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REVIEW

Reproductive mode and the genetic benefits of polyandry

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Behavioural ecology is currently undergoing a paradigm shift, with the traditional concepts of the choosy, monogamous female and the coadapted gene complex increasingly giving way to the realization that sexual reproduction engenders conflicts, promotes polyandry, and thereby provides females with a cryptic arsenal of postcopulatory processes with which to safeguard their investment in large, costly eggs. As research focuses on reproduction from the female perspective, evidence is emerging that polyandry can provide genetic benefits that enhance female reproductive success. In this review, we propose that reproductive mode is a critically important factor influencing the type of genetic benefits that females gain by mating with more than one male. Among the hypotheses that propose genetic benefits to polyandry, there is a distinction between those that posit benefits from intrinsic (additive) effects of paternal genes in offspring, and those that propose a benefit resulting from defence against incompatibility. Polyandry to acquire superior paternal genes and polyandry as a defence against incompatibility are not mutually exclusive hypotheses. However, evidence from reproductive physiology, immunology and evolutionary conflict theory suggest that development of the embryo within the female makes polyandry for incompatibility avoidance far more important for viviparous females than for females that lay eggs.

The now widespread use of DNA profiling in studies of animal behaviour has led to growing recognition that female mating strategies in many species cannot be determined reliably through field observation alone. Genetic techniques for assigning paternity are providing mounting evidence that females commonly mate with multiple males in a manner that is covert and therefore difficult to assess at the behavioural level (Hughes 1998). As a consequence, paternity cannot be inferred either from observed copulations and social relationships or from male dominance hierarchies. In Soay sheep, for example, comparison of rutting behaviour census data with genetic paternity assignment has demonstrated that only 27% of lambs were sired by rams seen in consort with the oestrous female (Coltman et al. 1999). In socially monogamous birds, females of many species produce offspring sired by extrapair males (Dunn & Lifjeld 1994; Birkhead & Møller 1995). Levels of extrapair paternity as high as 76% have been recorded for superb blue fairy-wrens, *Malrus cyaneus* (Mulder et al. 1994), and radiotelemetry has recently shown that these extrapair young result from predawn, extraterritorial forays and infidelity by fertile females (Double & Cockburn 2000). In a wild population of chimpanzees, *Pan troglodytes verus*, approximately 50% of offspring were sired by extragroup males, although extragroup copulations were never observed in 17 years of field study (Gagneux et al. 1999). Similarly, despite extensive genetic sampling and long-term behavioural observations, between 50 and 70% of pups in grey seal, *Halichoerus grypus*, breeding colonies were sired by unidentified males, apparently as the result of aquatic copulations (Wilmer et al. 1999, 2000). Microsatellite data have revealed that, contrary to the traditional assumption of extreme reproductive skew in such harem mating systems, 'behavioural dominance leading to enhanced fitness is a feature of only a handful of males located near the center of the breeding colony. The vast majority of pups are fathered by any of a large number of males who all share approximately equal success . . .' (Wilmer et al. 2000, page 283).

Polyandry as a pervasive feature of natural populations challenges the long-held view of females as the choosy, monogamous sex (Williams 1966; Trivers 1972), and

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raises the question of why females so commonly mate with more than one male, despite the potentially high risks and costs associated with copulation (Chapman et al. 1995; Watson et al. 1998; Holland & Rice 1999). Identifying the causes and consequences of polyandry is of general significance to a broad spectrum of biological disciplines. Polyandry not only impacts on the operation of sexual selection and the maintenance of genetic variability (Burke 1989; Zeh et al. 1997; Birkhead 1998; Jennions & Petrie 2000; Wilmer et al. 2000) but also generates postcopulatory conflicts that have profound implications for evolutionary processes, ranging from the evolution of parent-of-origin gene expression (i.e. genomic imprinting; see Moore & Haig 1991; Haig 1997; Spencer et al. 1999) to speciation via gametic isolation (Markow 1997; Rice 1998a; Howard 1999).

As behavioural ecologists increasingly recognize the importance of considering reproduction from the female perspective (Gowaty 1997; Hrdy 1999), evidence is accumulating that polyandry is an active mating strategy (Bateman 1998; Zeh et al. 1998; Archer & Elgar 1999) that significantly enhances female reproductive success (reviewed in Jennions & Petrie 2000; also see Kempenaers et al. 1999; Newcomer et al. 1999). A variety of hypotheses have been proposed to explain why selection should favour the evolution of polyandry, and these fall into two broad but distinct categories of material and genetic benefits (see Eberhard 1996; Reynolds 1996; Zeh & Zeh 1996, 1997; Jennions & Petrie 2000). The multifarious material benefits that females may gain by mating with more than one male are often conspicuous. Perhaps largely because of this, material benefits have been widely accepted as explanations for polyandry (see Parker 1992; Yasui 1998), while the argument that polyandry provides genetic benefits remains controversial (Stockley 1997). Certainly, there are numerous examples of mating systems, particularly in Orthoptera and Lepidoptera, in which males make material contributions that enhance the reproductive success (RS) and survivorship of their mates. However, most studies that have investigated material benefits have not adequately controlled for potential genetic benefits (Newcomer 1998). Furthermore, in many cases, such as the sheep, wren, chimpanzee and seal examples cited above, the species' natural history renders material benefit explanations tenuous at best. In other instances, correlative methods (Madsen et al. 1992; Olsson et al. 1994; Kempanaers et al. 1999) or manipulative experimental designs (Tregenza & Wedell 1998; Newcomer et al. 1999) have effectively eliminated material benefits, thereby isolating genetic benefits as the cause of the enhanced RS of polyandrous females.

