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Genetic Conflicts and the Paradox of Sex Determination: Three Paths to the Evolution of Female Intersexuality in a Mammal

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That sex determining systems ever change is paradoxical but can be explained by noting that conflict between selfish elements and their modifiers will often cause a shift in sex determining strategy. The evolution of the novel sex determining system of moles (*Talpa europaea* and *T. occidentalis*) may, we argue, be an example of just such a process. Three different models for the evolution of female intersexuality are presented. These all attempt to account for (1) the fact that a few years ago populations of moles had high frequencies of sterile XX individuals that were either morphologically male or intersex (other XX individuals were normal females) and (2) that presently, the XX individuals in the same population are exclusively fertile intersexes that are functionally female; i.e. have follicle producing ovotestes. This case history is compared to that of the wood lemming and two similarities are discussed. First, in both cases it is noted that one end product could be approached from different routes. Second, selfish elements may be involved in the evolution of both systems. In general, it is suggested that XY sex determination, far from being resilient to evolutionary change, is vulnerable to take-over by selfish elements. This is particularly the case in mammals in which transplacental interactions could allow manipulation of sex determination in one foetus by another. This, we also suggest, is a good candidate explanation for the evolution of novel sex determination in *Talpa*.

Introduction

Within clades there is often considerable variation in sex determining mechanism (SDM). In mammals the prevalent form of sex determination is an XY system, however, there are numerous exceptions to this rule. Mammalian SDMs involving the production of XY females have, for instance, been reported in two different rodent species, *Myopus schisticolor* (Lau *et al*., 1992) and *Akodon azarae* (Bianchi *et al*., 1989). Within the insects, intra-clade variation can be more considerable. Scale insects (Coccoids), for example, show a range of chromosomal systems from XX–XO with heterogametic males to a condition in which paternal chromosomes are eliminated in early development (Brown, 1964; Bull, 1979; Haig, 1993). Similarly, beetle sex determination can vary from XO heterogamety to mechanisms as complex as an $X_1X_2X_3X_4Y$ system (White, 1954). Some beetle species have abandoned X chromosomes and are haplodiploid. In total, haplodiploidy has evolved independently at least ten times within the animals. In a few species intra-populational variation in sex determining system has also been reported.

This variety of sex determining system is paradoxical. Once a reliable system for the production of differentiated sexes has been achieved, selection should, one might imagine, favour the conservation of this mechanism. It is thus not obvious why such a system should ever change. The numerous incidences of rapid transition between different sex differentiation pathways thus demand explanation.

In certain circumstances an adaptive explanation can be provided to account for the possession of one sex determining system rather than another. Particular ecological conditions are thought, for instance, to provide a selective regime favouring environmental sex determination (ESD). Ecological

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factors may thus explain the variation in effect of temperature in reptilian ESD (Bull, 1987), and the ability in some fish to switch from ESD to genetic determination when the disruption of the habitat temperature causes large sex ratio skews (Conover *et al*., 1992).

An alternative explanation is that turnover of SDMs is governed by non-adaptive factors. The stabilizing selection expected on a SDM would prevent genetic drift from being an important effect under most circumstances. However, it is possible that internal genetic conflicts could be sufficiently powerful to drive major changes to fixation. In broad outline, the spread of selfish genetic elements could create the conditions for the evolution of a novel sex determining strategy.

Several examples in which selfish genetic elements have influenced the evolution of sex determination strategies are known or have been proposed. Distortion of sex ratios mediated by manipulation of the native SDM is central to the action of many selfish cytoplasmic genes (Hurst, 1993). Where these factors are transmitted by females but not by males the selfish factor can spread in a population, even if deleterious, by converting males into females. In the isopod *Armadillidium vulgare*, the native SDM has become transformed into a similar, but novel, system by the spread of such a cytoplasmic feminizing gene. The spread of this cytoplasmic factor created the context for the spread of nuclear genes that regulate maternal transmission of the cytoplasmic factor. The population hence moved from one with a ZZ/ZW system to one in which the determinant of sex is the presence or absence of the cytoplasmic factor. This may not, however, be a stable end point and the invasion of a variant feminizing factor that is integrated into a Z chromosome is suspected (Juchault & Legrand, 1989; Juchault *et al*., 1992; Juchault & Mocquard, 1993).

Sex chromosomes are particularly vulnerable to invasion by genes exhibiting segregation distortion (Hamilton, 1967) and, at least in mammals, selfish growth factor effects (Hurst, 1994). The unusual sex chromosome systems in Coccoids may possibly be the result of the association of maternal genes with an X over 0 meiotic drive gene (Haig, 1993). Similarly, the incidence of XY females in the wood lemming *Myopus schisticolor* (Gropp *et al*., 1976; Bengtsson, 1977; Fredga *et al*., 1977; Bull & Bulmer, 1981; Bulmer, 1988) can potentially be explained in terms of a response to either X- or Y-linked meiotic drive genes (for review see Hurst *et al*., in press).

Natural occurrences of unusual sex determination-related phenomena may then represent episodes during the evolution of sex chromosome systems in response to selfish genetic elements. However, there are only a few cases, such as *Armadillidium*, in which there are any empirical data concerning the disruption of an SDM by a selfish genetic element, and the majority of supposed instances rely on *post hoc* postulation of intermediate steps (e.g. see Haig, 1993).

In this paper we present models of genetic conflict to explain the phenomenon of partial female sex reversal in populations of *Talpa occidentalis* (Jiménez *et al*., 1988; Jiménez *et al*., 1993) and *Talpa europaea* (Harrison Matthews, 1935). Based on observations on a Spanish population of *T. occidentalis* made over a period of 5 years (Jiménez *et al*., 1988; Jiménez *et al*., 1993), in which the SDM appears to have been dramatically and rapidly altered, three possible histories are proposed in which XX intersexes with follicle producing ovotestes can replace wild-type females.

