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GENETIC CONFLICTS

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ABSTRACT

Self-promoting elements (also called ultraselfish genes, selfish genes, or selfish genetic elements) are vertically transmitted genetic entities that manipulate their "host" so as to promote their own spread, usually at a cost to other genes within the genome. Examples of such elements include meiotic drive genes and cytoplasmic sex ratio distorters. The spread of a self-promoting element creates the context for the spread of a suppressor acting within the same genome. We may thus say that a genetic conflict exists between different components of the same genome. Here we investigate the properties of such conflicts. First we consider the potential diversity of genomic conflicts and show that every genetic system has potential conflicts. This is followed by analysis of the logic of conflicts. Just as Evolutionarily Stable Strategy (ESS) terminology provides a short cut for discussion of much in behavioral ecology, so the language of modifier analysis provides a useful terminology on which to base discussions of conflicts.

After defining genetic conflict, we provide a general analysis of the conflicting parties, and note a distinction between competing and conflicting genes. We then provide a taxonomy of possible short- and long-term outcomes of conflicts, noting that potential conflict in an unconstrained system can never be removed, and that the course of evolution owing to conflict is often unpredictable. The latter is most particularly true for strong conflicts in which suppressors may take surprising forms. The possibility of extended conflicts in the form of "arms races" between element and suppressor is illustrated. The peculiar redundancy of these systems is one possible trace of conflict,

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and others are discussed. That homologous conflicts may find highly different expression is discussed by referring to the mechanistic differences that are thought to underlie the action of the two best-described meiotic drive genes, and by the multiplicity of forms of cytoplasmic sex ratio distorters.

The theoretical analysis establishes a logical basis for thinking about conflicts, but fails to establish the importance of conflict in evolution. We illustrate this contentious issue through consideration of some phenomena for whose evolution conflict has been proposed as an important force: the evolution of sex, sex determination, species, recombination, and uniparental inheritance of cytoplasmic genes. In general, it is proposed that conflict may be a central force in the evolution of genetic systems. We conclude that an analysis of conflict and its general importance in evolution is greatly aided by application of the concept of genetic power. We consider the possible components of genetic power and ask whether and how power evolves.

INTRODUCTION

IN THE SOCIAL SCIENCES it is common to distinguish between two competing theoretical traditions. One tradition concentrates on the *function* of different social institutions, while the other prefers to view society as an arena for social *conflicts*. The phenomena studied, the terminology used, and the conclusions reached from the results obtained are widely different, depending on the perspective chosen. The American sociologist, Talcott Parsons, can be seen as a typical representative of the functionalist tradition, while Karl Marx stands as the arch-proponent of the conflict view of society.

In biology, the functionalist view is intuitively satisfying and it dominated our science well into the nineteenth century; it is, for example, strongly expressed in the ecological writings of Linnaeus. The break with the old perspective and the introduction of a distinctly conflict-based view of Nature came, of course, with the publication of *The Origin of Species* in 1859. According to Darwin, the impressive examples of biological functions, noted and commented upon by earlier observers, can only be satisfyingly understood if they are seen as the outcomes of conflicts among organisms.

This idea of conflicts among organisms has become so widely accepted since Darwin's time that today the word "conflict" is only rarely perceived as being anything other than a purely descriptive term in population biology. The concept is much more rarely used, however, in other areas of biology. For instance, intracellular relationships are normally described from an explicitly functional perspective. This applies, for example, to the relationship between mitochondria and the surrounding cell, which generally is regarded as a well-functioning symbiosis. But that the relationship can be regarded quite differently—as an uneasy balance between conflicting interests—is an idea we will return to later in this review.

Darwin's realization that "gemmules," what he thought was the heritable material, could compete for transmission (Darwin 1899), was perhaps the earliest understanding that everything *within* cells and organisms need not be for the common good. As the science of genetics developed, the same realization occurred several more times independently. One of the earliest critiques was formulated by the cytogeneticist Gunnar Östergren in 1945. He was interested in the supernumerary chromosomes that some plants carry, generally called B chromosomes (Östergren 1945). In discussing the maintenance of these B chromosomes in populations, Östergren reflected on the wisdom of the day (notably that of Darlington), which presumed that since they were maintained in equilibrium in the population, they must be beneficial.

Östergren, however, clearly understood that this need not be so, and probably was not so. B chromosomes, he notes, are generally associated with mechanisms by which they become over-represented in the gametic output of carrier plants. Individual plants with many B chromosome copies are at the same time only rarely found; Östergren concludes that this implies that they must be associated with some fitness disadvantage. Östergren proposed that they should be regarded as "parasitic chromosomes," and he summed up his position by stating thus:

> I agree with Darlington and Thomas that the existence of fragments in equilibrium shows that they have a use. But it is not nec-

> essary that they are useful to the plants. They need only be "useful" to themselves (p 163).

In presenting this argument Östergren provided one of the first clear enunciations of the gene's-eye view of evolution (also see Fisher 1930; Haldane 1932; Lewis 1941). He also provided the first understanding of what now are often called selfish genetic elements (of which the B chromosomes, assuming them to be deleterious, are but one example). Other names that have been used are selfish DNA, ultraselfish genes, genetic outlaws, and renegades (Dawkins 1976; Alexander and Borgia 1978; Doolittle and Sapienza 1980; Orgel and Crick 1980; Crow 1988; Werren et al. 1988). To avoid strongly value-laden words, we will use the term self-promoting (genetic) elements for these heritable units that act in a manner "useful" for themselves (i.e., competent to permit the invasion of the mutant when rare), but one that is not advantageous for other genes in the host.

Implicit in Östergren's statement is the understanding that a conflict can exist between different genetic entities: What is "useful" for one gene can be disadvantageous for another gene in a different linkage group in the same cell. It follows that any genetic system with potentially more than one linkage group (i.e., every genetic system) is at least potentially vulnerable to invasion by self-promoting elements. This article discusses the importance of this potential and its realization.

Although Östergren's paper was a very clear enunciation of the principles concerned, it did not attract much serious attention, nor did it address the possible impact of self-promoting elements on evolutionary change. Perhaps the first person to achieve this was Hamilton in his 1967 paper on sex ratio evolution; he considered the fate of various self-promoting sex ratio distorters, and conjectured that these factors might account for the inactivity of the Y chromosome, a conjecture not taken serious in all quarters (see Charlesworth 1991). Since then, the formal mathematical genetics of self-promoting elements has attracted considerable attention (see Prout et al. 1973; Thompson and Feldman 1975; Liberman 1976; Thompson and Feldman 1976; Charlesworth and Hartl 1978; Fine 1978; Uyenoyama and Feldman 1978; Charlesworth and Ganders 1979; Frank 1983; Eshel 1985; Werren 1987; Frank 1989; Bengtsson and Uyenoyama 1990; Crow 1991; Feldman and Otto 1991; Hurst and Pomiankowski 1991a), and many selfish elements have been extensively described (see Jones and Rees 1982; Werren et al. 1988; Lyttle et al. 1991; Saumitou-Laprade et al. 1994).

The idea that selfish elements may be an important evolutionary force has thus been around for a considerable time (also see Sandler and Novitski 1957). In the late 1970s and early 1980s, however, the idea was very much brought into focus, and to a large extent the domain of phenomena which might be the result of conflicts was greatly expanded (Alexander and Borgia 1978; Eberhard 1980; Cosmides and Tooby 1981; Hickey 1982; Birky 1983; Leigh 1983; Rose 1983). These latter authors considered the possibility that conflicts might explain major phenomena as wide ranging as anisogamy, dioecy and sexual reproduction.

More recently, with the upsurge in knowledge of the detailed workings of genetic systems, there has been a considerable bloom of interest, and genetic conflicts are increasingly coming to be seen as important in such areas as major evolutionary transitions (Maynard Smith and Szathmáry 1995; Szathmáry and Maynard Smith 1995) and in the turnover of genetic systems (Hurst 1995b).

Our aim here is to use examples, population genetic reasoning, and speculative suggestions to clarify and enrich the discussion of genetic conflicts. We start by describing the sorts of actions of self-promoting genetic elements that enable their over-representation. This section is not intended to be exhaustive, but rather to give a flavor of the underlying biology that may otherwise seem rather abstract.

The second section is devoted to providing a definition and general analysis of genetic conflicts. We discuss the terminology and population genetics of conflicts before considering some of the properties by which genetic conflicts can be classified. This part ends with a discussion of the dynamics of repeated conflicts, giving special attention to the possibility of a continued arms race. In the third section we illustrate how very similar conflicts can find very different modes of expression.

The fourth and final section is more speculative, focusing on the role genetic conflicts play in evolution at large. It is here that readers in the social sciences might perhaps find strongest resonance between the discourse within their field and that within evolutionary biology. The conflict perspective, as taken by Marx, for example, is never an exclusively negative viewpoint. Marx views the conflict between classes as a great dynamic force that—among all its implicit and explicit violence—leads to wide-range societal changes and, sometimes, improvements. Can an analogy be drawn to genetic conflicts? Do they play a crucial role in the generation of major evolutionary novelties, and in speciation, genome structuration, inheritance rules, and sex determination? We conclude with a discussion of the nature of evolutionary power and why genomes appear to be "well-behaved" most of the time, when there are good reasons to suppose that the contrary would be true.

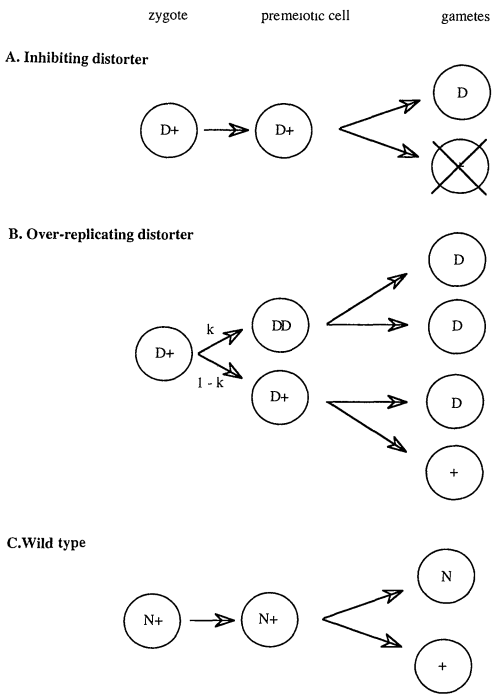


FIGURE 1. PREZYGOTIC SEGREGATION DISTORTION

Key: D = a driving gene, + = wild type (nondriving), and N = any other nondriving allele. It is assumed that all factors are located on nuclear chromosomes (and hence diploid), but this need not be so. D either inhibits the products of meiosis that do not contain it (type A) or over-replicates by some means prior to meiosis (type B). The former is often referred to as meiotic drive, but this term is also applied to type B events as well, particularly if the premeiotic over-replication involves a whole chromosome rather than a gene. Biased gene conversion is an example of type B that does not involve chromosomal distortion.

Advantage to distorter: increase in frequency owing to the higher number of zygotic progeny bearing driver than would be the case were driver not active.

Condition: viability/fertility D/+ heterozygous bearer must not be so low as to reduce the advantage gained by an increased number of carriers in the progeny. For this to occur under type A distortion there must be competition between haploid products of meiosis from a given individual.

Disadvantage for unlinked genes: reduced gamete production (type A). Overproduction of more common sex if D is sex-linked and involves chromosome distortion; possibly also a disadvantage possession of the self-promoting agent in heterozygous or homozygous condition.

Modifiers: suppressors of type A shown where fertility is reduced and where DD individuals are of reduced fertility/viability. Suppressors of sex chromosome drivers (type A) are also described. Enhancers of drive tightly linked to driving genes have been found.

Taxonomic distribution: type A: meiotic drive in mice, on chromosomes 17 (Silver 1993) and 1 (Agulnik et al. 1993), Drosophilids, both autosomal (Lyttle 1993) and sex-linked (Gershenson 1928; Sturtevant and Dobzhansky 1936; Faulhaber 1967; Miller 1971; Voelker 1972; Hauschteck-jungen and Maurer 1976; Wu and Beckenbach 1983; Curtsinger 1984; De Carvalho et al. 1989; James and Jaenike 1990), mosquitoes (sex-linked) (Wood and Newton 1977; Sweeney and Barr 1978; Sweeny et al. 1987; Wood and Ouda 1987), ascomycete fungi (Raju 1994), wheat and numerous other suspected examples in insects such as lepidopterans (Owen 1970; Scali and Masetti 1973; Smith 1975; Majerus 1981), angiosperms (Taylor 1994a) and mammals, e.g., lemmings (sex-linked) (Gropp et al. 1976; Gileva 1987). Some examples of B chromosomes and biased gene conversion are type B.

References: meiotic drive reviewed in Silver (1993), Ruvinsky (1995), and Lyttle (1991, 1993). One issue of *American Naturalist* is devoted to the subject (Lyttle et al. 1991). For biased gene conversion see Lamb (1984), and for B chromosomes see Jones and Rees (1982), Beukeboom (1994), and Shaw and Hewitt (1990).

THE DIVERSITY OF CONFLICTS

Self-promoting elements spread not because they increase the fitness of their carriers, but because their activity ensures that they are over-represented in the next generation. In principle, the spread of self-promoting elements is to a large extent fundamentally different from the selection that crafted the beaks of Darwin's finches, for example. In this latter case, the spread of the trait was due to the increased viability or fertility of the bearer of a novel variation of the trait.

The action allowing over-representation can occur at any time during the life cycle. Certain times in the life cycle are more vulnerable than others, however. Meiosis is probably the most vulnerable time, since it is at this point that the alliance set up between maternally and paternally derived nuclear genes breaks up. Many B chromosomes, for instance, manipulate meiosis in such a way that they become over-represented in the gametic cells produced (Figure 1) (Jones and Rees 1982; Shaw and Hewitt 1990). The mechanism for over-representation may also act at an earlier stage in the germ line, however. This is the case for some other types of B chromosomes, which gain their advantage in one or more of the premeiotic mitoses.

Nuclear genes on chromosomes cannot normally be over-represented as a consequence of strategies similar to those described above, because typically they obey the rules of mitosis and meiosis; if they do not the consequences are often heavily deleterious. Still, they can become over-represented in the offspring of a heterozygous individual by a number of different mechanisms. One of them is by biased gene conversion (Lamb 1984). In this process a copy of a particular small segment of DNA replaces the allele on the homologous chromosome more often than the reverse process occurs. Homing (allelic insertion of a sequence) and transposition (nonallelic insertion) are closely related processes.

A second such mechanism is when a gene spreads by inhibiting gametes carrying its allelic alternative, and by so doing increases its own frequency among the gametes (Figure 1). This is the tactic employed by the well-described meiotic drive genes, *Segregation distorter* on chromosome 2 of *Drosophila melanogaster*, and the *t* complex on chromosome 17 in mice (Lyttle 1991, 1993; Silver 1993). In these two cases, not only may heterozygotes suffer some fertility reduction, but individuals homozygous for the distorter also have a strong reduction in fertility or sterility. Despite these negative effects the distorters spread, and hence are in conflict with the interest of the rest of the host genome.

A chromosomal *Segregation distorter* on a sex chromosome will be a sex ratio distorter. A driver on the X (or Y) chromosome will result in an excess of females (or males). Such sex ratio distorters have been observed in numerous species (such as drosophilids, mosquitoes, mammals, and angiosperms), and several incidences are suspected in butterflies and moths (see Figure 1). Through their action on the sex ratio, sex-chromosome drivers will normally come into conflict with the autosomally inherited genes, which—with the logic pointed out by Fisher (1930)—in most situations favor a 1:1 segregation of the sexes.

The potential for conflict has not stopped after zygote formation: For instance, by means of a maternal effect, a gene can also spread by manipulating the frequency with which it is found among the offspring of heterozygous females. As with meiotic drive, this may be achieved by eliminating competitors—in this case the offspring that lack the self-promoting element. This elimination of competing offspring comes about during embryogenesis (Figure 2). The result is that half of the progeny are lost when a female heterozygous for the distorter mates with a male homozygous for the nondistorting allele. This process is of course highly deleterious for those genes not linked with the distorter. It is this high rate of offspring mortality that has led to the detection of the two known examples of such self-promoting elements. The first, recently found in the beetle *Tribolium castaneum* (Beeman et al. 1992), has been appropriately named *Medea* (she who killed her offspring). The second, in mice, is responsible for the heritable disease, Severe combined anemia and thrombocytopenia (Scat) (Hurst 1993c; Peters and Barker 1993).

As Trivers (1974) notes, parents and their progeny do not necessarily share precisely the same interests and are potentially in conflict

over, for example, the amount of resources any given progeny should receive. The maternal optimal allocation to a given offspring is typically lower than the optimum when envisaged from the offspring's point of view. The intimacy of contact between the mammalian mother and its young provides for the possibility not only of maternal manipulation of the young, but also of fetal manipulation of the mother and even possibly of other fetuses (Haig 1993d).

These interactions may be the source of still newer types of conflicts. In particular, paternally and maternally transmitted genes within an embryo are under contradictory selective pressures: Paternal genes, unrelated as they are to the mother, should be selected to maximize the embryo's chance of survival by obtaining the greatest amount of resources that does not endanger the survival of the mother (Haig and Westoby 1989; Moore and Haig 1991; Haig 1992a). Maternal genes, by contrast, should be selected to avoid any severe reduction in her future chance of reproduction, and should hence favor a lesser degree of resource transfer to the embryo. This logic has been invoked to explain the expression pattern of imprinted genes, i.e., genes that change their pattern of expression depending on whether they are maternally or paternally inherited (for a discussion of alternative theories of imprinting, see Hurst 1996).

In the best studied case, that of the mouse Insulin-like growth factor (IGF-II) with its two receptors (Haig and Graham 1991), paternally derived genes act to extract more resources from the mother, while maternally derived genes act to suppress the effect of the paternally derived genes (see Figure 3). A similar logic has been proposed as the reason for the presence of growth factors on the mammalian Y chromosome (Hurst 1994c) and for the existence of suppressors of Y-linked genes on the X chromosome (Hurst 1994b).