In this review, we focus on the potential genetic benefits of polyandry, and present the hypothesis that the nature of these genetic benefits is likely to be strongly influenced by whether a species is oviparous, ovoviviparous or viviparous. Among hypotheses proposing genetic benefits to polyandry (see below), there is a distinction between those that focus on benefits from intrinsic (additive) effects of paternal genes in offspring, and those that propose a benefit resulting from defence against incompatibility arising from detrimental maternal/paternal genome interaction (Zeh & Zeh 1996; Tregenza & Wedell 2000). These hypotheses are not mutually exclusive. However, evidence from reproductive physiology, immunology and evolutionary conflict theory suggests that the relative importance to female RS of male quality versus compatibility may depend critically on the degree to which embryological development involves physiological interactions between mother and embryo (also see Zeh & Zeh 2000). Here, we develop the hypothesis that polyandry for genetic incompatibility avoidance is likely to be far more important for viviparous females than for females that lay eggs.

GENETIC BENEFIT HYPOTHESES FOR POLYANDRY

Hypotheses that have focused on the intrinsic effects of paternal genes include (1) the 'intrinsic male-quality hypothesis' that sperm competition or female choice of sperm increases the probability of fertilization by high-quality sperm/males (Watson 1991; Madsen et al. 1992; Birkhead et al. 1993); (2) the 'trading-up hypothesis' (the intrinsic male-quality hypothesis in a socially monogamous context) that extrapair copulations compensate for a poor-quality mate (Kempenaers et al. 1992; Hasselquist et al. 1996; Petrie & Kempenaers 1998); (3) the 'bet-hedging hypothesis' that polyandry enables females to guard against mate choice errors (Watson 1991, 1998); (4) the 'sexually selected sperm hypothesis' that the sons of multiply mated females produce competitively superior sperm or ejaculates (Keller & Reeve 1995), and (5) the 'offspring diversity hypothesis' that increased offspring genetic variability enhances female fitness by reducing sibling competition (Ridley 1993) or by serving as a hedge against environmental uncertainty (Loman et al. 1988).

By contrast, the 'genetic incompatibility avoidance hypothesis' emphasizes the importance of interactions between maternal and paternal genomes and proposes that polyandry enables females to exploit postcopulatory mechanisms that minimize the risk and cost of fertilization by genetically incompatible sperm (Zeh & Zeh 1996, 1997). As a consequence of dominance, overdominance, intra- and intergenomic conflict, fetomaternal interactions and immune system function (see Table 1), sexual reproduction involves the merging in embryos of parental genomes likely to vary in the extent to which they are genetically compatible (Zeh & Zeh 1996, 1997, 2000; Brown 1997; 1998; Jennions 1997; Jennions & Petrie 2000; Tregenza & Wedell 2000). If offspring fitness depends on an interaction between maternal and paternal haplotypes, gene effects will not be strictly additive. More importantly from the perspective of female choice, genetic incompatibility, unlike intrinsic male quality, will generally not be apparent at the phenotypic level (Zeh & Zeh 1996). As Parker (1992, page 396) has pointed out, '. . . to expect selection to produce (pre-copulatory) mate choices which take account of the combined result of a female's genotype and that of her suitor is indeed to have faith'. By contrast, polyandry, in combination with an immunologically hostile female reproductive tract,

Table 1. Potential sources of genetic incompatibility

Causal agent	Effect	References†
Genetic relatedness between mates		
Dominance	Inbreeding exposes deleterious recessive alleles: homozygote lethality or low fitness	
Overdominance	Inbreeding reduces heterozygosity per se: homozygote lethality or low fitness	
Heterozygote superiority		
Classic overdominance (e.g. sickle-cell anaemia)	Homozygote lethality or low fitness	
Overdominance due to negative frequency dependent selection at highly polymorphic loci (e.g. MHC loci in vertebrates; self-incompatibility locus in plants)	Homozygote lethality or low fitness	
Intragenomic Conflict		
Segregation distorters (meiotic drive alleles)	Drive allele homozygosity: partial or complete sterility or inviability. Cost of mating with a heterozygous male depends on a female's genotype.	
Maternal-effect lethals	Dominant allele or gene complex (+) codes for both maternally produced, lethal compound and embryonically produced antitoxin: in (+/−) females, (−) eggs fail unless fertilized by (+) sperm.	
Cellular endosymbionts	Spiroplasmid bacteria: kill male embryos produced by certain male/female nuclear genotype combinations	Williamson & Poulson 1979
	Male-killing and feminizing *Wolbachia* bacteria: kill male embryos in some beetles and butterflies; in isopods, the bacterium can feminize males with particular nuclear/cytoplasmic genetic combinations	Hurst et al. 1999
	Wolbachia: cytoplasmic incompatibility (C.I.): in some arthropods, all embryos fail when females uninfected with the bacterium mate with infected males	
Transposable elements	Incompatibility can result from complex interaction between female nuclear genotype/cytotype and male nuclear genotype; similar to C.I.	
Genomically imprinted genes*	Spontaneous abortion, death of mother or stunted embryonic growth may result from imbalance in embryo between paternally expressed alleles that promote resource transfer from mother and maternally expressed alleles that down-regulate this transfer	
Y-chromosome genes*	Spontaneous abortion, death of mother or stunted embryonic growth may result from imbalance in embryo between X- and Y-chromosome gene expression (strictly paternal inheritance of Y favours evolution of aggressive growth factors)	Hurst 1994a, b
Intergenomic conflict		
Sexually antagonistic alleles	Imbalance between manipulative male seminal products and female resistance can lower female survival and/or fecundity in *D. melanogaster*	Holland & Rice 1999; Pitnick et al., unpublished data
Fetomaternal antagonistic alleles*	Can occur without genomic imprinting: imbalance may result in spontaneous abortion, death of mother or stunted growth of embryo	
The immune system		
Innate immune system fetomaternal incompatibility*	In vertebrates and invertebrates: recurrent spontaneous abortion in humans and mice	Clark et al. 1999b; Xu et al. 2000
Adaptive immune system fetomaternal incompatibility*	In vertebrates only: recurrent spontaneous abortion or impaired embryonic development resulting, for example, from nucleotide sequence similarity between MHC alleles of mother and paternally inherited allele in embryo (also overdominance) or from maternal antibody response to embryonic cell surface antigens (e.g. Rh blood factor incompatibility resulting in erythroblastosis fetalis)	Schumacher & Moise 1996
Adaptive immune system (MHC) enhanced heterozygote pathogen resistance	In vertebrates: overdominance (as above)	
Innate and adaptive immune reaction to sperm in female reproductive tract	In vertebrates and invertebrates: genotype-dependent barrier to fertilization	