Population genetical models are discussed and precedents for each situation are presented. Predictions of the models are compared to those of an adaptive explanation, and means of discriminating hypotheses are proposed. It is argued that the invasion of selfish genetic elements which disrupt native SDMs are likely to result in the evolution of strange sex-related phenomena, because large sex-ratio biases give extreme selective pressure to evolve *any* form of modifier that can return the sex-ratio towards Fisherian equilibrium. Further, it is noted that the same outcome can potentially be approached through several different pathways.

The Biology of the Mole

The reproductive biology of the European mole (*T. europaea*) is highly unusual. Females are externally indistinguishable from males, in that they possess a long, penis-like clitoris and, except during the brief breeding season, lack a vaginal opening (Harrison Matthews, 1935). In addition to a follicle producing region, ovaries also contain a highly variable amount of interstitial material that is homologous to testicular tissue (Harrison Matthews, 1935). Although this cannot produce sperm, all females are in effect XX intersexes with ovotestes; in contrast, all males are XY and have testes but no ovaries. Furthermore, within the intersexes there appears to be antagonism between the two regions of the ovotestes in that they show cyclic alternation of activity. The ovarian region is largest when the female is in oestrus and vice versa (Harrison Matthews, 1935). This suggests that both female and male

functions are present, each suppressing the other, with their relative magnitudes depending on the time of year.

Similar cases of natural partial sex reversal have also been described in the desman *Galemys pyrenaicus* (Insectivora, Talpidae) (Peyre, 1956), pig (Crew, 1927), freemartins (Jost *et al*., 1975) and ageing rats (Crumeyrolle-Arias *et al*., 1986). Given that gonadal tissue of any kind has a cost associated with its production then there is a disadvantage to producing any unnecessary material. Gonadal tissue of the opposite sex additionally acts in antagonism to that of the true genetic sex (mammalian male function both suppresses female development with anti-Mullerian hormone and promotes male development with testosterone), so the ubiquitous distribution of ovotestes in female moles is an intriguing paradox. Recent studies on the closely related species, *T. occidentalis*, may, however, present one possible explanation for this condition.

Rapid Transition Between Sex Determination Mechanisms in a Spanish Population of *Talpa occidentalis*

Individuals of *T. occidentalis*, a species with distinguishable sexual dimorphism, were sampled from the Vega de Granada in 1988 by Jiménez *et al*. They discovered a mixture of XY males, XX females, XX sterile intersexes and XX sterile males. Intersexes and sex reversed males appeared cytologically normal and no sex-chromosome/autosome interactions were seen at meiosis (i.e. no translocations had occurred; see Fredga, 1970). XX male testes appeared immature and lacked both meiotic activity and spermatozoa. However, the level of male specific antigens in XX and XY males was very similar; intersex levels were intermediate between males and females.

The same population was sampled 5 years later, by the same group. This time, all females examined were XX intersexes with follicle producing ovotestes and there were no recorded instances of either XX males or sterile XX intersexes (Jiménez *et al*., 1993). Detailed histological analysis of the testicular tissue in ovaries revealed numerous small seminiferous cord-like structures containing immature Sertoli cells (some of which appeared to be autolysing) and a complete absence of germ cells. As in *T. europaea* there was much variation in the amount of testicular tissue found, this being a good predictor of serum testosterone levels. Southern blot analysis failed to detect the presence of either *Sry* or *Zfy* in genomic DNA, multiple copies of the latter being found in two species with sex reversal, *Akodon azarae* (Bianchi *et al*., 1989) and *Myopus schisticolor* (Lau *et al*., 1992). This reinforces the earlier interpretation that no sex chromosome-autosome translocations are involved in the sex reversal. The explanation given for the discrepancy between samples is that in the first study not all XX females were histologically analysed and therefore could have possessed ovotestes. This, however, fails to explain either why XX sterile males were found only in the first sample, or why some of the XX female intersexes in the first study were judged sterile when none of those in the later sample were.

Genetic Conflict as a Possible Explanation of the Phenomenon

What explanations can we present for this phenomenon? Harrison Matthews (1935) suggests that the presence of testicular material in females of *T. europaea* is due to the faster growth rate of male tissues and is thus an effectively neutral by-product of the sex determination system. However, given the hormonally mediated antagonism between male and female gonadal tissue, the absence of testicular tissue in the majority of mammalian ovaries, and the large (though variable) quantities of testes in mole ovotestes, this explanation seems unparsimonious.

Could female intersexuality perhaps be advantageous? One possibility is that testosterone production is responsible for the aggressiveness of moles outside the breeding season. If this is true then the situation in moles may be similar to that of the spotted hyena (*Crocuta crocuta*). During the final third of pregnancy concentrations of androgen (particularly testosterone) in the female circulation reach the maximal values of those in adult males (Glickman *et al*., 1992; Licht *et al*., 1992). This results from the conversion of large quantities of ovarian produced androstenedione to testosterone by the placenta and has the effect of external masculinization of female foetuses and the destruction of their follicles. Consequently, at birth, females are morphologically indistinguishable from males, and while the serum testosterone concentration of females declines to ''normal'' levels by 26.5 months, the male phenotype is retained. This peculiar system is thought to be associated with female dominance and the high levels of aggressiveness exhibited by even the youngest animals, although why these features evolved originally is unknown.

