particular phenotype. For example, in terms of sex determination there is potential conflict between maternally expressed sex determining genes and embryonically expressed genes.

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 (49, 65). In contrast, autosomal genes (those residing on non-sex chromosomes) are generally selected to produce a balance in the sex ratio (69). 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 (108, 219). 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 excellent reviews on the diversity of sex determining mechanisms (20, 227, 228), sex ratio evolution (3, 35, 96, 220), somatic and germline sex determination in fruitflies (40,177, 200), vinegar worms (41, 99) and mammals (79, 103 124), sex determination in plants (81) and the evolution of heteromorphic sex chromosomes (30, 183).

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 upon the individual organism ("levels of selection") and the observation that some genetic elements can be "selfish" or "parasitic", i.e. gain a transmission advantage although they are detrimental to the organism in which they occur. The first publications on what is now known as the "intragenomic conflict" were theoretical studies by Lewis (139), who considered the fate of cytoplasmic male sterility genes in plants, and Howard (100), who investigated cytoplasmic factors causing all female families in animals. Both authors 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 (171) was the first to recognize that selection may operate in different directions on different parts of the genome. In his studies on B chromosomes, he realized that these genetic elements were "parasitic", and gained a transmission advantage relative to the rest of the "host's" genome. This notion of contrasting selection on genetic elements at the genomic level within an organism is now known as 'genomic conflict' or 'intragenomic conflict" (49). Intragenomic conflict is a special cases of the more general term 'genetic conflict'. Although long opposed (163-165, 167), the idea that B chromosomes are selfish elements is now widely accepted (8, 126, 196, 225). The discovery of meiotic drive chromosomes (192) also stimulated consideration of the gene as the level of selection . Evolution of these systems could be understood by invoking conflicting selective pressures between the driving genes and unlinked repressors (145). In particular, driving sex chromosomes discovered in several species lead to genetic conflict over sex determination. Models have been developed concerning how selection operates on chromosomal sex ratio distorters and the rest of the genome (e.g. 66,89, 92, 118, 233).

The concept that selection operates at the level of the gene was given broad attention and gained wider acceptance through publication of "The Selfish Gene" (57). Cosmides and Tooby (49) introduced the term "intragenomic conflict" and published a comprehensive paper on the possible role of genomic conflict in a number of evolutionary processes including cytoplasmic inheritance, the evolution of anisogamy, the transition of hermaphroditism to dioecy and the evolution of sex and sex determination. Several earlier studies have addressed the role of genetic conflict in evolution (1, 13, 65, 98, 188). However, the idea that DNA could be "selfish" or parasitic" only started to receive wider attention through simultaneous publications by Doolittle and Sapienza (60) and Orgel and Crick (173), and an accumulating number of discoveries of 'selfish" non-mendelian elements such as transposons, B chromosomes, and cytoplasmic sex ratio distorters. Werren et al (225) formerly defined selfish genetic elements and reviewed existing evidence.

The concept of genetic conflict is now widely accepted in evolutionary biology (e.g. 111, 149; reviewed in 113, 184). Recent theoretical and empirical work has focused on genetic conflict between cytoplasmic and autosomal sex ratio factors (50, 72, 94, 186, 190, 204, 219), conflict between sex chromosome drive factors and repressors of drive (87, 88, 231), the potential importance of genetic conflict in the evolution of sex (97, 111), and paternal-maternal genome conflict over allocation of resources to progeny (86). 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 (95) and development of the theory of heterogametic sex determination (151). Subsequent research focused on the basic mechanisms of sex determination in a wide range of organisms (reviewed by 56, 228), and revealed considerable diversity. Detailed genetic studies

of sex determination were limited to a few organisms, most notably *Drosophila melanogaster*, which has male heterogamety (XY males, XX females). In 'genic balance' systems, sex depends on a balance female-determining factors on the X chromosome and male determining factors on the autosomes. This system was uncovered in early genetic experiments by Bridges (15) who varied the number of X chromosomes in *Drosophila* and suggested that sex in *Drosophila* is determined by the ratio between X chromosomes and sets of autosomes. In 'dominant Y' systems (e.g. in some mammals), there is a dominant male determiner present on the Y chromosome. Bull (20), in a comprehensive treatise of the evolution of sex determining mechanisms, considered possible transitions between different sex determining systems. Evolution of sex chromosomes and heterogamety has also been considered (21, 23, 29, 30, 183).

At present, the molecular regulation of sex determination is known in detail from only a few organisms, including the house mouse (*Mus*), the fruitfly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* (reviews by 99, 200). These systems serve as a basis for comparisons with other systems, e.g., several dipteran species. However, it is difficult to extrapolate on the evolutionary changes leading to the differences between these species, due to their phylogenetic distance.

Complementary to studies of sex determination, there is an extensive theoretical and empirical literature on the evolution of sex ratios (35, 42, 77, 89, 96, 138, 220, 232). However, most of these studies have focused on how selection acts upon the parent to manipulate sex ratio of offspring under different circumstances. Very few studies have considered the coevolutionary interactions between sex ratio genes acting in the parent and sex determination genes acting within the zygote (but see 22).

CONCEPTUAL FRAMEWORK

The Sex Determining System

Sex ratio selection is the underlying force shaping the evolution of sex determining systems (20). Sex ratio selection basically 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, then selection will favor variants of that element that bias sex ratio (or sex determination) towards the transmitting sex.

To understand the evolution of sex determination, it is necessary to consider how selection acts upon each of 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 genes acting within the parents that influence either sex ratio or sex determination (Figure 1). Components of the sex determining system can be further categorized based upon their mode of inheritance. The mode of inheritance of a genetic element has a major influence on how sex ratio selection acts upon it. This is obvious, for instance, for cytoplasmically inherited elements. Due to uniparental transmission through females, cytoplasmic factors are subject to strong selection to bias sex ratios and sex determination towards females. Similarly, selection will act differently on sex chromosome genes than on autosomes. It is the interactions among the different components of the sex determining system that causes evolution of sex determination.

