PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Mate Choice and Maternal Selection for Specific Parasite Resistances before, during and after Fertilization

Claus Wedekind

Phil. Trans. R. Soc. Lond. B 1994 **346**, 303-311
doi: 10.1098/rstb.1994.0147

Mate choice and maternal selection for specific parasite resistances before, during and after fertilization

CLAUS WEDEKIND

Abteilung Verhaltensökologie, Zoologisches Institut, Universität Bern, CH-3032 Hinterkappelen, Switzerland

SUMMARY

As Hamilton & Zuk pointed out, some loci may be of special importance for sexual selection because they play a crucial role in the co-evolution between parasites and hosts. In previous work I have tried to extend Hamilton & Zuk's parasite hypothesis for sexual selection, partly by including findings of immunologists and endocrinologists: in some species, handicapping signals may specifically reveal the current needs of the immune system which depends on the host's susceptibilities to different parasites. In other species, depending on the constellation of some key variables, non-handicapping signals could directly reveal the identity of resistance genes. Despite the general conflict of interests between the sexes, sexual selection may, in these cases, lead to signallers (i.e. mostly the males) focusing on improving their offspring's survival chances instead of trying to maximize their number. Males achieve this by allowing choosy females to optimize costs and benefits of each resistance.

Both parts of the extended parasite hypothesis suggest that female choice for specific heritable mate-qualities aim to optimize the resistance genetics of the unfertilized eggs. However, intersexual selection could go further than just choosing a mate. Here, I list the possible selection levels at which the mother and/or her ova could select for specific sperm haplotypes before, during and after the formation of the zygote. For many of these possible selection levels, evidence suggests that selection after mating might favour heterozygosity or even certain specific allele combinations at loci which are involved in the parasite–host co-evolution (e.g. the major histocompatibility complex or the transferrin locus).

1. INTRODUCTION

At breeding time, members of one sex normally compete more intensively for being chosen by the other sex. Mostly, the females choose (see, e.g., Clutton–Brock & Parker 1993), and many studies have shown that they use male signals as a basis. However, it still remains unsolved *why* they use particular signals. Is there information in these cues especially relevant for the female's fitness manifested in her descendants?

Hamilton & Zuk (1982) suggested that mate choice could be based on signals which reveal a male's health and vigour. Health and vigour is dependent on a male's parasite load, which itself depends on his resistance genetics. By choosing a healthy male a female tends to acquire for her offspring those resistances which are at the moment important against the predominant parasites.

This suggestion implies that there are certain loci in the host genome which are under natural *and* sexual selection. Such loci should play a crucial role in the co-evolution between parasites and hosts. Since competition between these biological systems could produce rapid changes in the genetic optima over time, sexual selection on these loci may be a means to strongly and effectively react to an important environmental selection pressure. Moreover, this may be one of the most substantial benefits of sexual reproduction itself.

In Hamilton & Zuk's (1982) mating scenario, every male should try to signal best health and vigour to get chosen. Therefore, the signals could only be reliable if they are impossible to be cheated or if they are costly to produce. The latter argument, i.e. the 'handicap principle', has been suggested by Zahavi (1975, 1977) and proven to be feasible by Grafen (1990*a*,*b*) and others. However, Hamilton & Zuk's basic idea could be extended in two ways: (i) with handicapping signals revealing detailed information (Wedekind, 1992), or (ii) with cheap signals revealing the same (Wedekind 1994) (figure 1). Moreover, sexual selection on paternal resistance genes could still take place after mating, i.e. before, during and after the formation of the zygote.

Below, I will briefly outline the extended parasite hypothesis for sexual selection. Thereafter, I will propose several possible levels for maternal selection for certain allele combinations after mating, listing literature which gives some support to my suggestions.