This, then, is one possible explanation for the situation described. However, the presence of sterile XX intersexes and XX males in the first sample of

T. occidentalis (Jiménez *et al*., 1988) suggests that masculinization actually has a deleterious effect on female fertility in moles. If this is the case, then this cannot explain the initial spread of the trait through the populations (though it could explain its maintenance). Alternatively, it is possible that female intersexuality is a conserved feature of moles and that the XX males and sterile females in the first sample were simply fertile females undergoing a phase of acute masculinization with concomitant reduction in ovarian tissue. Whether this is true or not, this provides no explanation of why female intersexuality arose in the first place. Also, there is no evidence for the presence of ovotestes in female hyenas, and it appears that testosterone is produced constantly outside pregnancy by the testicular region of the ovotestes in adult female moles. This suggests that the situation in moles may well have a different explanation from hyenas.

If we assume then that the details presented above concerning the evolution of a novel sex determining system in populations of *Talpa* are correct, then this presents two separate problems. First, how did a population (which we presume originally had XX/XY sex determination), ever evolve to the position where nearly one third of all XX individuals are sterile? Second, how was it that the population changed from this position to one in which all XX individuals were fertile, follicle-producing intersexes, i.e. functional females?

The situation is suggestive of a possible role for selfish genetic elements for two reasons. First, the spread of genes that cause sterility in certain contexts is a frequently reported feature of selfish elements. Homozygotes for autosomal meiotic drive genes are sterile either due to intrinsic properties of the gene itself (as in the *t*-complex of mice) or linked sterility loci (as in "segregation distorter" in *Drosophila melanogaster*). Cytoplasmic male sterility in plants is usually caused by mitochondrial genes that sterilize male tissue and increase ovule production as a consequence. Second, the very fast rate of evolution, inferred by the dramatic change over a few years, is typical of many selfish elements and the spread of their modifiers. The selective coefficients associated with selfish elements are often so extreme that their spread through a population can be almost instantaneous if compared with "standard" advantageous alleles. Can, then, the case of *Talpa occidentalis* sex reversal be reinterpreted in the light of the vulnerability of sex chromosomes to segregation distorters and selfish growth factors? Below we present three possible models for the evolution of the novel sex determining system of *Talpa*.

All of the models attempt to account for the high frequency of sterile intersexes, and the principle differences between the models, concerns how the population came to have so many sterile individuals. All models then propose that a modifier arises which can convert these sterile intersexes into fertile functional females. The conditions for the spread of such modifiers are very broad and the only big unknown is how they effect their rescue function. The recovery of male fertility by restorers in hermaphroditic plants affected by cytoplasmic male sterility may be considered a precedent for such modifiers.

Three Models for the Evolution of Partial Sex Reversal in Moles Based on Genetic Conflicts

MODEL 1

Consider the origin of a Y-linked factor which causes female sibs to become sterile by masculinization of XX embryos. The mutant Y (Y*) could either label its X-chromosome carrying sister spermatids with a masculinizing signal during spermatogenesis or act *in utero* to androgenize surrounding sibs. As the population genetics of the two cases are similar (but not identical) they will be considered together.

For Y* to spread there must both be female sibs to masculinize and an advantage to males in causing masculinization of female sibs. This can either be a direct benefit, if the net effect of masculinization is to redirect resources away from sisters to the Y*-carrying males, or an indirect benefit, such as reducing the probability of sib-mating and hence inbreeding. The relative importance of each depends on the extent to which masculinization in females causes a reduction in resource demands (and the possibility of redirection of resources to males) as well as sterility.

The situation is similar to the evolution of cytoplasmic male sterility (CMS) in hermaphroditic plants (Gouyon & Couvet, 1987; Kaul, 1988; Saumitou-Laprade *et al*., 1994). In this instance, cytoplasmic genes causing male sterility (i.e. dysfunction in pollen production) will spread if they confer a fitness gain to female function via reallocation of resources or inbreeding avoidance. Cytoplasmic genes and Y-chromosomes are similar in that they are only usually transmitted through one sex (though opposite). Consequently, a mutant causing increased transmission of either may spread to fixation, despite its effect on the sex-ratio, as it never finds itself in the sex being discriminated against (potentially leading to the extinction of one sex; Hamilton, 1967).

As the Y* spreads through the population at the expense of the wild-type Y, conditions arise for the invasion of an X-linked (X^m) or autosomal (A^m) modifier that converts masculinized, sterile XX females into intersexes with follicle producing ovotestes. Because this can nullify the effect of Y*, if there is no cost to modifying, then the invasion of X^m drives the wild-type X to extinction (or wild-type autosome). The Y* will also remain at a high, stable level if it, too, is cost free. This has the effect of producing a population consisting almost entirely of X^mY^* males and X^mX^m intersex females (see Appendix 1). A similar final situation, but one in which most females are X^mX, and Y* is nearly at fixation, can be achieved by proposing a large cost to the modifier. Intermediate costs give lower equilibrium frequencies for Y* and X^m; however, it must be noted that it is not known if the situation described in moles is at equilibrium, and most feasible sets of parameter values predict an initial rise of both driver and modifier to high frequencies. Parenthetically, it is worth noting that the introduction of a costly modifier can have a large effect on the outcome of the system. The classical treatment of modifiers as being cost-free is thus perhaps a potentially important over simplification when considering the evolution of genetic systems.

Mole litters typically contain three to four offspring (recorded range of two to seven; Asdell, 1964) thus it is likely that a male will have at least one sister, as required by the models of intra-brood masculinization. The degree of inbreeding in moles is not known. Young disperse from the nest and adult moles are generally solitary. However, it has been observed that if one mole dies or is removed, another mole, often a sib, quickly assumes its territory. This suggests that sibs do not disperse far from the nest and so indicates that inbreeding may be a potential problem (J. R. Flowerdew, personal communication).

