Annu. Rev. Ecol. Syst. 2000. 31:9–32

THE KINSHIP THEORY OF GENOMIC IMPRINTING

David Haig
Department of Organismic and Evolutionary Biology, Harvard University, 26 Oxford Street, Cambridge, Massachusetts 02138; e-mail: dhaig@oeb.harvard.edu

Key Words genetic conflict, inclusive fitness, parent-offspring conflict, kin selection, sex chromosomes

■ **Abstract** The inclusive fitness effect attributable to an allele can be divided into an effect on matrilineal kin when the allele is maternally derived and an effect on patrilineal kin when paternally derived. However, the allele is not subject to selection on its effects on patrilineal kin when maternally derived nor on its effects on matrilineal kin when paternally derived. As a result, natural selection may favor alleles with effects that differ, depending on the allele's parental origin. At autosomal loci, this process is predicted to lead to the silencing of alleles when inherited from one or the other parent. At X-linked loci subject to random X inactivation, the process is predicted to lead to quantitative differences of expression between maternal and paternal alleles but not to complete silencing of one allele. The implications of this theory and some challenges to the theory are reviewed.

INTRODUCTION

Mendel observed that the progenies of reciprocal crosses appeared identical whether a dominant character was transmitted by the seed or pollen parent (56). Although reciprocal crosses do not always yield similar progenies, most exceptions can be explained by subsidiary hypotheses (sex-linkage, cytoplasmic inheritance, apomixis, maternal effects) that do not challenge the basic hypothesis that the phenotypic expression of a gene is unchanged by the sex of the transmitting parent. The general validity of this hypothesis has been overwhelmingly supported by classical and molecular genetics. Nevertheless, the phenomenon of genomic imprinting has shown that the hypothesis is not universally true. The *GNAS1* locus on human chromosome 20, for example, shows a complex pattern of expression in which some transcripts are expressed from both copies of the locus, some transcripts are expressed only from the paternally derived allele and other transcripts only from the maternally derived allele (34). Thus, a past environment—whether a gene was present in a male or female germ line in the previous generation—can affect how the gene is expressed in the current generation. Because an allele that is maternally derived in one generation may be paternally derived in the next, the

two alleles at the locus must be distinguished by some difference (an imprint) that is perpetuated through multiple cell divisions but that can be erased and reset.

The current paper addresses the question of why subtle differences between alleles passing through male and female germ lines have been elaborated by natural selection to become a mechanism of transcriptional control for some genes but not others, in some organisms but not others. The paper focuses on the hypothesis that such parent-of-origin effects are the outcome of conflicting selective forces acting on maternally derived and paternally derived alleles at loci that influence interactions among kin. This hypothesis has been known by various names (including the conflict hypothesis and tug-of-war hypothesis), of which I use the kinship theory of imprinting (85) because of the unique role the hypothesis ascribes to interactions among kin. The large literature on the nature of the marks that record parental origin and the mechanisms by which these differences affect transcription is reviewed in References 1, 5, 47, and 63 and provides examples of the expanding list of imprinted genes and parent-of-origin effects.

THE KINSHIP THEORY OF IMPRINTING

Symmetric and Asymmetric Kin

Descendants of the two alleles at a locus are potential competitors for future domination of the gene pool. Despite this divergence in long-term interests, the alleles have a common short-term interest in increasing the number of successful gametes produced by their shared individual. How then can maternally derived and paternally derived alleles be selected to express conflicting interests? An answer to this conundrum is provided by the observation that an individual may be more closely related to other individuals via his father than via his mother, or the reverse. If the individual's actions have fitness consequences for such relatives, the symmetry between the short-term interests of maternally derived and paternally derived alleles is broken.

Two different factors of one half have entered into traditional calculations of relatedness (23, 24, 85). The first arises when calculating forward from parent to offspring and reflects the random nature of meiotic segregation. The second arises when calculating backward from offspring to parent and reflects uncertainty about whether a randomly chosen allele entered a zygote in an egg or sperm. If this information were provided, the probability of one half that an allele entered the offspring via an egg would decompose into probabilities of one for maternally derived alleles and zero for paternally derived alleles (and the reverse for an allele that entered via a sperm). The forward calculation is unaffected by whether parental origin is specified, but the backward calculation is not. When one individual is related to another via a backward step, imprinting may change the coefficients of relatedness that are required in applications of Hamilton's Rule.

Consider the expression of an allele that causes a benefit (B) to the individual in whom it is expressed at a cost (C) to the individual's mother (where costs and benefits are measured as differences relative to some alternative allele). An allele

with these effects would be expressed when favored by natural selection if $B - rC > 0$, where r is a measure of how costs to mothers are weighted relative to benefits to offspring. If the implicit comparison were between two alleles, both of whose effects were independent of parental origin, 50% of the time the allele would be expressed when maternally derived (in which case costs to mothers should be given equal weight to effects on self), and 50% of the time the allele would be expressed when paternally derived (in which case costs to mothers should be given zero weight). The appropriate value of r would be the average of these weights ($r = 1/2$). By contrast, if the implicit comparison were between two alleles that were expressed only when maternally derived, an allele would be without cost or benefit when paternally derived and the appropriate weight would be one, whereas the weight would be zero if the comparison were between two alleles that were expressed only when paternally derived.

Suppose instead that the cost were experienced by a maternal half-sister of the offspring's mother. The traditional value of r for such a relative is one eighth, calculated as the product of two backward steps (from offspring to mother to grandmother) and one forward step (from grandmother to aunt). However, if alleles at the locus were expressed only when maternally derived, the appropriate value of r would be one quarter, whereas if alleles were expressed only when inherited from a maternal grandmother, the appropriate value would be one half. There is no evidence as yet that grandparental origin influences gene expression, and subsequent discussion assumes that all backward steps in calculations of relatedness contribute a factor of one half, except for the initial step from offspring to parent. If so, the traditional coefficient of relatedness (r) can be viewed as an average of distinct coefficients of matrilineal (m) and patrilineal (p) relatedness: $r = (m + p)/2$.

Kin can be classified as either symmetric ($m = p$) or asymmetric ($m \neq p$). An individual's symmetric kin include herself, her direct descendants, and her full sibs. Most other relatives are asymmetric kin, including her parents, grandparents, aunts, uncles, and cousins. The kinship theory proposes that genomic imprinting has evolved as a mechanism of transcriptional control at loci whose expression has fitness consequences for asymmetric kin. The theory was first developed in the context of postzygotic maternal care (mothers are asymmetric kin of their offspring) but was subsequently generalized to all kinds of asymmetric kin. For clarity, the general theory is presented first, with discussion of the special case of parent-offspring relations postponed to a subsequent section.

Matrilineal and Patrilineal Inclusive Fitness

Haig (21) proposed a partition of an allele's inclusive fitness effect (δW) into an effect on matrilineal kin (δW_m) and an effect on patrilineal kin (δW_p):

$$\delta W = \frac{1}{2}(\delta W_m + \delta W_p) = \frac{1}{2}\left(\sum_{i=0} m_i \delta a_i + \sum_{j=0} p_j \delta b_j\right).$$

Here, δa_i is the effect on individual i (when the allele is maternally derived); δb_j is the effect on individual j (when the allele is paternally derived); and m_i and p_j are the corresponding coefficients of matrilineal and patrilineal relatedness of these individuals for individual 0 (self). In this partition, kin are divided into a matriline (individuals with $m > 0$) and a patriline (individuals with $p > 0$). Some classes of relatives may belong to both matriline and patriline (e.g., self and self's symmetric kin). Effects on mothers are given equal weight to effects on self (both $m = 1$) in calculations of δW_m. Effects on fathers are given equal weight to effects on self (both $p = 1$) in calculations of δW_p.

An allele's effects on matrilineal kin when paternally derived (δV_p) and its effects on patrilineal kin when maternally derived (δV_m) are not included in δW, but they can be used to define what one might call the allele's excluded fitness effect:

$$\delta V = \frac{1}{2}(\delta V_m + \delta V_p) = \frac{1}{2}\left(\sum_{i=0} p_i \delta a_i + \sum_{j=0} m_j \delta b_j\right).$$

On average, an allele at an unimprinted locus has the same effects on patrilineal kin when it is maternally derived as when it is paternally derived. In other words, the allele's excluded fitness effect when paternally derived (δV_p) has the same expectation as its inclusive fitness effect when maternally derived (δW_m). Substituting δV_m for δW_m yields

$$\delta W = \frac{1}{2}(\delta V_p + \delta W_p) = \sum_{j=0}\left(\frac{m_j + p_j}{2}\right)\delta b_j.$$

Therefore, natural selection at unimprinted loci acts to increase average inclusive fitness (an equivalent result can be obtained by substituting δV_m for δW_p). This provides a justification for the standard practice of using coefficients of average relatedness rather than coefficients of parent-specific relatedness, but only at unimprinted loci. An allele at an unimprinted locus will not increase in frequency if its benefit to matrilines is outweighed by its cost to patrilines, or vice versa.