All genetic systems in which some genes are transmitted at a higher rate through one sex than the other will always provide potentials for conflict. Cytoplasmic genes, for instance,

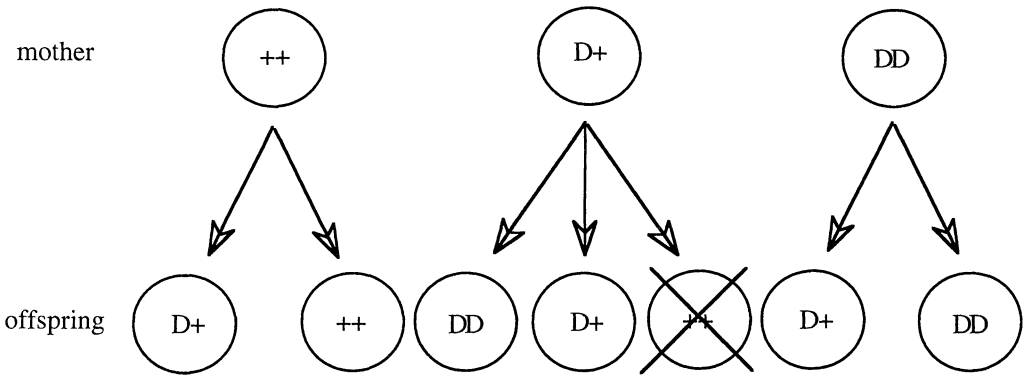


FIGURE 2. POSTZYGOTIC DISTORTION: MATERNAL-EFFECT LETHALS

Key: D = maternal-effect lethal distorter gene. By some means D, when in a female, kills progeny not containing D. The D gene, when derived from the father, is adequate to prevent mortality.

Advantage to D: increase in frequency owing to the decrease in number of progeny lacking it.

Condition: competition among progeny and/or small population size. Competition among progeny will ensure higher fitness of D-bearing offspring of D+ mothers when ++ die.

Disadvantage for unlinked genes: death of ++ progeny in D+ mothers.

Modifiers: there are no good examples. Spread to high frequency is possibly so rapid that modifiers do not have time to invade. At high frequency there is very little excess mortality, since mortality requires that mothers are heterozygous and that fathers lack D.

Taxonomic distribution: two well-described cases: *Medea* in *Tribolium*, and *scat*$^{+}$ in mice. Possibly quite common in eutherian mammals owing to intimacy of maternal/fetal interactions.

References: for *Medea* see Beeman et al. (1992); for *Scat* see Peters and Barker (1993) and Hurst (1993c).

typically do not gain much transmission through males, which implies that cytoplasmically inherited factors changing the common sex-determination system and/or transmission system may spread readily (Cosmides and Tooby 1981). Many of the self-promoting cytoplasmic elements act to bias the sex ratio, either by feminizing males (Figure 4), killing males (Figure 5), or sterilizing male tissue in hermaphrodites (Figure 6). Male-transmitted elements that convert daughters into sons have also been described (Werren et al. 1987). As for sex chromosome-linked sex ratio distorters, the spread of all such uniparentally transmitted sex ratio distorters is expected to set the stage for a secondary process of sex ratio evolution through the process of suppression of sex ratio distorters by nuclear genes.

Cytoplasmic agents can be over-represented without changing the sex ratio. This occurs, for instance, via sterilizing crosses with females without the self-promoting factor; so-called cytoplasmic incompatibility (Figure 7). A phenomenon resembling cytoplasmic incompatibility has been found in ciliates (Figure 8): A cytoplasmic factor in one mate acts to kill the partner after conjugation, but only if the partner is lacking the cytoplasmic factor (Beale and Jurand 1966). In both cytoplasmic incompatibility and ciliate mate killers, the self-promoting element may be regarded as "spiteful." Its increase in frequency is in large part owing to the alternative cytotype, which decreases in frequency as a result of the killer's action. Related cytoplasmic factors have been described in yeast (Wickner 1991) and other fungi (Puhalla 1968).

The above discussion of distortion processes is by no means complete from a theoretical point of view, but has been compiled with particular selfish genetic elements in mind. Other conflicts can be envisaged, but it is harder to find good examples of those. For

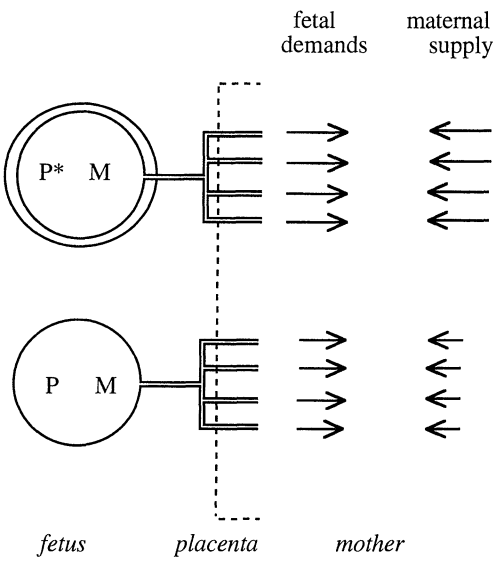


FIGURE 3. GENOMIC IMPRINTING: PATERNALLY DERIVED GROWTH FACTORS

Key: M = maternally derived genome; P = paternally derived genome. The fetus at the top has a gene expressed when paternally derived (P*). The expression increases the fetal growth demands, and hence, in competition with a fetus with lower demands, the gene tends to find itself in larger than average progeny. Competitor alleles (those in the other fetus) tend to find themselves in smaller-than-average offspring. If a female mates with more than one male, then the relatedness between the paternally inherited genomes of the two fetuses is less than 0.5. Regardless of mating system, the average relatedness between the maternally inherited genomes is 0.5. Alternatively, nonconflict-based hypotheses have also been proposed to explain imprinting.

Advantage to imprinted gene: increase in frequency owing to the increased size/survival of fetus.

Condition: multiple paternity either within or between broods (stricter conditions hold for invasion of growth-demanding genes under monogamy). Intimate parental (usually maternal–offspring) contact.

Disadvantage for maternally inherited genes: total output of progeny is less than what it might be.

Modifiers: maternally derived genes that oppose the function of the paternally expressed growth factors are interpreted as suppressors.

Taxonomic distribution: the above is illustrated for eutherian mammals. Paternal X–inactivation in marsupials is suspected to be a related phenomenon and a similar phenomenon probably occurs in angiosperms.

References: for imprinting in mammals and plants, see references by Haig and colleagues (Haig and Westoby 1989; Haig and Graham 1991; Moore and Haig 1991; Haig 1992a). For Y chromosome growth factors, see Hurst (1994b,c). For discussion of theories of imprinting, see Hurst (1996b).

instance, there may be conflicts over the rate of cell division; cytoplasmic factors may spread faster if host cell divisions were relatively slow, therefore ensuring 100% efficient vertical transmission rates. Rapid divisions may act to create parasite-free cells (Hurst 1990) and hence would be in the interests of the host. If diploids and haploids have different rates of cell division, then the relative length of diploid and haploid phases of the life cycle may be a domain of conflict (Hurst 1990).

Similarly, one might imagine that cytoplasmic factors derived from males may be excluded from being transmitted to the following generation by ensuring that the germ line is determined so early on that the cytoplasmic factors have not had the time to migrate to the necessary position. It is curious, for example, that germ line cells are produced very early in fly development and away from the point of entry of the giant sperm. Furthermore, there are organisms with highly unusual life cycles, and in them conflicts may appear at other moments than outlined above. It is also possible, at least in theory, for a self-promoting element to combine more than one of these modes of action. In practice, however, this seems to occur only rarely, and we know of no examples.

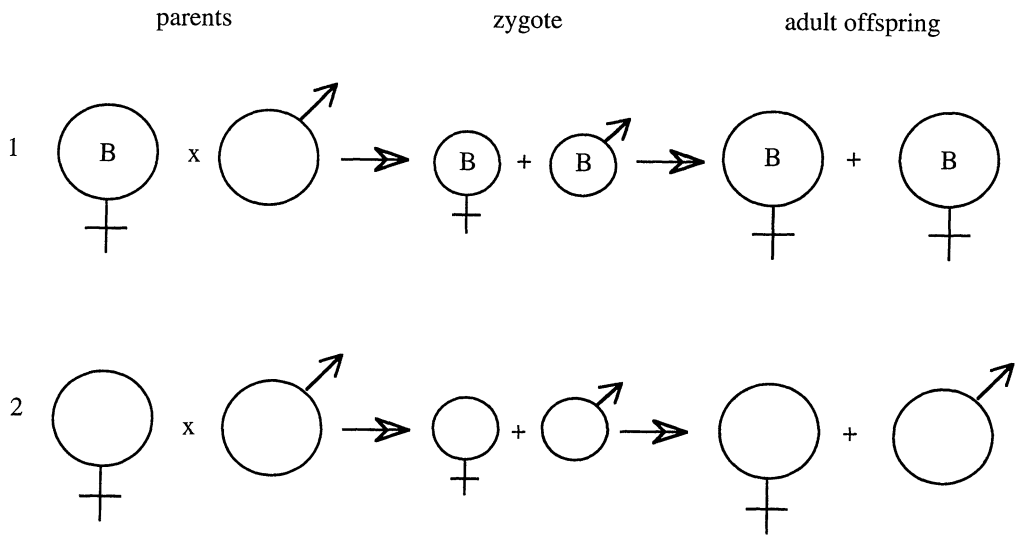


FIGURE 4. CYTOPLASMIC FEMINIZATION

Key: B = the maternally inherited agent (often bacterial in the case of feminization in isopods) capable of feminizing would-be males if the feminizing agent was not present.

Advantage to male feminizing agent: increase in frequency owing to higher number of daughters in cross 1 compared to number of daughters in cross 2.

Condition: invasion condition is very broad. Fitness reduction of agent on females must not be so great as to reduce the advantage of increasing the number of daughters.

Disadvantage for unlinked genes (nuclear genes): overproduction of the more common sex; possible metabolic disadvantage as in all other cases of symbiotic self-promoting elements.

Modifiers: strong suppressor detected in crustaceans. Modifiers yet to be shown in other systems.

Taxonomic distribution: well characterized in isopod and amphipod crustaceans. Inbred wasps contain bacteria that convert parthenogenetically derived would-be male offspring into females; similar cause is suspected in coccids.

References: reviewed in Hurst (1993a). The literature on the isopod sex ratio distorters is extensive (Juchault et al. 1992; Juchault and Mocquard 1993). Stouthamer et al. (1990) discuss induction of parthenogenesis in wasps and elsewhere. For the inverse (i.e., masculinization by male-transmitted factors), see work by Werren and colleagues (Werren et al. 1981; Werren and van der Assem 1986; Werren et al. 1987) and Hurst (1993a).

LOGIC OF GENETIC CONFLICTS

As seen from these examples, a remarkably wide array of situations can give rise to "genetic conflicts." What do they have in common? And why should these evolutionary processes be labeled "conflicts"? It seems appropriate at this time to attempt a definition followed by a discussion of some of its corollaries.

A DEFINITION OF GENETIC CONFLICTS

The following definition best describes what we mean by a genetic conflict: *There is a genetic conflict if the spread of one gene creates the context for the spread of another gene, expressed in the same individual, and having the opposite effect.* The second gene, which we generally think of as a suppressor, is assumed to be next to cost-free and to act only by countering the effects of the first factor. This definition is supposed to hold for all kinds of genetic factors (such as different chromosomes or genomes), and not just genes.

Evolutionary situations conforming to this definition can be said to suffer a genetic conflict because the different genetic elements may act to lead the population along opposite pathways. It should be noted that the definition describes what will happen if a certain modifier appears—it is not necessary that such a gene already exists. The conflict does not arise immediately when a modifier mutation occurs; it only becomes explicit at this moment in time. (For a related discussion see Cosmides and Tooby 1981.)

It is an important part of the definition that the genes considered should be expressed in the same individuals; i.e., that genetic conflicts are intra-individual. There are situations when this is not formally the case, but where we still find it useful to talk about genetic conflict. Such situations can arise when it is unclear what constitutes an individual exactly—consider, for example, maternal-fetal interactions across the placenta, which will be discussed later. In general, however, we do not wish to extend the notion of genetic conflicts to cases that clearly involve interactions between unrelated and independent individuals. Such interactions in population biology are well de-

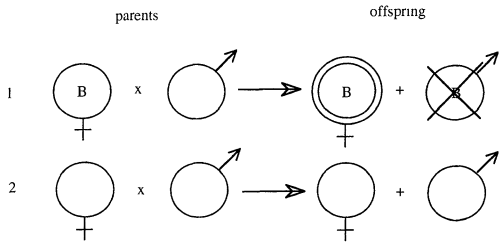


FIGURE 5. CYTOPLASMIC MALE KILLING

Key: B = maternally inherited agent responsible for male killing; the agent is often bacterial. The extra ring indicates some fitness advantage.

Advantage to male-killing agent: increase in frequency owing to increased fitness of daughters/female tissue in cross 1 compared to fitness of daughters/female tissue in cross 2.

Condition: assuming no horizontal transmission and no direct fitness benefits to females from possessing the agent, the death of sons must provide some advantage to surviving daughters. This could be owing to redistribution of resources and/or reduced probability of inbreeding. The former condition requires sib competition. The above assumes the agent is not directly advantageous to females.

Disadvantage for unlinked genes (nuclear genes): death of sons/male tissue reduces by half the average transmission of autosomes, although enhanced fitness of surviving daughters lessens this disadvantage. Overproduction of more common sex. The cost on sex chromosomes depends in this case, as with all other sex ratio distorters, on the degree of cotransmission of cytoplasm and sex chromosome.

Modifiers: there is no good evidence of strong suppressors, but some nuclear genes of weak effect have been described in *Drosophila*. Most male killers usually exist at low frequencies (dependent upon horizontal transmission efficiency and survivor advantage), and hence costly suppressors may not be able to invade.

Taxonomic distribution: quite widely found in insects (e.g., Diptera including fruit flies, wasps; Lepidoptera; beetles including ladybirds); possible reports in mites. Note that the examples in mosquitoes involving microsporidia rely on horizontal transmission of infective microsporidians and hence do not require the same advantages.

References: reviewed in Hurst (1991b, 1993a), Hurst and Majerus (1993), and Ebbert (1993). For details of the *Drosophila* male killers, see Williamson and Poulson (1979).

scribed by the standard term "competition," and little is accomplished by using the word "conflict." Nor do we include in our definition all those conflicts that develop from genetic elements (parasites) that to any noticeable degree spread horizontally from their host individual, living or dead. The key to understanding the genetic conflicts discussed here is that they interact with the genetic transmission system, not any infectious system.

The definition is expressed in terms of polymorphic genes at two separate loci. Thus, an important implicit assumption is that genetic factors can be in "different places" in the cells of an individual. If there were but one locus in the genetic material, it would be more natural to talk about competition between the alleles at this locus than of genetic conflicts between them.

If there are different genomes (e.g., cytoplasmic and nuclear) in the individuals, then there are obviously rich possibilities for genetic conflicts. But a genetic conflict can also exist intragenomically between genes that are more or less closely linked. For example, alleles modifying the strength of meiotic drive will often only spread if they are within the right recombinational distance of the affected locus (Bengtsson and Uyenoyama 1990). Recombination is thus another way by which genes come to lie in "different places."

Genes that never recombine can also be in conflict with each other, if only their transmission properties differ. Thus it is reasonable to speak about a conflict between driving genes and their suppressors on different sex chromosomes, even though the genes formally behave as allelic. The difference here is in their separate transmission properties.

Further complications arise when the genetic material is not homogeneously distributed over the considered individuals, and when the properties of genes are expressed in later life stages and generations. An example of the first is given by cytoplasmic factors in syncytial organisms, which have different probabilities for being included in tissues that undergo sexual or vegetative reproduction [for example, such syncytia are found in acellular slime molds (see Margulis et al. 1990)]. An example of the second situation arises in the case of chromosomal imprinting.

Implicit in the definition of a genetic conflict is the idea that the assumed modifier, at least in principle, is devoid of any specific properties other than counteracting the effect of the self-promoting factor. It is, however,

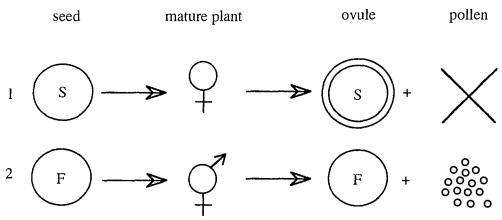


FIGURE 6. CYTOPLASMIC MALE STERILITY IN HERMAPHRODITIC PLANTS

Key: S = maternally inherited agent responsible for male sterility; the agent is often a mitochondrial gene. F = male-fertile cytotype. In both instance 1 and 2, the seed has the potential to develop both male and female functions. The extra ring indicates some fitness advantage. Note similarity between this system and cytoplasmic male killing.

Advantage to male sterilization agent: increase in frequency owing to the increase in numbers of ovules and/or higher fitness of progeny.

Condition: sterilization must provide some advantage to female tissue or to the progeny derived from female tissue. This could be the result of redistribution of resources and/or reduced probability of inbreeding. The above assumes agent is not directly advantageous to female tissue.

Disadvantage for unlinked genes (nuclear genes): overproduction of more common gamete. Sterilization of male tissue reduces by half the average transmission of autosomes, although enhanced fitness of female tissue lessens this disadvantage.

Modifiers: good evidence for common occurrence of nuclear restorers of male function.

Taxonomic distribution: very common in angiosperms (about 10% of species). Cytoplasmic male sterility (CMS) could potentially occur in hermaphrodite animals, but an example has yet to be found. CMS is found in a few dioecious animal hybrids; the relevance of this is uncertain.