Precedents

Analysis of brood composition suggests that mammalian foetuses can influence the development and fitness of their brood sibs during gestation. In Mongolian gerbils, females which have gestated between two males in the uterus (2M females) develop slower and reach puberty later than ones that have developed between two females (2F females) (see Clark *et al*., 1993 for references). A masculinizing male may hence be able to divert resources away from his sisters to himself. This effect is mediated by the import of testosterone into females from neighbouring male sibs in the uterus, an additional effect being that androgenized females produce litters with male-biased sex-ratios (Clark *et al*., 1993). In mice, Y-linked variants for the titre of testosterone in male foetuses have been described (Jutley & Stewart, 1985) and these same strains show a Y-linked sex-ratio effect (Weir, 1960, 1976). A similar situation is that of bovine freemartins. These are sterile, masculinized females which result from placental fusion with a twin male foetus *in utero* and the subsequent passage of an unidentified substance into the developing female gonad (Ohno, 1969). This causes the production of an excess of anti-Mullerian hormone in the female which leads to partial gonadal sex-reversal, though only slight masculinization of the external genitalia.

Possible mechanisms for a chromosome-labelling effect are less clear. Perhaps the best precedent is in *Heliothis* (Lepidoptera) which has ZW female heterogamety. Repeated backcrosses between two *Heliothis* species gives male sterility and this sterility is transmitted down the female line. This is consistent with either a cytoplasmic effect or the W labelling the Z (Roehrdanz, 1990). In XY systems one might consider an X-linked gene that has its imprinted status modified by a gene on the Y (this would hence effectively be X labelling by a Y). X-linked imprinted genes are known in mice, and their control must eventually be under the control of the Y (as imprinted status is dependent upon the sex of the parent). Whether Y-linked genes can directly influence the activity of X-linked genes is, however, unknown.

In this model the sterilization/masculinization of females is intrinsic to the spread of the selfish element. Hence the modifiers that restore fertility to these progeny are classical modifiers of a selfish element, the existence of which, in some cases, is well documented (e.g. restorers of fertilization to cytoplasmically sterilized male tissue in plants).

MODEL 2

Both this and the final model consider the effect of sex-chromosome-linked segregation distorters. In this model an X-linked meiotic drive gene (X^d) arises which achieves over-representation in eggs at oogenesis at the expense of the wild-type X-chromosome. As long as the reduction in fecundity is less than the increase in transmission, the selfish element invades. If, however, it has the property that there is an additional, non-proportional cost to possessing two copies of the gene (i.e. in the homozygous condition), then it will reach an internal equilibrium (Wright, 1969; Thomson & Feldman, 1975). The cost in this case would be masculinization of females, causing sterility. At this stage it is possible for an

autosomal modifier to invade which converts sterile intersexes into functional females with ovotestes. Increasing the fitness of mutant homozygotes (and assuming that possession of the modifier has only a low cost attached) allows the mutant X to spread to fixation, the effect being to convert all females into intersexes (see Appendix 2).

Precedents

No example of an X vs. X-driver is known to us. However, autosomal drivers, whose population genetics is to a first approximation similar, are known and all known ones are sterile (or have greatly reduced fitness) in the homozygous condition. Whereas in the previous model the sterility/reduced fertility of XX individuals was a necessary component of the spread of the selfish factor, here it is considered an unnecessary side product (though one that can be realistically assumed). There is, however, no precedent as to why homozygous driver sterility should be effected in females through masculinization.

MODEL 3

Consider a mutant Y chromosome (Y*) which drives against the X-chromosome in spermatogenesis and by so doing invades and spreads through the population (assuming the transmission bias is greater than its deleterious effect on fecundity). A male bias in the sex-ratio will result which could lead ultimately to an all male population (i.e. extinction, Hamilton, 1967). The spread of the Y-linked distorter hence provides broad invasion conditions for an X-linked suppressor (X^s) which restores the sex ratio to unity (Eshel, 1975). If the suppressor has the property that in the homozygous state it causes the X^sX^s female to become a partially sterile intersex, then while it will still invade (as it is at such a low initial frequency) it will reach an internal equilibrium as the chance of forming X^sX^s becomes greater (Wright, 1969; Thomson & Feldman, 1975). The equilibrium can be broken by the invasion of an autosomal modifier that converts sterile X^sX^s intersexes into functional females. If the increase in fertility outweighs the cost of the modifier, then it spreads to fixation. Again it is the persistence of Y* in the population that drives the wild-type X to extinction. All females thus become fertile intersexes. In principle the model could be generalized to the evolution of X-linked suppressors of any predominantly male transmitted factor that causes, by whatever means, a male bias to the sex-ratio. In general, the suppressors need not be X-linked but simply have homozygous sterilization/transformation activity restricted to XX individuals.

Precedents

There is no good evidence for precedents for this model, hence this must be counted the least likely of the three. Homozygous sterility of suppressors of drive has not to the best of our knowledge ever been described. Further, it is unclear why a suppressor that acted in males should cause female sterility. This model also requires more steps and predicts a strong initial XY/XX ratio bias that was not seen in *T. occidentalis*. The model is, however, worth discussing if only to illustrate the idea that the same end point can be arrived at by different routes (Models 1–3).

Weak evidence can, however, be mustered to support the possibility of Y-linked sex-ratio distortion. Y-linked meiotic drive genes are rare but have been described in mosquitoes (Wood & Newton, 1991) and can be suspected in lemmings (Hurst *et al*., 1995), although good evidence for the latter is absent. Male-biased broods have been reported in the wasp *Nasonia vitripennis* which are caused by supernumerary B chromosomes (Werren *et al*., 1981; Nur *et al*., 1988), however this is due to the elimination of the paternal set of chromosomes and is thus a peculiarity of the haplodiploid sex determination mechanism. Male-biased broods have also been described in other hymenopterans and a few crustaceans (Ginsburger-Vogel, 1989; Hunter *et al*., 1993). Weak, Y-linked sex-ratio distortion has been described in mice (Weir, 1960, 1976). One instance of a strong male-biased lineage has been described in humans but the reason for this is unknown (Stern, 1973).