Monoallelic expression uncouples inclusive and excluded fitness effects. At maternally silent loci, all δa_i are zero ($\delta V_m = \delta W_m = 0$). Therefore, natural selection acts to increase patrilineal inclusive fitness (δW_p) without regard for effects on matrilines (δV_p). An allele at a maternally silent locus can increase in frequency even if its cost to matrilines greatly exceeds its benefit to patrilines. At paternally silent loci, all δb_j are zero ($\delta V_p = \delta W_p = 0$), and natural selection acts to increase matrilineal inclusive fitness (δW_m) without regard for effects on patrilines (δV_m).

Quantitative Expression

Simple models suggest that imprinting of autosomal loci will usually be an all-or-none phenomenon. Suppose that an allele's strategy can be represented by a vector $\{x, y\}$, where x is the allele's level of expression when maternally derived and y its level of expression when paternally derived. Further suppose that each

δa_i and δb_j can be represented by a differentiable function of the total level of gene expression X. Then the kinship theory predicts that the evolutionarily stable strategy (ESS) at the locus will be either 'symmetric' or 'asymmetric' (21).

A symmetric ESS occurs when maternally derived and paternally derived alleles favor the same total level of gene expression. At such an ESS, matrilineal and patrilineal inclusive fitness would be decreased by mutant alleles that cause either small increases or decreases of expression. The ESS is described as symmetric because perturbations have the same effect on matrilineal and patrilineal inclusive fitness, not because the levels of expression of maternally derived and paternally derived alleles are necessarily equal. If both alleles favor X^*, any strategy $\{x^*, y^*\}$ for which $x^* + y^* = X^*$ is an ESS, including the unimprinted strategy $\{X^*/2, X^*/2\}$ and the imprinted strategies $\{X^*, 0\}$ and $\{0, X^*\}$. Of these, the unimprinted strategy appears the most likely to be observed in nature because it minimizes costs associated with deleterious mutations (58). However, imprinted strategies cannot be formally excluded, especially if maternally derived and paternally derived alleles have been previously subject to selection for different levels of total expression (61).

An asymmetric (or parentally antagonistic) ESS occurs when maternally derived and paternally derived alleles favor different total levels of gene expression. In the absence of imprinting, this conflict is resolved by a compromise, with the ESS level of production intermediate between the two parental optima. Small perturbations of expression in the neighborhood of the ESS would cause an increase in patrilineal inclusive fitness and a decrease in matrilineal inclusive fitness, or the reverse. In the presence of imprinting, the conflict is resolved by a fait accompli (14); the allele that favors the higher amount produces this amount and the other allele is silent (29). The strategy is stable because the silent allele cannot reduce its own production below zero. This form of conflict resolution has been called the loudest-voice-prevails principle (20). If maternally derived alleles favor a higher level of gene expression than paternally derived alleles, the paternal allele is silent. At such an ESS, small increases in gene expression would result in decreases of patrilineal and matrilineal inclusive fitness, whereas small decreases in gene expression would result in increases of patrilineal inclusive fitness but decreases of matrilineal inclusive fitness. If paternally derived alleles favor a higher level of gene expression than maternally derived alleles, the maternal allele is silent and the previous conditions are reversed (21).

Qualitative Effects

The models discussed in the previous section considered only quantitative mutations that change an allele's level of expression. However, the loudest-voice-prevails principle has important consequences for the kinds of qualitative mutations that can succeed at an imprinted locus. Suppose that it is paternally derived alleles that favor the higher level of gene product; then maternally derived alleles are predicted to be silent at the ESS. Once the established allele at a locus is silent when maternally derived, any mutation that does not reactivate maternal

expression—for example, a mutation that changes the coding sequence or causes the allele to be expressed in a new tissue—is subject to selection solely on its effects on patrilineal inclusive fitness. As a consequence, qualitative mutations with strongly deleterious effects for matrilines can become fixed at a maternally silent locus. Alleles at imprinted loci will therefore tend to accumulate parentally antagonistic effects. This long-term evolutionary process will reinforce imprinted expression because it results in the pleiotropic association of traits that enhance matrilineal interests at paternally silent loci and of traits that enhance patrilineal interests at maternally silent loci.

Why So Few Imprinted Genes?

A symmetric, unimprinted ESS appears balanced on a knife-edge. If maternally derived or paternally derived alleles favor different amounts of gene product—no matter how small the difference—simple models predict an asymmetric ESS at which one allele is silent. Despite this prediction, the vast majority of genes have biallelic expression. A number of suggestions have been made as to why this should be the case.

The principal effects of most genes may be to increase or decrease the fitness of the individual in which the gene is expressed, with minimal consequences for asymmetric kin. Even if a gene has effects on asymmetric kin, these effects must be dosage-sensitive for natural selection to favor changes in expression levels. At loci where loss-of-function mutations are recessive, inactivation of one allele has little discernible effect on phenotype, and selection in favor of imprinted alleles will be weak. Therefore, few genes may have the kind of dosage-sensitive effects on asymmetric kin that would favor the evolution of imprinting. Moreover, imprinting cannot evolve if there is no variation on which to select. The paucity of imprinted genes could partially be explained if mutant alleles with parent-specific expression are rare (21).

Imprinted expression of a locus would not be expected if the selective forces favoring monoallelic expression were outweighed by countervailing costs. The most obvious cost is increased exposure to the effects of deleterious recessives when one allele is silent (69), but there may be others. Mochizuki and coworkers showed that the cost of deleterious recessives could favor biallelic expression of a fetal growth enhancer despite multiple paternity of a female's offspring (58). This is likely to be an important consideration only at loci where parentally antagonistic effects are weak because the costs of deleterious mutations at an imprinted locus are small. At equilibrium there is only one selective death for each new deleterious mutation (25).

Imprinting may be rare because of conflicts between "imprinter" genes expressed in parents and imprinted genes expressed in offspring (3). For example, genes expressed in fathers will favor lower demands on mothers than will paternally expressed genes in offspring (see below). Therefore, genes expressed in the paternal germ line might be selected to erase any gametic marks responsible for imprinted expression of paternally derived alleles in offspring.

PARENT-OFFSPRING RELATIONS

Genes Expressed in Offspring

The matrilineal and patrilineal inclusive fitness effects of an allele (expressed in offspring) that modulates offspring demands on mothers are $\delta W_m = \delta a_o + \delta a_m$ and $\delta W_p = \delta b_o + \delta b_f$, respectively. Here, δa_o is the allele's effect on offspring when maternally derived; δb_o its effect on offspring when paternally derived; δa_m its effect on the residual reproductive value (RRV) of mothers when maternally derived; and δb_f its effect on the RRV of fathers when paternally derived. All four effects are associated with parent-specific relatednesses of one. An allele's effect on mothers when paternally derived (δb_m) and its effect on fathers when maternally derived (δa_f) are associated with zero relatedness and do not appear in δW_m and δW_p. Paternally derived alleles in offspring, however, need not always be selected to maximize benefits to offspring without regard to costs to mothers because costs to mothers may be associated with correlated costs to fathers. For example, a cost to a mother's RRV will be associated with an equal cost to her partner's RRV (and vice versa) if females and males have all of their offspring with a single partner.

Most previous formulations of the kinship theory (15, 27, 29, 60) have sidestepped the complication that costs to mothers may be correlated with costs to fathers by defining the cost to a mother's RRV as a cost to the mother's other offspring. The rate of multiple paternity appeared in these formulations as a discounting factor in the patrilineal relatedness of these other offspring. In the current formulation, the rate of multiple paternity appears as a discounting factor in δb_f. The new method of accounting is more easily extended to conflicts between maternally derived and paternally derived alleles that would arise if females are monandrous but interfere with their partners' ability to sire offspring with other females (3, 49). This method would extend as well to the absence of conflict that would occur, despite frequent partner change and half-sib families, if each and every cost of parental care were shared equally by an offspring's parents (49, 67).

When maternal care imposes greater costs on the RRVs of mothers than of fathers, the kinship theory predicts that alleles at paternally expressed loci of offspring will have been selected to make greater demands on mothers than will alleles at unimprinted loci, which will have been selected to make greater demands on mothers than will alleles at maternally expressed loci of offspring (3, 15). Therefore, if females have offspring by more than one male, fetal growth enhancers are predicted to be paternally expressed and maternally silent at evolutionary equilibrium whereas fetal growth inhibitors are predicted to be maternally expressed and paternally silent (58).