References: reviewed, for example, in Kaul (1988), Saumitou-Laprade et al. (1994), and Gouyon and Couvet (1987).

useful to regard it as being slightly deleterious on its own, since this implies that it would not be able to spread unless the primary factor was present.

From the viewpoint of theoretical population genetics, the situation outlined in the definition falls within the field of modifier studies, for which the methods and terminology outlined by Christiansen (1991) apply. In such studies, a formal mathematical model is built in which all selective effects and transmission properties are carefully specified. A mathematical analysis is then performed to find the condition under which an allele at a specific locus modifying the process will spread. Modifier studies can give important insights into the dynamic machinery of the population genetic process, but they often become technically impenetrable to readers not familiar with the method. Our aim here is to find a way to talk about complex genetic situations without having to go into the technicalities of the formal models. In its ability to produce a handy intermediary language between the logical workings of the population genetical machinery and the phenotypes of the considered organism, the theory of genetic conflicts is similar to evolutionary game theory (as outlined by Maynard Smith 1982). The primary difference between them is that the details of the genetic transmission system is virtually ignored in most game theoretical arguments, while it constitutes the central facet of genetic conflicts.

THE NATURE OF MODIFIERS

In real life, the effect of suppressor alleles is almost never restricted to counteracting the effect of a preceding self-promoting element exclusively. Neither is the suppressor always next to cost-free. However, if the conflict created by the self-promoting factor involves

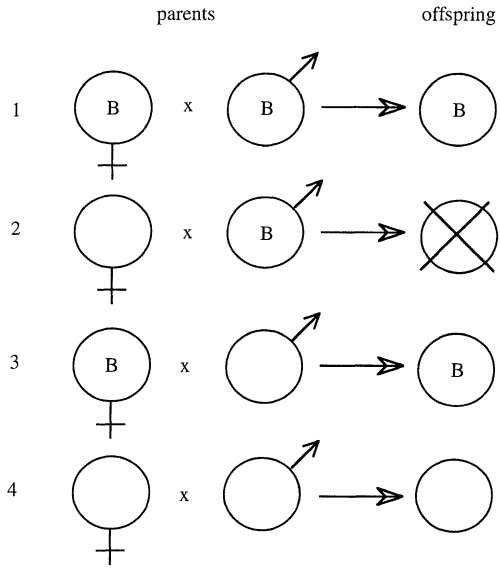


FIGURE 7. CYTOPLASMIC INCOMPATIBILITY

Key: B = maternally inherited bacteria responsible for cytoplasmic incompatibility. Although not typically transmitted by males, the bacteria affects the sperm of its host so as to ensure death of progeny not containing a clonal relative of the bacteria.

Advantage to bacteria: increase in frequency owing to the decrease in numbers of uninfected individuals after mortality of progeny in cross 2.

Condition: invasion is theoretically impossible in an infinitely large population (unless B is directly advantageous to females). Small population size and/or drift aids invasion. After an adequately high frequency is reached, further spread to, or close to, fixation is almost inevitable, even in very large populations.

Disadvantage for unlinked genes (nuclear genes): if male is infected and female uninfected, then all (or nearly all) progeny die.

Modifiers: there are no good examples. Spread to high frequency is possibly so rapid that modifiers do not have time to invade. At high frequency there is little excess mortality, as nearly all crosses are of type 1. Nuclear modifiers should, at this point, favor an increase in the vertical transmission rate of the bacteria, thus ensuring that no eggs die (i.e., there is no conflict as bacterial modifiers with the same effect will typically spread).

Taxonomic distribution: only one agent, the bacterium *Wolbachia*, has ever been shown to cause cytoplasmic incompatibility. *Wolbachia* is quite widely found in arthropods, but direct evidence of cytoplasmic incompatibility is largely restricted to insects: Diptera (including fruit flies and mosquitoes), Coleoptera (*Tribolium*), Lepidoptera, and isopod crustaceans.

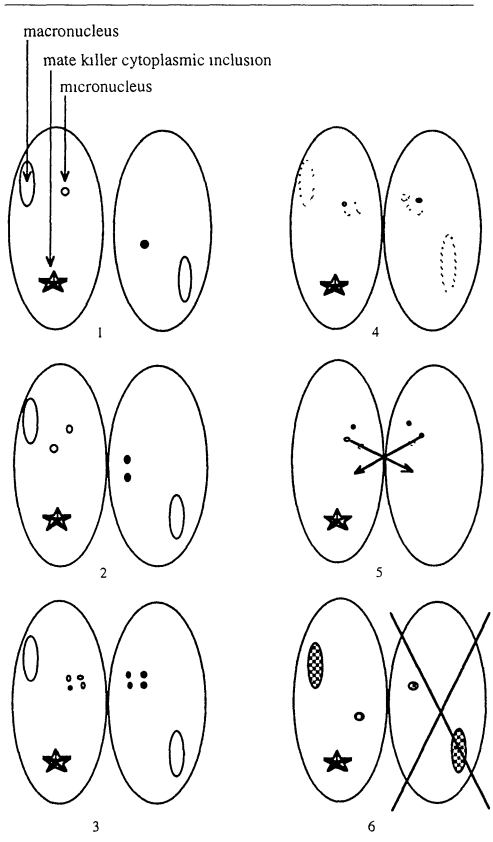
References: reviewed in Rousset and Raymond (1991), but see also O'Neill et al. (1992).

strongly deleterious genetic effects, then a modifier gene suppressing its worst negative properties will spread, even if it itself is associated with new and different, although weaker, deleterious effects. We can thus expect a difference in response to self-promoting genetic elements with weak and strong effects. Elements of the first type will, if at all, meet a response that comes close to reducing the conflict-generating effect, and not much more. The responses to a strong factor will, on the other hand, often be associated with surprising secondary effects that may themselves create possibilities for strong new *secondary* conflicts with surprising new responses, and so on.

An illustration of this potentially dramatic situation is given by the sex chromosome system in the wood lemming, *Myopus schisticolor* (Gropp et al. 1976; Bengtsson 1977; Fredga et al. 1977; Bengtsson 1980; Bull and Bulmer 1981; Bulmer 1988). A possible route to the present sex-determination system is as follows: On the X chromosome a mutation appeared (called X*) that 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 that 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 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 (owing to their production of YY embryos, assuming, quite reasonably, YYs to be lethal or sterile)—and it was on this phenomena that evolution acted. A system evolved (caused by genes on the autosomes or the X*) that changed the meiosis in the X*Y females so that they now produce exclusively X*-carrying eggs! Thus, the loss of fecundity was remedied but the sex chromosome segregation distortion was *increased.* As a logical consequence, the sex ratio in the population became even more female-biased than before. The drastic sex-reversing effect of the initial X* mutation therefore caused the spread of a modifier that, in some sense, perfected the unusual system rather than leading to its disappearance.

[An alternative history to the one described above is possible. The original mutation may have been a Y-driving chromosome. As this chromosome spread, 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 endeavors to restore the sex ratio. Selection could then favor those X*Y females that produced only X* eggs and hence avoided the production of YY embryos. Regardless of which explanation is correct (in future, we shall assume the former), both renderings make the



same heuristic point, that drastic crises provide the conditions for drastic solutions.]

DO ALL SELF-PROMOTING ELEMENTS INSTIGATE CONFLICTS?

A genetic factor that benefits from some self-promoting mechanism does not necessarily have to be an instigator of conflict. This is most easily seen by considering a factor that spreads by a non-Mendelian mechanism, but does so without being associated with any noticeable effect. In such a situation there can be no selective force acting on a suppressor to make it spread.

Self-promoting factors with no phenotypic effects are probably rare and would, if they ever exist, be relatively uninteresting from an evolutionary point of view. Many of the self-promoting factors studied are, instead, associated with strong effects—effects that are deleterious, if not to the factor itself, then at least to their carriers and/or to other genes in the organism. It is easy to understand how such self-promoting factors that impose a heavy cost to their carriers can be counteracted by suppressor genes. It is, however, much more important to understand that genes that cause no obvious loss of organismic resources can also be met with a strong response from other parts of the genome.

This would, for example, be the case after the spread in a bird population (with ZZ/ZW sex determination) of a W-linked factor that affected the meiotic reduction division in such a way that the W chromosome always got incorporated into egg cells, rather than into any of the other female meiotic products (the polar bodies). This W-driving factor would act in a self-promoting way without inducing death, decreasing fertility, or losing any other resources to individuals in the population. Nevertheless, it would initiate a conflict, since an

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FIGURE 8. CONJUGATION AND MATE KILLING IN A CILIATE

The stages in the process of conjugation in a typical ciliate are: (1) Two individuals of different mating type come together. Both have a diploid micronucleus and a highly polyploid macronucleus. The macronucleus is a much rearranged derivative of the micronucleus. In the above example, the cytoplasm of one partner also contains a cytoplasmic mate killer (mu) factor. (2) The diploid micronuclei undergo the first division of meiosis, followed by (3) the second division, resulting in four haploid nuclei. (4) Three of the haploid nuclei in each partner degenerate and the old macronucleus starts to decay as well. (5) The remaining meiotic product undergoes a division to produce two identical haploid nuclei, which pass through a small aperture to the partner. If no mate killer is present, then the two micronuclei fuse to produce new diploid micronuclei. These then divide to produce two diploid nuclei, one of which will stay as a micronucleus, while the other is converted into the new macronucleus. If, however, the mate killer is present in one of the mates, it somehow injects the opposite partner with a toxin. (6) This mate hence dies.

Note that the series of nuclear divisions and destructions results in the production of two haploid nuclei that, in any given cell, are identical. Following the nuclear transfer across the cell boundary (step 5), the resulting cells are identical twins. Hence, there is no competition between the nuclear genes of these two. This may indeed be why the peculiar nuclear process occurs (Reed and Hurst 1996). The absence of similar processes as regards the cytoplasmic genes predisposes towards the spread of mate killers, thus resulting in nuclear-cytoplasmic conflict.

Advantage to cytoplasmic factor: increase in frequency owing to the decrease in numbers of uninfected individuals after mortality of progeny (c.f., cytoplasmic incompatibility; Figure 7).

Condition: invasion is theoretically impossible in an infinitely large population (unless a direct advantage accrues owing to death of the mate). Small population size and/or drift aids invasion. After an adequately high frequency is reached, further spread to, or close to, fixation is almost inevitable even in very large populations.

Disadvantage for unlinked genes (nuclear genes): death of progeny in killer+/killer− matings.

Modifiers: the strength of the effect is known to be dependent upon nuclear factors.

Taxonomic distribution: the above example is given for a ciliate, but distribution within ciliates is uncertain. Other species with no fusion of cytoplasms during mating (e.g., some basidiomycetes) probably have similar factors.

References: for description and review see the following works: Beale and Jurand (1966), Beale et al. (1969), Jurand and Selman (1969), Preer et al. (1974), and Preer (1975).

autosomal suppressor of the effect would easily spread in the population. The selective advantage to the suppressor would come from its effect on the sex ratio produced by females carrying the W-driver. Without the suppressor, such females produce all-female broods, making the population sex ratio skewed; with the suppressor the females also produce males. Since this sex is under-represented in the population, the autosomal suppressor will invade even if it were associated with a clear detrimental effect on its carriers' fitness, as long as the sex ratio selection working in its favor was stronger than the natural selection acting against it.

Actually, the strength of a genetic conflict can be judged from how deleterious the modifier can be, and still be capable of spreading owing to its counteracting effect on the self-promoting factor. By this measure it is seen that self-promoting factors inducing much biological waste when spreading will always lead to strong conflicts, but the reverse is not true; situations associated with no obvious loss of resources may induce strong genetic conflicts.

From this insight it follows that the relationship between a genetic conflict and the fitness of individuals or a whole population is never self-evident. While some conflicts have strongly deleterious effects on some individuals, and thereby on the population mean fitness, other conflicts have much more subtle effects. Consider again the W-driver discussed earlier; it has no direct effect on the external phenotype or the fecundity of any individual. If it should be considered at all to affect its carriers' fitness, then a very technical and nonintuitive fitness concept must be used, based on the different "values" male and female offspring have in a population with a biased sex ratio.

Furthermore, in this example it is clear that as the frequency of females producing only female broods is increased, the "mean fitness" of the population is—from an ecological point of view—increased owing to the associated rise in the population's reproductive capacity. Thus, the concept of fitness is both difficult to use and of little heuristic value when genetic conflicts, as well as other changes of genetic systems (Bengtsson 1991) are considered.

According to the definition, there is a genetic conflict only when both the self-promoting element and its suppressor are able to spread *in the population.* This is, in effect, another reason why finding a gene that acts to over-represent itself does not automatically indicate the presence of a genetic conflict. Consider for instance a fast-replicating mitochondrial genome that may spread within an individual. If it is deleterious and if it is transmitted uniparentally, however, then it will not spread in the population; since it is uniparentally inherited, the cost it inflicts on its host will suffer to an equal degree. And when there is no spread of the fast replicator in the population, there is no genetic conflict.

The same fast replicator could spread in the population, however, if it were transmitted biparentally (the condition is that the disadvantage induced by fast replication should be outweighed by the transmission advantage). A conflict would then immediately develop between the self-promoting mitochondrial genome and all nuclear genes. Hence, the presence or absence of a conflict is not solely determined by the properties of a particular self-promoting element, but by the full genetic and biological context in which it appears.

WHO ARE THE CONFLICTING PARTIES?

Conflict is a term often employed in behavioral ecology; there one talks about conflicts between parents and offspring, between males and females, and so on. But who make up the fighting parties in the case of genetic conflicts? The obvious answer is the self-promoting element and its suppressor, since these are the direct actors in the conflict. However, it turns out that a better understanding of some of the phenomena associated with genetic conflicts is gained by analysing what can be called the different "conflicting parties," where each such party consists of a main actor with all its potential supporters.

The conflicting party associated with the self-promoting element will consist of all the genes so situated that enhancers of the self-promoting element will spread while its suppressors will become extinct. The size of the unit will be highly variable, depending on the particular self-promoting element. For example, in the case of an autosomal chromosomal driver, the conflicting party associated with the self-promoting element will normally be

the entire linkage group of the driver, or at least all genes closely linked to it. In the case of a Y driver, the conflict-instigating party is clearly the whole Y chromosome (assuming it to be nonrecombining), while in the case of a feminizing cytoplasm, the party consists of all genes that are consistently maternally inherited along with the feminizing factor.

The opposing conflicting party will, on the other hand, consist of all those loci to which alleles suppressing the effect of the self-promoting element could spread. In the case of an X-located distorter, a nearly cost-free suppressor of this drive would spread if it occurred on the Y or on any of the autosomes; they would make up the contending conflict party. Comparably, in the case of an autosomal distorter, the conflict-instigating party is the set of genes suitably linked to the distorter, while the responding party is all other nuclear loci. In the case of feminizing bacteria, the conflicting parties are the cytoplasm plus any cotransmitted loci on one hand (this could mean a W chromosome in a ZZ/ZW species), and any biparentally or paternally transmitted loci on the other hand. As shown by this last example, the key factor to consider when defining the conflicting parties is not their physical proximity, but their transmission properties.

When the two conflicting parties are in the same individual, as in the previous examples, the conflict may be specified as being "intra-individual," "intracellular," or "intragenomic," as best suits the particular case. This standard type of conflicts also includes the cases where the original self-promoting element is a taxonomically different organism; such as an endosymbiotic bacterium in an arthropod host. Here the conflicting party includes not only the bacteria, but also all the maternally transmitted genes of the host.

More remarkable are the genetic conflicts in which the conflict is expressed within individual organisms (as required by the definition), but where the conflicting parties belong to different individuals. For example, consider genomic imprinting: Imprinted genes have a different pattern of expression, depending on whether they are inherited from the mother or the father. The phenomenon of imprinting can be interpreted from a conflict perspective, as a situation where paternally derived gene copies act to manipulate the mother to provide the fetus with more resources, while maternally derived gene copies act in the opposite direction (Figure 3). The best studied instance of imprinting concerns the mouse Insulin-like growth factor (IGF-II) and its two receptors (Haig and Graham 1991).

IGF-II is one of a number of factors that promote the acquisition of resources from the mother by the developing embryo. In accordance with the interpretation above, paternally inherited genes that increase the production of IGF-II are expressed early in mammalian embryogenesis, while maternally inherited genes capable of the same function are shut off. Instead, maternal genes that *prevent* the action of IGF-II are expressed (most notably the IGF-II type 2 receptor). Another locus, *H-19* is closely linked to *Igf2*, but it acts to suppress it (although not by the same mechanisms as IGF-II type 2 receptor). This gene is transcribed from the maternally derived chromosome set. For discussion and references to the descriptive work, see Haig and Graham (1991) and Haig (1992a).

With this evolutionary interpretation, imprinting fits the definition of genetic conflicts given earlier. A gene whose expression depends upon having been transmitted by the father, and which acts to force the mother to give more resources to the offspring, even if this endangers her future reproduction, may well spread. But after this gene has become common in the population, any maternally transmitted gene that will prevent this overextraction of resources will also spread (Moore and Haig 1991; Haig 1992a). Interestingly, the suppressor could well be in the same linkage group as the enhancer and still spread; the factor of importance in this case is their separate sex-dependent expression.

The conflicting parties here are that part of the father's genome that is transmitted to the offspring (i.e., the nuclear genome) and the genome of the mother. In other words, imprinting is a type of father-mother conflict acted out in the offspring via transmitted genes.

One could argue that the term "genetic conflicts" is best restricted to those cases where the conflicting parties, and the conflict they entail, all belong to the same individual (e.g., an autosomal meiotic drive gene and its sup-

pressor acting in meiosis). We see, however, no particular advantage for such a restriction of the concept. Instead, we prefer to use a broader notion of genetic conflicts, but with the understanding that such conflicts can be of at least two different types: the standard type where all the elements of the conflict reside within the same individual (the drive gene and its suppressor), and the deferred (delayed, transmitted) type where the parties that set up the conflict belong to different individuals than those in which the conflict is acted out (e.g., imprinting in which the maternal and paternal alleles interact within the fetus, but the conflict was initiated in the male and female germ lines of the parents).