*Diploidy and sexual reproduction invariably generate some potential for genetic incompatibility as a threat to female reproductive success in both oviparous and viviparous taxa. However, as is indicated by the asterisks in this table, development of the embryo within the mother exposes females to sources of incompatibility that are not experienced by females that lay eggs.

†Unless otherwise indicated, see Zeh & Zeh (1996, 1997), Jennions & Petrie (2000) and Tregenza & Wedell (2000).

provides a physiological screening process capable of weeding out incompatible genotypes in sperm and/or embryos (Zeh & Zeh 1997). Finally, it should be noted that the inbreeding avoidance hypothesis that polyandry diminishes the cost of inbreeding when females cannot avoid mating with close relatives (Brooker et al. 1990; Stockley et al. 1993) is a special case of polyandry for genetic incompatibility avoidance.

THE GENETIC BENEFITS AND REPRODUCTIVE MODE HYPOTHESIS

The 'genetic benefits and reproductive mode hypothesis' presented here proposes that reproductive mode has important implications for both the potential for genetic incompatibility and the range of paternity biasing, postcopulatory mechanisms available to polyandrous females. The impact that reproductive mode may have on the forces underlying the evolution of polyandry has previously received little attention (but see Zeh & Zeh 2000), yet polyandry is a mating strategy that occurs in the context of oviparity, ovoviviparity or viviparity. Although most nonmammalian animal species are oviparous, some form of intrauterine embryonic dependence on the mother has evolved independently numerous times in a diverse range of animal taxa, including echinoderms (Byrne 1996), arthropods (Zeh & Smith 1985; Meier et al. 1999), fish (Wourms 1994; Dulvy & Reynolds 1997), amphibians (Wake & Dickie 1998) and reptiles (Blackburn 1998). The form that such embryonic dependence takes varies extensively between taxa, and even the definitions of the terms 'ovoviviparity' and 'viviparity' differ from lineage to lineage. The critical distinction for the genetic benefits and reproductive mode hypothesis is the degree to which embryological development involves physiological interactions between mother and embryo. For simplicity, in this paper, we will focus on the contrast between the two reproductive mode extremes of oviparity (egg laying immediately following fertilization) and true viviparity (complete intrauterine embryonic development supported by maternal nourishment).

We suggest that polyandry for genetic incompatibility avoidance is likely to be of greater general importance for viviparous females than for females that lay eggs. Development of the embryo within the mother creates a postfertilization arena for genomic conflicts that does not exist in oviparous species. As we argue below, such conflicts should generate perpetual antagonistic coevolution (sensu Rice 1998a), between genes expressed in embryonic development and genes involved in maternal reproductive physiology, thereby providing continual input of genetic incompatibility as a threat to the RS of viviparous females. At the mechanistic level, the immunological détente between mother and fetus necessary for embryonic development is an important additional factor influencing susceptibility of viviparous species to incompatibility.

Conflict-generated Genetic Incompatibility

Conflicts can, of course, arise prior to fertilization, and conflict-generated incompatibility manifested at this stage of reproduction is likely to impact female RS in all species, irrespective of reproductive mode. Indeed, recent experimental evolution studies of *Drosophila* indicate that intergenomic conflict can lead to the evolution of competitive ejaculates that actually depress female RS (Holland & Rice 1999; S. Pitnick, G. T. Miller, J. Reagan & B. Holland, unpublished data). The intergenomic conflict view of sexual selection (Rice & Holland 1997; Rice 1998a, b; Holland & Rice 1999) holds that conflict between genes residing in different individuals of the same species plays a fundamental role in the evolution of 'male versus female mating behaviour, male versus female genitalia, sperm versus egg, and seminal fluid proteins versus other seminal fluid proteins or the female's reproductive tract and physiology' (the 'intraspecific Red Queen'; see Rice 1998a, page 261). Although the intergenomic conflict model can encompass mate choice (Holland & Rice 1998; Rice & Holland 1997; but see Getty 1999; Rosenthal & Servedio 1999), the gametic stage of reproduction (i.e. the postcopulatory but prefertilization stage; Markow 1997), appears to be the arena for the most intense conflict, involving a three-way 'tug of war' between male offensive and defensive strategies and female resistance (Chapman et al. 1995; Rice & Holland 1997; Rice 1998a; Clark et al. 1999a; Karr & Pitnick 1999; Prout & Clark 2000; Pitnick et al. 1999).