Haig (20) modeled the quantitative expression of a placental hormone (secreted into the maternal bloodstream) that increased nutrient supplies for all members of the current litter at the expense of members of future litters. In this model, multiple

paternity within litters and changes of paternity between litters had opposite effects on the level of hormone production. Multiple paternity within litters reduced the expression of paternally derived alleles because benefits were then shared with a larger proportion of potential freeloaders of zero patrilineal relatedness. Paternity change between litters reduced the patrilineal relatedness of future litters and thereby favored increased hormone production by members of the current litter.

Genes Expressed in Parents

Although parents are asymmetric kin of offspring, offspring are symmetric kin of parents. If the fitness effects of the previous section were caused by alleles expressed in mothers rather than offspring, $\delta W_m = \delta a_o/2 + \delta a_m$ and $\delta W_p = \delta b_o/2 + \delta b_m$ (for alleles expressed in fathers, $\delta W_m = \delta a_o/2 + \delta a_f$ and $\delta W_p = \delta b_o/2 + \delta b_f$). At unimprinted loci expressed in parents, $\delta W_m = \delta W_p$ because $\delta a_o = \delta b_o$, $\delta a_m = \delta b_m$, $\delta a_f = \delta b_f$. Therefore, loci responsible for parental care are not predicted to be imprinted (with the proviso that δW_m and δW_p may differ if they contain additional nonzero terms for asymmetric kin of the parent (25).

When genes that modulate offspring demands are expressed in parents rather than offspring, benefits to offspring are discounted by a relatedness of one half. That is, genes expressed in mothers are selected to favor a lower level of maternal investment than are maternally expressed genes in offspring (15). Similarly, genes expressed in fathers are selected to favor a lower level of maternal investment in offspring than are paternally derived genes expressed in offspring, if the father has some chance of having other offspring by the same mother. Genes of parents express different interests from genes of offspring because of asymmetric information. Once a gene finds itself in offspring the gene "knows" the outcome of one toss of the meiotic coin, but the outcome remains "unknown" for genes in the parent. Burt & Trivers suggested (3) that this difference in information can result in conflicts between imprinter genes of parents and imprinted genes of offspring.

OTHER ASYMMETRIC RELATIONS

The logic of the kinship theory applies to all interactions with asymmetric kin, not just with parents and half-sibs (23, 85). Nevertheless, the selective forces favoring imprinting are likely to be weaker when an allele's expression affects other kinds of asymmetric kin because asymmetries of relatedness are maximal for relations with a parent ($m = 1$ versus $p = 0$ for a mother, the reverse for a father) but become progressively weaker for more distant kin. Moreover, there is no selection for imprinting if an allele's effects on asymmetric kin are unbiased with respect to matrilines and patrilines. Biased effects require either direct recognition of matrilineal and patrilineal kin or an asymmetry in social relations that ensures individuals interact preferentially with one side of the family.

The different parental roles of mothers and fathers provide a reason why an allele will often have disproportionate effects on mothers compared to fathers

(and on maternal half-sibs compared to paternal half-sibs) but a question remains, how could an allele discriminate in its effects between maternal and paternal first half-cousins? Two social asymmetries have been discussed in this context (23, 85). First, if the variance of reproductive success is greater for males than for females, a population will contain more paternal half-sibs and their descendants than maternal half-sibs and their descendants. Second, if there is preferential dispersal of one sex, an individual may interact predominantly with kin of the non-dispersing parent. These factors can interact to produce complex asymmetries of relatedness. For example, if male offspring disperse, female offspring remain in their natal group, and paternity within the group is dominated by a single male immigrant until he is supplanted by a new unrelated male, then an individual will often have higher patrilineal than matrilineal relatedness to members of her own age class and their offspring, but higher matrilineal than patrilineal relatedness to members of older age classes and their offspring (23).

CHALLENGES TO THE THEORY

One of the most effective ways to clarify the predictions of a theory is to show how it would explain what appears, at first sight, to be contradictory evidence. In this section, I outline some challenges to the kinship theory and how these challenges can be rebutted. Presenting a case for the defense seems preferable to maintaining a pretense of impartiality in a debate in which I have been an active participant. Although there is no reason why a single hypothesis should explain all examples of imprinting, it is desirable to minimize superfluous hypotheses and expand the explanatory domain of an already successful theory.

Diallelic Models

The models discussed above find an ESS $\{x^*, y^*\}$ from among an infinite set of alleles $\{x, y\}$ in which maternal expression x and paternal expression y are allowed to take any non-negative value (26). A different approach has been taken by Spencer and coworkers (76, 77), who presented a series of models in which there are two alleles: an unimprinted allele $\{z, z\}$ and an imprinted allele $\{0, z\}$ or $\{z, 0\}$. In their models, the level of expression z is implicitly a constant that does not evolve. Contrary to predictions of ESS models, these authors found that imprinted alleles can invade in the absence of multiple paternity, that multiple paternity has no effect on the dynamics of models with maternal-silencing, and that stable polymorphisms of imprinted and unimprinted alleles are possible.

When models have such different structures, it is hardly surprising that they make different predictions. A choice between the models' predictions therefore devolves upon which set of simplifying assumptions are deemed more relevant to the question of interest. Haig (26) argued that the diallelic models of Spencer and colleagues ignore the effects of ongoing mutation and therefore describe a process of short-term rather than long-term evolution (see 10, 30 for discussion

of this distinction). From this perspective, the demonstration that an imprinted allele can displace an unimprinted allele in the absence of multiple paternity is merely a demonstration that a total level of expression z is sometimes superior to $2z$ when no constraints are placed on the evolutionary plausibility of z. Consistent with this interpretation, a dominant genetic modifier that alters expression from $\{z, z\}$ to $\{z/2, z/2\}$ can invade a population fixed for $\{z, z\}$ under the same conditions as can imprinted alleles $\{z, 0\}$ or $\{0, z\}$ if multiple paternity is absent, whereas if multiple paternity is present, the imprinted alleles can invade under a subset of conditions for which the modifier cannot invade, but the modifier can never invade under conditions for which neither imprinted allele can invade (39).

Reverse Imprinting

Some loss-of-function mutations of imprinted genes and some uniparental disomies—i.e., an individual with both copies of a chromosome derived from one parent—have phenotypes that have been interpreted as contradicting the kinship theory (40, 41). *Mash2*, for example, is a paternally silent locus that is strongly expressed in early mouse trophoblast. Mutational inactivation of the maternally derived allele results in embryonic death with major placental defects, specifically, absence of spongiotrophoblast and poor development of labyrinthine trophoblast, but excess development of trophoblast giant cells (13, 83). *Mash2* has thus been interpreted as a paternally silent enhancer of placental growth, whereas the kinship theory predicts that placental growth enhancers will be maternally silent. Similarly, paternal disomies in mice of proximal chromosome 7 and distal chromosome 17 are associated with deleterious postnatal effects that have been interpreted as contradicting the kinship theory (4).

For the most part, these criticisms appear to result from a simple misunderstanding of the nature of an asymmetric ESS. If maternally derived alleles favor a level of gene product X_m and paternally derived alleles favor a level of gene product X_p, where $X_m < X_p$, then the theory predicts that the paternal allele will produce X_p and the maternal allele will be silent at the ESS. Between X_m and X_p, changes in the level of gene product are predicted to have opposite effects on patrilineal and matrilineal inclusive fitness, but increases above X_p and decreases below X_m will be detrimental to both (21). A maternal disomy at this locus, or knockouts of the paternally derived allele, would result in zero gene product, whereas a paternal disomy would result in $2X_p$. Therefore, both kinds of perturbation would result in levels of gene expression that lie outside the zone of conflict and would be associated with phenotypes that are detrimental to both patrilineal and matrilineal inclusive fitness. Nevertheless, uniparental disomies and loss-of-function mutations can provide evidence for testing the kinship hypothesis in the clues they provide about the phenotypic effect of changes in gene expression within the zone of conflict.