Phil. Trans. R. Soc. Lond. B (1994) **346**, 303–311
Printed in Great Britain

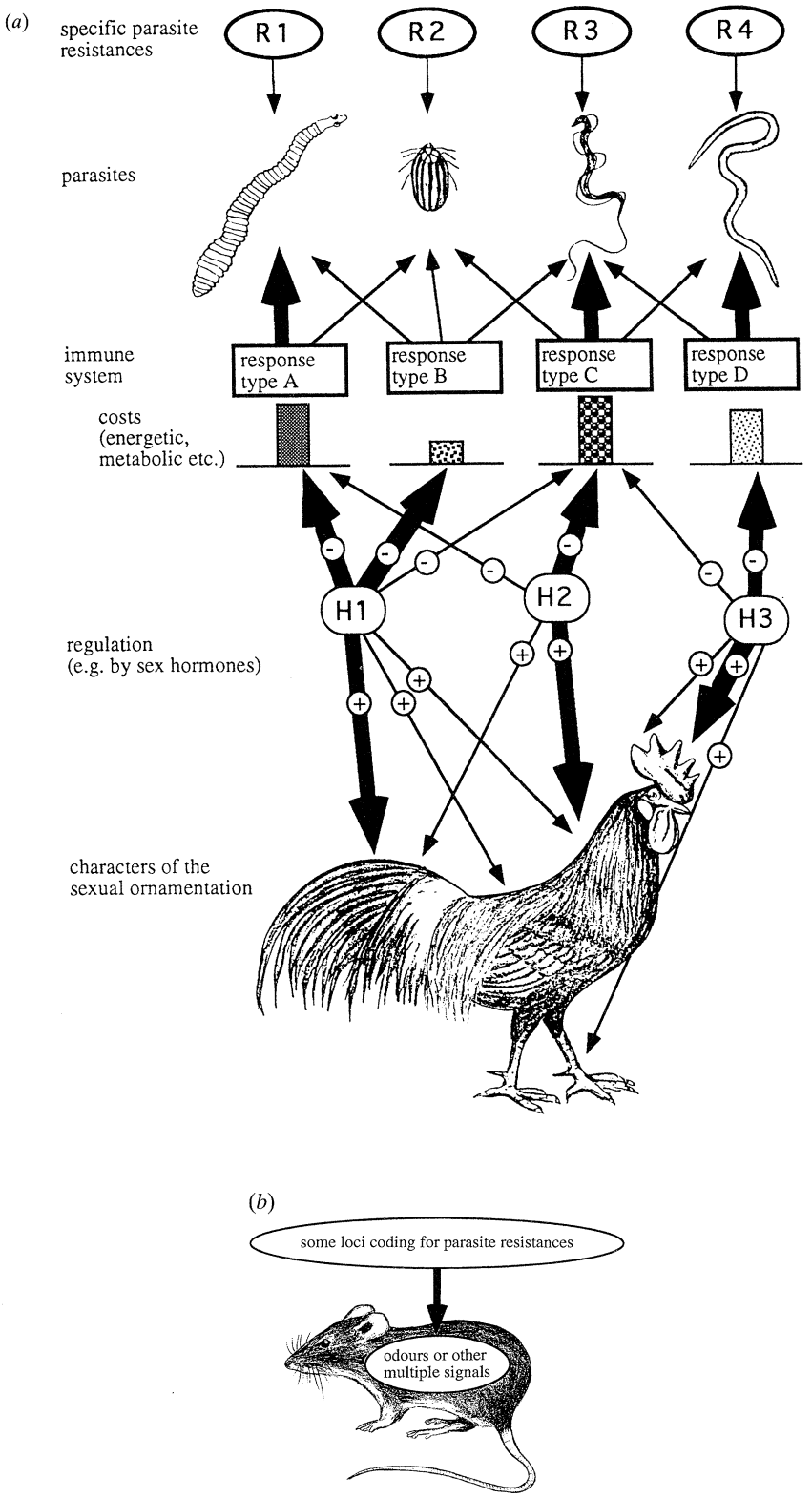

Figure 1. Schematic illustration of the extended parasite hypothesis (*a*) with the need for handicapping signals, i.e. with signals whose reliability bases on their energetic and metabolic costs to a parasitized signaller. While building the different ornaments, a signaller should optimally weigh the redistribution of his resources according to the parasites that have to be fought against, i.e. resources that are urgently needed by the immune system to fight a certain infection should be invested there while other resources could be withdrawn from the immune system for building the ornaments. Therefore, the relative and absolute extent of the different ornaments could signal detailed information about the signaller's parasites, which themselves should depend on his resistances. To optimally use this information, a female's preference should be coupled with her own resistances to achieve an optimal mix of resistance genes in the progeny. (*b*) Under some circumstances the signals need not be handicapping but can still bear detailed information about the signaller's resistance genes (see text). The connection between resistance genes and the signal could be very direct, e.g. odours as multiple signals could contain volatile parts of the gene products themselves.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

2. THE EXTENDED PARASITE HYPOTHESIS

(*a*) *With handicapping signals*

Males of many species display several ornaments (e.g. the cock in *Gallus gallus*), or single ornaments which could vary in several properties, e.g. the red coloration of many fish often varies in colour intensity (dull to bright) as well as in colour quality (yellowish to purple-red). If these multiple ornament are costly to produce or to maintain, a male might be forced to re-allocate his resources such as energy and certain metabolites from other uses. Naturally, he should be selected to optimally weigh the redistribution of any essential resources as based on the needs of every tissue as well as the benefit expected from his signal.

The immune system might be one of the few systems whose needs may greatly differ between males, as these needs depend on the actual pathogen load that has to be fought. Therefore, the kind and amount of resources that can be withdrawn from the immune system might reflect the kind and burden of different parasites the male carries. As a consequence, detailed information about parasites could be encoded by the relative and absolute extension of the different ornaments or ornament properties.