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 not only influenced by selection acting on genes in the zygotic sex determining pathway, but also genes

acting within the parents to determine the sex ratio among progeny. Based upon this dichotomy, Werren (219) defined two broad categories of genes that influence sex determination, *sex ratio genes*, which are genes that act within the parent to influence the sex ratio among its progeny, and *sex determination genes*, which are genes that act within the developing zygote to influence its sex. However, there is a third intermediate category that needs to be considered, *parental effect sex determiners*. Parental effect sex determiners are genes that are expressed in the parent (i.e. dependent upon parental genotype) but that act in the developing zygote to influence sex. For example, maternal effect sex determining genes have been described in *Drosophila melanogaster* (39, 200) and *Musca domestica* (116). In addition, maternal effect sex determining genes occur in species demonstrating monogeny (e.g. *Chrysomya*, 215) and in coccids that show paternal genome loss early in development (20, 166-168, 169). These three categories 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 functional X and Y (or Z and W) bearing gametes, 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 haplodiploids, females manipulate the sex ratio among progeny by altering the probabilities that the egg is fertilized (77). Unfertilized eggs develop into males and fertilized eggs develop into females. Genetic variation for fertilization proportion has been documented in some species (174) and is inferred in many others (77). 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 (e.g. males) parental phenotypes could alter selection acting upon 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 (187) and western painted turtle (120). This, in turn, will affect how selection operates upon environmental sex determining genes expressed in the zygote. Recent studies have shown that some birds (e.g. the Seychelles warbler, 134) alter sex ratio among progeny based upon available resources. This is due to either preferential segregation of Z or W chromosomes during meiosis (a parental sex ratio affect) or to maternal modification of zygotic sex determination (see below).

2. PARENTAL EFFECT SEX DETERMINERS: As described, parental effect sex determiners are expressed in the parent (i.e. are dependent upon the genotype of the parent), but act in the zygote to determine its sex. Functionally, these genes are similar to zygotic sex determiners because they act within the developing zygote to determine its sex. However, in terms of selection, parental effect sex determining genes are subject to the same selection pressures as sex ratio genes because they are expressed in the parent and dependent upon parental genotype. Parental effect genes can be either maternal effect or paternal effect sex determiners. Examples of both types are presented in 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 the process is

therefore dependent upon products placed in the eggs. This creates the situation where 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 *Drosophila melanogaster*, daughterless (*da*) is a maternal effect nuclear gene that produces a transcription factor involved in sex determination (39, 200). A maternal specific *da* gene transcript is placed in eggs (prior to meiosis), and therefore presence of *da* product is dependent upon the maternal genotype. However, action of the maternal *da* product occurs during early development of the zygote (after meiosis), where the transcribed protein activates the Sex-lethal gene (*Sxl*), resulting in female development. Similar maternal effects on zygotic sex determination have been detected in the flies *Musca domestica* (116) and *Chrysomya rufifacies* (215). Nur (166) modelled maternal control of sex determination.

Evidence for paternal effect sex determiners is sparse. One example appears to be the paternal sex ratio chromosome (psr), which occurs in the parasitic wasp *Nasonia vitripennis* (170, 221). Normally these wasps "control" the sex among their progeny by either fertilizing eggs (diploid female progeny) or withholding fertilization (haploid male progeny). The psr chromosome is a supernumerary (B) chromosome present in some males. 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. This "haploidizes" the fertilized egg, causing it to develop into a male. Indirect evidence suggests that psr acts during spermatogenesis to modify the developing sperm, although its expression occurs in the fertilized egg (12). Although there are 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 (157, 161). Differential parental imprinting has been proposed as a possible mechanism for complementary sex determination (CSD) in haplodiploid insects (9). The extent to which paternal and maternal effect sex determiners have evolved will partly depend on whether divergent selective pressures occur on parental versus zygote sex determining genes.

3. ZYGOTIC SEX DETERMINERS: Studies of sex determination classically consider genes acting in the zygote to determine its sex. For most organisms, sex is determined early in development. Examples of zygotic sex determiners include *SrY* in mice and humans (79). Sex Lethal in *Drosophila melanogaster* (200) and the *xol* and *sdc* genes in *Caenorhabditis elegans* (99). 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 (99). 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 does the system evolve from a major effect gene to multiple female determining elements on the X and male determiners on the autosomes? Wilkins (230) proposes, 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 proposes 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 by other mechanisms (see below)

This contrasts to the dominant male determiner in mice and humans (*SrY*), although it is still unclear whether *SrY* is the primary signal, or other signals induce the SrY testis determining cascade (124).

4. OTHER DEFINITIONS:
In addition, the terminology below will be useful for considering genetic conflict over sex determination.
1. *sex ratio distorters*: non-mendelian elements (meiotic drive chromosomes, cytoplasmically inherited organelles and microorganisms, supernumerary B chromosomes) that alter parental sex ratios or zygotic sex determination.
2. *repressors & enhancers*: genetic modifiers that either increase (enhance) or reduce (repress) phenotypic expression of a sex ratio gene, sex determining gene or sex ratio distorter.
3. *resistance genes*: for microbial sex ratio distorters, these are "host" genetic modifiers that reduce or eliminate the infection or reduce transmission of the infection.
4. *restorer genes*: modifiers that suppress a sex ratio distorter, restoring sex determination to the background state. Suppressor, repressor and restorer are used synonymously.
5. *compensatory genes*: genes that, in populations polymorphic for a sex ratio distorter, cause a compensatory shift in sex ratio or sex determination in individuals without the distorting element.