Iwasa and coworkers (42, 44) have developed models to explain how the anomalous cases of *Mash2* and of paternal disomies with retarded embryonic growth can be made compatible with the kinship theory. In the case of paternal disomies, they

considered expression of a locus that increased an offspring's relative allocation of resources to placental, rather than embryonic, growth. Paternally derived alleles were shown to favor greater proportional allocation to placental growth because this increased the total uptake of maternal resources. The ESS at such a locus would therefore have the form $\{0, y^*\}$, with paternal disomies producing $2y^*$, a level of production that could result in excessive allocation to the placenta at the expense of the embryo's own growth ("overshoot"). Thus, their model is a special case of the general principle that disomies will result in phenotypes that are detrimental to both matrilineal and patrilineal inclusive fitness. In the case of *Mash2*, these authors argued that preferential maternal expression of an embryonic growth enhancer would be predicted if high growth rates were associated with an increased risk of early abortion (44). Although the model is ingenious, it seems simpler to explain the phenotype of *Mash2* knockouts as an example of "overshoot" in the allocation of various cell types during placental development (21).

Imprinting Where Not Predicted

Imprinting in Oviparous Vertebrates The kinship theory posits that the principal selective force favoring the major effects of genomic imprinting on mammalian development has been conflict between the maternally and paternally derived genomes of offspring over the level of maternal investment. As a corollary, genomic imprinting is not expected to have major developmental effects in oviparous taxa because an offspring's paternally derived genome can do nothing to influence the level of maternal investment (with the caveat that post-hatching interactions among asymmetric kin could favor imprinting of genes affecting social behaviors). Therefore, the observation of methylation differences between maternally and paternally transmitted transgenes in zebrafish (54)—a species without postzygotic parental care—has been interpreted as inconsistent with the theory (55).

The supposed inconsistency with the kinship theory appears to be a misinterpretation of the theory's domain of explanation. In fact, the theory presupposes the existence of differences between maternal and paternal alleles; otherwise there would be nothing to select upon. What the theory does claim is that given a mechanism that causes alleles at some loci to have different levels of maternal and paternal expression—even if these differences are initially small—the cumulative processes of natural selection and new mutation will result in qualitative differences in gene expression resulting in major phenotypic effects when there is a conflict of interests between maternal and paternal genomes, but not when such conflicts are absent. Thus, the existence of differential methylation in zebrafish adds weight to the kinship theory because it provides evidence of a pre-existing mechanism for generating parent-specific differences, but only so long as differential methylation does not have major phenotypic effects. The kinship theory therefore receives support from the observation that androgenetic and gynogenetic zebrafish are phenotypically normal (8, 78). The adaptive function of methylation and why it should differ between male and female germlines are important questions upon which the kinship theory is silent.

Imprinting in Monogamous Species In the context of parent-offspring relations, the kinship theory predicts that the "interests" of maternally derived and paternally derived alleles are identical when all costs to a mother's RRV are associated with an equal cost to the father's RRV, and vice versa. This would be the case, for example, if individuals of both sexes were constrained to have all of their offspring with a single partner. Therefore, there would be no selective force favoring the origin of imprinted expression in a species with strict lifetime monogamy. For this reason, Hurst (38, 41) argued that the existence of imprinting in "monogamous" *Peromyscus polionotus* (88) and in predominantly self-fertilizing *Arabidopsis thaliana* (70) adds to accumulating evidence against the kinship theory.

The kinship theory can parry this thrust in two ways. The first is to question whether *P. polionotus* and *A. thaliana* are truly monogamous (25). The rate of partner change between successive litters of *P. polionotus* is substantial (20% in one study; 11) and the rate of outcrossing in *A. thaliana* probably exceeds the per locus mutation rate (74). Thus, serial monogamy in *P. polionotus* is consistent with continuing selection for imprinting (25), and the same may be true of the mating system of *A. thaliana*, although this case is less strong. The second is to note that if maternal and paternal alleles agree on the same level of combined gene expression X^*, the unimprinted strategy $\{X^*/2, X^*/2\}$ is the midpoint on a continuum of possible symmetric ESSs from $\{0, X^*\}$ to $\{X^*, 0\}$. If a locus evolved imprinted expression because maternal and paternal alleles previously favored different levels of expression—but the mating system changed so that maternal and paternal alleles favor the same level—there are many ways to adjust gene expression to achieve the new consensus that do not involve the loss of imprinting (61).

For the above reasons, the kinship theory does not predict a rapid loss of imprinting when a species' mating system shifts toward greater monogamy. However, the theory does predict that the shift will result in reduced expression of paternally expressed genes and reduced conflict costs. Thus, the kinship theory is supported by the observation that in both *P. polionotus and A. thaliana* the growth-promoting effects of paternal alleles appear attenuated relative to related taxa with a higher incidence of partner change (70, 88).

Imprinting of Genes Affecting Maternal Behavior Natural selection for imprinted expression is not expected at loci whose effects are limited to symmetric kin. Offspring are symmetric kin of their mothers (i.e., a mother's maternally derived and paternally derived alleles are equally likely to be transmitted to each of her offspring). Therefore, the kinship theory does not predict imprinting of loci affecting maternal behavior unless maternal care has fitness consequences for other (asymmetric) kin of the mother (such as the female's own mother or her matrilineal half-sisters). However, null mutations of two paternally expressed loci in mice result in impaired maternal care (48, 50). The implications for the kinship theory are ambiguous because both null mutations also cause prenatal growth retardation. Imprinting of these loci could therefore be explained by their effects on growth, without requiring a separate explanation for the parent-of-origin effects on maternal behavior. The more interesting possibility is that the promotion

of prenatal growth and postnatal maternal behavior are pleiotropically associated because both serve patrilineal interests. If so, this would imply that increased care for a female mouse's own offspring has occurred at the expense of investment in other matrilineal kin (25).

Other Hypotheses

Alternative explanations for the evolution of imprinting have continued to proliferate since the reviews of Haig & Trivers (28) and Hurst (37), but I do not attempt a new review here. Rather, I limit myself to some brief comments on the ovarian time-bomb hypothesis (87) because this is perhaps the most commonly cited alternative to the kinship theory, and the minimization of variance hypothesis (37) because this has been claimed to explain many of the same phenomena as the kinship theory.

Varmuza & Mann proposed (87) that genomic imprinting is an adaptation to protect eutherian females from the development of invasive trophoblast in ovarian germ cell tumors (87; see 19, 59, 75 for critiques). My previous argument that this hypothesis could not explain the existence of paternally silent growth inhibitors (19, 28) has been shown to be fallacious (44). Nevertheless, I believe that the kinship theory—with its emphasis on the conflicting interests of maternal and paternal genomes—provides a more satisfying general explanation for the evolution of imprinting because it can explain many more phenomena, including the imprinting of genes affecting seed development where there is no risk of germ cell tumors (29, 30). Moreover, theories based on genetic conflicts can explain why trophoblast is often invasive (16), whereas this is merely accepted without explanation in Varmuza & Mann's hypothesis.

Hurst & McVean (41, p. 702) claimed that most of the features of imprinting that are explained by the kinship theory are also explained by a model in which "imprinting is an adaptation to control growth rates in embryos in which the uptake of resources is continuous and flexible over time." This appears to be Hurst's (40) proposal that imprinting is a means whereby cooperative offspring minimize the variance in resource extraction from their mother. The central assumption of this hypothesis is that a lower variance in the rate of transcription can be achieved with monoallelic expression than with biallelic expression. This assumption is questionable. One could argue instead that coefficients of variation will be lower in a biallelic system because stochastic processes occur independently at the two loci (6).

There is an important sense in which neither of these hypotheses—nor any other hypothesis that attempts to explain the origin of imprinting—is an alternative to the kinship theory. An allele's effects when paternally derived are subject to selection solely on their consequences for patrilines, whereas an allele's effects when maternally derived are subject to selection solely on their consequences for matrilines, whether or not its locus is imprinted, and whether or not other factors have played a role in the origin of imprinting. Therefore, if imprinted expression evolves—for whatever reason—the logic of the kinship theory will apply if an allele's expression has consequences for asymmetric kin. Trophoblast growth in Varmuza &

Mann's hypothesis and resource extraction in Hurst's hypothesis clearly have consequences for at least one asymmetric relative (an offspring's mother). Therefore, formal models of these hypotheses will need to take account of the different selective forces acting on alleles of maternal and paternal origin.

SEX CHROMOSOMES

X-Linked Relatedness

Mammalian fathers transmit an X chromosome to their daughters but a Y chromosome to their sons. Thus, an offspring's sex reveals the outcome of meiosis for sex-linked loci of males: forward steps from fathers to daughters (and backward steps from sons to mothers) contribute a factor of one to coefficients of X-linked relatedness, whereas forward steps from fathers to sons (and backward steps from sons to fathers) contribute a factor of zero. As a consequence, coefficients of relatedness will differ for autosomal and X-linked loci if individuals are related via a father-to-offspring link in which the offspring's sex is specified, and any individual that is related to another via a chain that contains a father-to-son link is a nonrelative from the perspective of X-linked loci. As a corollary, X-chromosomal matrilines and patrilines contain fewer individuals than autosomal matrilines and patrilines, but some of the included individuals have higher X-linked than autosomal relatedness. For example, at an autosomal locus, patrilineal relatedness is one half for a paternal half-sib of either sex, whereas at an X-linked locus of a female, patrilineal relatedness is one for a paternal half-sister (all of a father's daughters receive an identical X chromosome) but zero for a paternal half-brother.