Predictions and Testing the Hypotheses

The conflict hypotheses make a number of testable predictions. The first model requires either a degree of inbreeding or a gain in male fitness via resource reallocation. The importance of each depends on whether the primary effect of masculinization in females is sterility or reduction in resource demands. It is also possible to make experimental predictions. If the first model, chromosome-labelling scenario, is correct then females should be vulnerable to masculinization even if they have no male sibs in the brood: the trait will segregate with the Y chromosome and Y-linked gene products (transcripts and/or proteins) will be present in early female embryos. In contrast, the androgenization scenario would predict

that female masculinization could only occur if there are male sibs in the brood. However, this may not necessarily be the case as the hormonally mediated growth rate and sex-ratio effects in gerbils mentioned above exhibit inheritance of acquired characteristics, 2M females producing male-biased sex ratios (Clark *et al*., 1993). If this effect were mediated by serum testosterone, then an androgenized mother may be able to masculinize her offspring through the import of testosterone in the uterus even without the presence of male sibs (as occurs in hyenas). In either situation it is predicted that rescue of XX intersex phenotype is a non-Y trait, most likely X-linked.

The second and third models predict that there is a sex-chromosome segregation distorter that creates the context for the spread of modifiers of homozygous sterility effects or sex-ratio distortion. Mutant phenotypes may well be expressed in cross-strain or cross-specific hybrids, thus under Model 2, first generation females from a hybrid cross would show a bias in gametic X-chromosomes in favour of that from the Vega de Grenada *T. occidentalis* population, and that two such X-chromosomes together on a different autosomal background would cause female sterility. In contrast, Model 3 predicts that females from strains lacking the X-suppressor (or possessing it but separated from the native strain for many years) would produce male-biased broods if mated with males from the Vega de Granada.

Discussion

We do not wish to claim that any of the above models are the right model for the evolution of the novel sex determining strategy in *Talpa*, only that they could be at least partially correct. More importantly we wish to illustrate two points. First, that the spread of selfish elements may be associated with major selective forces and rapid transitions in features that might ordinarily be thought of as being under stabilizing selection. The invasion of selfish elements thus provides the conditions for the spread of modifiers that need not be the "best solution", but are the best available solution. This need neither be "optimal" nor predictable. In short, drastic crises provide the conditions for drastic solutions. Second, that the same result can be reached via several different routes (Models 1–3).

These same two points can be equally well illustrated by reference to the case history of the wood lemming *Myopus schisticolor* (Gropp *et al*., 1976; Bengtsson, 1977; Fredga *et al*., 1977; Bull & Bulmer, 1981; Bulmer, 1988). In this species, a variant X chromosome (X*) is present in both wild populations and laboratory stocks, which causes X*Y individuals to develop as males; XY animals develop as normal males. The sex-ratio bias this causes is exaggerated by the preferential inclusion of X* in eggs produced by X*Y females, the result being that populations can have sex ratios of as low as 0.2. The history of this animal's novel sex determining strategy can be run in at least two ways.

First, an X-chromosome mutation appeared (X*) which turned X*Y carriers into females. These females produced both X* and Y eggs, but with a presumed numerical dominance of the first type (in accordance with X0 female mice which produce more eggs with the X than without it) (Kaufman, 1972; Luthardt, 1976; Deckers *et al*., 1981; Sakurada *et al*., 1994; but see also Brook, 1983). This created a genetic conflict to which many responses were possible. If a Y-chromosome mutation had evolved which switched off the female inducing effect, then it would have spread and the population would have evolved back to the standard XX/XY sex determination system. An autosomal gene that similarly suppressed the feminization effect of the X* chromosome would also have spread. The actual evolutionary route taken (at least in this model of history) was, however, another one. Since the X*Y females produced a fraction of Y* carrying eggs, they must have had a lower fecundity than other females (due to their production of inviable YY embryos) so a system evolved (caused by genes at the autosomes or the X*) that changed X*Y female meiosis so that they now produce exclusively X*-carrying eggs. Thus, the loss of fecundity was remedied, but the sex chromosome segregation distortion was increased, with the consequence of creating an even greater female bias. The modifier has thus perfected segregation distortion rather than suppressed it.

The alternative history to the one described above proposes that the original mutation may have been a driving Y-chromosome. As this spread so the population became increasingly male-biased. A novel X that forces the progeny to be female regardless of whether it is associated with a Y or not will invade as it goes some way to restoring the sex ratio. Selection could then favour those X*Y females that produced only X* eggs and hence avoided the production of YY embryos.

What conclusions does this lead us to about the evolution of sex determination mechanisms in general? First, one must reiterate the problem; that major changes in pathways leading to the production of differentiated sexes are most likely to be deleterious, yet there are several instances of highly

unusual systems, even within mammals. It is possible that these changes could simply be due to the spread of favourable, adaptive mutations, but, we would argue, it does not have to be the case. The sex-ratio bias resulting from the spread of sex-related selfish genetic elements presents such drastic conditions that almost any mechanism which can reduce costs will spread. Two alternative solutions to this dilemma are available; either the driving phenotype must be suppressed [a route that appears to have been taken by populations of *D. melanogaster* with the SR X-chromosome distorter (Lyttle, 1981) and also *Silene alba* (Taylor, 1994)], or an alternative means of sex determination must be found (as we suspect in the cases of *Myopus*, *Talpa* and *Armadillidium*). Which option is taken in any given situation depends entirely on what alternatives are available, thus the outcome of such a crisis is impossible to predict, and may well lead to unexpected ends. To ask why a sex determination mechanism works in the way it does may not then be a question of why this is adaptive for this organism, but a question of what its genetic history is. If selfish genetic elements have been important, then there is no necessary logical progression to the current state (unlike with the evolution of obviously adaptive elements such as morphology) and several different routes are possible from the same starting point. This is important not only because it can solve the problem of how major changes can occur, but also because it illustrates the potential power of selfish genetic elements to create a variety of novel genetic situations. Though the cases discussed above have all been resolved in a particular way, other populations, in similar situations, may evolve in completely different directions.