Findings from endocrinologists support this view: steroids seem to regulate this redistribution of resources because they are known to induce the development of the ornamentation while suppressing the activity of the immune system (reviews e.g. in Grossman 1985; Folstad & Karter 1992, however, Folstad & Karter's evolutionary explanation of this phenomenon has been critically discussed in Wedekind & Folstad 1994). Every sex hormone might have a different influence on the ornamentation and on the immune system which could ensure a very precise allocation of resources. This regulation, however, need not be restricted to the action of hormones. (see figure 1*a* for a schematic overview)

The multiple ornamentation of roach (*Rutilus rutilus*, a common European fish), for example, is induced by several sex hormones (Wiley & Colette 1970), and seems to encode detailed information about the males' current parasite load (Wedekind 1992). Also, some poultry breeders seem to be able to estimate the kind of diseases of their fowl from some of the secondary sexual characters (Zuk 1984).

Females could try to use such detailed information, indeed could try to reach an optimal level of each resistance in the offspring. In the most extreme case – which is at the moment purely hypothetical – they would be able to weigh the costs and benefits of each specific resistance and combine their own and those of their mate according to the expected parasite pressure. Here, several assumptions are made whose plausibility is still to be proven: (i) the females should be able to accurately decode several male signals, (ii) they should 'know' their own level of resistances, and (iii) they should be able to estimate the future parasite pressure.

At the moment, little is known about the ability of females to be discriminating to this degree. However, some speculations exists which support points (ii) and (iii): The immune system and the nervous system seem to communicate back and forth (Blalock 1984, 1994). This has led Blalock to suggest that the immune system might act as a sensory organ for 'feeling' for pathogens which could not be recognized by other sensory systems. Furthermore, females with different resistances might show, innately or otherwise, different mate preferences, opposite to the predictions derived in the original parasite hypothesis where all females are assumed to go for the most healthy male (Hamilton & Zuk 1982). Few studies have tested this new prediction. In roach, however, different females tend to exhibit different mate preferences (Wedekind 1994). Also, studies which have demonstrated additive genetic variance in female preference could indicate the proposed polymorphism in mate preferences (see reviews in Bakker 1990; Bakker & Pomiankowski 1994), although these observations have been mainly discussed as evidence for a Fisher–Lande process (Fisher 1958; Lande 1981).