Genetic Conflict over Sex Determination
Genetic conflict will occur when the different components of the sex determining system are selected to "push" zygotic sex determination or parental sex ratios in different directions. Given the apparently divergent selective pressures acting upon genes with different inheritance patterns (cytoplasmic, autosomal and sex chromosomal) and site of expression (maternal, paternal and zygotic), genetic conflict appears to be an inherent feature of sex determining systems. Here we list the general "arenas" of conflict over sex determination and sex ratios.

1. 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 108). In plants, cyto-nuclear conflict has been documented between maternally inherited organelles inducing cytoplasmic male sterility and autosomal suppressors of CMS (reviewed in 44, 190). In the absence of suppression or other counterbalancing forces, cytoplasmic sex ratio distorters can spread to or near fixation, potentially driving the population (and species) to extinction (100, 204). Cyto-nuclear conflict is discussed in more detail below.

2. SEX CHROMOSOME DRIVE & B CHROMOSOME DRIVE CONFLICT: Sex chromosome drive is just one manifestation of selection favoring meiotic drive loci, which also occur on autosomes (reviewed in 144). 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 either favor enhancement of drive or suppression of drive, depending upon how tightly linked the gene is and whether linkage disequilibria are

maintained (233). However, the possibility that X-drive induced sex ratio distortion favors compensatory shifts in zygotic sex determination (or maternal affect sex determiners) has not been extensively explored.

Genetic conflict is also expected between Y-drivers, and the X and autosomes. Interestingly, there is a concordance in the "genetic interests" of W-driving chromosomes and cytoplasmic factors in female heterogametic species (ZW females), but not between X-drivers and cytoplasmic factors in male heterogametic species (XY males). Sex chromosome drive can also potentially cause population extinction (89, 142, 143).

B chromosomes are supernumerary chromosomes that occur in a wide range of species (126). Many B chromosomes are "parasitic" genetic elements which have an increased transmission in gametes (transmission drive), thus maintaining the chromosomes within populations despite the fitness costs they impose on the "host" (164, 167). In many cases, transmission of B's 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 towards the transmitting sex. However, detailed studies in a few coccid species with biased transmission of B chromosomes have failed to show an affect of B on sex determination (Nur, pers. com.). There is one striking example of a sex ratio distorting B chromosome - the *psr* chromosome in *Nasonia vitripennis*. *N. vitripennis* is a haplodiploid parasitic wasp - males normally develop from unfertilized (haploid) eggs and females from fertilized (diploid) eggs. Males with the psr B chromosome produce functional sperm, but following fertilization, the paternal chromosomes (except psr) form a chromatin mass and fail to participate in subsequent mitotic divisions. The psr chromosome is transmitted to the zygote, which develops as a (haploid) male due to loss of the other paternal chromosomes (170, 221). Subsequent work has shown that conversion of females to males is selectively advantageous for the B chromosome because it has high transmission through male (mitotic) gametogenesis but low transmission through female (meiotic) gametogenesis. Hunter et al (102) and Stouthamer (pers. com.) have also discovered paternally transmitted non-mendelian elements that cause male-biased sex ratios, but the causative agents have not yet been determined.

3. PARENT-OFFSPRING CONFLICT: Trivers (211) 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 and Hare (212) proposed that Queen-Worker conflict occurs over sex ratios in social insects (workers are typically the offspring of the queen). Empirical studies now strongly support that such conflict exists (203).

The role of parent-offspring conflict (or more appropriately parental gene-zygotic gene conflict) over sex determination has not been widely considered. Given the growing evidence for maternal effect sex determining genes, this possibility needs to be considered more thoroughly. There are two situations where maternal gene-zygotic gene sex determination 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 the other, natural selection will favor the parent to overproduce the less costly sex (69). 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 (43). Under these circumstances, genetic conflict theory predicts that maternal effect sex determiners will push the sex determination towards the less expensive sex and zygotic sex determiners will push sex determination towards a reduced bias. The dynamics of this interaction have not been explored theoretically. Depending upon the mating system, paternal effect sex determiners will either have "genetic interests" more concordant with 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 for these genes due to 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.

4. MATERNAL-PATERNAL CONFLICT: Interest has primarily focused 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 (85, 86). Nevertheless, there are some interesting applications to sex determination evolution. Brown (16) and Bull (18, 20) 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. The selective advantage (termed the automatic frequency response by Brown) results from a higher maternal genome transmission in the next generation through haploid males relative to through diploid males (i.e. no reduction due to meiosis). The advantage accrues so long as haploid males have a greater than ½ fitness of diploid males.

In addition, intergenomic maternal-paternal conflict clearly occurs in species with haplodiploid and paternal genome loss sex determination (88). In haplodiploids, males are under selection to increase the proportion fertilized eggs (proportion 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, 16, 101, 168, 169), 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 (162) and the flatworm *Polycelis nigra* (10).

Alternative Models For Sex Determination Evolution

From the discussion above, it should be apparent that 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. Here we briefly review some models currently in the literature. The focus is on factors that destabilize sex determining systems, causing evolutionary transitions in the sex determining mechanism.

1. TRANSIENT COVARIANCE OF FITNESS AND SEX (HITCHIKING): Bull (20) 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 *Musca domestica*, where some sex determination variants appear to be linked to pesticide resistance alleles (132, 156, 189). In the platyfish, several body color genes are tightly linked to the different sex chromosome loci (128). Differential selection for body color in males and females could possibly play a role in the variation in sex determination among platyfish (20, 129). Karlin and Lessard (130) models for when viability factors are linked to sex determining genes, and found a diversity of resulting sex determining mechanisms.