Given any kind of ongoing conflict, can there be genes that do not belong to any of the conflicting parties? In principle the answer must be yes, since one can construct theoretical examples where a modifying allele to the expression of a self-promoting factor, depending on its exact genetic location, will neither increase nor decrease in frequency, thus defining a "neutral" ground. However, such situations must in practice be rare, and most loci will belong to one or the other of the conflicting parties. With few exceptions, the responding party will contain more genes than the conflict-instigating party. (We will return to this point at the end of the review, when we discuss the question of power in genetic conflicts.)

Aside from neutrals and the two conflicting parties, it is necessary to distinguish a fourth class of party: those genes that are allelic to the self-promoting element and hence in *competition* with it (Cosmides and Tooby 1981). The allelic competitors are different from the components of the genome that are in conflict with the self-promoting element for a variety of reasons. First, an increase in frequency of the self-promoting element must by definition cause a reduction in the frequency of the allelic competitors. The same is not true of the parties in conflict with the element. This distinction is important, insomuch as the invasion conditions for suppressive modifiers at competing and conflicting alleles are very unlike because of the above difference. Furthermore, unlike the conflicting parties, the competing alleles need not be in the same organism as the self-promoting element. For example, the competing party to a cytoplasmic sex ratio distorter is the set of nondistorting cytoplasms. If, as in the case of meiotic drive, the competing party is in the same individual, unlike the parties in conflict, then the alleles of the self-promoting element have a possible tactic not open to unlinked suppressors, namely, cis-acting insensitivity to distortion.

OPEN-ENDED EVOLUTION

Given a well-defined conflict with well-characterized conflicting parties, what will happen? In brief, the answer is that no one can know for certain; genetic conflicts are by their nature *unpredictable.* We are not interested here in how the end results of conflicts can best be described and classified (which is discussed below), but in the fact that a genetic conflict will evolve in a direction determined by which responding genes exist or first arise in the population. One may well assume that there can be two different modifier loci that may act on the challenge of the self-promoting element, although in quite different ways. It will then be a question of the locus at which the relevant modifier allele first appears. Thus, the pure stochasticity of the mutation process will determine the way the conflict will evolve. In cases with strong conflicts, this effect can become very important, since the initial response will determine what secondary conflicts will develop.

The wood lemming story told earlier can be used to illustrate this point very well. The primary conflict developed in a way that could only be seen in hindsight: a primary conflict over the X*Y females' fecundity now exists as an unresolved conflict over the population sex ratio. Thus the stage has been set for a further genetic change, which presumably will make the frequency of males, today approximately 25% to 30% at birth, more in accordance with that of other mammals. As with all ongoing genetic conflicts, however, the next step in the development of the conflict cannot be foreseen with certainty.

CONFLICT OUTCOMES

From everyday life we know that conflicts may develop in a multitude of ways. Some conflicts have outcomes that are easy to character-

ize, while with other conflicts it is difficult to tell afterwards exactly what happened to them. In this section on the evolution and outcomes of simple genetic conflicts, we look at four types of end results, using terms that are normally used to describe conflicts in the social sphere.

Extinction of conflict. The simplest outcome of a genetic conflict is that the self-promoting element decreases in frequency and becomes lost from the population, as a function of the effects of a suitable modifier. If the modifier is almost but not completely cost-free and has no other particular effect of its own, it will also be lost from the population. Afterwards, it will be very hard to know that a conflict has ever taken place, since all direct traces have been lost. The same result can also come about in cases where the self-promoting element spreads to fixation, but has no net effect at fixation. For instance, both cytoplasmic incompatibility agents (Figure 7) and certain autosomal meiotic drive genes (Figure 1a) can easily spread to fixation, at which point no incompatibility/drive will be witnessed. Selection could then favor the decay of the incompatibility/drive mechanism.

Stalemate. In this outcome, genetic conflicts do not become resolved, in any standard meaning of the term, nor do they lead to compromises. They may well develop into situations of stalemate, however, at least temporarily. This is the case with the *Segregation distortion* (*SD*) system in *Drosophila*, where affected populations tend to be polymorphic for both the self-promoting element and its modifiers. A stalemate can be regarded as a failure of the self-promoting element to win, as well as a failure of the population to "invent" a modifier with such precise effect and low cost that by its spread the self-promoting element becomes lost from the population. It is likely that such a temporarily locked situation will develop in a new direction when, with time, new genetic variants arise for the two types of factors involved.

Joint annihilation. A conflict may end with the extinction of not only the self-promoting element and its possible modifier(s), but of the population itself. This would occur if the self-promoting element has a strongly deleterious effect, and no (or only weak) responders appear before the spread of the self-promoting element had decreased the population size to a dangerously low level. Another possibility is that the self-promoting element acts like a strong Y driver, which increases the frequency of males, and by its ultimate success the population becomes all male and extinct. Instances of this type of conflict possibly could be found in species with relatively isolated populations that show unexpected patterns of extinction.

Conflict transformation. An interesting possibility is that the modifier of the self-promoting element either has only partial effects on the action of the self-promoting element or has some specific new phenotypic properties of its own. When this modifier spreads and mitigates the action of the self-promoting element, then there will still be a conflict, even if it looks different. Thus, an original modifier of a conflict may turn into a coconspirator with the self-promoting element for a second conflict. The evolution of the sex-determination system in the wood lemming discussed earlier offers a nice illustration of this possibility. There, a conflict leading to problems with the fertility of some females has been turned into a conflict over the population sex ratio.

EXTENDED CONFLICTS

Perhaps the most important characteristic of a genetic conflict is whether it reoccurs over a reasonable time period. A conflict that occurs but once will only rarely produce any long-lasting results. For example, an autosomal meiotic drive gene that appears and either becomes fixed or lost, owing to the action of a suitable modifier gene, cannot easily be detected afterwards; neither will it tend to lead to any serious secondary effects. If such mutants were to appear constantly, however, the situation would be quite different. Then there would be many more possibilities for modifiers of different types to appear, and a complicated extended conflict between the self-promoting factors and their modifiers would develop, which could in turn lead to important secondary effects.

Genetic systems undoubtedly differ with respect to how likely they are to be drawn into such repeated genetic conflicts. Some systems are decidedly conflict prone, while others ap-

pear to have a high conflict threshold. An example of the first type is found in the relationship between mitochondrial genes in plants that may cause male sterility, and their nuclear restorers that counteract this effect. It is known that almost ten per cent of angiosperm species exhibit a high frequency of male-sterile (female) individuals (Delannay 1978) owing to the presence of one or several mitochondrial male-sterility genes. In some species, such as *Thymus vulgaris*, it has been shown that *all* individuals contain a cytoplasmic male-sterility gene, so that presence of pollen-producing plants is completely dependent upon appropriate nuclear responders (Belhassen et al. 1991). In what appear to be pure hermaphroditic species, male-sterile individuals are not found within the species, but are frequently obtained in between-species crosses (Kaul 1988). This result has been interpreted as evidence for a common co-occurrence of male-sterility genes with appropriate nuclear restorers (Gouyon and Couvet 1987). It is impossible to determine whether this apparent vulnerability of angiosperms to nucleocytoplasmic conflicts have in any way restricted their evolutionary success.

Still, it seems reasonable to propose that most genetic systems must have a fairly high conflict threshold since systems that are very conflict-prone will, in most cases, probably rapidly annihilate themselves. Such a higher-level sieve in favor of genetic systems with considerable conflict thresholds would be an example of clade selection (Williams 1992). A change in conflict propensity can sometimes be caused by a simple and "innocent looking" genetic change. For example, without a preceding X-autosome translocation the complex sex-determination conflict(s) in the wood lemming would probably never have evolved (Bengtsson 1980).

It is not very helpful to describe situations leading to repeated genetic conflicts by the outcomes of individual single conflicts, since the process will occur over and over again. Such situations, however, can still be usefully characterized by their long-term trend.

Decrease in vulnerability. An important possibility, when repeated conflicts occur, is that the probability for new conflicts to develop continually decreases, as do the negative effects of each round of conflict. Over time the conflict may tend to disappear, or at least be much less important than before. One might, for example, consider a suppressor of meiotic drive that remains in the population even after the removal of the original drive allele (the modifier may, for example, be one that increases the recombination rate, thus breaking up the drive gene pairing). The activity of the suppressor may perhaps reduce the probability of invasion of new drivers (increased recombination rates do tend to do this). If some meiotic drive genes do invade, selection may favor the modifier to be stronger (e.g., an even higher recombination rate), thus making subsequent invasion still less probable than it was before. If the modifier is one increasing in recombination rates, then the drive alleles will be restricted to small chromosomal domains of limited recombination, which is where they are typically found.

Uniparental inheritance of mitochondria is probably another example of such a decrease in vulnerability. As will be discussed in detail later, there are strong reasons to believe that the competition between maternally and paternally inherited mitochondria often led to conflicts between mitochondrial and nuclear genes. These conflicts may well be the cause underlying the evolution of uniparental inheritance of mitochondria and chloroplasts, since with this mode of inheritance intra-individual competition between unrelated cytoplasmic genomes is impossible. Thus, this is a case where the ultimate response to a repeated conflict eliminated the roots to the conflict (even though it created the background for a whole new class of repeated conflicts, as just seen earlier in the discussion of cytoplasmic male sterility).

Escalation. Repeated conflicts may also develop in the opposite direction, away from stability. A first conflict between two factors may continue into a second conflict between the same factors, but now with "raised voices" (Haig 1993d), which continues on to a third round of escalated conflict, and so on. Such escalations are, of course, threatening to the continued existence of the whole population or species. However, if the upper limit of the decrease in fitness that the process may inflict on the organism is less than unity, then many

rounds of increasing conflicts may occur. Such situations of "arms races" are important, though perhaps not very common, in that these situations of extended genetic conflicts are likely to leave observable traces behind. We will therefore illustrate the possibility of repeated genetic conflicts by two examples. The first is that of an arms race between a putative meiotic drive gene and its suppressor, while the second is a case of maternal-fetal relationship leading to a conflict over the control of maternal blood sugar levels.

ARMS RACE 1: *STELLATE* AND *SUPPRESSOR OF STELLATE*

Stellate (*Ste*) is a multicopy gene on the X chromosome of *Drosophila melanogaster* that is transcribed only in the testes (Hardy et al. 1984). Copy number of the repeat varies among strains, up to about 200. Expression of *Stellate* is normally suppressed in males by *Suppressor of Stellate, Su(Ste),* on the Y chromosome (Livak 1984, 1990). Absence of this suppression results in the production of large amounts of Stellate protein that crystallizes into star-shaped bodies found in the sperm. That a *Stellate* sequence is not found in all drosophilids is taken as an indication that the gene may not be necessary for normal spermatogenesis (Livak 1990). An X-chromosome lacking *Stellate* has not been created as yet despite extensive effort (Palumbo et al. 1994) and hence it remains to be seen whether this inference is correct.

The possibility that *Stellate* is an X-chromosome meiotic drive gene—which has evolved in an arms race with its suppressor—has been presented (Hurst 1992b) as a solution to the problem of how a gene that is possibly not required for spermatogenesis, and that renders the host sterile unless suppressed, could have ever evolved.

The suggestion is that the original *Stellate* gene interfered with DNA packing in such a manner that the Y chromosome was more profoundly affected than the X. This might simply be due to the fact that the large Y had more heterochromatin requiring packing than the X, or because the Y has more sites of interaction with the mutant protein. Whatever the mechanism, the consequence would be that an X-bearing *Stellate* would be present in more than 50% of the viable sperm when it is present in low dose without suppression. As long as host fertility was not reduced too dramatically, the gene would invade. Of all positions on the X, the centromere—being a region of low recombination—is the most likely location for a meiotic drive gene. The main body of *Stellate* copy repeats is not centromeric, but two copies of *Stellate* are present at this position (Shevelyov 1992). It might be suggested that these are the original two.

As the driver invaded it would impose a cost, both reducing male fertility and biasing the sex ratio towards females. Thus a suppressor of this condition, for example *Su(Ste)* on the Y chromosome, could also invade and go to a stable equilibrium, at least in the short term. If this suppressor acted in a dose-dependent fashion, then a multiplication of the driver gene would produce a gene family that evaded suppression and once again produced drive. Selection would then act to increase suppressor copy number, and so on. When (and if) a balance between driver and suppressor was ultimately reached, selection would favor deletion of the driving genes if driving has a cost. It can therefore be seen that the dynamics of driving genes are complex, with selection sometimes favoring an increase in copy number, at other times a decrease. Although the mechanism by which *Su(Ste)* inhibits the production of *Ste* product is not fully known, what is understood supports the assumption that *Su(Ste)* acts in a dose-dependent fashion.

This model has recently received considerable empirical support from analysis (Hurst 1996a) of segregation data (Palumbo et al. 1994) from males with no *Su(Ste)* on the Y, but that varied in copy number of *Stellate* repeats on the X. As predicted by the model, it was found that with low copy number (< 35) of *Stellate,* males transmitted the X chromosome to significantly more than 50% of their progeny. Furthermore, as predicted (Hurst 1992b), although against previous empirically derived expectations (Hardy et al. 1984), it was found that the relative survival of X-bearing sperm, compared to that of Y-bearing sperm, increases as *Stellate* copy number goes up (Hurst 1996a).

A similar arms race has been proposed for a multicopy repeat on the murine Y chromo-

some (Conway et al. 1994). Males with a deletion of the Y that removes some but not all copies of the repeat produce a female-biased sex ratio. This is consistent with the action of an X versus Y meiotic drive gene. Whether the mouse X has a multicopy repeat responsible for the sex ratio effect has yet to be investigated.

ARMS RACE 2: MATERNAL BLOOD SUGAR LEVELS

Stellate is a clear example of "the raising of voices" resulting in a large number of copies with no apparent function. Haig (1993d) has illustrated a similar example of raised voices in the case of a maternal/fetal conflict over the control of blood sugar. As previously pointed out, mothers would prefer to retain resources in order to nourish many additional offspring, yet each offspring can advantage itself by extracting more resources than its mother would prefer to give. In numerous kinds of organisms, such as birds, this potential conflict cannot be expressed during embryonic stages, since the egg is provisioned with a fixed amount of resources (in the form of yolk), and hence the embryo cannot affect the titer of nutrients that it will receive. In mammals, however, the flow of nutrients across the placenta ensures that the conflict is real. Not only is the amount of resources flowing across the placenta not fixed, but the embryo can also secrete factors into the maternal blood stream, and thus affect maternal metabolism. These types of interactions are not formally genetic conflicts since the parties involved belong to different individuals. However, if the fetal attempts to manipulate the mother or the maternal response genes are under imprinting control, as is almost certainly the case for the beta subunit of human chorionic gonadotrophin (Degroot et al. 1993; Haig 1993e) and insulin (Haig 1994), then the circumstance may have components of intra-individual conflict.

The control over maternal blood sugar level is one such area of conflict, since the rate of transfer of sugars from mother to fetus is positively correlated with the level of sugar in the maternal blood. Haig (1993d) argues that if fetal demands went unopposed, the fetus would remove more glucose from maternal blood than was in the mother's interests. He suggests that the mother's best interests are served by reducing her blood sugar in order to limit fetal uptake. Furthermore, he argues that a mother and her fetus will compete after every meal for control of the blood sugar. Although the mother would prefer to take sugar out of the blood rapidly, the fetus would prefer that the sugar remain in circulation so that it can be taken across the placenta. Haig proposes that this conflict between mother and fetus has resulted in an evolutionary arms race in which a trait permitting a fetus to increases its output of anti-insulin hormone (keeping blood sugar high) will spread, and in response, a trait that sees the mother increase her production of insulin (reducing blood sugar levels) can also spread (cf. *Ste* increasing copy number allowing an increase in copy number of *Su(Ste)* to spread). The outcome of this genetic arms race is a very high fetal production of an anti-insulin hormone and an equally high maternal production of insulin. The high production of these two hormones has practically no net effect on the flow of sugars into the fetus, as the two effects cancel each other out (just as *Ste* and *Su(Ste)* balance out and at equilibrium, no drive is seen).

In mechanistic terms, human placental lactogen (hPL) and human placental growth hormone (hPGH) are proposed to be the fetal anti-insulin hormones. hPL is the most abundant peptide hormone produced by primates. Its concentration in maternal serum increases throughout pregnancy, reaching the remarkably high titer of 5μg/ml to 15μg/ml near term. At this stage the syncytiotrophoblast is secreting 1g/day to 3g/day. For comparison, the plasma concentration of human growth hormone (hGH), integrated over a day, is about 0.003μg/ml to 0.006μg/ml in young, nonpregnant adults. Levels of hPGH are much lower than those of hPL, but follow a similar temporal pattern. At term their levels exceed 0.015μg/ml. As expected, concentrations of hPL and hPGH in fetal serum are much lower than concentrations in maternal serum.

Changes in titer of anti-insulin agents and maternal insulin cause a number of changes

in maternal blood sugar levels that are confusing if not understood in terms of conflict. First, the level of fasting blood sugar falls during early pregnancy. It stabilizes after week 12 and after that it is held at the new low level. This is interpreted as a maternal device to limit fetal access to sugars. Second, fasting insulin remains close to nonpregnant levels during first and second trimester, but then, in parallel with the growth of the fetus, increases during third trimester. That is, the mother is apparently attempting to take sugar out of the blood just as the fetus requires more nutrients. This is probably to compensate for increased fetal attempts to increase blood sugar levels. Third, after a meal in late pregnancy, maternal blood glucose and insulin both reach higher peaks than they would have in the nonpregnant condition. The peaks remain elevated for longer periods than normal. A high glucose peak is probably owing to manipulation by the fetus. The high insulin level is the mother's attempt to counter the fetal demand.