(*b*) *Without the need for handicapping signals*

Although the necessary prerequisite for the handicap principle, namely the conflict of interests between sender and receiver of an information, is probably always present between the sexes during mate choice (Clutton–Brock & Parker 1993), there might be conditions that allow for a liberation from the handicap principle (Wedekind 1994).

To maximize their fitness, males (or females) may sometimes do better by switching their mating strategy from trying to get as many offspring as possible to trying to enhance the survival rate of fewer offspring. They could achieve this by honestly signalling their parasite resistances because this would allow choosy females (or males, respectively) to optimize cost and benefits of their own resistances. If cheating, i.e. showing dishonestly the resistance type most often preferred, is not possible (because cheaters need to have lots of information which may not be available in time) or does not pay (because honest signalling enhances the offspring survival chances, and cheaters may not be able to outweigh the lower survival chances of offspring by having more of them), handicaps are no longer necessary for ensuring the reliability of signals.

Therefore, there could exist species or populations where cheap and unspectacular signals encode detailed information about parts of the resistance genetics of the signaller. This could be the case for many mammals since they often base their mate choice on body odours which may be cheap to produce.

3. POSSIBLE SELECTION LEVELS FOR SPECIFIC ALLELE COMBINATIONS

Figure 2 indicates the different selection levels at which sexual selection for specific allele combination has been shown or would be plausible. In the following, the discussion is concentrated on mice and humans (as these two species are best studied in this

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

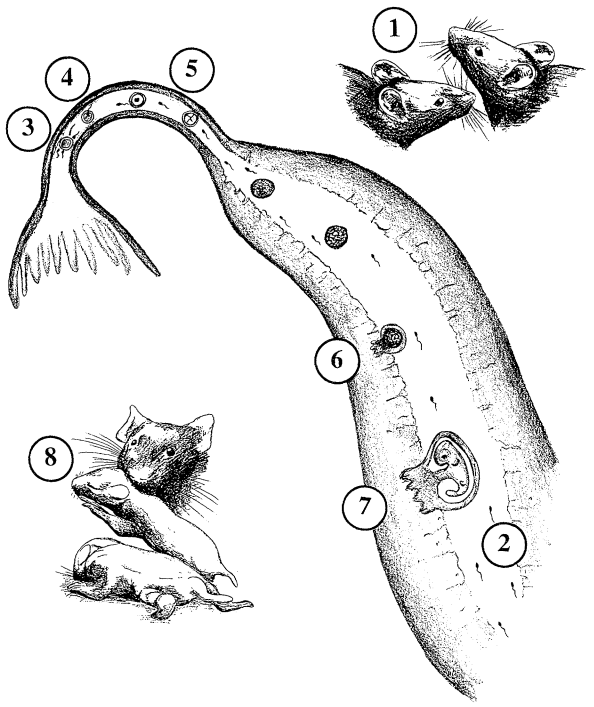

Figure 2. Schematic illustration showing the possible selection levels at which females or their ova could select for heterozygosity or even specific allele combinations in the offspring on loci which are important in the parasite–host co-evolution: (1) mate choice, (2) selection on sperm by the female within her reproductive tract, (3) egg choice for the fertilizing sperm, (4) meiotic drive influenced by the fertilizing sperm, (5) selection on the early embryo by the oviduct, (6) implantation, (7) nutrition supply to the embryo and spontaneous abortion, (8) selective feeding or selective killing of newborns.

respect), and on loci which are known to be important in the parasite–host co-evolution. I will therefore not include the *t*-complex which has been shown to influence mate choice (review in Lenington *et al.* 1992) and reproduction (for reviews see Bennett 1975; Klein 1986), but does probably not play any role in the parasite–host co-evolution.

(*a*) *Mate choice*

Behavioural ecologists who study mate choice normally measure some characteristics of possible signals of one sex and the preference for them of the other sex (reviews in Møller 1990*a*; Read 1990). Normally, this approach has to deal with disturbing influences of many different variables and lots of measuring errors, while large sample sizes are difficult to achieve. These may be some of the reasons why only few such studies have found evidence for a significant genetic influence on signals and/or preference (Møller 1990*b*; Bakker 1993). Furthermore, behavioural ecologists very often concentrate on spectacular secondary sexual characters like bright colours or long feathers. Here, the connection between genes and signals is not expected to be very direct (see section 2(a) and figure 1*a*).