In addition to incompatibility arising from gametic-stage conflict, the viviparous mode of reproduction engenders further potential conflicts because development of the embryo within the mother provides a direct conduit for manipulation of the mother's physiological system by genes expressed in the embryo. Application of the intraspecific Red Queen to viviparous species requires extension of conflict-based coevolution to interactions between: (1) individual embryos within the mother; (2) the mother's reproductive system and the developing fetus, and (3) paternally and maternally derived genomes within individual embryos (Haig 1993, 1997; Spencer et al. 1999). The evolutionary interests of embryonic genes are likely to conflict with genes in the mother, particularly in the case of paternally inherited, genomically imprinted alleles and genes unique to the Y chromosome, since the latter never pass through females (see Hurst 1994a, b).

Genomic imprinting and incompatibility

Among the various viviparity-specific factors that can contribute to genetic incompatibility (Table 1), genomically imprinted genes play a critical role in embryonic development. Originally coined to describe inactivation of entire paternal chromosomes in sciarid flies (Crouse 1960), genomic imprinting is now generally (and in this paper) applied to transcription patterns of individual gene loci. As such, it is known definitively from only marsupials (O'Neill et al. 2000), eutherian mammals (Constancia et al. 1998) and angiosperms (Grossniklaus et al. 1998; Mora-Garcia & Goodrich 2000), and Haig & Westoby (1989) have proposed that it is the 'placental habit' (Harper et al. 1970) that underlies the evolution of imprinted gene expression. Genomic imprinting is a form of non-Mendelian, autosomal inheritance in which

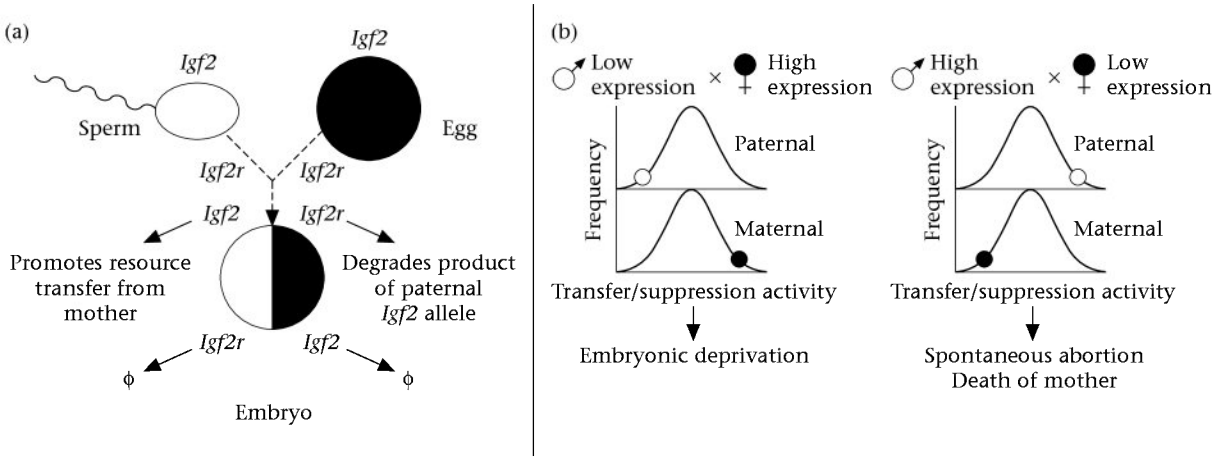

Figure 1. Genomic imprinting and fetomaternal genetic incompatibility. (a) *Igf2* (insulin-like growth factor type 2) and *Igf2r* (insulin-like growth factor type 2 receptor) are reciprocally imprinted genes in marsupials and placental mammals. In the developing embryo, gene expression occurs only from the paternally inherited copy of the *Igf2* locus and only from the maternally inherited copy of the *Igf2r* locus. The two loci function in opposition: insulin-like growth factor type 2 promotes resource transfer from the mother to the embryo but is degraded by the product of the *Igf2r* locus. The null symbol (Ø) indicates that no gene expression occurs. (b) With a number of loci contributing to the stimulation of resource transfer by the paternal genome and suppression by the maternal genome, maternal and paternal genomes are likely to vary in the extent to which they are genetically compatible (modified from Zeh & Zeh 2000).

methylation and expression of an allele depend on whether it is inherited through sperm or egg (Sapienza 1995; Bartolomei & Tilghman 1997). During embryonic development, maternally and paternally inherited alleles at imprinted loci exhibit radically different patterns of expression. In mice, for example, insulin-like growth factor II (IGF-II), which stimulates nutrient transfer from the mother, is transcribed only from the paternal copy of the *Igf2* gene (Fig. 1a). This pattern is reversed at the *Igf2r* locus where the paternal allele is inactive and transcription of the maternal allele results in degradation of IGF-II (Barlow et al. 1991). Development involves a precise balance between the opposing effects of maternal and paternal genes, and imprinting disruption has been implicated in a growing list of embryonic abnormalities, growth disorders, cancers and unstable DNA diseases in humans (reviews in Hall 1999; Tycko 1999; Ariel et al. 2000).