Just as *Stellate* is possibly not required for spermatogenesis, neither hPL nor hPGH is essential for a successful outcome of pregnancy, despite their high concentrations. And just as a *Stellate*-bearing X chromosome should occasionally obtain a transmission benefit, so should a fetus gain a marginal benefit from hPL production, at least under some circumstances. A positive correlation between birthweight and hPL concentration in maternal serum during third trimester has been identified. However, as Haig cautions, this could reflect either a direct effect of hPL or an indirect correlation with placental weight. The absence of direct maternal regulation of hPL is another accurate prediction of the conflict hypothesis.

TRACES OF CONFLICT

No genetic system is immune to conflicts, but just how common are they? This is a surprisingly difficult question to answer. A minority of genetic conflicts can be immediately recognized, such as those due to sex ratio distorters and cytoplasmic male sterility, but many are hard to detect because of their lack of obvious phenotypical effect. In addition, since the spread of a self-promoting genetic element (and its suppressor) may be very rapid, conflict events have a high probability of going unnoticed. Hence, to understand whether conflicts are of general importance, it may be necessary to look for traces of conflicts. There are also technical difficulties: Highly detailed observations, usually involving the analysis of individual lineages, are often necessary to prove convincingly the presence of a self-promoting element.

An example of traces of conflicts are those involving "raised voices" where—as discussed earlier—repeated genes and/or high levels of expression produced by the process give indications about the evolutionary past. In general, redundancy in genetic systems can be a sign of a preceding history of conflict: a situation where one unnecessary gene (e.g., *Suppressor of Stellate*) regulates another unnecessary gene (*Stellate*) could probably have evolved only through conflict.

It is likely that the current efforts in genome mapping and sequencing will produce a number of strange examples that are best interpreted as traces of earlier genetic conflicts. Let us consider one possible example: The conflict theory of genomic imprinting is consistent with the possibility of a dosage-mediated arms race between paternally and maternally derived genes for control of fetal growth demands. Such an arms race may be expected to lead to dramatic selection for increased transcription rates of the genes concerned. This may, as in the case of *Stellate*, select for increased copy number. An excess of retroposed genes within the known set of imprinted genes is consistent with this possibility (Hurst et al. 1996). Furthermore, if gene size limits transcription rate (it certainly affects it), then the finding that imprinted genes have both few and small introns, when compared to a randomly selected control set, may be a trace of a past or ongoing conflict (Hurst et al. 1996). In contrast, however, the same theory would have probably predicted rapid sequence evolution of imprinted genes (a mutant *Igf2* that can avoid binding to *Igf2r* should spread), but no evidence for such an effect could be found when six imprinted genes were compared with a control set of over 350 genes in the mouse-rat comparison (Hurst 1996b).

Evidence for past conflicts do not come only

from molecular genetics; they can also be unearthed by laboratory crosses between populations and species. Such crosses will sometimes reveal dormant self-promoting agents and thus tell about earlier conflicts. The activation of transposable P elements in certain *D. melanogaster* crosses is well known (Rose and Doolittle 1983), and above we discussed how male sterility in angiosperm hybrids may be indicative of a breakdown of nuclear control over mitochondrial male-sterility genes. Let us consider here a case where crosses have reactivated a factor involved in segregation distortion.

In some *D. simulans* populations, males homozygous for a particular recessive autosomal gene are known to produce heavily female-biased progeny sex ratios (Faulhaber 1967). This was interpreted as evidence of a past history of meiotic drive (Hurst and Pomiankowski 1991a), where an earlier X/Y meiotic drive system led to the spread of a dominant autosomal suppressor of the drive. This postulated co-occurrence of factors for both drive and drive suppression has now, indeed, been observed in some Seychellian populations of *D. simulans*. Here a strong X driver is present in high frequencies, but not normally expressed because a suppressor of drive is fixed. The driving effect of the X therefore becomes observable only in the progeny of males obtained from crosses between the Seychelles populations and populations lacking the suppressor (and the driver) (Merçot et al. 1995).

Both cytoplasmic incompatibility agents and autosomal meiotic drive genes (with no homozygous deleterious effects), can potentially go to fixation, at which point they will not be visible. However, in a cross between two populations with differing histories of the self-promoting agent, the action of the agent may well re-emerge. For instance, if one species has a cytoplasmic incompatibility factor and the other does not, then unidirectional incompatibility is to be expected.

If two species have disparate cytoplasmic incompatibility factors, then bidirectional incompatibility, and hence full isolation, is to be expected. Such a situation has been detected in hybrids between *Nasonia vitripennis* and *N. giraulti* (Breeuwer and Werren 1990, 1993) and between distant populations of *D. simulans* (Montchamp-Moreau et al. 1991). Actually, many of the known examples of cytoplasmic incompatibility have been uncovered in finding unidirectional or bidirectional incompatibility in hybrids (Rousset and Raymond 1991). Similarly, *Medea*—the autosomal selfish maternal-effect lethal found in flour beetles (*Tribolium castaneum*)—was uncovered because of its effects in hybrids (Beeman et al. 1992).

In the examples above, the phenotypes found in hybrids are taken to illustrate phenotypic variation that existed earlier within a population. The correlation between the phenotypes of the original intrapopulation variation and the phenotypes of the hybrids need not, however, be complete. Thus, Frank (1991a) and Hurst and Pomiankowski (1991a) have conjectured that hybrid sterility might be the consequence of the release from dormancy of meiotic drive genes. This is supported by analysis of genes such as *Stellate* and the *t* complex (Hurst 1993b); for both of these cases there are good explanations as to why sterility rather than drive could emerge in hybrids. An absence of drive in hybrids cannot hence be taken as evidence for the lack of a past history of drive (but also see Johnson and Wu 1992; Charlesworth et al. 1993; Coyne and Orr 1993). Even so, we wish still to point out that a few cases are known in which drive, and not sterility, is seen in hybrids (see e.g., Tsujimoto and Tsunewaki 1984, 1985). The exposure of Y-linked restorers of what is probably an X-linked meiotic drive gene has been demonstrated in *Silene* hybrids (Taylor 1994b).

In at least one instance, such drive is the cause of genetic isolation between two species. In a hybrid between *Rana ridibunda* and *R. lessonae*, the complete genome of *R. ridibunda* drives against the genome of *R. lessonae*. In essence, the two genomes, and hence the two species, are as a consequence kept genetically isolated (reviewed by Schmidt 1993). Unfortunately, it is very difficult to show that the appearance in a hybrid cross of what could be a self-promoting element is not the product of de novo production of a gene with properties resembling a self-promoting element. Particular caution should be paid to the expression of cytoplasmic male sterility (CMS) in hybrids, as male sterility may often be a trivial mutational event.

HOMOLOGOUS CONFLICTS, DIFFERENT EXPRESSIONS

The transmission pattern of a linkage group defines the potential conflicts which that linkage group can initiate. Cytoplasmic genes, for instance, are typically uniparentally inherited and hence are in conflict with the autosomal chromosomes over the sex ratio. Until this point in our analysis, we have chosen to down play an important dimension of genetic conflicts, namely, that "structurally similar" conflicts may in practice be highly diverse. In this section we illustrate this possibility by considering two cases where homologous conflicts are expressed differently. First, we discuss how systems with uniparental inheritance can be subverted by a wide array of different "types" of sex ratio distorters. Each type uses a different mechanism to obtain the same basic overrepresentation of a self-promoting factor. The logic behind some of these mechanisms has already been briefly outlined in Figures 4 through 7. Second, factors using the same "type" of manipulation to become over-represented do not necessarily have to utilize the same molecular mechanism. We illustrate this by considering the remarkable mechanistic differences between *SD* and the *t* complex. While these are both meiotic drive factors acting in males to inhibit sperm not containing the driver, they function in manners as different as chalk from cheese.

CONSEQUENCES OF UNIPARENTAL INHERITANCE OF CYTOPLASMIC GENES

When cytoplasmic genes are transmitted mainly by female gametes, the production of male gametes constitutes a waste of resources for the cytoplasmic factors. As a result, maternally inherited cytoplasmic genes are selected to increase the investment into female tissue, whatever the consequences on male reproductive function may be. In particular, the sacrifice of a male individual, or of a male gamete,

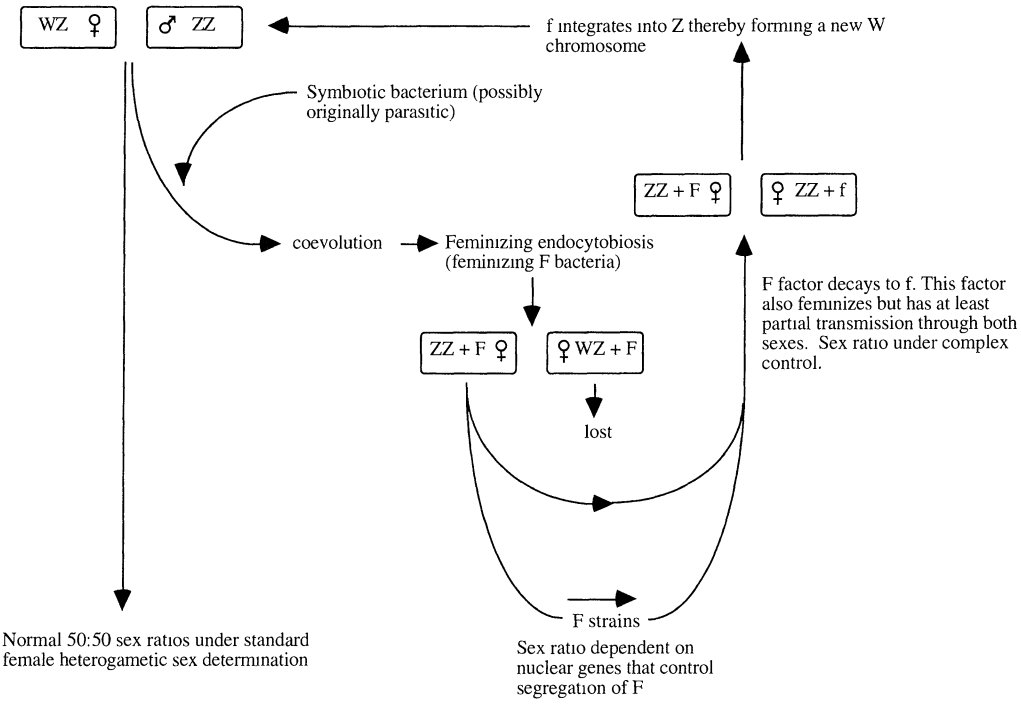

FIGURE 9. A SCHEME FOR THE EVOLUTION OF SEX DETERMINATION IN *ARMADILLIDIUM VULGARE* (ISOPODA).
Based on Juchault and Legrand (1989), Juchault and Mocquard (1993), and Juchault et al. (1992).

does not affect the cytoplasmic fitness. Since the male gamete production is a component of the fitness of nuclear genes, this creates a conflict between the nucleus and the cytoplasm. This conflict potentially exists in all species with maternally inherited genomes. Not all maternally inherited genomes, however, seem capable of the required manipulation. Plant mitochondria—as well as maternally transmitted bacteria, protists, and virus-like parasites of all kinds—seem quite adept at host manipulation; the genome of chloroplasts and animal mitochondria are not known to be able to distort sex ratios.

Maternally transmitted factors in animals manipulate their hosts in several different ways (Hurst 1993a). A first category of selfish cytoplasm acts by manipulating the sex of its host. This seems relatively easy to do when the normal differentiation between male and female individuals is limited. In some crustaceans, for example, cytoplasmic parasites present in genetic males transform their hosts into phenotypic females, thereby ensuring their transmission to the next generation (Rigaud and Juchault 1993) (see Figure 9). A second category of selfish cytoplasm acts by manipulating the sex ratio of its host's offspring. Perhaps the simplest way to ensure the production of female offspring is to induce parthenogenesis, as does a cytoplasmic parasite (a bacterium of the genus *Wolbachia*) in the wasp *Trichogramma* (Stouthamer et al. 1990; Rousset et al. 1992; Stouthamer et al. 1993). Another mechanism occurs in several species of *Drosophila*, where cytoplasmic parasites kill their male carriers at a very early stage, so that the only surviving offspring are females (Williamson and Poulson 1979) (Figure 5). This does not reduce the fitness of the parasite since they were already of zero fitness (being in a nontransmitting host), but presumably enhances the fitness of their relatives in female hosts by diminishing sibling competition. Such male-killing cytoplasmic genes have been shown to occur in ladybirds, where the mechanism for female advantage has been elucidated (Hurst et al. 1992c): Broods of ladybirds are cannibalistic. The death of male offspring then ensures that, on the average, a young female is more likely to be consumer than consumed.

Self-promoting cytoplasmic genes may also increase their transmission without any effect on the sex ratio. This is the case for factors underlying the cytoplasmic incompatibility observed in *Drosophila simulans*, the mosquito *Culex pipiens*, and a variety of other insects and crustaceans (Rousset and Raymond 1991). When the cytoplasmic parasite is present in a male, it prevents the hatching of eggs from that male and a noninfected female (Figure 7). This drastically reduces the fitness of the nuclear genome of the infected male and the uninfected female, but the fitness of the cytoplasmic parasite is not reduced, because the dead offspring are exclusively those lacking the symbiont. As a result, the presence of infected males in a population results in an increased frequency of females carrying the cytoplasmic parasite.

In hermaphroditic plant species, it is the male gametes (pollen grains) that constitute a dead-end for cytoplasmic genes. Hence, when the loss of male gamete production results in enhanced seed production or survival, cytoplasmic genes are selected to inhibit pollen production (Lewis 1941; Cosmides and Tooby 1981). However, the effect of these selfish cytoplasms may be prevented by nuclear genomes, which are more efficiently transmitted by hermaphrodites (see Figure 6). As discussed earlier, this conflict seems to be expressed very often. The forms of dysfunction in pollen production have been shown to be highly variable, ranging from the absence of anthers to the production of seemingly normal but inviable pollen grains (Kaul 1988). The genes responsible for distortion are often mitochondrial, but sometimes viral.

How can we account for this wide range of types of conflicts over the sex ratio in organisms with uniparental inheritance of cytoplasmic genes? It has been proposed that in every example cited above, the host systems are particularly vulnerable to the spread of particular classes of selfish elements (Hurst 1993a). Assuming an absence of horizontal transmission, in order for cytoplasmic male killers and for cytoplasmic male sterility to spread, it is required that the death/sterilization of male function should result in an advantage to the germ line that contains relatives of the self-promoting element and transmit it. Vulnerable systems then are those where this

"transfer of fitness" easily occurs. Accordingly, animals with male killers are typically those with gregarious broods. And in plants, hermaphroditism can be thought of as a special form of gregariousness, making cytoplasmically inherited male sterility a real possibility.

Vulnerability does not necessarily imply that the organism somehow easily provides the condition needed for spread. It can also mean that the organism is unusually easy for a conflict instigator to manipulate. The crustaceans, for instance, have a sex-determination mechanism where the default strategy is the pathway to female development. A feminizing agent needs then only to inhibit perhaps a single masculinization gene to convert its host into a perfectly normal female. Similarly, the induction of parthenogenesis has mainly been reported from inbred hymenopterans, in which the sex determination system is such that haploid eggs develop into males and diploid eggs into females. In this case, a parasite needs only to prevent the first cleavage division of haploid eggs, and parthenogenetically derived females will result.

SD AND *T* COMPLEX: DIFFERENT MECHANISMS FOR THE SAME EFFECT

Although few meiotic drive factors have been carefully investigated for their underlying mechanisms, it is possible to make some general predictions about the ways they function. When they act by eliminating the gamete that contains the other allelic form, a closely linked two-locus system can be expected. The main distorting factor should produce a "poison" and, at the same time, the chromosome should contain a second factor providing an "antidote" to this poison, so that this particular chromosome remains unaffected. There is, however, no reason to suppose that exactly the same mechanisms for killer and the antidote functions should be used by different distorters. Furthermore, it can be predicted that the two factors, determining the killer and the antidote functions, should be tightly linked to ensure that they normally end up in the same gamete. "Suicide" chromosomes, with killer effects but with no antidote, will otherwise frequently be produced. For this reason, autosomal two-locus distorters are expected to be found in nonrecombining parts of the chromosome; e.g., the region around the centromere and/or a chromosomal inversion.

This is not the only meiotic drive system that is theoretically possible. Any one-locus factor acting for itself in meiosis would act as a *Segregation distorter* and increase its own transmission. However, efficient mechanisms for such one-unit meiotic terrorists seem difficult to invoke and none have been found in nature (but see McKee 1991).

Although a general theoretical outline can be made of how a two-locus system for meiotic drive is expected to appear, it would be wrong to assume that all such systems would function mechanistically in the same way. The relationship among meiotic drive systems between structural similarity and underlying molecular differences can be illustrated by a comparison of *Segregation distorter* (*SD*) on chromosome 2 of *D. melanogaster* and the *t* complex on chromosome 17 in the mouse, *Mus domesticus*. The structure of the two meiotic drive systems are very similar (Lyttle 1991, 1993): Both factors are autosomal meiotic drivers with about the same strength (90% to 99% recovery from heterozygotes); they both act by causing gametic dysfunction; both have their action limited to males; both involve two types of separable loci (killer and sensitivity/antidote); both involve heterochromatic elements; both are linked to the centromere; both are associated with chromosomal rearrangements and recombinational blocks; and both systems are widespread in nature. The mechanisms of distortion, however, differ widely in the two systems.