An illustration of the variety of solutions that can occur in response to selfish genetic elements is the demonstration by Lyttle (1981) that populations of *D. melanogaster* subject to pseudo sex-chromosome drive (SD genes attached to Y-chromosome) can evolve in two different directions. The majority responded by evolving X-linked suppressors of the drive, however, in one population the sex ratio distortion was effectively neutralized by the accumulation of sex chromosome aneuploids (XXY females and XYY males). The primary sex determining switch of X:A ratio is maintained, however, as all individuals now carry a Y-chromosome, the drive can spread through to fixation without an effect on the sex ratio. Neither solution is completely reproductively compatible with populations lacking the driving chromosome, thus the evolution of sex determination mechanisms in response to selfish genetic elements not only produces novel systems, but can also act to genetically isolate potentially interbreeding populations.

If selfish elements do underlie much of the evolution of novel sex determining strategies, we might then ask whether certain sex determining strategies are more likely to change than others. It has, for instance, been claimed that XY sex determination may be thought of as an evolutionary black hole out of which no alternative emerges (Bull & Charnov, 1988). If this is so (this being an empirical issue) then it is perhaps paradoxical, as sex chromosomes are in general vulnerable to being parasitized by selfish genetic elements. In general, the absence of recombination between X and Y leaves these chromosomes vulnerable to parasitism by two-locus segregation distorters (Hamilton, 1967; Frank, 1991; Hurst & Pomiankowski, 1991). All distortion loci investigated so far involve gene complexes, with co-segregation of the driving and insensitive responder alleles, thus close genetic linkage of loci is required. Heteromorphic sex chromosomes which lack recombination thus present broad conditions for the invasion of distortion systems as there is no necessity for close physical linkage between driver and responder loci.

In mammals, lack of recombination between sex chromosomes, coupled with the patrilineal inheritance of the Y-chromosome, makes the region carrying the male sex determining gene particularly vulnerable to genes exerting selfish growth effects (Hurst, 1994). Mammalian embryos receive all nutrition from the mother until parturition (except indirectly from paternal feeding of mother), thus in breeding systems where there is a degree of uncertainty of paternity (both within and between broods), mutant paternally-derived genes demanding more resources from the mother than wild-type sibs will spread. This is one possible explanation of the phenomenon of genomic imprinting in mammals and angiosperms (Moore & Haig, 1991) with the corollary that the Y-chromosome is a potential attractor for selfish growth factors (Hurst, 1994). The Y-chromosome can then act as a haven for any selfish gene that exerts a male-specific fitness effect, such as the reallocation of resources from, or the induction of sterility in, female sibs.

If sex determining pathways evolve through bouts of suppression of selfish elements then these pathways may also be expected to end up as a series of dosage mediated suppression events. Although the male mammalian sex determination gene *Sry* has been discovered in all species investigated so far, including marsupials (Foster *et al*., 1992; Gubbay *et al*., 1992), it is not the only gene involved in the

sex determination pathway. The short arm of the mouse X-chromosome contains a dosage sensitive suppressor of *Sry* function, DSS (Bardoni *et al*., 1994 and references therein), and a variety of dosage dependent autosomal loci (including that for campomelic dysplasia in humans, *Sox*-9) have been implicated in *Sry*-independent sex reversal (Tommerup *et al*., 1993; Biddle *et al*., 1994; Foster *et al*., 1994). This suggests that while there may now be a single underlying mechanism of sex determination in the majority of mammals, its evolutionary history is highly complicated and there is potential for change. Cases of sex reversal in mouse hybrids (Eicher *et al*., 1982; Coward *et al*., 1994), instances of population wide sex determination perturbations such as seen in *Talpa* (Harrison Matthews, 1935; Jiménez *et al*., 1988, 1993) and the frequent occurrence of unusual sex chromosome inheritance in mammals (Fredga, 1970) all suggest that sex determination mechanisms in mammals are far from the centre of an evolutionary black hole.

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APPENDIX A

Simulation of a Population with a Y-Linked Selfish Genetic Element and X-Linked Modifier

Suppose an X-linked modifier (X^m) arises such that it converts the sterile, masculinized XX intersexes into fertile intersexes with follicle producing ovotestes. Assume that in every brood there is exactly one male and one female, both fathered by the same male, and that if a brood male has a Y* chromosome (sterilizing mutant) then a wild-type female sib will be completely sterilized. A single copy of the modifier completely rescues the sterile phenotype, however there is a cost attached, which is U in the homozygous condition and hU in heterozygotes. D is the gain in fitness for males carrying Y* and S is the cost of possessing this gene. If the frequencies of the female genotypes XX, XX^m and X^mX^m are f_1, f_2, and f_3 respectively, and the frequencies of the male genotypes XY, X^mY, XY* and X^mY^* are m_1, m_2, m_3, and m_4 respectively, then the proportions of genotypes in the next generation can be calculated from the mating combinations presented in Table A1. This gives the following recursion equations:

$$f_1' = \{\tfrac{1}{2}(f_1 + \tfrac{1}{2}f_2)m_1\}/\bar{W}_f \quad \text{(A.1)}$$

$$f_2' = \{\tfrac{1}{2}(1 - hU)[f_1(m_2 + m_4) + \tfrac{1}{2}f_2(m_1 + m_2 + m_3 + m_4) + f_3(m_1 + m_3)]\}/\bar{W}_f \quad \text{(A.2)}$$

$$f_3' = \{\tfrac{1}{2}(1 - U)(f_3 + \tfrac{1}{2}f_2)[m_2 + m_4]\}/\bar{W}_f \quad \text{(A.3)}$$