2. ACCUMULATION-ATTRITION: Graves (82) has 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 those 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) (182, 183) and the idea that male growth enhancers will accumulate on the Y (109, 110).

3. POPULATION STRUCTURE & INBREEDING: Hamilton (89) pointed out that subdivided populations with local mating (and inbreeding) selects for parents that female-biased sex ratios. There is considerable empirical evidence that local mate competition (LMC) does lead to female biased sex ratios (reviewed in 3, 90). Studies have focused upon haplodiploid insects, where females have 'control" over the sex ratio among progeny (35, 77, 78, 218). However, there has been little consideration of how inbreeding and LMC will shape the zygotic sex determining mechanism in species without parental sex ratio control. Even relatively low levels of inbreeding and local mate competition can select for female-biasing maternal and zygotic sex determiners. Temporal variation in inbreeding levels could select for sequential accumulation of male and female sex determiners. However, this has not been explored theoretically or empirically. Local pollen competition is likely to be important in shaping the sex allocation of hermaphroditic plants (35)

Two other population structure effects may also be relevant to sex determination evolution. These are local resource competition (LRC) (38) and local resource enhancement (LRE) (195). For species with differential dispersion of the two sexes, selection will favor a sex ratio bias toward the more dispersing sex when there is competition among the non-dispersing siblings for resources (Local Resource Competition). Conversely, if proximity of relatives enhances the fitness of non-dispersing sex (e.g. due to sharing of resources or cooperation), then a bias towards the non-dispersing sex would be favored (Local Resource Enhancement). There is some empirical evidence to support both these models (53).

Basically, 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. due to dispersal), then biased sex ratios will be selected (71, 72, 207). However, the models implicitly assume parental sex ratio control. The same selective force (differential dispersal of the sexes)

should also select for biases in the zygotic sex determining genes (due to genetic relatedness among siblings), although less strongly than for parental sex ratio and parental affect sex determining genes. Such affects have not been investigated theoretically.

4. VARIABLE FITNESS OF MALES & FEMALES: Facultative adjustments in sex ratio and sex determination are expected when male and female fitness varies. For example, Trivers and Willard (213) 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 to overproduce the sons when in good condition and daughters when in bad condition. Variable fitness affects are also invoked to explain a shift from male to female as a function of age in sequential hermaphrodites (34) and sex ratio shifts as a function of host size in parasitic wasps (37, 77).

In terms of sex determination, variable fitness effects almost certainly are important in the evolution of environmental sex determination (ESD) (19, 36). ESD is observed in some marine worms and molluscs, parasitic nematodes such as mermithids, a few fish and some lizards, turtles and crocodillians (reviewed in 20, 121) as well as some plants (175). 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 environmental sex determination in reptiles is still unclear. Conover et al (47) subjected Atlantic silversides (*Menidia menidia)*, which have ESD, to highly unbalanced sex ratios under high and low temperature regimes. They were able to select for a balanced sex ratio within 8-10 generations. At high, but now low temperature, the level of ESD was reduced or virtually eliminated suggesting selection for temperature-insensitive sex determining genes. These results show that highly skewed sex ratios can cause shifts in the degree of ESD and the underlying sex determiners. Kraak and Looze (135) propose that the change from ESD to genotypic sex determination was due to selection for embryonic development rates, with a selection for larger male size favoring XY male sex determination and larger female size favoring ZW female sex determination.

"Locked-In" Sex Determination?

Some sex determining systems may be more rigid than others, reducing or precluding further evolution of sex determination. One example is the evolution of heteromorphic sex chromosomes. Heteromorphic sex chromosomes are believed to evolve primarily by mutational degeneration of chromosome maintained in the heterozygous state (the Y in XY males and W in ZW females) following suppression of recombination between homomorphic sex chromosomes (30, 183). 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 (24). For instance, in mice and humans, male fertility factors are present on the Y chromosome, restricting the potential fitness of XX males (82). Phylogenetic patterns support the view that evolution of sex chromosome heteromorphisms increases conservation of sex determining mechanisms (20, 172); some large phylogenetic groups have conserved heteromorphic sex chromosome systems. Nearly all mammals have an XX/XY sex determining system (but see below), snakes and birds have a ZW/ZZ system. Haplodiploid sex determination also shows phylogenetic conservation, with complete orders showing this form of sex determination (e.g. hymenopterans, thysanurans, oxyurid nematodes). It is apparently difficult

for haplodiploid sex determination to evolve (16, 93); however once evolved it is a highly stable and successful mode of sex determination.

Bull (20) makes the interesting point that sex chromosome heteromorphism may reduce evolutionary changes in sex determination, and conversely, that lack of change in sex determining mechanisms will lead to the evolution of heteromophic sex chromosomes from a homomorphic sex determining system. The flux in sex determination caused by genetic conflict (or other forces) could be a factor preventing sex determining mechanisms from evolving heteromorphic chromosomes. We would like to make the additional point that strong selective forces will be required to move highly stable ("locked in") sex determining systems. The highly distorted sex ratios resulting from sex ratio distorters (e.g. chromosomal or cytoplasmic) is the most likely mechanism causing changes in these otherwise stable systems. Several such genetic conflict models have been proposed for the evolution of unusual sex determination in mammals (22, 153).

Pleiotropic effects of sex determining genes can constrain sex determination evolution. For example, complicated interactions between sex determination and dosage compensation likely restricts 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 (191). In humans, *SrY* and related sex determining genes (*DAX1, SF1*) have pleiotropic effects on other developmental processes, such as skeletal, nervous and adrenal development (131, 181).

