Letter to the Editor

Multiple Paternity and Genomic Imprinting

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IN its simplest form, the genetic-conflict hypothesis for the evolution of genomic imprinting posits that multiple paternity of a female's offspring, in combination with postzygotic maternal care, favors differential expression of maternal and paternal alleles in offspring such that the expression of paternal alleles increases the cost of the offspring to its mother, whereas the expression of maternal alleles reduces the cost to the mother (Haig and Westoby 1989; Moore and Haig 1991; Mochizuki *et al.* 1996). The hypothesis has often been phrased in terms of effects on offspring growth, but the underlying logic applies to all fitness-related costs to a mother that benefit her offspring, not only those that affect offspring size. In its more general form, the hypothesis applies to all interactions among relatives that have different maternal and paternal coefficients of relatedness (Haig 1992a, 1997).

Spencer *et al.* (1998) have recently presented a series of diallelic models that appear to contradict key predictions of the genetic-conflict hypothesis. Specifically, Spencer *et al.* (1998) argue that multiple paternity is not necessary for the evolution of imprinting and is irrelevant for understanding maternal inactivation of growth-enhancing genes. If two well-formed evolutionary models come to different conclusions, both models will be correct in their own terms, and their different conclusions must result from different initial assumptions. A choice between the models must then be based on each reader's judgment about which set of initial assumptions is more appropriate to the question being asked. The purpose of this letter is to clarify why Spencer *et al.*'s models and the genetic-conflict hypothesis come to different conclusions and to argue that diallelic models are not appropriate for modeling long-term evolutionary change, although such models are useful for answering questions about short-term changes within populations.

COMPARISON OF MODELS

In the language of evolutionary game theory, the genetic-conflict hypothesis describes a game in which the players are alleles at a locus, strategies are the alleles' patterns of expression, and an unbeatable (Hamilton 1967) or evolutionarily stable strategy (Maynard Smith and Price 1973) is a pattern of expression, which, when adopted by most of the alleles in a population, is noninvasible by alternative strategies. The definition of alleles as players and patterns of expression as strategies means that most, if not all, genetic models can be interpreted as descriptions of games played by genes, even if the models are not expressed in these terms by their authors. This equivalence between game-theoretic and genetic models does not exist if individuals, rather than genes, are the strategists.

For purposes of comparison among models, let an allele's strategy be represented by a two-element vector $\{x, y\}$ of which the first element is the allele's level of expression when maternally derived and the second element the allele's level of expression when paternally derived. An unimprinted strategy occurs when $x = y$ and an imprinted strategy when $x \neq y$. The models of Haig (1996a, 1997) and Mochizuki *et al.* (1996) treat x and y as continuous variables and find a strategy $\{x^*, y^*\}$ that cannot be invaded by alternative strategies $\{x^* + \delta x, y^*\}$ or $\{x^*, y^* + \delta y\}$. Thus, these models implicitly select an unbeatable strategy from among an infinite set of alleles. By contrast, the models of Spencer *et al.* consider only two alleles, imprinted and unimprinted, and then derive fitness criteria that allow one allele to displace the other, or that allow both alleles to coexist at a polymorphic equilibrium. These alleles can be represented by strategies $\{x, x\}$ and $\{x, 0\}$ in Spencer *et al.*'s models of paternal imprinting (*i.e.*, paternal inactivation) and $\{x, x\}$ and $\{0, x\}$ in their models of maternal imprinting. The models do not consider alternative strategies in which there is quantitative, rather than qualitative, variation in gene expression. Therefore, x is implicitly a constant rather than a continuous variable.

Over the long-term evolutionary time scale, mutation generates many different alleles with different expression levels (including different degrees of imprinting), and these alleles are tested against previously established alleles by natural selection. The "infinite-strategy" models of Haig (1996a, 1997) seek a monomorphic equilibrium at which the established allele cannot be invaded by any alternative allele. Thus, these models emphasize noninvasibility and do not consider the pos-

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sibility of polymorphic equilibria. Because the models do not preclude the possibility that no strategy will be unbeatable, the models can be interpreted as demonstrations of the existence or nonexistence of a monomorphic equilibrium as an absorbing state of the system. By contrast, the "two-strategy" models of Spencer *et al.* represent the full dynamics of a diallelic system, including the possibility of polymorphic equilibria, but do not address the stability of equilibria to the introduction of additional alleles.

COMPARISON OF PREDICTIONS

The genetic-conflict hypothesis proposes that genomic imprinting evolves at a locus when maternal and paternal alleles "favor" different total levels of gene product, a condition that Haig (1997) has called parental antagonism. If so, the hypothesis predicts that either the paternal allele or the maternal allele will be silent at an unbeatable strategy, $\{z, 0\}$ or $\{0, z\}$. At such an evolutionary equilibrium, the allele favoring the higher level of gene product produces its favored amount, and the other allele is silent. The strategy is evolutionarily stable because neither allele has an "incentive" to change: the active allele produces its favored amount, so any increase or decrease would be selected against, whereas the silent allele would benefit from a lower level of gene product but cannot reduce its own expression further. Haig (1996a) has called this the "loudest-voice-prevails" principle. The principle does not apply for genes with cell-autonomous effects that are subject to random X-inactivation because, in this case, maternal and paternal alleles can each produce their favored amount in different cells. For this reason, imprinted genes may be more difficult to detect on X chromosomes than on autosomes.