On the other side, while studying histocompatibilities on congenic inbred mouse strains, immunologists have accidentally found strong influences of genes of the major histocompatibility complex (MHC) on mate choice (Yamazaki *et al.* 1976; Egid & Brown 1989; Potts *et al.* 1991; for a comprehensive introduction into the natural history of the MHC, see Klein 1986). Here, the signals used are not very spectacular. Information about an individual's MHC can be sniffed in body odours, urinary odours or odours of faeces, either by conspecifics in mice (Yamazaki *et al.* 1979) and rats (Singh *et al.* 1987; Brown *et al.* 1989) or by members of other mammalian species, e.g. rats on mice odours (Beauchamp *et al.* 1985), humans on mice odours (Gilbert *et al.* 1986), and mice on human odours (Ferstl *et al.* 1990). Mice acquire their MHC-dependent odour preferences at least partly during ontogenesis (Yamazaki *et al.* 1988). For recent reviews on mate choice and MHC see e.g. Boyse *et al.* (1987) and Potts & Wakeland (1993).

Shortly before Yamazaki *et al.* (1976) first found that the MHC influences mate choice, Zinkernagel & Doherty (1974) discovered that the MHC plays an important role in the immune defence against pathogens. Therefore, MHC genes are resistance genes. Accordingly, the presence of one allele or another correlates with specific parasite susceptibilities of its bearer (review in Tiwari & Terasaki 1985). MHC genes are codominant, i.e. heterozygotes can respond to any pathogens recognized by either parental MHC haplotype (Doherty & Zinkernagel 1975). Therefore, heterozygotes may often have a selective advantage.

Boyse *et al.* (1987) estimated that about half of the genetically based odour individuality in mice is determined by the MHC, while the other half may be influenced by other genes. These genes could have an impact on mate choice as well. Suspicious candidates might be loci which are polymorphic and have one or several functions in the host's defence against pathogens, e.g. the transferrin loci (see below). To my knowledge, however, any influences of these loci on mate choice have not been studied so far.

In most species where mate choice has been studied, a chosen male is diploid and often heterozygous at the interesting loci. Therefore, females who choose a mate for his alleles often need further selection mechanisms to ensure heterozygosity at the important loci or to reach epistatic allele combinations with a selective advantage.

(*b*) *Haplotype-specific signals on sperm membrane and survival of sperm until the oviduct*

The female reproductive tract is very hostile to sperm. Physiochemical and immunological factors in the vagina and the cervix play an important role in sperm survival and transport (e.g. Overstreet 1983; Hafez 1987; Birkhead *et al.* 1993). In many mammals, most of the sperm of an ejaculate do not even pass the cervix (Mortimer 1983; Overstreet 1983). Until reaching the oviduct the sperm have to survive strong selection by physical and chemical barriers,

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

phagocytosis by leukocytes and high concentrations of antisperm antibodies which coat a majority of ejaculated sperm (Overstreet 1983; Birkhead & Møller 1993; Birkhead *et al.* 1993). Therefore, maternal selection for specific spermal haplotypes could be possible by several means between the vagina and the oviduct. However, as a necessary prerequisite, sperm should signal their haplotype with respect to resistance alleles. Therefore, haplotype-specific cell surface components should be transcribed and produced after meiosis.

In general, haploid expression of mammalian genes in sperm is possible, because during spermatogenesis, e.g. in mice, RNA synthesis is terminated only during the early postmeiotic phase (Eddy *et al.* 1993). Protein synthesis continues until late in the postmeiotic phase (Eddy *et al.* 1993).