Arguing against the notion that sex determination mechanisms can become "locked in" is the mounting evidence that superficially similar sex determination mechanisms can have different underlying genetic structures. In haplodiploid hymenoptera the genetic mechanism can either involve a single locus, or more complex mechanisms (48). Murine rodent species differ in the number of *SrY* genes (141) and *SrY* can differ in potency even between different geographic strains of *Mus musculus*, resulting in production of hermaphroditic and XY females in interstrain crosses (160). Furthermore, it is clear that even groups believed to be conserved by heteromorphic sex chromosomes (e.g. mammals) show variation in this basic feature. Unusual sex determination systems are for example found in lemmings (74) (see below). A growing number of studies are showing that vertebrates previously believed to have genetic sex determining systems, actually have a mixture of genetic and environmental sex determination (51) and that transitions between these mechanisms may be relatively easy (52, 125). Studies are likely to reveal further diversity in sex determination, even in groups previously believed to be conserved.

GENETIC CONFLICT SYSTEMS

Sex chromosome drive

Meiotic drive chromosomes inherit in a non-Mendelian fashion typically ending up in 70-100% of gametes (192). The best known examples are Segregation Distorter in *Drosophila* (54, 208, 234) and the *t*-locus in *Mus* (142, 144, 197). 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 114). The majority of examples are driving X chromosomes that are typically

referred to as "Sex-Ratio" (SR) chromosomes. Driving Y chromosomes are rare, probably due to their stronger drive capacity leading to fast extinction in the absence of counter selection (89).

Recent evidence (118, 154) in concordance with predictions by (73, 114) that they are frequent but hidden, indicate that driving sex chromosomes are much more common than previously thought. Without counterbalancing selection, meiotic drive of sex chromosomes would quickly lead to extinction of carrier populations (89). Counterbalancing selection of driving sex chromosomes can occur at the gene, individual and group level (see 118). At the individual level, driving sex chromosomes often cause a reduction in male fertility (145). This is the result of their mode of action that typically involves dysfunction of gametes due the breakage of the non-driving sex chromosome homologue (179). If the driver genes are associated with chromosomal inversions, females may have reduced fitness as well (see 119). Wilkinson et al (231) found that the frequency of Y drive increased as a correlated response in populations selected for increased stalk-eye size, suggesting that genes involved in this male character are Y linked.

At the level of genes, Fisher's sex ratio theory (69) predicts that selection will favor alleles on the autosomes and the non-driving 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 (144, 233). The drive allele is expected to show coupling with enhancer and repulsion with suppressor alleles, which might be further promoted by chromosome inversions (145). Interestingly, the evolution of autosomal suppressors to drive is not inevitable, and depends on the specific fitness effects of driver chromosomes in males and females (Wu 1983). Jaenike (118) has invoked frequency-dependent selection in the absence of linkage. Modifiers of Sex Ratio have been found in a number of organisms (26, 27, 144, 154, 180, 199). For example, Cazemajor et al (28) showed that in *D. simulans* the 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 (206). Hurst (107, 112) has argued that the Stellate locus in *Drosophila melanogaster* is a relict driver gene on the X chromosome that has been silenced by modifier genes on the Y chromosome.

Driving sex chromosomes are a clear example of conflict at the genomic level between chromosomes that are selected to produce an equal sex ratio and ones that bias the sex ratio towards their own transmission gain. However, what has not been widely investigated is whether sex chromosoome drive selects for compensatory changes in the zygotic sex determining mechanism. So far, there is not strong evidence for this. All known modifier genes appear to counteract the action of driver within the parent, rather than by compensatory changes in sex determining genes. The only clear cut example of a genetic conflict induced change in the sex determining system is provided by Lyttle's experiments (143). He constructed laboratory populations with driving Y chromosomes containing Segregation Distorter (SD) genes. 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). Although this is an artificial example, it 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 solutions at the gene level to escape from sex chromosome drive induced extinction. 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 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 64, 104, 108). In most cases, cytoplasmic sex ratio distortion is caused by maternally inherited microorganisms that distort sex ratio towards females. Cytoplasmic sex ratio distorters can cause a various phenotypes, which can be classified into the following categories: male-killers, primary sex ratio distorters, feminizers and parthenogenesis inducers. Examples of male-killing microbes include spiroplasms in *Drosophila willistoni* (84), gamma proteobacteria in *Nasonia* wasps (224), rickettsia, spiroplasms and flavobacteria in lady-bird beetles (104, 224) and microsporidia in mosquitoes (2). Feminization of genetic males is caused by *Wolbachia* rickettsia in isopods (185) and microsporidia in amphipods (62). Wolbachia induced parthenogenesis is found in an array of hymenoptera (202; reviewed in 201) and is implicated in other organisms. Primary sex ratio distortion towards females is caused by the msr element in *Nasonia* (198); although the causative agent is unknown, it is possibly due to a mitochondrial variant. As described previously, cytoplasmically inherited elements are selected to cause shifts towards females because females transmit these elements to future generations. Interestingly, cytoplasmic incompatibility inducing *Wolbachia* (reviewed in 222) in haplodiploids appear to run counter to the expectation because they actually cause a male-biased sex ratio. However, this is selectively favored because these bacteria reduce female productivity in lineages not harboring the bacteria, thus increasing the frequency of infected females.

Coevolutionary interactions between cytoplasmic sex ratio distorters and nuclear genes can be complex. For example, when transmission of the sex ratio distorter is incomplete, selection for compensatory shifts in the parental sex ratio can lead to an "positive feedback" that results in monogeny - some females producing all-female progeny (cytoplasmic control) and some producing all-male progeny (nuclear control following compensation) (20, 219). However, Werren (219) found that this effect would not occur when transmission of the distorter was near 100%. Under this circumstance, presence of a distorter, even at high frequency, had no effect on selection for compensatory sex ratio shifts. A similar effect was shown for cytoplasmic sex determiners (63). In contrast, selection for autosomal repressors of cytoplasmic distorters of parental sex ratio is favored (216), due to sex ratio selection. Theoretical studies indicate that there is no selection for compensatory sex ratio alleles in response to male-killing microorganisms, at least in panmictic populations (219), although repressors to male-killers are expected to evolve.