The two loci involved in the *SD* system are Responder (*Rsp*) and *Segregation distorter* (*Sd*). The latter is what might be called a "killer" locus; it has two alleles, Sd^+ (the wild type) and *Sd* (the distorter). In a heterozygote male carrying a wild type chromosome (Sd^+ Rsp^s) (Rsp^s being the sensitive form), in addition to an *Sd* Rsp^i (Rsp^i being the insensitive form) chromosome (the usual form of driving chromosome), most of the sperm containing Rsp^s are destroyed. Although the mechanism of action of *SD* is not fully understood, some basic facts about the mechanism of distortion and insensitivity are known. *Rsp* probably has its resistance to the action of *Sd* conferred by its structure. *Rsp* is an array of a particular sequence recognized by its XbaI (restriction enzyme)

markers (Wu 1991), and the copy number of this repeat correlates positively with the degree of sensitivity to distortion, i.e., a few copies makes the chromosome insensitive to drive. Examination of restriction maps of the *SD* region indicates that *SD* chromosomes have a 5kb tandem duplication that is absent from wild type alleles (Powers and Ganetzky 1991). The biochemistry of the peptide product coded by the 5kb duplication is uncertain, but it probably affects the binding of proteins to the *Rsp* locus (Lyttle 1991, 1993). This suggestion is strengthened by the finding that the XbaI repeats are thought to curl naturally (Doshi et al. 1991). Possibly this curl helps the chromosomal packing during spermatogenesis under normal circumstances and in the absence of *Sd*, a high copy number is selectively advantageous. It is thus reasonable to assume that *Sd* codes for a protein that interferes with DNA packing, although such a protein is unknown. This simple mechanistic model for the action of the *SD* system is attractive in many ways, but gives no good explanation of the phenomena of antidrive (Hiraizumi 1989), a situation in which the driving chromosome is recovered at less than 50% frequency.

Even though there still is little known about the functioning of *SD*, it certainly functions very differently from the *t* complex, both with respect the action of distortion and to the mechanism of sensitivity (Lyon 1992; Hurst 1993b). Lyon (1992) has shown that at least one of the *t* complex distorter loci (of which there are three or four termed *tcd1–4*) is either a hypomorph or an amorph (i.e., they produce no product or only small amounts of a product). Thus, whereas killing in *SD* is done by the production of something that is toxic in a high dose, in the *t* complex it is performed by the underproduction of a necessary substance. Similarly, whereas insensitivity in the case of *SD* does not require transcription, in the case of the sensitivity/antidote locus *t-complex responder* (*tcr*), transcription is necessary. Furthermore, the transcriptional product of the *t-complex responder* has haploid-specific expression. In this respect *tcr* is very rare if not unique. A possible suggestion is that the *tcd-4* gene is a chaperone necessary for the packing of tubulin and other structural proteins, which could explain why the malfunctioning sperm in *t* complex heterozygotes have malformed tails. In sum, although the *t* complex and *SD* have a number of similarities, in particular with respect to their formal population genetics, the mechanisms by which they achieve their meiotic drive effects are very different.

Genetic Conflict as an Evolutionary Force?

So far this article has concentrated on small-scale phenomena and short-term effects. We have not considered the broader evolutionary consequences of conflict, only its mechanistic and population genetical aspects. We have kept speculation to a minimum and, although we might be accused of over-interpreting some examples, at least the theory presented has been well founded and logically consistent. After we address the issue of the evolutionary importance of genetic conflicts, we will feel free to be more speculative.

At a minimum, genetic conflicts are interesting to evolutionary biologists, insomuch as incidences of self-promoting elements and their suppressors clearly demonstrate that the gene (with its associated conflict party) is the ultimate unit of selection. A corollary of this view is that the organismic individual is the outcome of potentially self-promoting elements whose transmission genetics overlap to such a degree that cooperation between them is generally the favored strategy. This then is the resolution of the paradox of the organism (Dawkins 1990). The insight provides no binding demonstration, however, as to whether genetic conflict is important to the process of evolution; only that it is necessary for a logically consistent understanding of the process of evolution. Were there only one example of a self-promoting element, the logical point would still be illustrated and hence shown to be valid. Under such a circumstance, however, it would be incorrect to claim that conflict is important to the process of evolution. But the preceding sections have demonstrated that potential conflicts are often made real. The question is not whether conflict plays a role in evolution, but rather how big a role.

A possible role for genetic conflict has been presented for just about every major evolutionary phenomena. From the emergence of linkage groups (Szathmáry 1991; Maynard

Smith and Szathmáry 1993; Szathmáry and Maynard Smith 1993a), through bacterial genome evolution (Eberhard 1990), the initial evolution of sex (Hickey 1982; Rose 1983; Hickey and Rose 1988; Hickey 1992, 1993) and its maintenance (Moore and Haig 1991) as well as its absence (Hamilton 1979; Hurst et al. 1990; Stouthamer et al. 1990; Hurst 1993a), sexual selection and mate choice (Lenington and Egid 1989; Hastings 1994; Haig and Bergstrom 1995), meiosis (Hurst and Pomiankowski 1991b; Haig 1993a; Reed and Hurst 1996), crossing over (Haig and Grafen 1991), multicellularity (Buss 1987; Hurst 1990), diploidy (Hurst 1990), anisogamy, sexes, and mating types (Grun 1976; Cosmides and Tooby 1981; Hoekstra 1987, 1990a; Hastings 1992; Hurst and Hamilton 1992; Law and Hutson 1992; Bell 1993b), sexual and somatic incompatibility (Nauta 1994), sex determination (Brown 1964; Hamilton 1967; Bull 1979, 1983; Haig 1993b,c; Hurst 1993a; McVean and Hurst 1996), sex chromosome evolution (Hamilton 1967; Hurst 1994b,c; Moore et al. 1995), senescence (Bell 1993a), eusociality (Haig 1992b), monospory (Haig 1986), dioecy (Charlesworth and Charlesworth 1978; Cosmides and Tooby 1981), speciation (Powell 1982; Kidwell 1983; Rose and Doolittle 1983; Thompson 1987; Frank 1991a; Hurst and Pomiankowski 1991a; Levy 1991; Beeman et al. 1992; Hurst 1993b; Pomiankowski and Hurst 1993; Taylor 1994b), genome size (Doolittle and Sapienza 1980; Orgel and Crick 1980; Cavalier-Smith 1985; Charlesworth et al. 1994), organelle behavior (Eberhard 1980), and many other phenomena besides (Hurst et al. 1992a). To our knowledge there has been no suggestion that genetic conflict has been responsible for the extinction of the dinosaurs, although it is worth noting that sex ratio distorters have often been considered as possible causes of extinction of individual species (Gershenson 1928; Williams 1966; Hamilton 1967).

We do not propose to discuss every suggestion of a role for genetic conflict in evolution. Rather, in this section we examine five suggestions that conflict may be important in major evolutionary events. The five topics have been chosen not only because they are major issues, but also because they illustrate the diversity of phenomena that might be explicable in terms of conflict, the variation in time scales over which conflict is assumed to act, and the variable degrees of speculative thinking that have gone into the explanations. We start with a consideration of the evolution of sex in which a role for conflict is difficult to demonstrate, at least in eukaryotes, and conclude by considering the field in which conflict-based models might potentially be most important: the evolution of genetic transmission systems.

ORIGIN OF SEX

Hickey and Rose (1988) presented the elegant idea that sex might have evolved initially as a means by which a self-promoting gene may increase its transmission frequency, even at the expense of its host organism. A gene without such a means of transfer is forever stuck in the vertical lineage that descends from the original parent cell, yet one with horizontal transmission capability has the potential to infect numerous other lineages (see also Hickey 1982; Rose 1983; Hickey 1992, 1993).

How might a gene achieve such a transfer? The horizontal transfer of bacterial plasmids today is promoted by a variety of plasmid products (Eberhard 1990). At least thirteen different genes on the F plasmid of *E. coli* are involved in the transfer of plasmid DNA from a donor to a recipient bacterium. The functions of these genes include making cell extensions (sex pili) that serve both as grappling hooks and tubes for the transfer of DNA during conjugation; anchoring the plasmid at the site of transfer; opening the circular DNA ring and unwinding it; and replicating the DNA ring and transferring one copy to the recipient bacterium. In addition, *Streptococcus* plasmid genes code for aggregation substances that induce the formation of clumping in the presence of "sex pheromones" from nearby plasmid free cells. It is unclear whether the sex pheromone is possibly a degradation product rather than a specific product designed to elicit the observed response.

These and related adaptations of plasmids (Eberhard 1990) are clearly supportive evidence for the notion that sex—in this case meaning the transfer of genetic material from one prokaryotic cell to another—is under the control of accessory elements and to the benefit of these elements. The idea is further

strengthened by the finding that the reduction in the rate of conjugation with the age of the colony is under plasmid control, and thus the process makes sense from the point of view of the plasmid (Eberhard 1990). As the frequency of uninfected cells falls, the expense of attempting conjugation, which remains constant, makes a reduction in the rate of conjugation a sensible strategy. In general terms, the genes encoded by plasmids and their behavior are best understood and explained in terms of the selfish interest of the plasmid (Eberhard 1990). Similar kinds of arguments can be applied for those plasmids that induce trans-kingdom sex, and for transposons that induce conjugation.

Whether these accessory elements are truly parasitic (i.e., impose a cost on their hosts) is unresolved. The transfer of a plasmid from one cell to another is time consuming, however, and it would not be unreasonable to assume that the transfer is made at some cost. Thus the original spread of the sexual process presupposes that, at least initially, the plasmid could assume control over its cell, i.e., to avoid being suppressed by the host genome and turning part of its machinery into functions favoring horizontal transmission of the plasmid. Once established, the transfer process would have become adapted to better suit the host genome. When an F plasmid does not exist in its independent state, but as an integral part of the host's circular DNA, the latter is cotransferred to the recipient cell during conjugation. Recombination is much more frequent when the plasmid is included in the host DNA than when it is independent, and the first DNA to be transferred is that of the host DNA, with the plasmid going last (Willetts and Skurray 1980). This position is indicative that the host is taking control of a parasitic selfish gene. In sum, it seems reasonable to suppose that sex among prokaryotes has conflict at its initiation, and that possibly it plays a role in its maintenance, although the latter need not be implied.

Can the same argument be applied to sex in eukaryotes? In no case has a bacterial plasmid been seen to induce sex in a conventional eukaryotic manner, i.e., with full fusion of the reproductive partners and with mutual exchange of information rather than one-way transfer, as in prokaryotes. However, one example of plasmid-induced neo-eukaryotic sex has been described: Hurst (1991c) has drawn attention to a plasmid that inhabits the mitochondria of the slime mold *Physarum polycephalum* (Kawano et al. 1991). Zygotes are formed by the fusion of two isogamous gametes, each of which has its own mitochondria. If one set of mitochondria has the plasmid but the other does not, then the mitochondria fuse, recombine, and then split apart. The plasmid is thereupon found in all the mitochondrial products. In the absence of the plasmid, mitochondrial fusion is not seen. Kawano et al.'s (1991) finding is significant because it reveals that plasmids are capable of complex manipulations of their hosts: they can force the fusion of two otherwise asexual lineages. Mitochondria are, however, transformed prokaryotes, so this fascinating case of plasmid-induced sex in a eukaryote is not of direct relevance for the origin or maintenance of the sexual process involving the nuclear genes in *Physarum*. Hence, it is uncertain whether conflict has had anything to do with the origin(s) of eukaryotic sex. Perhaps of greatest interest is the way the above case illustrates how conflict potential still abounds even in basically asexual organisms. These conflicts are not then among genes with different transmission patterns, but among ones with potentially different transmission routes.

In a related example, Keeling and Roger (1995) note that the HO endonuclease necessary for mating-type switching in yeast is almost certainly a derivative of a self-promoting translated intron (what they refer to as an "intein"). This example may allow us to suppose that components of the sexual cycle have been altered by self-promoting elements, but this finding does not support the authors' view that self-promoting elements had anything to do with the initial evolution of sex.

SEX DETERMINATION

Within clades sex-determining systems tend to be either highly variable or remarkably invariable. For instance, crustaceans can have variation in their sex-determining mechanism even within populations. Similarly, among beetles XO, XXO, XXXO, XY, XXY, and XXXY systems exist, and there have been at

least three instances of independent evolution of haplodiploidy. In contrast, Bull and Charnov (1985) have argued that XY sex determination is often a black hole from which it is difficult for evolution to escape. For instance, within mammals there is practically no variation from the standard XY/XX (male heterogamety) system (for exceptions, see Fredga 1988).

Although we shall not discuss why some sex-determining systems do not change, we shall discuss the question why sex-determining mechanisms do change in some lineages. The basic problem is simple: Once a system for sex determination has been achieved, why should selection favor its change? One possible explanation is that certain sex-determination systems are better for certain environments. For instance, environmental sex determination is probably adaptive under certain ecological conditions (Adams et al. 1987; Bull 1987; Korpelainen 1990). In contrast, it could be that the turnover of sex-determination systems is independent of their adaptive values, and that the process is driven instead by internal genetic conflicts. We believe this latter alternative to be generally correct, but it is difficult to support in the abstract since, almost every change to such systems is unique in some respect. Therefore we have chosen to describe two illustrative case histories. The first is based on a single, well-studied case and shows how deeply genetic conflicts can affect systems for sex determination. The second is less specific, but illustrates an effect that is probably of great importance for the evolution of sex-determination systems in many groups of organisms.

Armadillidium vulgare: A Case Study in Conflict and Sex Determination

One way for a cytoplasmic gene in an animal to control the sex ratio and to increase its own fitness is to force the host to become female. This raises the possibility of an arms race between cytoplasm and nucleus for control of the determination of sex. A feminizing cytoplasmic gene may invade, be suppressed by a nuclear gene, after which a new cytoplasmic gene will appear, and so on. The end result will be a complicated series of genetic events, all related to the control of sex differentiation. Taylor (1990) has suggested that the invasion of a cytoplasmic feminizing agent, like the type known to occur in crustaceans, might lead to nuclear compensation, so that genes supporting the female development all end up being cytoplasmic. Juchault and Legrand (1989) provide support for such a notion, and argue that the invasion of cytoplasmic feminizing factors in populations of the isopod *Armadillidium vulgare* has resulted in the continuous evolution of new sex-determining systems (see Figure 9).

A. vulgare has ZW females and ZZ males as its basic sex-determining system. Some populations are infected with a cytoplasmic feminizing factor (F), which renders would-be males female. This feminizing factor can spontaneously change into a different feminizing factor (f), which acts as a mobile (possibly nuclear) genetic element. The feminizing factors may spread in the population, and standard ZW females may then be entirely replaced by feminized ZZ males. In such populations the sex-determining system is no longer female heterogamety, but one in which nuclear genes support male development while specific cytoplasmic genes force the host to become female (Juchault and Legrand 1989; Juchault et al. 1992; Juchault and Mocquard 1993). The sex ratio is then controlled, not by the segregation of Z and W in females, but by those nuclear genes that regulate the transmission from mother to progeny of the cytoplasmic factor (Rigaud and Juchault 1993).

The conflict does not, however, stop there. The f factor has at least two modes of inheritance. First, it can be transmitted as a cytoplasmic gene, though possibly with some paternal leakage. Second, it has been known to integrate into a Z chromosome, thereby converting ZZ + f individuals into ZZ_f females, and in the process rebuild the recipient Z chromosome into what functionally is a new W chromosome (Juchault and Mocquard 1993). In this later mode the f factor undergoes Mendelian transmission and the carrier females can be considered as normal "genetic females" (Juchault and Mocquard 1993). In such populations, where all females end up having f stably incorporated into the Z chromosome, the sex ratio returns to 50:50 and all females are genetic females. This is probably where the population started before the cycle

of conflict; hence, the system has gone full circle (see Figure 9). Note, however, that it is unclear whether the newly formed W chromosome could or does spread in the population.

The Evolution of Unusual Chromosomal Systems in Coccoids

Bull (1979), following Hartl and Brown (1970) and Brown (1964), has argued that meiotic drive might be central to the evolution of sex-determination systems involving male haploidy (or genetic equivalents). Such systems have originated independently at numerous times over a wide taxonomic breadth: rotifers, oxyuridian nematode worms, mites, ticks, bees, wasps, saw flies, bark beetles, micromalthid beetles, sciarid flies (and probably cecidomyids as well), thrips, and coccoids. Here we consider a detailed model for the evolution of one of these systems (Haig 1993b); the unusual chromosome system in scale insects—coccoids.

Four basic types of chromosomal systems can be delineated within the coccoids. The most primitive of these is an XX/XO system, in which males are the heterogametic sex. This condition is considered ancestral to the lecanoid (L) system, in which the paternally derived chromosome set is inactivated (heterochromatized) in males and not transmitted to progeny because of elimination during meiosis. This system in turn is believed to be ancestral to the Comstockiella (C) system, in which the inactive paternal chromosomes are eliminated before the first prophase in meiosis. Derived from the C system is the diaspid (D) system, in which the paternal genome is already eliminated in early cleavage. The end point would be pure haplodiploidy, in which the paternal genome would never even enter the eggs that will undergo male development. This type of sex determination has indeed been found in coccoids, but not in species presumed to be derived from an earlier L system.

The above pattern of evolution suggests an obvious problem: If the XX/XO system is perfectly efficient at determining sex, then why change it? As was illustrated above, changes in sex-determining systems need not occur because it is "good for the species," or even the individual, to alter the system; it may just be forced onto the species by the outbreak of a conflict. Haig (1993b), following Bull (1979), has suggested that this is just what is going on in the coccoids. Rather than a cytoplasmic sex ratio distorter, Haig envisages the spread of an X versus O meiotic drive gene at the start of the process. The next step that Haig envisages (also see Bull 1979; Hartl and Brown 1974; Brown 1964) is that the maternally derived chromosomes at meiosis somehow were able to join up with the driving X chromosome and, by so doing, jump onto the drive through the population. The genetic material associated with the driving X should be under selection not to recombine with the paternally derived genome during spermatogenesis, and this is indeed what is found in the L system. As the X/maternal genome spreads, however, the population sex ratio becomes increasingly female-biased. Thus, Haig argues, strong selection is then placed on the mother to affect the sex of her XX offspring to render some of them male. This results in a system in which sex determination is no longer XX/XO, but where the sexual development of an egg is determined by the mother prior to fusion with the sperm.