TABLE A1

Proportions of genotypes produced by possible mating combinations

Genotype fitness	XX 1	X^mX $1-hU$	X^mX^m $(1-U)$	$(XX)'$ 0	XY 1	X^mY $1-hU$	XY* $(1-S)(1+D)$	X^mY^* $(1-S)(1-hU)$ $(1+D)$	$(XY^*)^o$ $1-S$	$(X^mY^*)^o$ $(1-S)(1-hU)$
Mating										
XX × XY	1/2				1/2					
XX × X^mY		1/2			1/2					
XX × XY*				1/2			1/2			
XX × X^mY		1/2							1/2	
XX^m × XY	1/4	1/4			1/4	1/4				
XX^m × X^mY		1/4	1/4		1/4	1/4				
XX^m × XY*		1/4		1/4			1/8	1/8	1/8	1/8
XX^m × X^mY^*		1/4	1/4						1/4	1/4
X^mX^m × XY		1/2			1/2					
X^mX^m × X^mY			1/2			1/2				
X^mX^m × XY*		1/2								1/2
X^mX^m × X^mY^*			1/2							1/2

Y* is a mutant Y-chromosome that sterilizes female sibs, X^m is an X-linked modifier that can restore female fertility. In each brood there is exactly one female and one male, both sired by the same father. $(XX)'$ refers to sterile XX intersexes, fertile wild-type females are indicated by XX. $(XY^*)^o$ and $(X^mY^*)^o$ refer to males carrying the mutant Y-chromosome but which do not receive a fitness benefit as their female sib carries the modifier.

$$m_1' = \{\tfrac{1}{2}(f_1 + \tfrac{1}{2}f_2)[m_1 + m_2]\}/\bar{W}_m \quad (A.4)$$

$$m_2' = \{\tfrac{1}{2}(1 - Uh)(f_3 + \tfrac{1}{2}f_2)[m_1 + m_2]\}/\bar{W}_m \quad (A.5)$$

$$m_3' = \{\tfrac{1}{2}(1 - S)[m_3(f_1 + \tfrac{1}{4}f_2) + (1 + D) + f_1 m_4 + \tfrac{1}{2}f_2(\tfrac{1}{2}m_3 + m_4)]\}/\bar{W}_m \quad (A.6)$$

$$m_4' = \{\tfrac{1}{4}(1 - S)(1 - hU)[f_2(\tfrac{1}{2}m_3 + m_4) + 2f_3(m_3 + m_4) + \tfrac{1}{2}f_2 m_3(1 + D)]\}/\bar{W}_m. \quad (A.7)$$

Where;

$$\bar{W}_f = \sum_i w_i f_i \text{ and } \bar{W}_m = \sum_j w_j m_j \quad (A.8)$$

The conditions for invasion of X^m can be calculated by letting the initial frequency of the modifier be equal in both sexes, i.e. in females $f_1 = 1 - r$, $f_2 = r$, and $f_3 = 0$, and in males $m_2 = m_4 = r/2$, $m_1 = 1 - p - r$, and $m_3 = p$. The frequency of X^m in the next generation is:

$$\tfrac{2}{3}(f_3' + \tfrac{1}{2}f_2') + \tfrac{1}{3}(m_2' + m_4') = X^{m'},$$

For invasion of X^m, $\delta X^{m'}/\delta r > 1$ at $r = 0$.

From which it can be found that,

$$hU < \frac{p^2[11D(1-S) - 10S] - p[5D(1-S) - 4s - 10] - 4}{p[7D(1-S) - 8S - 2] - p^2[D(1-S) - 2S] + 8}. \quad (A.9)$$

Which, when D and S are small, approximates to,

$$hU > \frac{5p - 2}{4 - p}. \quad (A.10)$$

The different sex-linked fitness effects of the X-linked modifier create the conditions for sex-related linkage disequilibrium, thus an analytical solution to final equilibria becomes impossible and the system has to be investigated by means of computer simulations. The results of these are discussed in the text. Substituting an autosomal location for the modifier simply has the effect of slowing down the spread of the gene as it will spend a half, rather than a third, of its time in males where it has no fitness benefits.

APPENDIX B

Analysis of X-Linked Meiotic Drive Gene with Autosomal Modifier

X-LINKED OOGENIC MEIOTIC DRIVE

Suppose that an X-linked mutant (X^d) arises which causes X^d over X meiotic drive during oogenesis and is inactive in males. Following the method of Wright (1969) this system can be written as:

	Zygotic frequency	Fitness
Females		
XX	$(1 - q_f)(1 - q_m)$	1
XX^d	$(1 - q_f)q_m$	$1 - hs$
X^dX	$q_f(1 - q_m)(1 + k)$	$1 - hs$
X^dX^d	$q_f q_m(1 + k)$	$1 - s$
Males		
X	$1 - q_f$	1
X^d	$q_f(1 + k)$	$1 - hs$

Where q_f is the frequency of X^d in females, q_m is the frequency in males and k is the degree of meiotic drive (with 1 being complete drive and 0 being Mendelian segregation). There is a cost to the driver which is s in homozygotes and hs in heterozygotes. From this it follows that the average fitnesses of males and females are, respectively;

$$\bar{W}_f = 1 + q_f[k(1-hs) - hs] + q_m[q_f s[h(2+k) - (k+1)] - hs] \quad \text{(B.1)}$$

and

$$W_m = 1 - q_f[hs(1+k) - k]. \quad \text{(B.2)}$$

If it is assumed that $h = 0$, then these simplify to;

$$\bar{W}_f = 1 + q_f[k - q_m s(k+1)] \quad \text{and} \quad \bar{W}_m = 1 + q_f k \quad \text{(B.3)}$$