Imprinting at X-linked loci will be restricted to females because males lack paternally derived alleles (the distinction between symmetric and asymmetric kin is meaningless for X-linked loci of males). The kinship theory predicts that natural selection favors imprinting when expression of alleles at a locus has fitness consequences for kin with different degrees of matrilineal and patrilineal relatedness at that locus. Symmetric kin at autosomal loci may be asymmetric kin at X-linked loci, or the reverse (the latter requires some degree of inbreeding). For example, a female's full-sibs and their descendants are symmetric autosomal kin, but they are asymmetric X-chromosomal kin whenever sibs are distinguished by sex. That is, a female's full-sisters have higher patrilineal than matrilineal relatedness at X-linked loci ($m = 1/2$, $p = 1$), whereas her full-brothers are matrilineal kin but patrilineal non-kin ($m = 1/2$; $p = 0$). Maternally silent X-linked alleles are therefore predicted to favor full-sisters without regard for costs to brothers (3, 23), whereas paternally silent X-linked alleles are predicted to oppose these effects.

X-Linked Inclusive Fitness

Over the course of several generations, an average X-linked allele spends one third of its time as a maternally derived allele in males, one third as a maternally

TABLE 1 Invasion criteria for new alleles at an X-linked locus

Type of X-linked locus	Expression[a]	Mutant alleles favored if
Biallelic expression, not sex-limited	$\{x, y, z\}$	$\delta W_x + \delta W_y + \delta W_z > 0$
Biallelic expression, female-limited	$\{0, y, z\}$	$\delta W_x + \delta W_z > 0$
Male-limited	$\{x, 0, 0\}$	$\delta W_y > 0$
Paternally silent	$\{x, y, 0\}$	$\delta W_x + \delta W_y > 0$
Maternally silent	$\{0, 0, z\}$	$\delta W_z > 0$
Paternally silent and female-limited	$\{0, y, 0\}$	$\delta W_x > 0$

[a]An allele's strategy is represented by the triplet $\{x, y, z\}$, where x is the allele's level of expression when maternally derived in males; y, its expression when maternally derived in females; and z, its expression when paternally derived in females.

derived allele in females, and one third as a paternally derived allele in females. Therefore, the allele's inclusive fitness effect, δW, will be an equally weighted sum of its effects in each of these circumstances (δW_x, δW_y, δW_z respectively);

$$\delta W = \frac{1}{3}(\delta W_x + \delta W_y + \delta W_z) = \frac{1}{3}\left(\sum_{i=0} m_i \delta a_i + \sum_{j=0} m_j \delta b_j + \sum_{k=0} p_k \delta c_k\right)$$

where m_i, m_j, p_k are the appropriate coefficients of X-linked relatedness.

Conditions favorable to the invasion of a new allele are summarized in Table 1 for different patterns of expression at an X-linked locus. Monoallelic and/or sex-limited expression reduce one or more of δW_x, δW_y, δW_z to zero. At paternally silent loci, δW_z is zero. Therefore, natural selection favors alleles that increase matrilineal inclusive fitness ($\delta W_x + \delta W_y > 0$) without regard for effects on patrilines. As a corollary, experimental or mutational reactivation of paternally silent loci is predicted to be particularly detrimental to patrilines. At maternally silent loci, δW_x and δW_y are zero. Natural selection favors alleles that increase patrilineal inclusive fitness of females ($\delta W_z > 0$) without regard for effects on matrilines.

Haplodiploidy and Other X-Linked Genomes

The entire genome of haplodiploid taxa is effectively X-linked: haploid males develop from unfertilized eggs and lack paternally derived alleles; diploid females develop from fertilized eggs and receive alleles from both parents. These genetic systems thus provide a "natural experiment" in which the selective forces acting on X chromosomes are not masked by selection acting on autosomes.

Hamilton proposed that the repeated evolution of nonreproductive helpers in the haplodiploid Hymenoptera was a consequence of increased relatedness among sisters: daughters of a singly mated female share three quarters of their genes by descent, rather than half, because all of their haploid father's sperm carry an identical genome (31). The boost to relatedness among sisters caused by haplodiploidy

(and X-linkage) results solely from increased patrilineal relatedness; $r = 3/4$ is an average of $m = 1/2$ and $p = 1$ (14). From this perspective, the daughters of a singly mated female are a matrilineal sibship but a patrilineal clone. Thus, the kinship theory predicts that paternally derived alleles will be under stronger selection than maternally derived alleles to promote behaviors that benefit sisters if single-mating is common. If a female mates with many males, most of her daughters will be maternal half-sibs, and the relatedness asymmetries are reversed; it is maternally derived alleles that are more strongly predisposed to favor sisters. Recent evidence for the existence of imprinting in a parasitoid wasp (9) strengthens the possibility that imprinted genes will also be found to play an important role in the control of hymenopteran social behaviors (14, 22).

Many of the kinship theory's predictions about X-linked loci and haplodiploidy also apply to parahaplodiploid systems of paternal genome loss that occur in coccoid scale insects and sciarid flies, among other taxa (35). In these groups, males develop from fertilized eggs, but only a male's maternally derived alleles are transmitted to his offspring. The similarity to haplodiploidy is particularly close for scale insects because the paternal genome of males is inactivated or eliminated during early development (64). Therefore, paternally derived alleles of males are expected to have minimal phenotypic effects. In sciarid flies, on the other hand, paternally derived alleles of males are expressed (57) and are therefore subject to selection on their effects on patrilineal kin. Paternally derived alleles of males might therefore be selected to promote reproduction by sisters in their own sibship at the expense of the males' own reproduction. This possibility does not arise in most sciarids because females produce offspring of a single sex only, either all sons or all daughters (12).

The elimination of the paternal genome in scale insects and sciarid flies provides a dramatic demonstration that maternally derived and paternally derived genomes are not equivalent in these taxa, but this form of imprinting does not directly compare with the locus-specific imprinting of mammals in which alleles of both parental origins are transmitted to offspring. I have argued that these genetic systems have evolved as the outcome of a system of meiotic drive in which parental origin marks one set of chromosomes for elimination (17, 18).

X Inactivation

Two patterns of X inactivation occur in female mammals. Paternal X inactivation is observed in the somatic cells of female marsupials (7) and in trophoblast and yolk sac of mice (66, 82). Random X inactivation occurs in the somatic cells of female eutherians and (probably) in human trophoblast (51); only a single X is active in any given cell, but the paternal and maternal X are active in different cells of the same female (52). This section discusses some of the implications of X inactivation for the kinship theory and briefly comments on possible implications of the theory for understanding the evolution of paternal X inactivation.

Paternal X Inactivation Natural selection at paternally silent loci favors alleles that increase matrilineal inclusive fitness without regard for effects on patrilines (Table 1). Therefore, X-linked genes expressed in female marsupials and in trophoblast and yolk sac of female mice are predicted to evolve strong biases in favor of matrilineal interests. In the specific context of maternal-embryo relations in mice, reactivation of the inactive paternal X chromosome is predicted to retard embryonic growth.

Evidence that murine X chromosomes harbor inhibitors of placental growth comes from a recent knockout of *Xist* (53). When a disabled copy of *Xist* was inherited maternally, female offspring were viable because the paternal X chromosome (with an intact copy of *Xist*) was inactivated in extraembryonic membranes. By contrast, there was a profound failure of placental development, associated with early death, when an embryo's paternal copy of *Xist* was disabled, presumably because both copies of the X chromosome remained active in placental tissues. The lethal effect could be ascribed to the increased number of active X chromosomes (rather than to the expression of imprinted genes on the paternal X) because an XO mouse that inherited a disabled paternal copy of *Xist* was viable.

Moore and colleagues (60, 62) have suggested that paternal X inactivation may be the outcome of an evolutionary conflict between maternal and paternal interests. In this view, inactivation of the paternal X was initiated by maternally derived genes because the paternal X of an ancestral mammal carried imprinted growth enhancers that benefited patrilines at the expense of matrilines. An alternative hypothesis would view the evolution of paternal X inactivation as a response to a matrilineal bias in the effects of X-linked genes. In this scenario, paternally derived alleles would have gained an advantage from shutting down their own chromosome because ancestral X chromosomes carried unimprinted growth inhibitors that benefited the matriline at the expense of the patriline.