The differential tagging of imprinted loci during spermatogenesis and oogenesis enables alleles to exhibit condition-dependent, that is, parent-of-origin, expression during embryonic development (Haig & Westoby 1989). Because embryonic paternal genes are unrelated to genes of the mother (and genes in half-siblings), the optimal rate of nutrient transfer from mother to embryo is likely to be greater for paternally inherited alleles than it is for maternally inherited alleles (Haig & Westoby 1989). The resultant tug-of-war conflict between embryonic maternal and paternal alleles over maternal resource transfer is hypothesized to be the driving force behind the evolution of genomic imprinting (Haig & Westoby 1989; Moore & Haig 1991; Haig 1997). If this conflict hypothesis is correct, the components of this interplay should be constantly evolving in viviparous species, due to a coevolutionary arms race over maternal resource allocation. Since stimulation of resource transfer by the paternal genome and suppression by the maternal genome are likely to be polygenic traits (approximately 100 loci are estimated to be imprinted in mammals; see Mochizuki et al. 1996), maternal and paternal genomes will vary in extent of genetic compatibility (Zeh & Zeh 1996, 2000). For example, a maternal multilocus genotype of high suppression activity will produce normal offspring only when paired with paternal genotypes of similarly vigorous resource transfer activity. Matings between males and females on the opposite ends of their respective distributions of gene expression are likely to result either in overdemanding progeny (Haig 1993) or embryos unable to sequester adequate maternal resources (Fig. 1b).

Y-linked growth factors and incompatibility

It has been demonstrated in a number of mammals that male embryos develop significantly faster than female embryos, as a consequence of Y-linked gene expression (Burgoyne 1993; Erickson 1997). The nonrecombining region of the Y chromosome may, indeed, serve as a 'safe haven' for paternally inherited selfish growth factors (Y-SGFs) whose interests conflict with those of the mother in a manner analogous to that of paternally inherited, genomically imprinted autosomal genes (Hurst 1994a, b). However, unlike imprinted genes, Y-SGFs are never transmitted through females and therefore do not require a mechanism for parent-of-origin gene expression. Consequently, they are likely to spread easily through populations of a viviparous species (Hurst 1994a).

In multiparous species, accelerated preimplantation growth rate can give embryos carrying Y-SGFs a competitive advantage, with negative consequences for the mother's RS (Hurst 1994a). By developing rapidly and implanting early, such embryos can trigger a change in

uterine endocrinological status that reduces the probability of subsequent implantation by less rapidly developing blastocysts (Pope 1988). Y-linked selfish growth factors can thus promote their own transmission by causing females to differentially abort XX embryos and produce male-biased litters (Weir 1960, 1976). Such manipulation of the mother's reproductive physiology can be countered either by X-linked inhibition of Y-SGF activity or by counterbalancing growth factors on the X chromosome (Hurst 1994b), resulting in a coevolutionary arms race with concomitant scope for sex chromosome-based incompatibility. Although characterization of mammalian Y-chromosome evolution is still in its early stages (Burgoyne 1998; Roldan & Gomendio 1999), the rapid rate of molecular divergence documented for the house mouse, *Mus domesticus*, Y chromosome and its role in reproductive isolation between subspecies (Boissinot & Boursot 1997) are consistent with the above model of conflict-driven rapid evolution generating postzygotic incompatibility in viviparous species.

Immunologically Based Incompatibility

Viviparous reproduction depends on a complex sequence of two-way interactions between fetal and maternal tissues that involves humoral, cellular, innate (invertebrate and vertebrate) and adaptive (vertebrate only) immune responses (Hill 1995). As is clear from the rapidly expanding field of human reproductive immunology, intolerance of the embryo, as an antigenetically foreign body growing within the female, can constitute a significant barrier to reproduction within an apparently genetically cohesive species (Zeh & Zeh 2000). An estimated 70% of human conceptions fail (Hill 1995), with similar estimates of early fetal loss in other mammals (Baker & Bellis 1995). In humans, ca. 45% of recurrent spontaneous abortions are attributed to immunological factors (Clark 1999). In other species, the proportion of spontaneous abortions attributable to incompatible feto-maternal immunological interactions remains to be determined. Recent findings indicate that immune tolerance is established through innate immunological interactions between mother and embryo, involving complement system regulation (Xu et al. 2000), production of pro- and anti-inflammatory cytokines, and modulation of uterine natural killer cells (Clark et al. 1999b). Although previously thought to exhibit only a generalized response, the innate immune system in arthropods is now known to be capable of discriminating between different classes of microorganisms and inducing the appropriate effector response (Lemaitre et al. 1997; Meister et al. 1997; Williams et al. 1997). Of course, in mammals, the adaptive (MHC-based) immune system adds additional potential for fetomaternal incompatibility. At polymorphic MHC loci, expression is minimal following implantation but increases through pregnancy in placental and cytotrophoblast tissues (Kurpisz et al. 1995). Restriction of polymorphic MHC gene expression to later stages of embryonic development may serve to prevent rejection of the fetus. Interestingly, immunologically based incompatibility results, in some cases, from difference and, in other cases, from similarity between maternal and embryonic genotypes. Perhaps the best characterized example of the former is that of erythroblastosis fetalis in which antibodies produced by the Rh^- mother pass through the placenta to attack erythrocytes of her Rh^+ fetus (Avent & Reid 2000). By contrast, MHC haplotype similarity between mates increases spontaneous abortion rates in humans (Ober et al. 1998) and other primates (Knapp et al. 1996). Intrauterine selection favouring MHC dissimilarity may be at least partially responsible for the high levels of MHC allelic diversity in mammals (Edwards & Hedrick 1998).