The frequency of X^d in females and males in the next generation then becomes;

$$q_{f(o)} = \left[\tfrac{1}{2} q_m(1-q_f) + q_f(1+k)(1-q_m) + q_m q_f(1+k)(1-s)\right] \Big/ \bar{W}_f \quad \text{(B.4)}$$

$$q_{m(o)} = q_f(1+k)/\bar{W}_m \quad \text{(B.5)}$$

At equilibrium, $q_{m(o)} = q_m = \hat{q}_m$, thus;

$$\hat{q}_m = \frac{\hat{q}_f(1+k)}{1+\hat{q}_f k} \quad \text{(B.6)}$$

The change in frequency of X^d per generation in females can be written as,

$$\Delta q_f = q_{f(o)} - q_f \quad \text{(B.7)}$$

By substituting the above value of $\hat{q}_m$ (from B.8) into eqn (B.9), and putting $\Delta q_f = 0$ at $\hat{q}_f$, the equation for the solution of $\hat{q}_f$ becomes;

$$\hat{q}_f^2[(1+k)^2 s - k^2] + \hat{q}_f[(1+k)^2 s - k^2 + k] + k. \quad \text{(B.8)}$$

This is in the form $ax^2 - (a+b)x + b = 0$; the solutions of which are $x = 1$ and $x = b/a$. Thus the equilibrium values of $\hat{q}_f$ are;

$$\hat{q}_f = 0, 1 \quad \text{and} \quad \frac{k}{(1+k)^2 s - k^2} \quad \text{(B.9)}$$

Thus, there is an internal equilibrium where both alleles are present, X and X^d. It can be shown that for the internal equilibrium to be stable,

$$s > \frac{k}{1+k} \quad \text{(B.10)}$$

It follows that for there to be an equilibrium $\hat{q}_f < 1$, $s > k/1+k$. Thus if there is an internal equilibrium, it is stable.

INVASION CONDITIONS

Without a cost to the heterozygote XX^d or XY^d, the conditions for invasion are trivially $k > 0$. If the costs described above are implemented then it can be shown that at

$$q_f = 0, \frac{dq_{f(o)}}{dq_f} > 1 \quad \text{if} \quad k > \frac{hs(3+hs)}{2 - hs(3-hs)}, \quad \text{and,} \quad \text{as } k \leqslant 1, hs \leqslant \tfrac{1}{3} \quad \text{(B.11)}$$

If a similar anaylsis to that above is carried out for the situation with a heterozygote cost, then the internal equilibrium frequency becomes

$$\hat{q}_f = \frac{k - \frac{1}{2} hs(1+k)(3-hs)}{(1+k)^2 s - k^2 - hs[s(1+k) \times (1+k-h) + k(1-k) + 2]} \quad \text{(B.12)}$$

ANALYSIS OF AUTOSOMAL MODIFIER

Throughout this analysis it shall be assumed that there is no cost to the heterozygote and homozygote sterility is complete. A single copy of the autosomal modifier A^m is sufficient to rescue the phenotype of X^dX^d females to complete fertility, however, there is a cost associated with the modifier which is the multiplier $1 - U$ in the heterozygous condition and $(1-U)^2$ in homozygotes. A table similar to that above can be constructed to work out zygotic frequencies in which it is assumed that the modifier is in complete linkage equilibrium.

From this it follows that;

$$\bar{W}_f = (1+q_f k)(1-rU)^2 - q_m q_f s(1+k)(1-r)^2$$

$$\bar{W}_m = (1+q_f k)(1-rU)^2$$

$$\bar{W}_t = 2(1+q_f k)(1-rU)^2 - q_m q_f s(1+k)(1-r)^2$$

$$W_{x^d f} = q_m[\tfrac{1}{2}(1+q_f k)(1-rU)^2 - q_f s(1+k)(1-r)^2] \times \frac{q_f(1+k)(1-r)^2}{2}$$

$$W_{x^d m} = q_f(1+k)(1-rU)2$$

$$W_{A^m} = 2r(1+q_f k)(1-U)(1-rU). \quad \text{(B.13)}$$

Where r is the frequency of the modifier (A^m), $W_{x^d m}$ is the total fitness of X^d in males and $W_{x^d f}$ is that in females. The frequencies in successive generations

can then be found from the following recursion equations;

$$q_{f(o)} = \frac{W_{x^{df}}}{\bar{W}_f},\ q_{m(o)} = \frac{W_{x^{dm}}}{\bar{W}_m} \quad \text{and} \quad r_{(o)} = \frac{W_r}{\bar{W}_t}. \quad \text{(B.14)}$$

INVASION CONDITIONS

The condition for invasion of A^m is;

$$U < \frac{q_m q_f s(1+k)}{2(1+q_f k)} \quad \text{(B.15)}$$

which, at the equilibria $\hat{q}_f > 0$, gives

$$\text{at } \hat{q}_f = 1,\ U < \frac{s}{2},\ \text{and}$$

$$\text{at } \hat{q}_f = \frac{k}{(1+k)^2 s - k^2},\ u < \frac{k^2}{2s(1+k)^2}. \quad \text{(B.16)}$$

Thus the conditions for invasion of the modifier are quite broad.

EQUILIBRIA

It can also be shown, that if U is small enough to permit invasion of A^m, then it will allow the fixation of X^d. The equilibrium frequency of the modifier is;

$$\hat{r} = \frac{s(1+k) - 2U}{s(1+k) - 2U^2}. \quad \text{(B.17)}$$

The third model proposes that there is a Y-linked meiotic drive and X-linked suppressor of meiotic drive which creates sterile female intersexuality in the homozygous condition. An autosomal modifier then invades which rescues the homozygote phenotype. The population genetics of this system will give a result similar to that described above for the oogenic X-linked drive, however, as this is the least likely scenario, no detailed analysis is presented here.