Why might unimprinted X-linked loci have possessed a matrilineal bias in their effects? At an autosomal locus with biallelic expression in both sexes, a new allele cannot increase in frequency if its costs when present in females outweigh its benefits when present in males (or vice versa), nor can it increase in frequency if its costs to matrilineal kin when maternally derived exceed its benefits to patrilineal kin when paternally derived (or vice versa). Therefore, evolution at autosomal loci is not expected to systematically favor females over males nor matrilines over patrilines. By contrast, at an X-linked locus with biallelic expression in females and hemizygous expression in males, a new allele's effects when present in females are given twice the weight of its effects when present in males, and its effects on matrilines when maternally derived are given twice the weight of its effects on patrilines when paternally derived. Therefore, allelic substitutions at such loci will tend to favor females at the expense of males and matrilines at the expense of patrilines.

Random X Inactivation At an autosomal locus, maternally derived and paternally derived alleles are expressed in the same cells and contribute their gene

products to a single pool. Whichever allele favors the higher level of gene product is predicted to produce its favored amount with the other allele silent. By contrast, at a locus subject to random X inactivation, maternally derived and paternally derived alleles contribute their gene products to different pools: Each allele can seemingly produce its favored amount in different cells. Thus, the logic of the loudest-voice-prevails principle does not apply at imprinted loci subject to random X inactivation (particularly at loci with cell-autonomous effects). Therefore, if both alleles are expressed, but at different levels, imprinting may be more difficult to detect at X-linked loci than at autosomal loci. Moreover, if both alleles are active, "qualitative" mutations at imprinted X-linked loci will be subject to natural selection on their effects for both matrilines and patrilines.

Sex-Specific Expression Hypothesis

Paternally derived alleles at X-linked loci are restricted to females. Therefore, it has been proposed that there will be selection for imprints on the paternal X which are specifically favorable to females (45); that genomic imprinting may function as a mechanism of haplodiploid sex determination (68); and that imprinting of X-linked loci may be a hormone-independent mechanism of achieving sexual dimorphism during mammalian development (43, 72).

Could imprinting be favored at X-linked loci independently of effects on asymmetric kin? There is no reason in principle why not. Indeed, the presence of a paternally derived genome appears to determine female development in *Nasonia vitripennis* (9). Once imprinting has evolved at an X-linked locus, for whatever reason, the selective forces acting on an allele's effects when paternally derived will be female-specific and specific to patrilineal kin; both sets of forces must be considered in evolutionary models, and their relative importance becomes an empirical question.

Iwasa & Pomiankowski (43) have argued that the pattern of X-linked imprinting in humans and mice contradicts predictions of the kinship theory. They proposed instead that imprinting has evolved to control sex-specific gene expression in early embryos before gonadal sex determination. Two lines of evidence are claimed to be inconsistent with the kinship theory. First, experimental data from mice show that X^p inhibits embryonic growth relative to X^m (superscripts refer to the maternal or paternal origin of the X chromosome). Second, X^p0 humans have greater social skills than X^m0 humans (73).

The claim that X^p inhibits embryonic growth relative to X^m is based on the observation that X^mY and X^m0 embryos are larger at 10.5 days post coitum than X^mX^p embryos, which, in turn, are larger than X^p0 embryos (84). In comparisons of X^p0 with X^m0 embryos and X^mX^p with X^m0 embryos, X^p is indeed associated with poorer growth. However, in comparisons of $X^mX^mX^p$ with X^mX^p embryos (71) and X^mX^mY embryos with X^mX^pY embryos (79), X^m is associated with poorer growth. A plausible interpretation of these data is that trophoblast develops very poorly if its only X chromosome is a normally inactive X^p (46), but that the presence

of two active X^m chromosomes also inhibits development of trophoblast (80). The slow growth of X^mX^p relative to X^m0 embryos appears to be an effect of having two (rather than one) active X chromosomes during early development (2, 81). These interpretations are consistent with predictions of the kinship theory that the effects of unimprinted loci on the X chromosome will show a matrilineal bias and that X-linked loci expressed in tissues with paternal X inactivation will have been selected to favor matrilineal interests without regard for costs to patrilines.

For Iwasa & Pomiankowski (43), the observed differences between X^p0 and X^m0 humans suggested sexual dimorphism in the adaptive value of social skills (43). These authors did not discuss effects on kin, but if their hypothesis is to be made maximally distinct from the kinship theory, such sex differences would be reflected solely in the individual fitness component of inclusive fitness. From the perspective of the kinship theory, the observed differences would be interpreted as evidence that the expression of social skills has had fitness implications for asymmetric kin of females. I suspect that not enough is currently known about the context of human social evolution, nor about the properties of imprinted loci on the X chromosome, to make predictions that discriminate between the hypotheses.

On a final note, marsupials show substantial sexual differentiation before gonadal sex determination (65, 86), yet inactivation of the paternal X has the effect that the single active X of females is maternally derived (as is the single X of males)—not what one would expect if the principal function of X-linked imprinting were to achieve sex-specific expression. A similar argument applies to paternal X inactivation in mouse trophoblast.

Y Chromosomes

X and Y chromosomes segregate at male meiosis I and have opposite patterns of inheritance with respect to the sex of a male's offspring. Genes on the Y chromosome are transmitted to all of his sons but none of his daughters, and from these sons to their sons, and so on, in an unbroken chain of male-to-male transmission. Because Y-linked genes are restricted to males and are always paternally derived, they are expected to favor the growth of their own embryo at the expense of the mother (36) and to favor the growth of full-brothers at the expense of full-sisters and maternal half-siblings of either sex (85).

PROSPECTS

During the life of an individual organism, gene expression responds adaptively to information from the organism's internal and external environment. These responses are not limited to effects of the contemporaneous environment but include effects of past environments. If such evolved responses are possible within a generation, there seems no reason in principle why they could not also occur between generations. Until recently, however, it was generally believed that each individual

starts life with a blank slate; historical (epigenetic) information was not transferred between generations. Somatic cells, it was believed, might retain information acquired during the current generation, but either germ cells were quarantined from such effects or all information was wiped clean during gametogenesis.

Genomic imprinting conclusively demonstrates that at least one bit of information (maternal versus paternal origin) can be transmitted epigenetically from one generation to the next. If so, could not other useful information be similarly transmitted? For example, the optimal allocation of resources in good times between fat stores and growth might differ for individuals in environments with, on average, a famine every two generations versus a famine every ten generations. If past famines could leave an epigenetic trace in the germ line, these modifications could adaptively modulate gene expression in the current generation. Many similar examples can be envisioned.

The initial selective advantage favoring the evolution of contingent responses to information from past environments need have nothing to do with effects on asymmetric kin, but there are at least two reasons why such information would not be symmetrically transmitted by both sexes. First, males and females may have different information. The nondispersing sex, for example, would have better information about local conditions. Second, male and female germ lines are so different that it seems unlikely that identical DNA modifications would occur in both. Because of these profound differences between the biochemical environments of male and female germ lines—one actively dividing in adult life, the other arrested at mid-meiosis since early development—parental origin is perhaps the simplest information that could be transmitted to the next generation. Future work will show whether it is an exception to a general rule that information is not transmitted or is just one piece of information among many.

ACKNOWLEDGMENTS

Austin Burt, Glenn Herrick, Rolf Ohlsson, Jon Seger, and Robert Trivers have all made helpful comments on the manuscript.