Haig argues that the future evolution of the L system is simply meiotic drive against the paternal set, acting before meiosis. Why there should be an intermediary such as the C system and why no derivative of the L system has become fully haplodiploid is unclear. That some of the "true" haplodiploid systems have evolved by an analogous path is suggested, Haig argues, by the presence of ghost meiotic products in some of their haplodiploid males.

If the above two examples establish anything, it is that conflict is potentially important for the alterations in systems of sex determination. Indeed, in any case of a change in sex-determination system, conflict will always be a reasonable explanation. Changes in sex-determining systems are, for the most part, rare (although there is much clade-specific variation). Can conflict be generally important on a shorter time scale? We might, for instance, ask whether turnover of conflicts is important for every species, in which case it may be an important force in postzygotic isolation.

SPECIATION AND POSTZYGOTIC HYBRID DISRUPTION

It is not immediately obvious why two populations evolving in isolation for some short time should not be able to produce viable fer-

tile progeny in crosses. It is even less obvious why particular patterns to the inviability and sterility should exist. One well known generalization is that if one of the sexes in a hybrid is sterile, then it is usually the sex with the heterogametic chromosome constitution (Haldane 1922). The genes for such sterility are often located on the X chromosome (Coyne and Orr 1989). Other general patterns have also been recognized. Often unisexual sterility affects males, regardless of heterogamety (Hurst and Pomiankowski 1991a), and the genes for this condition are often cytoplasmic. Other crosses have particular asymmetries instead: males from species 1 mated to females from species 2 produce perfectly adequate progeny, whereas the reciprocal cross produces only inviable or sterile progeny, if any. The genes for this outcome may be both nuclear and cytoplasmic. Under still other circumstances there exists no particular pattern in the dysfunctioning of the hybrids, and the progeny of every cross is inviable or sterile.

One broad explanation to account for many of the above patterns of dysfunction, and for the general phenomena of hybrid breakdown, is that they are the effects of normally quiescent but potentially harmful self-promoting elements. This suggestion can only be taken seriously if reasonable explanations exist as to why the elements have spread in the first place, and now are normally quiescent. The system easiest to understand is probably cytoplasmic incompatibility (CI) (Figure 7).

This system is well known in many insects and crustaceans, and is determined, to a first approximation, by the presence (and absence) of a maternally transmitted symbiont. In crosses, females carrying symbionts are compatible with all males, regardless of whether they are infected. Similarly, uninfected females are compatible with uninfected males (the symbionts are thus not necessary for the development of embryos). However, uninfected females are incompatible with infected males; the eggs laid by females after such crosses do not hatch. This killing of eggs (or more accurately, the prevention of their fertilization) is of adaptive significance for the cytoplasmically transmitted genes of the symbiont, in that it eliminates competing individuals that do not harbor clonal relatives (Caspari and Watson 1959; Fine 1978; Hurst 1991a; Rousset and Raymond 1991; Turelli and Hoffmann 1991; Turelli 1994). By killing uninfected eggs the frequency of the cytoplasmic factor increases and can reach a stable level close to fixation, or may even go to fixation.

Once at a high frequency, the rate at which incompatibility is observed in intraspecific crosses will be negligible, since all mating partners will be infected. In interspecific crosses, however, the incompatibility may once again become expressed (Turelli and Hoffmann 1991). If, for instance, one species has a cytoplasmic incompatibility factor that the other one lacks, then unidirectional incompatibility is expected: males with the factor will be incompatible with females without it, but not vice versa. If the two species have disparate cytoplasmic incompatibility factors, then bidirectional incompatibility and, hence, full isolation is to be expected. Why two populations might have disparate incompatibility elements is unclear, yet this is what has been reported, for example, from hybrids between *Nasonia vitripennis* and *N. giraulti* (Breeuwer and Werren 1990, 1993). Many of the known incidences of cytoplasmic incompatibility have indeed been uncovered because of such unidirectional or bidirectional incompatibility in hybrids (Rousset and Raymond 1991).

The male sterility commonly found in angiosperm hybrids is normally due to a system very similar to cytoplasmic incompatibility. As discussed earlier, the most likely interpretation is that genes for cytoplasmic male sterility (CMS) are commonly hidden under the control of nuclear suppressor genes, but that this control is disturbed in the combination of nuclear genes existing in hybrids (Kaul 1988; Levy 1991).

A more contentious suggestion is that meiotic drive might be the underlying cause of hybrid disruption. A few cases exist in which drive, unseen in intraspecific crosses, emerges in hybrids and there typically causes a reduced fertility (e.g., Tsujimoto and Tsunewaki 1984, 1985). As noted above, in at least one instance meiotic drive is the cause of genetic isolation between two species. In hybrids between *Rana ridibunda* and *R. lessonae*, the genome of *R. ridibunda* drives against the complete genome of *R. lessonae* and the two genomes (hence the

two species) are kept genetically isolated as a consequence (Schmidt 1993). Whether this drive was present in a latent form because of an earlier intraspecific spread or whether it appeared as a de novo side product of the hybrid condition is unknown.

Most contentiously it has also been suggested that meiotic drive genes might cause hybrid sterility, and hence that meiotic drive genes, with their action restricted to the heterogametic sex, would be responsible for some of the instances of Haldane's Rule (for debate see Coyne et al. 1991; Frank 1991b; Johnson and Wu 1992; Charlesworth et al. 1993; Coyne and Orr 1993; Pomiankowski and Hurst 1993). One of the objections to this idea is that driving genes should cause drive—not sterility—in hybrids; therefore driving genes should not be considered as candidates for hybrid sterility loci (Coyne and Orr 1993). By analogy to the above instances (CI, CMS), in which selfish agents act in hybrids as they do in interspecific crosses, this is a valid criticism. The objection has, however, been rebutted, first by a detailed consideration of the mechanism of *Stellate* (Hurst 1992b, 1995a) and of the *t* complex (Hurst 1993b), and second by the accumulation of literature supporting a link between meiotic drive and sterility (Pomiankowski and Hurst 1993). Whether drive is of general importance as regards hybrid sterility is undecided.

Judging by the variability in patterns of hybrid disruption, it is unwise to suppose that there is a single genetic cause of postzygotic isolation (Orr 1992). Many instances of hybrid disruption are, however, consistent with the involvement of selfish genetic elements (see Kidwell 1983; Jablonka and Lamb 1991; Forejt and Gregorova 1992; Hurst and Pomiankowski 1992). As various self-promoting genetic elements, including sex ratio distorters, have been implicated in a number of well-studied cases of hybrid disruption, the question is not whether such agents can be involved, but rather how often they are involved (Pomiankowski and Hurst 1993).

WHY THE GENOME IS NOT ONE LINKAGE GROUP

What is the advantage of having multiple chromosomes and why do they randomly assort? Prokaryotes typically manage with one circular loop of DNA for all their vital genes, so why cannot eukaryotes? One factor that may help maintain the large number of independent eukaryote linkage groups, plus the recombination process within them, is the frequent conflict instigator: meiotic drive.

Recorded incidences of meiotic drive typically have been shown to rely on genes at two loci: one gene that encodes the information to kill certain chromosomes or gametes (e.g., *Sd*), and one locus that determines the sensitivity to being killed (e.g., *Rsp*). This two-locus structure has consequences for the fate of meiotic drive genes at different positions within the genome, but potentially for the evolution of recombination as well.

If the insensitive allele is not constrained as to how costly it may be, it is expected that drive will be much more common on X chromosomes than on autosomes (Frank 1991a,b; Hurst and Pomiankowski 1991a; Wu and Hammer 1991; Pomiankowski and Hurst 1993). The logic is relatively simple and based on the classic population genetical results on segregation distortion (e.g., Prout et al. 1973; Thompson and Feldman 1975, 1976; Charlesworth and Hartl 1978; Bengtsson and Uyenoyama 1990; Feldman and Otto 1991). Driving chromosomes must be insensitive to their own action, at the same time that the chromosomes they oppose must be sensitive to the drivers' action. As X and Y never recombine their sex-specific parts, all X chromosomes in a species can become fixed for insensitivity without affecting any of the Y chromosomes. In general, the higher the frequency of insensitivity, the more likely an X-linked driver directed against the Y is to invade (a corresponding argument holds for Y-linked drivers).

The reverse is true of autosomes, however. For invasion of autosomal drive, the insensitivity allele must be rare at the beginning, since if insensitivity is at all common, most chromosomes in the population will be immune to drive and the driver will not be associated with any strong transmission advantage. The most likely reason for the rarity of insensitivity is that it is mildly deleterious (Wu et al. 1989) in the absence of drive. But with insensitivity rare at the start, severe restrictions are put on exactly where a driving factor with a chance to spread may appear. When the driver enters it

should not only be on the same chromosome as the insensitivity property, but also it must be very tightly linked to it. Otherwise the driver will lose its association with insensitivity through recombination and be lost from the population owing to the lack of any transmission advantage. Contrast this with the case of an X driver when insensitivity is fixed on the X: under this circumstance the driver can appear anywhere on the sex-specific part of the X chromosome.

Thus it has been postulated that recombination (both random assortment of chromosomes and crossing over) may have arisen or be maintained as a means to minimize the size of linkage groups, and hence to prevent the formation of potential meiotic drive allegiances (Haig and Grafen 1991). Extending the previous theory on why meiotic drive genes are normally found on sex chromosomes and in inversions, Haig and Grafen have shown that an allele at a third locus promoting recombination can invade if the population is afflicted with a driver, and if recombination breaks up the deleterious alliance between the driver and its insensitivity gene. In general, it follows that a major advantage of having the genome organized into multiple chromosomes is that it provides a context in which any given gene will have the large majority of other genes freely recombining with it (Eshel 1985) and, therefore capable of acting as its suppressor. Conversely, with only a few linkage groups, Mendelian segregation may well be evolutionarily unstable, given any limitations on segregation (Liberman 1976).

The classical Mendelian genetic process involving crossing over and random assortment of chromosomes may indeed be viewed as a method for reducing intragenomic conflict. It is not known whether the primary function of crossing over is to counter meiotic drive or something else. It could be that its ability to hinder drivers is a fortunate consequence of some other role for crossing over. However, the conflict idea does make the prediction that genes involved in meiosis should normally be separated by sites accessible to recombination. This should hold both for genes that are actively transcribed during meiosis and for those whose function is influenced by their physical structure. This hypothesis has yet to be tested.

The theory also predicts that there may be conflicts over recombination rates and recombination sites. Genes in the same conflict party as a meiotic drive gene are selected to strengthen the linkage between the killer and the insensitive loci, whereas unlinked genes are selected to increase the recombination rate at such locations. Hence, if genes previously unlinked to a driver become linked to a self-promoting locus, then selection should favor a switch in the selective forces acting on these newly linked genes, in that they now should favor the absence of recombination relative to the drive locus. This is what has been described above for coccoids, in which the maternally derived chromosome set aligns with a driving X chromosome and subsequently favors the absence of recombination between the maternal and the paternal chromosomes—which is what is observed.

THE EVOLUTION OF TRANSMISSION SYSTEMS

In sexual species cytoplasmic genes are often uniparentally inherited (or with a strong bias in this direction of transmission), whereas nuclear genes come from both parents. Why is this? We shall approach this question first by asking why cytoplasmic genes are uniparentally inherited. Then we shall ask, why, if uniparental inheritance is so advantageous, do nuclear genes not behave similarly?

It should first be noted that uniparental inheritance cannot be explained simply as a consequence of anisogamy (but see Godelle and Reboud 1995). Numerous isogamous organisms have uniparental inheritance enforced by nuclear alleles (usually linked to the mating-type locus) and numerous anisogamous organisms have significant levels of biparental or even paternal inheritance.

Hoekstra (1990b), in reviewing theories of the uniparental inheritance of cytoplasmic genes, concluded that one category of explanation, based on the same simple idea, seemed in principle adequate (also see Hurst 1994a): Uniparental inheritance of cytoplasmic genes is a means to prevent self-promoting deleterious cytoplasmic genes from spreading in the population.

The spread of a self-promoting cytoplasmic gene could come about in at least two different ways. First, an "aggressive" cytoplasmic

gene which managed to destroy cytoplasmic competitors would spread, as long as the costs due to killing did not outweigh the transmission benefit gained from it (Hoekstra 1987; Hurst and Hamilton 1992). The costs associated with such genes could either be due to a direct consequence of the killing action or to the spread of linked deleterious genes that such aggressive mutants would help hitchhike through the population. A related process favoring spread would be the type of insertional gene conversion shown by the ω^+ factor found in yeast mitochondria (Dujon 1981). This process should also have an associated cost resulting from the production of flanking mutations or the hitchhiking of deleterious genes.

Alternatively, Grun (1976), Hoekstra (1990b), Hastings (1992), and Hurst (1994a), have considered the possibility that cytoplasmic genomes carrying deletions (and thus being deleterious to their host organism) can replicate faster than wild type ones and therefore spread within a cell, and possibly within a lineage. Such over-replicating mitochondria have been reported in fungi (e.g., petite mutants of yeast, reviewed in Jinks 1964)) and are suspected to exist in animals (see Rand and Harrison 1989; Wallace 1992).

Whatever selective factors favoring self-promoting cytoplasmic genes, modifier analysis supports the conclusion that their presence can be the driving force behind the evolution of uniparental inheritance. One can show, for instance (Hastings 1992), that a haploid cell without any deleterious cytoplasmic genome would, at zygote formation, do best to kill off its partner's cytoplasm, since it may carry disadvantageous factors. A nuclear gene supporting this behavior would spread because it would always occur in a positive linkage disequilibrium with the beneficial cytoplasm.

A number of authors (see e.g., Law and Hutson 1992) have argued that uniparental inheritance might be a consequence of a *general* defense against deleterious cytoplasmic heritable components. Although such theories may be valid in some cases, they cannot generally be applicable, since cytoplasmic inheritance in some organisms is not controlled by a general mechanism (meaning one that acts to eliminate all of the cytoplasmic genes from one of the two parents). For instance, *Chlamydomonas reinhardtii* mitochondria are inherited from the minus-type parent, while chloroplasts are inherited from the plus-type. Similarly, in a number of gymnosperms mitochondria are inherited from one parent, whereas chloroplasts are inherited from the other. This being said, however, the proposed explanation works well with animals: One possible advantage to anisogamy over isogamy is the fact that producing small sperm may act as a general mechanism for preventing the transmission of cytoplasmic parasites (Grun 1976; Coleman 1982; Hurst 1990; Law and Hutson 1992). Several details of sperm morphology and spermatogenesis can be given likely interpretations from this viewpoint (Hurst 1990, 1992a).

Usually the polarity of inheritance is associated with a distinct sexual asymmetry: Within a species a particular class of cytoplasmic genes is always inherited from either the mother or the father—though normally from the mother ("cytoplasmic inheritance" is often synonymous to "maternal inheritance"). In isogamous organisms this relationship with sexual asymmetry translates into different kinds of cytoplasmic genes always being inherited from either the plus-type or minus-type. It has been proposed that the fundamental asymmetry between the sexes (between + and −, or between male and female) is owing to the fact that they evolved to control conflicts between cytoplasmic genes (Hurst and Hamilton 1992; Hutson and Law 1993). There is some empirical support for this idea (Hurst and Hamilton 1992; Hurst 1995), but the evolution of sexes will not be further discussed.

Evidence supporting the notion that uniparental inheritance can evolve as an adaptive response to counter self-promoting cytoplasmic genes has been obtained from an organism previously believed to be an exception to the rule of maternal cytoplasmic inheritance. In the mussel *Mytilus* two different mitochondrial genomes (types F and M), which exhibit about 10% to 20% sequence divergence, have been detected (Fisher and Skibinski 1990; Hoeh et al. 1991). There is a large sex difference in the probability that an individual carries copies of F or M or both (Fisher and Skibinski 1990; Skibinski et al. 1994; Zouros et al. 1994a,b). Whereas females usually (if not

always) have only the F genome (hence the name), males harboring both M and F genomes have been found (Fisher and Skibinski 1990). This variation is owing to a difference in the way the mitochondrial types are transmitted to offspring of opposite sex (Skibinski et al. 1994; Zouros et al. 1994a,b). Sons receive F type mitochondria via the egg from their mother, but also M type mitochondria via the sperm from their father. Daughters, in contrast, usually receive only the F type from their parents. It is then generally assumed that all, or nearly all, of a daughter's mitochondria are maternally derived. Hence, the mitochondria of *Mytilus*'s are functionally differentiated into two uniparentally transmitted lineages: F mitochondria are transmitted through a maternal lineage, while M mitochondria are transmitted through a paternal lineage. A distinction has developed here between inheritance and transmission: males inherit both F and M mitochondria, but in effect they transmit only the second type. Only some theories of uniparental inheritance are therefore also theories for uniparental transmission. This subset, of which the conflict hypothesis theory is one, is vindicated by the *Mytilus* data (Hurst and Hoekstra 1994). The *Mytilus* case, however, is very good at showing the key prerequisite for the conflict theory—namely, that there can be competition within the same individual between cytoplasmic genomes with different abilities to gain representation. In *Mytilus*, this follows from the fact that M type mitochondria numerically dominate in the germ line of males, despite their initial low frequency in the fertilized egg (Fisher and Skibinski 1990).

Assuming then that there is convincing support for the idea that uniparental inheritance evolved as an efficient means to control the spread of self-promoting elements, we must now ask: How do nuclear genes succeed in being biparentally inherited? The evolution of crossing over, as noted above, must play some large role. However, by analogy to the problem of over-replicating mitochondrial genomes, the answer may be that the process of mitosis—characteristic of all eukaryotic organisms—functions in such a way that it strongly prevents nuclear genes from becoming self-promoting elements. First, mitosis usually acts successfully to prevent the appearance of over-replicating chromosomes (see below for exceptions), and prevents potentially lethal, random unequal segregation. It is interesting to note that trypanosomes have both evolved a means to segregate the mitochondrial DNA by a novel mitosis-like process (Borst 1991; Robinson and Gull 1991; Perez-Morga and Englund 1993) and, unlike all other cytoplasmic genomes, have little if any redundancy of each separate circular chromosome.