Some of the surface antigens on spermatozoa seem to be transcribed from the haploid genome. Several studies using different methods have demonstrated that at least the MHC and the *t*-complex of the haploid genome may be expressed in the sperm membrane (haploid expression of the MHC-type in humans: class I: Fellous & Dausset 1970; Arnaiz-Villena & Felsenstein 1976; Halim *et al.* 1982; class II: Halim & Felsenstein 1975; haploid expression of the *t*-complex in mice: Yanagisawa *et al.* 1974; haploid signalling of the MHC in mice suggested by Goldberg *et al.* 1970). However, these findings may still be controversial, because Haas & Nahhas (1986) could not find any MHC antigens on human sperm, and Kurpisz *et al.* (1987) reported that sperm of only few men in their sample showed HLA expression.

Nicol & McLaren (1974) found a strong influence of female genotype on sperm transport in two mouse strains. Furthermore, about 1.5 h after mating females of both strains tended to have more sperm in their oviduct if mated with males of the other strain each than if mated with males of their own strain. These findings suggests that the female reproductive system may favour certain sperm genotypes according to their own genotype. Since the sperm probably signal specifically their own MHC-haplotype, the females may select for certain MHC-types in their reproductive tract. Since MHC-heterozygotes may well have higher fitness expectations (see previous chapter), maternal choice for MHC-haplotype in sperm could be adaptive.

Further support for this hypothesis comes from the self-nonself recognition system which is known in the angiosperms. The 'self-incompatibility' (SI) is a genetically controlled mechanism which ensures that a plant is fertilized by a genetically dissimilar individual of the same species (Haring *et al.* 1990). If the pollen that landed on the stigma carries the same allele as one of the two in the pistil, the female tissue will hinder the pollen from growing into the pistil.

In vertebrates there is some evidence that the MHC is not the only system which could be important in parasite-driven maternal selection: Transferrin is a protein that binds iron and zinc. In most vertebrates studied this protein shows a polymorphism within a population (Ashton & Dennis 1971). In humans, transferrin is encoded by a single locus on chromosome 3 with codominant expression. The protein has several important functions in immunoregulation (Vodinelich *et al.* 1983) and in defence against pathogens (Weinberg 1978). Since it also shows a polymorphism it seems to be one of the important genes involved in host–parasite co-evolution.

Canham *et al.* (1970) found anomalous segregation at the transferrin locus of the deer mouse (*Peromyscus maniculatus borealis*) in a breeding experiment. The same has been found in mice and other species (Ashton & Dennis 1971, and references therein). Canham *et al.* (1970) and Ashton & Dennis (1971) listed several arguments supporting their favoured hypothesis that selective sperm transport might be the cause for the observed deviations in phenotype frequencies. In humans, Weitkamp *et al.* (1985) found that the maternal transferrin genotype influences the transmission ratio of the transferrin genes from heterozygous fathers to the offspring. They discussed this distortion as probable maternal selection on sperm during their way to the oviduct, at the egg itself (see next section), or even as maternal selection on the early embryo (see section 3(f)). Hence, it is still not clear where the selection on paternal transferrin type really takes place. However, as transferrin lies on a different chromosome from the MHC it is evident that it is probably another important gene in a parasite-driven maternal selection in vertebrate (next to MHC).

(*c*) *Egg choice for sperm*

Normally, oocytes are surrounded by envelopes such as the zona pellucida in mammals or the vitelline envelopes in amphibians or many invertebrates. Both the zona pellucida and the vitelline membrane appear to contain specific receptors for the binding of the spermatozoa (Moore & Bedford 1983; Bazer *et al.* 1987). Here, the possibility for sperm selection by the ovum is evident.

The mammalian zona pellucida is important in the initial stages of fertilization: it plays a role in blocking polyspermy, and it is, in some species, important in sperm capacitation, i.e. the changes that enable the sperm to fertilize the egg (Dunbar 1983). Furthermore, the sperm must bind to the zona and penetrate it before fusing with the oocyte plasma membrane. Several zona antigens are important in the sperm–egg interactions. However, the communication between sperm and egg which takes place at the zona pellucida and, on a later stage, at the egg membrane itself is not yet fully understood (review in Dunbar 1983; Moore & Bedford 1983).