LITERATURE CITED

1. Bartolomei MS, Tilghman SM. 1997. Genomic imprinting in mammals. *Annu. Rev. Genet.* 31:493–525
2. Burgoyne PS, Thornhill AR, Boudrean SK, Darling SM, Bishop CE, Evans EP. 1995. The genetic basis of XX-XY differences present before gonadal sex differentiation in the mouse. *Philos. Trans. R. Soc. London B* 350:253–61
3. Burt A, Trivers R. 1998. Genetic conflicts in genomic imprinting. *Proc. R. Soc. London B* 265:2393–97
4. Cattanach BM, Barr JA, Evans EP, Burtenshaw M, Beechey CV, et al. 1992. A candidate mouse model for Prader-Willi syndrome which shows an absence of Snrpn expression. *Nat. Genet.* 2:270–74
5. Constância M, Pickard B, Kelsey G, Reik

W. 1998. Imprinting mechanisms. *Genome Res.* 8:881–900
6. Cook DL, Gerber AN, Tapscott SJ. 1998. Modeling stochastic gene expression: implications for haploinsufficiency. *Proc. Natl. Acad. Sci. USA* 95:15641–46
7. Cooper DW, Johnston PG, Watson JM, Graves JAM. 1993. X-inactivation in marsupials and monotremes. *Semin. Devel. Biol.* 4:117–28
8. Corley-Smith GE, Lim CJ, Brandhorst BP. 1996. Production of androgenetic zebrafish (*Danio rerio*). *Genetics* 142:1265–76
9. Dobson S, Tanouye M. 1996. The paternal sex ratio chromosome induces chromosome loss independently of *Wolbachia* in the wasp *Nasonia vitripennis*. *Dev. Genes Evol.* 206:207–17
10. Eshel I. 1996. On the changing concept of evolutionary population stability as a reflection of a changing point of view in the quantitative theory of evolution. *J. Math. Biol.* 34:485–510
11. Foltz DW. 1981. Genetic evidence for long-term monogamy in a small rodent, *Peromyscus polionotus*. *Am. Nat.* 117:665–75
12. Gerbi SA. 1986. Unusual chromosome movements in sciarid flies. In *Germ Line – Soma Differentiation, Results and Problems in Cell Differentiation*, ed. W Hennig, 13:71–104. Berlin: Springer Verlag
13. Guillemot F, Caspary T, Tilghman SM, Copeland NG, Gilbert DJ, et al. 1995. Genomic imprinting of *Mash2* required for trophoblast development. *Nat. Genet.* 9:235–41
14. Haig D. 1992. Intragenomic conflict and the evolution of eusociality. *J. Theor. Biol.* 156:401–3
15. Haig D. 1992. Genomic imprinting and the theory of parent-offspring conflict. *Semin. Devel. Biol.* 3:153–60
16. Haig D. 1993. Genetic conflicts in human pregnancy. *Q. Rev. Biol.* 68:495–532
17. Haig D. 1993. The evolution of unusual chromosomal systems in sciarid flies: intragenomic conflict and the sex ratio. *J. Evol. Biol.* 6:249–61
18. Haig D. 1993. The evolution of unusual chromosomal systems in coccoids: extraordinary sex ratios revisited. *J. Evol. Biol.* 6:69–77
19. Haig D. 1994. Refusing the ovarian time bomb. *Trends Genet.* 10:346–47
20. Haig D. 1996. Placental hormones, genomic imprinting, and maternal-fetal communication. *J. Evol. Biol.* 9:357–80
21. Haig D. 1997. Parental antagonism, relatedness asymmetries, and genomic imprinting. *Proc. R. Soc. London B* 264:1657–62
22. Haig D. 1998. Mother's boy or daddy's girl? Sex determination in Hymenoptera. *Trends Ecol. Evol.* 13:380–81
23. Haig D. 1999. Genomic imprinting, sex-biased dispersal, and social behavior. *Ann. NY Acad. Sci.* 907:149–63
24. Haig D. 1999. Asymmetric relations: internal conflicts and the horror of incest. *Evol. Hum. Behav.* 20:83–98
25. Haig D. 1999. Genomic imprinting and the private life of *Peromyscus polionotus*. *Nat. Genet.* 22:131
26. Haig D. 1999. Multiple paternity and genomic imprinting. *Genetics* 151:1229–31
27. Haig D, Graham C. 1991. Genomic imprinting and the strange case of the insulin-like growth factor-II receptor. *Cell* 64:1045–46
28. Haig D, Trivers R. 1995. The evolution of parental imprinting: a review of hypotheses. See Ref. 65a, pp. 17–28
29. Haig D, Westoby M. 1989. Parent-specific gene expression and the triploid endosperm. *Am. Nat.* 134:147–55
30. Haig D, Westoby M. 1991. Genomic imprinting in endosperm: its effects on seed development in crosses between species and between different ploidies of the same species, and its implications for the evolution of apomixis. *Philos. Trans. R. Soc. London B* 333:1–13
31. Hamilton WD. 1964. The genetical

evolution of social behaviour. II. *J. Theor. Biol.* 7:17–52
32. Hamilton WD. 1972. Altruism and related phenomena, mainly in social insects. *Annu. Rev. Ecol. Syst.* 3:193–232
33. Hammerstein P. 1996. Darwinian adaptation, population genetics and the streetcar theory of evolution. *J. Math. Biol.* 34:511–32
34. Hayward BE, Moran V, Strain L, Bonthron DT. 1998. Bidirectional imprinting of a single gene: *GNAS1* encodes maternally, paternally, and biallelically derived proteins. *Proc. Natl. Acad. Sci. USA* 95:15475–80
35. Herrick G, Seger J. 1999. Imprinting and paternal genome elimination in insects. See Ref. 65a, pp. 41–71
36. Hurst LD. 1994. Embryonic growth and the evolution of the mammalian Y chromosome. I. The Y as an attractor for selfish growth factors. *Heredity* 73:223–32
37. Hurst LD. 1997. Evolutionary theories of genomic imprinting. In *Genomic Imprinting*, ed. W Reik, A Surani, pp. 211–237. Oxford, UK: Oxford Univ. Press
38. Hurst LD. 1998. *Peromysci*, promiscuity and imprinting. *Nat. Genet.* 20:315–16
39. Hurst LD. 1999. Is multiple paternity necessary for the evolution of genomic imprinting? *Genetics* 153:509–12
40. Hurst LD, McVean GT. 1997. Growth effects of uniparental disomies and the conflict theory of genomic imprinting. *Trends Genet.* 13:436–43
41. Hurst LD, McVean GT. 1998. Do we understand the evolution of genomic imprinting? *Curr. Opin. Genet. Dev.* 8:701–8
42. Iwasa Y. 1998. The conflict theory of genomic imprinting: How much can be explained? *Curr. Top. Devel. Biol.* 40:255–93
43. Iwasa Y, Pomiankowski A. 1999. Sex specific X chromosome expression caused by genomic imprinting. *J. Theor. Biol.* 197:487–95
44. Iwasa Y, Mochizuki A, Takeda Y. 1999. The evolution of genomic imprinting: abortion and overshoot explain aberrations. *Evol. Ecol. Res.* 1:129–50
45. Jablonka E, Lamb MJ. 1990. The evolution of heteromorphic sex chromosomes. *Biol. Rev.* 65:249–76
46. Jamieson RV, Tan SS, Tam PPL. 1998. Retarded postimplantation development of X0 mouse embryos: impact of the parental origin of the monosomic X chromosome. *Dev. Biol.* 201:13–25
47. Latham KE. 1999. Epigenetic modification and imprinting of the mammalian genome during development. *Curr. Top. Dev. Biol.* 43:1–49
48. Lefebvre L, Viville S, Barton SC, Ishino F, Keverne EB, Surani MA. 1998. Abnormal maternal behaviour and growth retardation associated with loss of the imprinted gene *Mest. Nat. Genet.* 20:163–69
49. Lessels CM, Parker GA. 1999. Parent-offspring conflict: the full-sib–half-sib fallacy. *Proc. R. Soc. London B* 266:1637–43
50. Li LL, Keverne EB, Aparicio SA, Ishino F, Barton SC, Surani MA. 1999. Regulation of maternal behavior and offspring growth by paternally expressed *Peg3*. *Science* 284:330–33
51. Looijenga LHJ, Gillis AJM, Verkerk AJMH, van Putten WLJ, Oosterhuis JW. 1999. Heterogenous X inactivation in trophoblastic cells of human full-term female placentas. *Am. J. Hum. Genet.* 64:1445–52
52. Lyon MF. 1999. Imprinting and X-chromosome inactivation. See Ref. 65a, pp. 73–90
53. Marahrens Y, Panning B, Dausman J, Strauss W, Jaenisch R. 1997. *Xist*-deficient mice are defective in dosage compensation but not spermatogenesis. *Genes Dev.* 11:156–166
54. Martin CC, McGowan R. 1995. Parent-of-origin specific effects on the methylation of a transgene in the zebrafish, *Danio rerio*. *Dev. Genet.* 17:233–39
55. McGowan R, Martin CC. 1997. DNA methylation and genome imprinting in the

zebrafish, *Danio rerio*: some evolutionary ramifications. *Biochem. Cell Biol.* 75:499–506