Postcopulatory paternity-biasing mechanisms

In both oviparous and viviparous species, polyandry and the accumulation of sperm from several males shifts the arena for sexual selection from the external environment to the female reproductive tract where sperm competition and female choice of sperm can act as selective mechanisms favouring fertilization by more competitive (Keller & Reeve 1995), genetically superior (Birkhead et al. 1993) or more compatible sperm (Zeh & Zeh 1996, 1997). To date, the best evidence for the existence of postcopulatory paternity-biasing mechanisms involves incompatibility avoidance (Birkhead 1998; Tregenza & Wedell 1998; Newcomer et al. 1999; Stockley 1999). Polyandry as a mechanism for inbreeding avoidance has been demonstrated in adders (Olsson et al. 1996), ascidians (Bishop et al. 1996) and crickets (Stockley 1999). At a more general level of incompatibility avoidance (i.e. in the absence of inbreeding effects), postcopulatory paternity-biasing mechanisms resulting from polyandry have been shown to reduce spontaneous abortion rate in pseudoscorpions (Newcomer et al. 1999) and to increase hatching rate in birds (Kempenaers et al. 1999) and crickets (Tregenza & Wedell 1998). At the level of recently diverged populations, assortative fertilization, in which homopopulation (or conspecific) sperm are used in preference to heteropopulation (or heterospecific) sperm, is increasingly being shown to be among the most rapidly evolving of reproductive isolating mechanisms. Fertilization by homopopulation (or conspecific) sperm has been found to override even strong mating-order effects in grasshoppers (Hewitt et al. 1989; Bella et al. 1992), crickets (Gregory & Howard 1994; Howard et al. 1998; Howard 1999), *Drosophila* (Price 1997), *Tribolium* (Wade et al. 1994, 1995) and *Macrohaltica* beetles (W. G. Eberhard, personal communication).

Reproductive mode has important implications not only for the diversity of factors that can generate genetic incompatibility but also for the range of paternity biasing, postcopulatory mechanisms available to polyandrous females (Zeh & Zeh 1997, 2000). In addition to the prefertilization processes of sperm competition and female choice of sperm, a postfertilization paternity-biasing mechanism is available when embryonic development takes place within the female. For the viviparous female that mates with several males and produces mixed paternity litters, the option may exist to shunt maternal resources from genetically inferior to superior embryos or

to viable embryos from embryos that are inviable because of incompatibility. Known as 'reproductive compensation' (see Charlesworth 1994), such reallocation could be particularly advantageous, if females typically ovulate more eggs than the number of embryos they are capable of carrying to term. Female mice, for example, eliminate as many as one third of their fertilized eggs without affecting total litter size (Hull 1964). A similar pattern of reproductive compensation has been documented in the South American field mouse, *Akodon azarae* (Espinoza & Vituzo 1996), and may explain the multiple origins of heterogametic (XY) females in the *Akodon* genus (Hoekstra & Edwards 2000). Although progeny of XY *A. azarae* females show a biased 1:2 male to female sex ratio that is presumed to result from early loss of YY zygotes, litter size at birth does not differ between XY and XX females (Espinoza & Vituzo 1996). Interestingly, although rarely multiparous, human females retain the capacity for embryo resorption and thus reproductive compensation (Landy & Keith 1998). In a recent analysis of the outcome of 38 pregnancies in which three gestational sacs were identified following assisted reproductive techniques, embryo resorption was found to occur primarily during the first 7 weeks of gestation, resulting in delivery rates of 47% for triplets, 32% for twins and 18% for singletons (Manzur et al. 1995). The relative extent to which pre- versus postfertilization processes contribute to paternity biasing in polyandrous, viviparous females is an important question that awaits empirical investigation. However, polyandry followed by reproductive compensation based on assessment of paternal gene expression in early-stage embryos could provide females with a particularly sensitive mechanism for biasing paternity.

The Cruel Bind of Polyandry

Central to the genetic benefits and reproductive mode hypothesis is the thesis that incompatibility generated by intra- and intergenomic conflict acts as a selective force favouring the evolution and maintenance of polyandry. Mating with multiple males provides females with a cryptic arsenal of postcopulatory processes with which to safeguard their investment in large, costly eggs (Thornhill 1983; Eberhard 1996; Zeh & Zeh 1997). Ironically, however, polyandry also creates postcopulatory conditions that intensify conflict and thus increase the evolutionary potential for incompatibility as a threat to female RS. As Rice (1998a) has pointed out, the intensity of sexual conflict depends critically on mating system. With strict monogamy, both sexes achieve highest fitness by maximizing the female's lifetime RS. The opportunity for conflicts of interests increases with deviations from strict monogamy and intergenomic conflict is greatest when both sexes copulate with multiple partners. Evidence of such antagonistic coevolution comes from recent experimental evolution studies of *Drosophila*, in which multigenerational imposition of monandry on laboratory lines of a naturally polyandrous species resulted in males whose sperm fared poorly in competition with sperm from polyandrous-line males (Holland & Rice 1999; Pitnick et al., unpublished data). However, standard females mated singly to these monandrous-line males showed greater fecundity and higher offspring survival than females singly mated to polyandrous-line males (Pitnick et al., unpublished data). These results suggest the existence of polyandry-driven competitive ability/compatibility trade-offs operating at the gametic stage in an oviparous species.