Taylor (204) 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 element. If this process is common in nature, then interspecies crosses may reveal cytoplasmic sex ratio distorters, due to their release from suppressing genotypes. It has been have proposed that hybrid lethality and sterility can result (73, 114). One interesting feature is of cytoplasmic sex ratio distorters is hitchhiking by associated mitochondria. Eventually, the mitochondrial variant associated with the cytoplasmic distorter can become fixed in the population, if transmission of the distorter is incomplete or restorer genes are present. 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) (204) and interdemic selection against local populations with male scarcity (20, 223).

Although it is expected, there is not extensive empirical evidence for nucleo-cytoplasmic 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 feminizing factor of unknown etiology (*f*), masculinizing autosomal genes and suppressors of the feminizing factors (186; reviewed in 185). The *f* feminizing factor shows a complex inheritance pattern, with primarily cytoplasmic transmission but also some paternal transmission. An apparent association between *Wolbachia* and *f* led Legrand and Juchault (137) to propose that *f* was a bacterial phage carrying feminizing elements from the *Wolbachia* which occasionally incorporates into the isopod genome. It is still 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 different elements, although 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 (due to sex ratio selection). Juchault and Mocquard (127) have 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; integration of the *f* factor onto an autosome would then result in a neo-W (female determining) chromosome. This process would effectively prevent the evolution of degenerate (heteromorphic) sex chromosomes. What is less clear, although intriguing, is whether nucleo-cytoplasmic conflict could result 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 (185) points 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

Cytoplasmic male sterility (CMS) is the failure of anther or pollen development caused by a cytoplasmically inherited factor. CMS is widespread in plants, occurring as a polymorphism in species with a mixture of hermaphroditic and male sterile individuals (referred to as gynodioecy). Lewis (139) first pointed out that male sterility is much more readily selected for when caused by a cytoplasmic gene than a nuclear gene. CMS will be selectively favored so 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 (50, 59).

This conflict is manifested by complex interactions between cytoplasmic male sterility genes and nuclear repressor of CMS. Because many plant species showing CMS are of economic importance, extensive molecular genetic analyses of CMS have been conducted (reviewed in 190). In all such cases examined, CMS genes occur within the mitochondria and are chimeric genes resulting from genetic rearrangements. Examples include CMS genes found in maize, *Petunia*, rice, the common bean and sunflower. 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. Most gynodioecious species harbor more than one CMS cytotype and multiple interacting nuclear restorers segregating within populations. For example, Haan et al (59) found three different CMS types in *Plantago lanceolata*, each with a set of specific nuclear restorer loci. These ranged 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 (72, 150). Under some circumstances, CMS cytotypes can go to fixation within a species, but be repressed by restorer alleles and therefore 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 form of hybrid sterility in plants (139).

There is an extensive theoretical literature on the coevolutionary dynamics of CMS and nuclear genes (e.g. 31-33, 72, 80, 147, 150, 194). 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 (147) document 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 (31, 33, 147, 194)

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 towards male function can be favored, Atlan et al (4) observed such sex allocation shifts in gynodioecious populations of *Thymus vulgaris*. Explicit genetic models are necessary for investigating these complex processes because phenotypic models do not capture the non-random association of alleles (gametic phase disequilibria) that can be crucial to the ultimate fate of different genotypes (147). But, in general, the clearest and most compelling examples of genetic conflict causing turnover in sex determining alleles occur within these plant systems.

Other systems

Genetic conflict as a driving force in the evolution of sex determining systems has been invoked in a number of cases that we describe below. In addition, we consider a few systems to which genetic conflict theory has not been applied. These systems show that the role of genetic conflict in the evolution of sex determining systems (a) is still hypothetical in most cases, (b) cannot be fully interpreted due to lack of enough information in some cases, and (c) is worth considering because it points to critical bits of information that need to be collected in order to understand the evolution of particular mechanisms.

LEMMINGS. The evolution of aberrant sex chromosome systems of lemmings have been extensively considered (74, 75, 83). In the wood lemming (*Myopys schisticolor*) there exist three types of individuals: XX are normal females, XY are normal males and X*Y are females. The variant X chromosome (X*) shows drive in X*Y females resulting in a strongly biased sex ratio towards females in carrier populations. X* is considered to suppress the male determing effect of the Y so that X*Y individuals are female. X*Y females have X*X* oocytes through non-disjunction (YY cells die) and produce nearly all daughters. A somewhat similar system has been described from varying lemmings (*Dicrostonyx groenlandicus* and *D. torquatus*) (75, 76). 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 (7, 22, 25, 148). 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 22 for a comprehensive treatment). Relevant to our discussion is to what extent X*Y females may select for changes in the sex determining system. One of the most straightforward means of eliminating XY females would be evolution of an Y-linked restorer gene of X*, but invasion of a restorer 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 showed that selection for autosomal restorer genes was even weaker than for Y-linked suppression. The actual path that evolution has taken in the wood lemming seems to involve first , 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 overcomes their reduced fertility (half of the Y oocytes die when they are fertilised by Y sperm). As an alternative scenario, McVean and Hurst (153) have 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 of lemming may be interpreted from a genetic conflict perspective, but its exact role is unclear.