In the absence of parental antagonism, maternal and paternal alleles favor the same overall level of gene product z, and there is no systematic selection for different levels of maternal and paternal expression. Two caveats are necessary. First, if $\{z/2, z/2\}$ is an unbeatable strategy, then any strategy $\{x, y\}$, where $x + y = z$ is also unbeatable (Haig 1997). However, there is no selective reason why x and y should initially depart from equality, and the inevitable occurrence of loss-of-function mutations provides a selective force (albeit weak) against x or y close to zero (Mochizuki *et al.* 1996; Spencer and Barnett 1996). Second, nonequality of x and y could reflect past parental antagonism. That is, if parental antagonism is eliminated by a change in mating system, and this change is associated with natural selection for a lower level of gene product, then the reduction of gene product is most readily accommodated by maintaining silence of the inactive allele and decreasing expression of the active allele.

In Spencer *et al.*'s models of monogamous females, imprinted alleles are sometimes able to supplant, or coexist with, unimprinted alleles. Moreover, the parameter values that allow invasion of the imprinted allele are identical for maternal and paternal imprinting. Therefore, Spencer *et al.* argue, genomic imprinting can evolve in the absence of genetic conflict between maternal and paternal genomes. From a game-theoretic perspective, these results are not unexpected because their two-strategy models do not require that the unimprinted strategy $\{x, x\}$ be superior to all $\{y, y\}$ where $x \neq y$. Thus, Spencer *et al.*'s results merely demonstrate that an imprinted allele is sometimes superior to an unimprinted allele if no constraints are placed on the level of expression of the unimprinted allele. Their models do not address whether it is evolutionarily plausible that a population would initially be fixed for an unimprinted allele that is expressed at such a high level that natural selection would favor a mutant allele that reduced its average expression by half.

Contrary to the predictions of the genetic-conflict hypothesis, multiple paternity of a female's offspring had no effect on the evolution of maternal imprinting in Spencer *et al.*'s models. Once again, the result is a simple consequence of considering only two options, $\{x, x\}$ and $\{0, x\}$. Multiple paternity does not affect the level of gene product favored by maternal alleles, but it does affect the level favored by paternal alleles. In the models of Haig (1996a, 1997), paternal and maternal expression levels are both allowed to evolve. As a result, increases in paternal expression of growth enhancers (due to multiple paternity), $\{x, x + \delta\}$, provide the selective factor that favors alleles with reduced maternal expression, $\{x - \delta, x + \delta\}$. This, in turn, favors further increases in paternal expression, and so on, until maternal alleles are silent and paternal alleles produce their favored amount.

In Spencer *et al.*'s models, stable polymorphisms of imprinted and unimprinted alleles are possible. The authors correctly state that stable polymorphism is not predicted by the genetic-conflict hypothesis in its current form. This is because the models of Haig (1996a, 1997) are designed to find a monomorphic equilibrium, if such exists. Therefore, such models are inadequate, and inappropriate, when imprinting status is polymorphic within populations. On the other hand, these models suggest that Spencer *et al.*'s polymorphic equilibria will not be stable to the introduction of new alleles by mutation.

Population mean fitness sometimes decreases in the models of Spencer *et al.*, and the authors claim that this result is not predicted by game-theoretic models. Evolutionary game theory, however, often predicts a decrease in mean fitness, and suboptimal allocation of parental resources is a general feature of models in which genes expressed in offspring influence how much an offspring receives from its parents (Haig 1992b, 1996b).

Finally, it should be noted that some of Spencer *et*

al.'s conclusions can be interpreted as supportive of the genetic-conflict hypothesis. In this category, I would include the observation that recursion equations are identical for maternal and paternal imprinting when females are monogamous, and the observation that paternal inactivation of growth inhibitors is favored in some regions of the parameter space when females are bigamous but not when females are monogamous.

CONCLUSIONS

Eshel (1996) has contrasted two concepts of equilibrium in evolutionary genetics, which he identifies with models of short-term and long-term evolution. The short-term concept is stability of genotype frequencies within a given finite set of genotypes, and the long-term concept is stability of genotype frequencies against the introduction of any of a large set of potential mutations. Eshel (1996) has shown that the two concepts correspond to equilibria of radically different processes and that the behavior of long-term evolution cannot be fully understood by extrapolation from models of short-term evolution. Many pointless arguments in evolutionary theory are based on one camp modeling the short-term process, and the other the long-term process, with neither camp acknowledging that their models make different assumptions and address different questions. Spencer *et al.*'s criticism of the genetic-conflict hypothesis is an example of this confusion: their models employ the short-term concept of evolutionary stability, whereas the models they criticize address long-term stability.

Given that a gene is imprinted, and that the active allele's level of expression is such that it is deleterious in double dose, short-term models are appropriate in deriving the equilibrium frequency of deleterious loss-of-imprinting mutations (Spencer and Williams 1995), but such models have little to say about the reasons why a single copy of the locus should have such a high level of expression. An answer to this question is the province of long-term models that consider a much larger class of alternative patterns of expression, including alleles with quantitative, as well as qualitative, variation in expression.

J. J. Bull, A. Burt, A. Grafen, M. Ridley, R. L. Trivers, M. Westoby, and C.-I Wu all made helpful comments on earlier drafts of this letter.

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Communicating editor: C.-I Wu