For viviparous females, the cruel bind of polyandry extends to the postzygotic stage, with physiologically mediated conflicts predicted to be most intense in polyandrous species. By generating relatedness asymmetries, multiple paternity favours the evolution of an aggressive paternal genome in the embryo (Haig 1997, 1999; Burt & Trivers 1998; Rice 1998a; Hurst 1999) and is argued to be critical to the evolution of genomic imprinting (Haig & Westoby 1989; Moore & Haig 1991; Haig 1997). Although recent single-locus models suggest that imprinting could evolve without multiple paternity (Spencer et al. 1999), the weight of theoretical evidence indicates that multiple-paternity-driven conflict, either within or across broods, is essential to the evolution of parent-of-origin gene expression (Mochizuki et al. 1996; Haig 1997, 1999; Iwasa 1998; Hurst 1999). It should be pointed out, however, that genomic imprinting is not essential for viviparity-driven conflict. Indeed, according to inclusive fitness theory (see Mock & Parker 1997), multiple paternity within a brood generates conflict and can influence offspring growth rates, even in species lacking imprinting (Lessels & Parker 1999). Between-embryo competition should be intensified as average relatedness declines (Queller 1994; Lessels & Parker 1999).

Experimental evolution studies that manipulate mating system to investigate the effects of polyandry-driven conflict have yet to be carried out on a viviparous species. However, evidence from crosses between closely related *Peromyscus* species suggest that polyandry does favour aggressive paternal genomes in embryos at the cost of reduced fetomaternal compatibility (Dawson 1965; Rogers & Dawson 1970). Matings between males from the polyandrous *P. maniculatus* (Birdsall & Nash 1973) and females from the (essentially) monogamous *P. polionotus* (Foltz 1981) resulted in a high incidence of spontaneous abortion, near-term fetal death or death of pregnant females during late stages of gestation, with only 17% of pairings leading to offspring birth. Surviving fetuses were, however, 33% heavier at birth than either parental species and almost 200% heavier than the reciprocal hybrid (Dawson 1965). By contrast, the reciprocal cross (*P. polionotus* male × *P. maniculatus* female) was much more frequently successful (46%), but the resulting neonates were likely to have been noncompetitive due to their small size. Similar patterns of asymmetrical postzygotic incompatibility have been detected in crosses between *P. leucocephalus* and *P. maniculatus* and between *P. nasutus* and *P. comanche* (reviewed in Gray 1972) but molecular data on the extent of the difference in the level of polyandry are lacking. Most attempts at hybridization between other *Peromyscus* species have proved unsuccessful (Gray 1972).

Polyandry as a mating strategy that defends against current risk of incompatibility at the cost of fueling future

incompatibility may drive females into an evolutionary cul de sac. Initially, mating with multiple males may evolve for material benefits or for genetic benefits that do not involve polyandry-driven conflict. For example, in mammals, sperm are relatively short-lived, and serial polyandry may have evolved simply as a by-product of remating to enable the production of multiple litters. Alternatively, polyandry may evolve as a mechanism for inbreeding avoidance (Brooker et al. 1990; Stockley et al. 1993) or as a defence against selfish genetic elements such as segregation distorter alleles (Haig & Bergstrom 1995) and cellular endosymbionts (Zeh & Zeh 1996, 1997). Once evolved, however, polyandry can rapidly become a self-perpetuating process that generates genetic incompatibility by promoting postcopulatory conflict and competition between rival paternal genomes. As the results of experimental imposition of monandry on laboratory lines of *Drosophila* (Holland & Rice 1999; Pitnick et al., unpublished data) suggest, the population as a whole might well benefit over the long term from relaxation of polyandry-driven conflict and the evolution of more benign paternal genomes. Monandry is unlikely to evolve in natural populations of polyandrous species, however, in the face of short-term selection that favours the maintenance of polyandry at the level of the individual female. With their heightened susceptibility to genetic incompatibility, viviparous females would seem particularly prone to becoming locked into polyandry by this cruel bind. An evolutionary transition from polyndry to monandry might then require extreme ecological conditions that either enabled males to effectively monopolize females or tipped the cost/benefit ratio against mating with more than one male (see Say et al. 1999).

EVIDENCE FOR THE GENETIC BENEFITS AND REPRODUCTIVE MODE HYPOTHESIS

Comparison of levels of polyandry in marsupial and placental mammals might be used to test the genetic benefits and reproductive mode hypothesis, with short marsupial gestation predicted to reduce the potential for conflict and hence the genetic benefits of polyandry. Unfortunately, however, few studies estimating levels of polyandry and multiple paternity have been carried out on natural populations of marsupials (but see Spencer et al. 1998; Sarre et al. 2000; Taylor et al. 2000). Moreover, selection for polyandry is likely to be influenced by both material and genetic benefits, as well as by ecological constraints (Emlen & Oring 1977; Say et al. 1999). Simple comparison of levels of polyandry in taxa varying in the degree to which embryonic development involves physiological interactions between mother and embryo would therefore suffer from confounding effects and would thus provide an inadequate test. Assessment of the extent to which polyandry acts as a defence against genetic incompatibility in a representative sample of oviparous and viviparous taxa (for an overview of the independent origins of viviparity, see Zeh & Zeh 2000) would provide a more powerful test but such data are currently unavailable. The following patterns are, however, at least consistent with reproductive mode influencing the type of genetic benefits that females gain from polyandry.