56. Mendel G. 1909 [1865]. Experiments in plant hybridisation. In *Mendel's Principles of Heredity*, transl. W Bateson. Cambridge, UK: Cambridge Univ. Press. (From German)
57. Metz CW. 1938. Chromosome behavior, inheritance and sex determination in *Sciara*. *Am. Nat.* 72:485–520
58. Mochizuki A, Takeda Y, Iwasa Y. 1996. The evolution of genomic imprinting. *Genetics* 144:1283–95
59. Moore T. 1994. Refusing the ovarian time bomb. *Trends Genet.* 10:347–48
60. Moore T, Haig D. 1991. Genomic imprinting in mammalian development: a parental tug-of-war. *Trends Genet.* 7:45–49
61. Moore T, Mills W. 1999. Imprinting and monogamy. *Nat. Genet.* 22:130–31
62. Moore T, Hurst LD, Reik W. 1995. Genetic conflict and evolution of mammalian X-chromosome inactivation. *Dev. Genet.* 17:206–11
63. Morison IM, Reeve AE. 1998. A catalogue of imprinted genes and parent-of-origin effects in humans and animals. *Hum. Mol. Genet.* 7:1599–1609
64. Nur U. 1989. Reproductive biology and genetics. In *Armoured Scale Insects, Their Biology, Natural Enemies and Control*, ed. D Rosen, A:A179–90. Amsterdam: Elsevier
65. O WS, Short RV, Renfree MB, Shaw G. 1988. Primary genetic control of somatic sexual differentiation in a mammal. *Nature* 331:716–17

65a. Ohlsson R, Hall K, Ritzen M. 1995. *Genomic Imprinting: Causes and Consequences*. Cambridge, UK: Cambridge Univ. Press

66. Papaioannou VE, West JD. 1981. Relationship between the parental origin of the X chromosomes, embryonic cell lineage and X chromosome expression in mice. *Genet. Res.* 37:183–97
67. Parker GA. 1985. Models of parent-offspring conflict. V. Effects of the behaviour of the two parents. *Animal Behav.* 33:519–33
68. Poirié M, Périquet G, Beukeboom L. 1992. The hymenopteran way of determining sex. *Semin. Dev. Biol.* 3:357–61
69. Sapienza C. 1989. Genome imprinting and dominance modification. *Ann. NY Acad. Sci.* 564:24–38
70. Scott RJ, Spielman M, Bailey J, Dickinson HG. 1998. Parent-of-origin effects on seed development in *Arabidopsis thaliana*. *Development* 125:3329–41
71. Shao C, Takagi N. 1990. An extra maternally derived X chromosome is deleterious to early mouse development. *Development* 110:969–75
72. Skuse DH. 1999. Genomic imprinting of the X chromosome: a novel mechanism for the evolution of sexual dimorphism. *J. Lab. Clin. Med.* 133:23–32
73. Skuse DH, James RS, Bishop DVM, Coppin B, Dalton P, et al. 1997. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* 387:705–8
74. Snape JW, Lawrence MJ. 1971. The breeding system of *Arabidopsis thaliana*. *Heredity* 27:299–302
75. Solter D. 1994. Refusing the ovarian time bomb. *Trends Genet.* 10:346
76. Spencer HG, Clark AG, Feldman MW. 1999. Genetic conflicts and the evolutionary origin of genomic imprinting. *Trends Ecol. Evol.* 14:197–201
77. Spencer HG, Feldman MW, Clark AG. 1998. Genetic conflicts, multiple paternity and the evolution of genomic imprinting. *Genetics* 148:893–904
78. Streisinger G, Walker C, Dower N, Knauber D, Singer F. 1981. Production of clones of homozygous diploid zebra fish (*Brachydanio rerio*). *Nature* 291:293–96
79. Tada T, Takagi N, Adler ID. 1993. Parental imprinting on the mouse X chromosome: effects on the early development of

X0, XXY and XXX embryos. *Genet. Res.* 62:139–48
80. Takagi N. 1991. Abnormal X-chromosome dosage compensation as a possible cause of early developmental failure in mice. *Dev. Growth Different.* 33:429–35
81. Takagi N, Abe K. 1990. Detrimental effects of two active X chromosomes on early mouse development. *Development* 109:189–201
82. Takagi N, Sasaki M. 1975. Preferential inactivation of the paternally derived X chromosome in the extraembryonic membranes of the mouse. *Nature* 256:640–42
83. Tanaka M, Gertsenstein M, Rossant J, Nagy A. 1997. *Mash2* acts cell autonomously in mouse spongiotrophoblast development. *Dev. Biol.* 190:55–65
84. Thornhill AR, Burgoyne PS. 1993. A paternally imprinted X chromosome retards the development of the early mouse embryo. *Development* 118:171–74
85. Trivers R, Burt A. 1999. Kinship and genomic imprinting. See Ref. 65a, pp. 1–21
86. van der Schoot P, Payne AP, Kersten W. 1999. Sex difference in target seeking behavior of developing cremaster muscles and the resulting first visible sign of somatic sexual differentiation in marsupial mammals. *Anat. Rec.* 255:130–41
87. Varmuza S, Mann M. 1994. Genomic imprinting—defusing the ovarian time bomb. *Trends Genet.* 10:118–23
88. Vrana PB, Guan XJ, Ingram RS, Tilghman SM. 1998. Genomic imprinting is disrupted in interspecific *Peromyscus* hybrids. *Nature Genet.* 20:362–65
89. Whitney G. 1976. Genetic substrates for the initial evolution of human sociality. I. Sex chromosome mechanisms. *Am. Nat.* 110:867–75

Annual Review of Ecology and Systematics
Volume 31, 2000

CONTENTS

PREFACE: A Millennial View of Ecology and Systematics, and ARES at Age 30, *Richard F. Johnston* 1

THE KINSHIP THEORY OF GENOMIC IMPRINTING, *David Haig* 9

CENOZOIC MAMMALIAN HERBIVORES FROM THE AMERICAS: Reconstructing Ancient Diets and Terrestrial Communities, *Bruce J. MacFadden* 33

CONSERVATION ISSUES IN NEW ZEALAND, *John Craig, Sandra Anderson, Mick Clout, Bob Creese, Neil Mitchell, John Ogden, Mere Roberts, Graham Ussher* 61

THE EVOLUTION OF PREDATOR-PREY INTERACTIONS: Theory and Evidence, *Peter A. Abrams* 79

THE ECOLOGY AND PHYSIOLOGY OF VIVIPAROUS AND RECALCITRANT SEEDS, *Elizabeth Farnsworth* 107

INBREEDING DEPRESSION IN CONSERVATION BIOLOGY, *Philip W. Hedrick, Steven T. Kalinowski* 139

AFRICAN CICHLID FISHES: Model Systems for Evolutionary Biology, *Irv Kornfield, Peter F. Smith* 163

SHRUB INVASIONS OF NORTH AMERICAN SEMIARID GRASSLANDS, *O. W. Van Auken* 197

THE GRASSES: A Case Study in Macroevolution, *Elizabeth A. Kellogg* 217

THE ECOLOGY OF TROPICAL ASIAN RIVERS AND STREAMS IN RELATION TO BIODIVERSITY CONSERVATION, *David Dudgeon* 239

HARVESTER ANTS (POGONOMYRMEX SPP.): Their Community and Ecosystem Influences, *James A. MacMahon, John F. Mull, Thomas O. Crist* 265

ORIGINS, EVOLUTION, AND DIVERSIFICATION OF ZOOPLANKTON, *Susan Rigby, Clare V. Milsom* 293

EVOLUTIONARY PHYSIOLOGY, *Martin E. Feder, Albert F. Bennett, Raymond B. Huey* 315

MECHANISMS OF MAINTENANCE OF SPECIES DIVERSITY, *Peter Chesson* 343

TEMPORAL VARIATION IN FITNESS COMPONENTS AND POPULATION DYNAMICS OF LARGE HERBIVORES, *J.-M. Gaillard, M. Festa-Bianchet, N. G. Yoccoz, A. Loison, C. Toïgo* 367

IMPACTS OF AIRBORNE POLLUTANTS ON SOIL FAUNA, *Josef Rusek, Valin G. Marshall* 395

ECOLOGICAL RESILIENCE - IN THEORY AND APPLICATION, *Lance H. Gunderson* 425

QUASI-REPLICATION AND THE CONTRACT OF ERROR: Lessons from Sex Ratios, Heritabilities and Fluctuating Asymmetry, *A. Richard Palmer* 441

INVASION OF COASTAL MARINE COMMUNITIES IN NORTH AMERICA: Apparent Patterns, Processes, and , *Gregory M. Ruiz, Paul W. Fofonoff, James T. Carlton, Marjorie J. Wonham, Anson H. Hines* 481

DIVERSIFICATION OF RAINFOREST FAUNAS: An Integrated Molecular Approach, *C. Moritz, J. L. Patton, C. J. Schneider, T. B. Smith* 533

THE EVOLUTIONARY ECOLOGY OF TOLERANCE TO CONSUMER DAMAGE, *Kirk A. Stowe, Robert J. Marquis, Cris G. Hochwender, Ellen L. Simms* 565