SCIARA COPROPHILA. In the fungal gnat *S. coprophila* sex determination occurs through paternal genome loss (17, 155). 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. All zygotes are initially XXX and sex is determined by an unknown maternal cytoplasmic factor. Haig (87) has suggested an evolutionary scenario based on genomic conflict to explain this unusual sex determining mechanism. He envisages the following steps: (1) origin of a driving X chromosome causing female-biased sex ratios, counteracted by (2) conversion of XX daughters into sons by elimination of one paternal X, and (3) origin of dispensable L chromosomes derived

from X chromosomes that favor male-biased sex ratios, followed by (4) 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 towards females and the maternal autosomes and variant (doubling) X' which counteract their effects. Although this model is still completely hypothetical some of its predictions are testable, e.g. that the L chromosomes are derived from X chromosomes.

COCCIDS. The evolution of unusual chromosome systems of scale insects (169) has been explained in the context of genetic conflict (16, 18, 93, 88). Using similar reasoning as for *Sciara*, Haig (88) has attempted to explain the origin of haplodiploidy from heterogamety through a number of evolutionary transitions. Several of these transitory stages are presently found within the scale insects (Cocoidea). Many species of scale insects exhibit paternal genome loss meaning that paternally derived chromosomes are not transmitted by males because they are eliminated from their germ lines at different developmental stages (see 88 for details and references). Haig's model involves three steps (1) meiotic drive by the X chromosome in XO males causing female-biased sex ratios, (2) linkage of the maternal set of autosomes in males to exploit X-drive, and (3) conversion of XX daughters 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*.

In the above scenarios, conflict between sex chromosome drive and autosomal suppressors is considered as the driving force in the evolution of these systems. The importance of Haig's models is that they also illustrate how genetic conflict may lead to novel (pathways in) sex determining mechanisms, such as parental specific elimination of sex chromosomes and the origin of dispensable supernumeraries affecting sex determination. However, although evolutionary plausible, there is currently no supportive empirical evidence that the observed systems are indeed the outcome of conflict between sex determining genes.

MOLE (*TALPA EUROPAEA*). Using genetic conflict theory, McVean and Hurst (153) have proposed three evolutionary pathways to explain the high frequencies of intersexes observed in moles (*Talpa europaea* and *T. occidentalis*) (122, 123). In moles, males are XY and have only testes, but females are XX and essentially intersexes with ovotestes, i.e., functional ovaries and a variable amount of non-functional testicular tissue. In their first model they consider the evolution of a Y-linked factor (a paternal effect sex determing gene in our terminology) that masculinizes XX embryos and that is counteracted by a modifier on the autosomal or X-chromosome. In their second model they consider 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 the authors that there is currently very little empirical evidence for any of these models.

MUSCA DOMESTICA. In *Musca domestica* male sex is determined by a dominant zygotic sex determiner, M, which can be located on the Y, X or any of the autosomes (see 61 for references). Northern European populations have standard XX females and XY males with the Y

chromosome determining sex (70). Populations in Central and Southern Italy have XX males and females; sex being determined by autosomal determinants for maleness and femaleness. Hybrid zones are found between populations with different sex determining systems.

The *M* factor counteracts the maternal effect sex determiner F which, in the absence of *M*, is expressed during oogenesis leading to maternal product F in embryos and female development. Because the various M factors appear functionally homologous, they are considered homologous copies that have translocated (193), although this has not yet been confirmed by DNA sequence analysis. Two maternal effect mutants are known, *tra* and *Ag*, but these are interpreted as hypomorphic alleles of *F* and *M* respectively.

At present, there are no ready evolutionary explanations for the translocation of *M*, but several scenarios can be thought of. One possibility is linkage of the sex determining locus to a gene under selection (i.e. the hitchhiking model). On at least two seperate occasions, *M* factors have been translocated near DDT resistance genes (*MII* and *MIII* "translocations"; 132, 156, 189). What remains unclear is why an male determining zygotic sex determiner would serrendipitously become linked to resistance genes repeatedly like this. Another possible explanation is that hybrid zones have acted as a source of selection for various modifiers of sex determination through destabilization of the sex determining mechanisms and population sex ratios.

Translocations of sex determining genes (so-called 'jumping sex factors') have also been reported from the midge species *Chironomus* (136, 146) and the fly *Megaselia scalaris* (210). Although these male determiners appear functionally similar as well, there is no evidence yet that they are genetically homologous. Genetic conflict theory may provide an explanation for why a sex determining gene would move positions in the genome. For example, XX females may have evolved in response to a driving X that drove the Y out of the population, which in turn may have created selection for translocation of a male determining factor onto an autosome. Alternatively, other genes may have been recruited for a male or female determining function. For example, maternal effect genes may have been selected to balance the sex ratio towards 50:50 in the presence of a male distorting sex determining gene (*M*). However, before more molecular genetic information on the nature and regulation of the sex determiner genes in *Musca* is present, these scenarios based on genetic conflict remain pure speculation.

CONCLUSIONS

Support for the role of genetic conflict in the evolution of sex determining systems is growing. Genetic conflict theory is consistent with much of the observed diversity, including sex chromosome drive systems, cytoplasmic sex ratio distorters in animals and cytoplasmic male sterility in plants. A number of plausible scenarios have been developed for specific systems. However, convincing evidence for the role of genetic conflict only exists in a few cases, notably the genetic diversity in sex determination of *Armadillidium vulgare*, and cytoplasmic male sterility in plants. In a number of systems, the invoked role of genetic conflict is still purely speculative and future empirical work is needed. There is also ample scope for further theoretical investigations. Investigations of parental gene - zygotic gene conflict could prove particularly interesting given the growing evidence of the role of maternal effect zygotic sex determiners in sex determination.