(1) In birds, which are, of course, oviparous, evidence is accumulating that polyandrous females generally seem to enhance their RS through the acquisition of superior paternal genes for their offspring (reviewed in: Petrie & Kempenaers 1998; Jennions & Petrie 2000).

(2) Female promiscuity is common in mammals (Ginsberg & Huck 1989; Stockley et al. 1993; Schenk & Kovaks 1995; Hoogland 1998; Berteaux et al. 1999; Coltman et al. 1999; Matsumoto-Oda 1999; Say et al. 1999) and occurs even within the constraints of female or resource defence polygyny (Inoue et al. 1990; Amos et al. 1993; Gust et al. 1996, 1998; Wilmer et al. 1999, 2000). In several of these studies, mating with multiple males was associated with enhanced female RS that was attributed to the effects of good genes. Incompatibility avoidance was not considered as a possible explanation, despite the high rates of early embryonic failure experienced by many mammalian species (see above). In the one mammal study capable of distinguishing between good genes and compatibility, the results clearly supported incompatibility avoidance, manifested as a lower rate of still births and preweaning offspring mortality in females mated to multiple males (Keil & Sachser 1998).

(3) Data on the relationship between divergence time and hybridizability across vertebrate clades (Prager et al. 1974; Wilson et al. 1974a, b; Prager & Wilson 1975; see Figure 1 in Zeh & Zeh 2000) strongly implicate viviparity as a factor in the rapid evolution of postzygotic incompatibility. Bird and anuran species pairs retain the capacity to produce viable hybrid offspring for up to 60 million years, an order of magnitude longer than mammals. Embryo transfer experiments and observations of spontaneous abortion and female death during pregnancy demonstrate that fetomaternal incompatibility rather than gametic (i.e. prefertilization) incompatibility is frequently responsible for the inability of mammalian species to produce hybrids (Gray 1972; Kraemer 1983; Rossant et al. 1983; Tate et al. 1997). Thus, diversification in mammals is associated with rapid evolution of incompatible fetomaternal interactions (Zeh & Zeh 2000), suggesting that viviparous females are particularly vulnerable to genetic incompatibility-based embryonic failure.

(4) An increasing number of 'infertility' and reproductive problems in humans are being linked to partner incompatibility. Incompatibility results from both similarity (MHC allele sharing; Hill 1995) and dissimilarity (e.g. Rh blood factors) between mother and fetus. Quantitative evidence that fetomaternal incompatibility represents a serious risk to female RS comes from extensive clinical data on premature births, demonstrating that women who change partners after a premature birth significantly reduce their risk of subsequent preterm delivery (Li 1999). By contrast, medical advances and public health measures have failed to reduce the high incidence of premature births (10% of pregnancies) over the last three decades, suggesting that environmental factors, such as poor nutrition or lack of prenatal care, are not the underlying cause of preterm delivery (Li 1999).

TESTING THE GENETIC BENEFITS AND REPRODUCTIVE MODE HYPOTHESIS

Given the growing evidence that postcopulatory, paternity-biasing mechanisms can enhance female RS by defending against genetic incompatibility (Bishop et al. 1996; Olsson et al. 1996; Zeh 1997; Birkhead 1998; Keil & Sachser 1998; Tregenza & Wedell 1998; Newcomer et al. 1999; Stockley 1999), testing for incompatibility avoidance is likely to be increasingly incorporated in studies aimed at determining the potential adaptive significance of polyandry. Experimental designs that control for both potential material benefits and intrinsic male-quality effects provide the strongest tests for genetic incompatibility avoidance. A particularly simple but ingenious design is patterned after that used by Keil & Sachser (1998) and Tregenza & Wedell (1998). The experiment consists of two treatments: (1) females mated n times to a single male, and (2) females mated once to each of n different males (where $n \geq 2$). Control for inherent male genetic-quality effects is achieved by utilizing the same set of males in both treatments, making average male quality identical for the two treatments. In addition to standardizing the number of ejaculates each female receives, control for material benefits should incorporate randomization of male mating order across treatments, since virgin, once-mated, twice-mated, and so forth, males might differ in material contributions donated to females (see Newcomer et al. 1999).

An alternative, more complex experimental design, again controlling for material benefits and male mating history would enable partitioning potential genetic benefits of polyandry into intrinsic male effects and compatibility components. In this design, males used in the multiple-male treatment would also each be singly mated to n different females in the single-male treatment. An analysis of covariance controlling for such effects as female size (Zeh 1997; Newcomer et al. 1999) could be used to partition variation in female RS into within-male and between-male components. The ratio of between-male to within-male variation would then provide an index of the importance of intrinsic male effects for female RS. With a sufficient number of these types of studies carried out on a representative sample of both oviparous and viviparous species, the data should ultimately be available to rigorously test the genetic benefits and reproductive mode hypothesis.

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