A parallel problem can be envisaged in organisms such as the slime mold *Physarum polycephalum* that have multiple nuclei within the same cell, all of which are potentially in competition with each other to enter the germ line of that cell. One can well imagine a nuclear mutant that over-replicates to gain excess transmission into the germ line, while at the same time it is less competent than other nuclei in supporting the necessary vital functions of the organism. The slime molds appear to have solved this problem by forcing a synchronous division of all nuclei: Several million nuclei within a single cell will divide within the space of a few minutes, and then will not divide for several hours or days. This enforced synchronicity is a parallel to mitosis as a means to prevent over-replication. Perhaps this too is the function of telomeric sequences: these limit the number of divisions any chromosome can make and, therefore, prevent unlimited over-replication. Parenthetically, it is interesting to note that a similar kind of competition within an organism, but between cells rather than genetic entities, has been considered as a force behind the evolution of multicellularity and of the sequestered germ line (Buss 1987).

The above analysis suggests how over-replication of specific parts of the nuclear genome generally is contained. However, it still leaves the problem of why nuclear gene conflict does not break out in the form of "killer chromosomes" that annihilate their "competitors," the homologs inherited from the other parent. In part we discussed this earlier when asking why the genome is not contained in a single linkage group. Killer chromosomes that act after meiosis are meiotic drive genes, and recombination appears to be a successful means of defense against such genes when they require two or more loci in alliance.

Other characteristics of meiotic forms may

have evolved in response to spreading self-promoting elements. Consider, for example, the evolution of ciliate meiosis. Ciliates are unicellular protists with an unusual sexual process. Rather than two gametes fusing, two cells pair closely and exchange haploid nuclei (Figure 8). Each cell prior to pairing will have gone through meiosis to produce two such haploid nuclei: one remains in the cell and one is transferred. The manufacture of these nuclei is, however, unusual. One might imagine that to make two haploid nuclei one might go through meiosis I, digest one nucleus, and resolve the other in meiosis II to produce two nuclei. Or perhaps one might go through meiosis to produce four haploid nuclei and digest two. Ciliates, however, produce four nuclei and digest three, then let the remaining one go through mitosis to produce two nuclei.

Why go to such a length? A ciliate that uses one of the simpler, less costly, forms of meiosis will always end up, prior to nuclear exchange, with two nuclei that are not identical. This leaves the system vulnerable to a variety of self-promoting factors. The presently employed form always results in identical nuclei and is immune to the spread of the same self-promoting factors (Reed and Hurst 1996). Consider for example a nuclear linkage group that produces both toxin and antitoxin (i.e., a classic two-locus distorter). If the diploid cell is initially heterozygous for this gene, then with the simpler forms of meiosis the two nuclei produced may be different at this locus. If then the toxin/antitoxin nuclear gene is exchanged, then the cell that the nucleus leaves contains the toxin but not the antitoxin and dies—if the toxin is more stable than the antitoxin, as is true in numerous instances (Gerdes et al. 1990). The only cells that ever die are those that do not contain the toxin/antitoxin complex; hence this mate-killing factor can invade a population under relatively broad conditions (if the death of the cell gives some advantage, the invasion conditions are particularly broad).

The spread of this element, however, creates the context for the spread of a nuclear modifier of the form of meiosis (converting meiosis to the form of current ciliate meiosis). In effect, by doubling one product of meiosis, the system is geared such that the nucleus that remains in the cell is the identical twin of that which is passed into the partner cell. Such a system will never be affected by the "killer" trait. Under this circumstance the fitness of cells with the modifier may be higher than that of those without the modifier, and hence the trait spreads and may become fixed (Reed and Hurst 1996).

But the other part of the problem remains: Prior to meiosis, why does one of the homologs of a pair not attempt to annihilate the other? This process can occur and has been well documented. Genome against genome annihilation has been reported (for instance see the earlier discussion of coccids), and the excess of transmission of the remarkable X chromosome in lemmings (also previously discussed) is managed by deleting the Y and duplicating the X in the germ line (maize B chromosomes do a similar trick). Therefore we can only suggest here that much of mitosis might have evolved to guard against exactly this sort of self-promotion. The full details of this remain, however, to be elucidated.

THE LANGUAGE OF POWER

Earlier discussions have considered the possible consequences of the expression of conflicts. We have shown that there are conflicts within every genetic system, and that conflict is potentially a continuous force in evolutionary change. We have also illustrated a wide range of actual, and often very bitter, conflicts. For us, however, the most remarkable conclusion from this investigation is the fact that self-promoting elements, with their concomitant conflicts, are only occasionally seen. Meiosis is not always being plundered by meiotic drive genes, and the sex ratio is not usually corrupted by sex ratio distorters. Nuclei and cytoplasms generally live in harmonious relationships. If conflicts are potentially ever-present, then why are genomes so well behaved? And why are some of the potential conflicts realized more often than others?

One possible answer to the paradox of the well-behaved genome is that it is not a problem. Genetic systems may evolve to a position where a self-promoting element with an adequate ratio of transmission advantage to cost cannot be found, in which case the system is stable (Hurst 1994a; Godelle and Reboud

1995, 1996). The validity of this "evolved constraint" type of argument is hard to assess. What is known, at least as regards cytoplasmic genetics, is that it cannot explain all the data (Hurst 1994a). An inability to produce an adequately cheap distorter, however, could possibly explain the stability of some genetic systems.

If self-promoting elements are a potential problem, then the paradox is subsumed, in large part, under the general problem of the evolution of cooperation. Unbiased meiosis and undisturbed sex ratios provide evidence that genes are cooperating. Genes, like organisms, may cooperate for one of two reasons: either it pays for them to cooperate or they are forced to do so. General theory of virulence, compared with cooperation that can be considered the inverse of it, establishes that, as the degree of cotransmission goes up, potentially independent entities should become less virulent with respect to each other. Parasites are under selection not to damage their host to the extent that their damage limits the spread of the parasite (e.g., see Ewald 1988; Frank 1994a,b). In general, a parasite that is cotransmitted with its host is under direct selection to minimize the harm done to that host, as the host's fitness correlates to a high degree with that of the parasite.

The diverse linkage groups in an organism can be understood as parasites with a high degree of cotransmission. And according to theory, mitochondrial genomes, for instance, should be minimally virulent when residing in females. But the logic does not need to be thought of only in negative terms. Possibly the most successful of all strategies available to cotransmitted linkage groups is to boost the fitness of the pairing combination by producing a phenotype good for the grouping. The most cunning strategy of a selfish gene is, thus, to be a standard advantageous gene helping its carrier to see better, run faster, and such. In large part then, as made explicit in Maynard Smith and Szathmáry's (1993) analysis of the evolution of chromosomes, linkage (cotransmission) provides the context for a cooperating genome [this point is further discussed by Leigh (1971b, 1983), Wade (1985), and Dawkins (1982, 1990)]. The method introduced by Price (1970, 1972) to make the effect of selection at varying levels dependent upon the fitness covariance, is in effect a global methodology for considerations of these issues.

Within a sexual organism, however, the cotransmission of genetic elements is never absolute. Mitochondria typically are not transmitted through males; a given autosome is transmitted only by half of the gametes. It is this absence of cotransmission that creates the window of opportunity for self-promoting elements. By definition, in the short term, it does not pay for a linkage group not to become a self-promoting element unless the ensuing costs are too high. [However, see Axelrod and Hamilton (1981) for a consideration of the possibility of reciprocal altruism as a solution to conflict in the genome, and Kloss and Nesse (1992) for an evaluation.] Our underlying basic assumption of partial cotransmission (i.e., the restriction that we only consider here self-promoting elements with no important horizontal transmission) ensures that the key condition for "selfishness" is moderately restrictive and that their negative fitness effects cannot be too strong. Meiotic drive genes, for instance, must not reduce the viability/fertility of heterozygotes by more than the transmission advantage they receive. Male-killing bacteria must not hinder females to such a degree that the advantage accruing from male death is outweighed. This generally benign situation can be contrasted, for example, to microsporidian male killers of mosquitoes, which receive horizontal transmission from both males and females. Under this circumstance, both male and female mortality promotes the maintenance of the microsporidian. This could not be true for any vertically transmitted component of the genome.

Although partial cotransmission limits self-promoting elements to being relatively benign, this cannot be the whole answer to the problem of cooperation within the genome, since self-promoting elements harmful to their carriers do exist. Perhaps the standard situation is instead that the multitude of different genetic elements are made to cooperate. As discussed earlier, one way this may develop is when self-promoting elements come under the control of suppressors. The coevolution of self-promoting elements and their suppressors is a process that may very accurately be

analysed by the tools of theoretical population genetics. For a self-promoting element, the costs it may confer and still invade, and its equilibrium values, and so on, can more or less be easily calculated. Likewise, we can describe the population genetics of any suppressor, the limits to the costs it may inflict and still invade, and its equilibrium conditions. An analysis of this kind will, however, miss many important components of the underlying problem. For instance, what is the probability that a linkage group will come to harbor a self-promoting element? And what is the likelihood that a suppressor will arrive before the conditions are such that it will not invade?

Population genetics will attempt to approach these kinds of problems by comparing the parameter spaces within which initial increase conditions hold. The smaller the permissible parameter space, the less likely the effect. Similarly, the range of recombination values under which suppressors will spread reflects, at least crudely, how likely suppressors are to appear. However, under the cover of extreme exactness, these population genetical approaches often come to hide the simple, more structural than quantitative, evolutionary forces that underlie the results. It would therefore be useful sometimes to have recourse to a language better suited than theoretical population genetics for the treatment of higher order problems, such as why the genome is so well behaved. Social scientists already have such a device, the language of power.

Any two actors in a system may be regarded as having between them some power relationship. The actors that we are interested in are the potential conflicting parties: the genomic regions (usually linkage groups) in which self-promoting elements may reside versus the genomic regions in which suppressors of them can develop. Just as one country can be made to cooperate peacefully with another because the latter exercises power over the former, so too the genome may appear well behaved because certain parts of the genome have genetic power over others (Leigh 1991; Haig 1993d; Hurst 1993a). But what would such genetic power be and how might it operate?

Genetic power is a function of a variety of parameters of the inheritance system. As Leigh (1971a, 1991) notes, the genome appears to have a majority voting scheme. He argues that the genome is a "parliament of the genes" (also see MacArthur 1961). There are often more genes (larger stretches of DNA) in the potential suppressor party than in any given potential self-promoting region. As the recombination rate goes up, this difference becomes more marked: regions in close linkage become smaller and hence the total amount of DNA pitted against any given element becomes larger. This effect acts both with respect to the probability that a suppressor will evolve (Eshel 1985; Crow 1991) and, in turn, the probability that a suppressor of the suppressor can be found.

In addition to this numerical advantage for the suppressor party, a more physiological factor may also be relevant. In many conflicts it seems mechanistically and/or physiologically quite "easy" to invent a number of possible suppressors, while in contrast the strategies available for potential enhancers are much more rare. Mitigating against the factors tending to control self-promoting elements is, however, the asymmetry in the conditions for spread of enhancer and suppressors. Unlinked parts of the genome may lose something from the spread of a self-promoting element, but what an average gene loses is not as great as what genes linked to the self-promoting element gain—crudely put. In sum, however, the situation seems loaded against the conflict-instigating party.

This broad generalization must, of course, be qualified. In particular, systems in which suppression is performed in a dosage-dependent fashion may well be predisposed towards continuous rounds of conflicts involving an arms race. A new distorter is always easy to find in such systems (all that is needed is an increase in expression or copy number), as is a new suppressor.

The expression and fates of conflicts is not, however, simply a matter of the number of genes that may self-promote or suppress such activity. The rate of mutation for these genes is almost certainly of importance as well. For instance, mammalian mitochondrial genomes have extremely high mutation rates. On the basis of this observation it has been suggested that the remarkably strict enforcement of uni-

parental inheritance in homeothermic mammals is a suppressive response to prevent the spread of frequently produced fast-replicating mitochondrial genomes (Hurst and Hoekstra 1994).

Still, these components of power—number and propensity to change—probably do not tell the whole story. There is not only an issue of quantity, but also an issue of quality. We noted above that a self-promoting element cannot be too deleterious. But most importantly it must be able to perform some manipulation of the standard genetic machinery. Certain potential conflicts may not ever be realized, simply because the manipulation required is too elaborate to be achievable. Consider for instance the case of genomic imprinting. There, it is postulated that mammalian fetal genes attempt to manipulate the mother into provisioning the fetus with more than would be optimal for the mother. The intimacy of the maternal-fetal transplacental interactions can be said to predispose the expression of such conflicts. In birds, for instance, the same potential conflict between mother and fetus is present. There it cannot, however, be expressed because the required manipulation would be too complex.

Above we have framed the operation of power mostly in terms of a post hoc response to an invading self-promoting element. In human societies, however, policing acts as a general purpose means to prevent the possible spread of selfish elements. Does the genome have a police force? In general, we might ask if power is more a matter of prevention than of cure (Hurst and Pomiankowski 1991b). With any gametic redundancy it may well pay an individual to kill some of its own gametes if these gametes look as if they may contain self-promoting elements. Evidence for meiotic policing against abnormalities in meiosis has been provided (Burgoyne et al. 1992). In general, however, and in contrast to social insects), policing of the genome is not well documented. [For general discussion of conflicts in social insects, see Leigh (1991) and Ratnieks and Reeve (1992).]

In sum a variety of properties of a genetic system add up to determine the power relations within it. We may then expect that, of all potential conflicts, the ones most frequently found are the ones in which the power relations are unusually equitable. Genomic imprinting, for instance, is a conflict between maternal and paternal genes in a fetus. These genes are about equal in number, and the balance of power between them is therefore much more delicate than in many other conflicts. Similarly, plant mitochondria often induce male sterility, while animal mitochondria never seem to disturb sex ratios. Animal mitochondria are typically small and are maintained small, and have little opportunity for adding mutations with new functions. Plants mitochondrial genomes, on the other hand, are large and have little or no selection on them to make them smaller. Additional genetic functions can hence be relatively easily incorporated. The vertically transmitted elements that disturb sex ratios in animals are not only never mitochondrial, but also tend to exploit some vulnerability on the part of the host (Hurst 1993a): Crustaceans will develop as females if any block on male development is provided, and inbred hymenopterans will be female if diploid. These aspects of vulnerability can be figured as components reducing genetic power of the nuclear genome.

Any change in the parameters discussed previously will change the power relations within the genetic system in question. So, we must ask, what underlies the evolution of power relations in nature? In principle we can envisage two extremes. First, it may be that power changes because there is direct selection on power. For instance, certain models (see above) of uniparental inheritance are based on the idea that this reproductive system, which gives much more power to the nuclear than the cytoplasmic genome, has selectively evolved as a response to the spread of self-promoting cytoplasmic elements. Once uniparental inheritance has evolved, then the absence of recombination between distantly related cytoplasmic genomes might act to reduce the power that cytoplasmic genomes have. Alternatively, new genetic systems may come about owing to selective forces completely independent of power relations. There are, for instance, numerous models for the modification of recombination rates that do not evoke what effects such changes will have on the invasion and creation of new self-promoting elements.

For any given change in a power relationship, both types of argument are imaginable. In addition to these suggestions that give power a high or low explicatory value for its own change, a third possibility must also be considered. Whatever the reason for short-term changes of power relations, high level (clade) selection (Williams 1992) may act as a long-term filter on inheritance systems (Nunney 1989). Systems vulnerable to self-promoting elements just may be less likely to persist over evolutionary time. This form of reasoning has been applied to the emergence and maintenance of, for example, the earliest cells and replicators (Niesert et al. 1981; Szathmáry and Demeter 1987; Szathmáry and Maynard Smith 1993b, 1995). At the other extreme, the notion that group selection might act in favor of conflict-reducing mechanisms in human societies has recently found forceful advocates (Wilson and Sober 1994). However, a long-term filter on genetic systems may also be independent of power relations and still filter away certain ones. It will be very difficult to distinguish these two possibilities—major or minor role of power relationships in high level selection—since multiple independent evolutions will be needed to resolve the comparative analysis.

Clade selection may also be evoked to account for the persistence over evolutionary time of certain self-promoting elements. Higher level selection may explain why symbionts (and transposable elements such as Mariner) that are deleterious tend not to have a phylogeny, which matches that of their hosts (Hurst et al. 1992b; Hurst and McVean 1996), whereas those that are mutualistic never seem to undergo transmission between species (Moran and Baumann 1994).

It seems clear to us that genetic conflicts often, although not always, lead to selective forces that may change the power relationship among the genes in an organism. We also know that genetic systems may change without any effects whatsoever of conflicts. Yet with respect to a given evolution of a genetic system, it must be up to the good sense of the analysing biologiogist to decide when to invoke selection for a change in power. But there is a final question about tendency that we would like to know more about: Does power generally beget power?

Typically in human societies power leads to enhanced power. In simplistic terms, money may buy power and power allows the acquisition of more money. By this means, power relations may become canalized. The regulated transmission of power (by social standing and resources) across the generations is also important to this maintenance of power relations. Does the same situation hold for genetic systems? Could the canalization of genetic power be the reason that Mendel's rules are generally obeyed and sex ratios are typically somewhere near Fisherian and Hamiltonian equilibria? Perhaps then, most paradoxically, the lack of variation in sex ratio (Bull and Charnov 1988) may be the result of a successful suppression of elements that could usurp the sex ratio to their own ends (Leigh et al. 1985). Far from being evidence for the irrelevance of conflicts, such absence of variation should be evidence of the pervasive role of conflict in evolution. Perhaps then Nietzsche (1889) was not far from the truth when he wrote:

> *Anti-Darwin.* As for the famous "struggle for *existence*," so far it seems to me to be asserted rather than proved. It occurs, but as an exception; the total appearance of life is not the extremity, not starvation, but rather riches, profusion, even absurd squandering —and where there is struggle, it is a struggle for *power* (p 522).

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