Caution should be exercised in comparing highly divergent sex determining systems and trying to draw inferences on the evolutionary transitions between them (e.g. between *D. melanogaster* and *C. elegans*, or even flies in different families). Because sex determining mechanisms evolve quickly, comparisons between phylogenetically closely related species are needed. Such studies are still very scarce and have only begun in mammals and flies (Diptera). However, comparisons between *C. elegans* and *D. melanogaster* do reveal an interesting case of convergent evolution in sex determining mechanisms.

There are a number of extremely interesting questions concerning genetic conflict and the evolution of sex determing systems. These include (a) how X:A balance systems evolve from major sex determing gene systems and whether genetic conflict is involved (b) to what extent does sex chromosome drive cause compensatory changes in zygotic sex determination mechanisms, (c) why translocations of sex determining genes translocating appear to be frequent in some genomes, and (d) what is the potential role of parental gene - zygotic gene conflict in sex determination evolution. Although the verdict is still out, we believe that genetic conflict will prove to be an important force shaping sex determining mechanisms.

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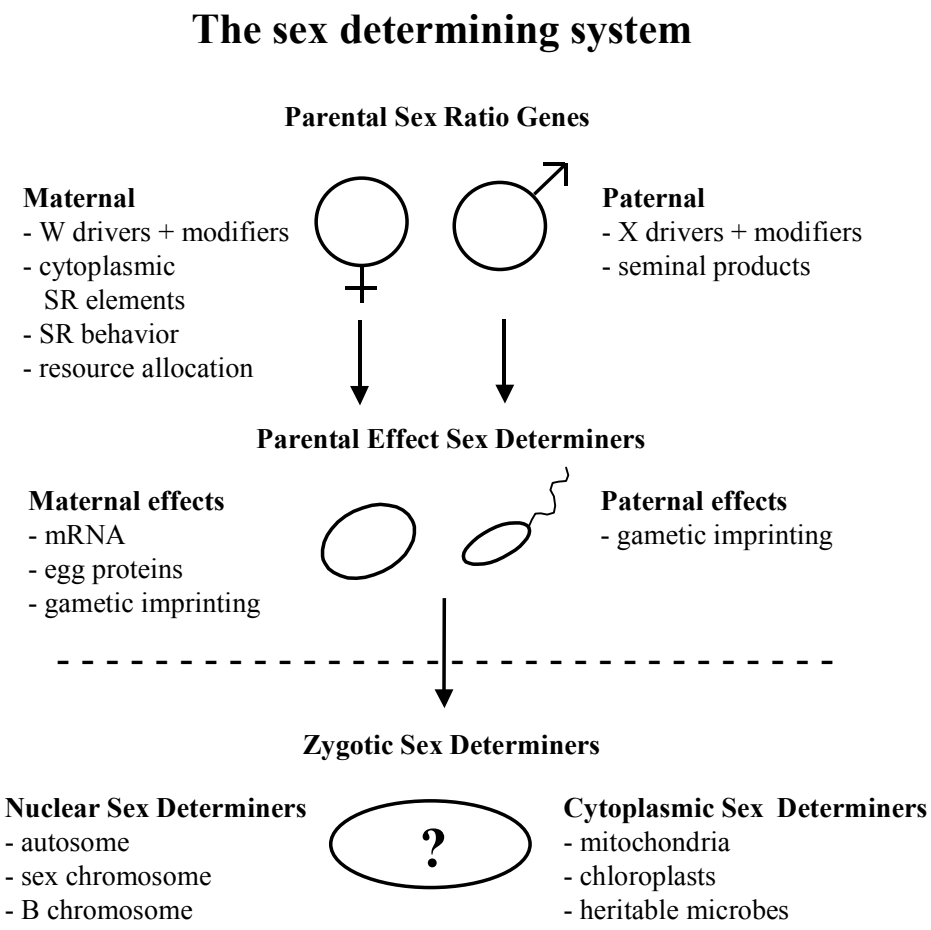
Figure 1. The Sex Determining System: The different interacting components of the sex determining system are shown, including parental sex ratio genes, maternal and paternal effect sex determiners and zygotic sex determiners.



Zygotic sex determiners and parental effect products interact in the developing zygote

TABLE 1. Catergories of genetic elements involved in sex determination.

Category	Expression	Action	Examples	Ref
Sex Ratio Genes				
Maternal	Maternal	Maternal	sex ratio control in parasitic wasps	77
			oviposition site selection (ESD systems)	120
			sex ratio meiotic drive (ZW females)	20
			msr cytoplasmic factor in N. vitripennis	128
Paternal	Paternal	Paternal	X-chromosome drive in many species	114,144
			Suppressors of sex chromosome drive	154
Parental Effect Genes				
Maternal Effect	Maternal	Zygotic	Maternal effect SD in coccids	166
			da in *Drosophila melanogaster*	200
			F factor in *Musca domestica*	193
			monogeny in *Chrysomia rufifacies*	215
			cytoplasmic sex ratio distorters (*Wolbachia*, CMS in plants)	108
Paternal Effect	Paternal	Zygotic	paternal imprinting of sd genes (hypothetical)	9
			psr chromosome in *N. vitripennis*	170
Zygotic Sex Determining Genes	Zygotic	Zygotic	*D. melanogaster* sd cascade (X:A balance genes, *Sxl*, *tra*, *dsx*)	200
			C. elegans sd cascade (*sdc*, *her*, *tra*, *fem*)	99
			SrY in humans, housemice	124
Other (Social) Interactions				
Sex Ratio	Individual 1	Individual 1	worker sr manipulation in social insects	212
Social Effect	Individual 1	Individual 2	sibling hormonal influences in utero in mice	xx
			social influences in ESD species (*Heterodera* nematodes, *Mytilicola* copepods)	20