Gametes of many lower organisms (yeast, algae, fungi and protozoa) seem to choose mates on the basis of pheromones (Pagel 1993 and references therein). In higher organisms, however, eggs may even be able to choose for a specific sperm haplotype. *Botryllus* sp., for example, are colonial tunicates which are likely to be sometimes subject to natural tissue transplantations. The *Botryllus* fusibility is controlled by a polymorphic locus with similar properties to the vertebrate MHC.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Scofield *et al.* (1982) found that this locus not only controls allorecognition but also the fusion of gametes: *Botryllus* eggs resisted fertilization by sperm from the same colony for longer time than by sperm from a strange allele on the fusibility locus. Thus, the eggs strongly select for heterozygosity on this locus in the zygote.

(*d*) *Meiotic drive influenced by sperm haplotype*

The eggs of most vertebrate and invertebrate species are in some stage of meiotic arrest at the time of fertilization (exceptions are the coelenterates and echinoids, which complete meiosis prior to ovulation (Lopo 1983)). In mammals, the second maturational division is completed only when the sperm has digested a pathway through the zona pellucida and is penetrating the vitelline membrane of the ovum. Then, the first and/or the second polar body is expelled into the perivitelline space (Wolgemuth 1983; Bazer *et al.* 1987; Hafez 1987).

The significance of this suspension of meiosis is not yet clear but in the context of this paper it raises a suspicion. The decision of the ovum (or parental zygote) about which haplotype will go into the zygote and which will be lost in the polar body could be influenced by the haplotype of the fertilizing sperm to ensure higher fitness of the zygote. But again, several prerequisites need to be fulfilled to make this plausible: (i) the ovum should be able to detect the sperm's haplotype on the important loci, and (ii) it should have a regulatory mechanism to decide accordingly which of its own haplotypes will stay in the zygote.

After fusion of the membranes of the two gametes the spermatozoan nuclear envelope disintegrates and the released chromatin material undergoes decondensation for a short time (Wolgemuth 1983). This decondensation seems to be at least partly controlled by the egg since it requires specific components (e.g. the 'sperm nucleus-decondensing factor') in the ovum's cytoplasm (Wolgemuth 1983; Bazer *et al.* 1987). Here, the egg could have the possibility of analysing the allelic specificity of the spermal haplotype, as an alternative to the potential signalling between the gametes before fusion (see above). Correspondingly, it appears that transcription of pronuclei occurs, i.e. before fusion of the paternal and maternal genomes and probably even before the egg has decided which of the two maternal haplotypes goes into the polar body (Wolgemuth 1983). After decondensating, the sperm nuclear envelope is replaced by a new envelope provided by the egg's cytoplasm before male and female pronuclei migrate to the ovum centre (Bazer *et al.* 1987).

(*e*) *Zygotic cleavage and implantation*

If it is beneficial for the mother to be able to select after fertilization she should decide as soon as possible whether to support an embryo or not, minimizing her costs. However, the formation of the zygote is the start of the conflict between the embryo and the mother (Haig 1993), i.e. the embryo might develop some mechanism of self-protection.

The oviductal epithelium is in close contact to the early embryo and most active near it. Therefore, oviductal secretions seem to provide metabolic support for the early embryo (Hafez 1987). Also, the descent of the embryo depends strongly on the oviduct. A premature entry of the embryo into the uterus (e.g. during the morula stage) often causes its degeneration (Hafez 1987). After entrance of the blastocyst into the uterus, it must implant into the uterus tissue to establish the necessary close contact to the mother during pregnancy. Until this stage, a majority of embryos get lost for various reasons (e.g. for humans see Chen 1986). It is still unclear whether maternal selection for certain offspring genotypes is one of these reasons. However, several possibilities for maternal selection might be given from the very beginning of the embryo's existence.

Until reaching the uterus the embryo is still covered by the zona pellucida (Bazer *et al.* 1987). This could be a mechanism of self-protection of the early embryo against the mother, since for example, the sperm's MHC type can be identified in the membrane of the early embryo as late as the eight-cell stage (Bazer *et al.* 1987) while neither MHC class I nor class II molecules are detectable on the zona pellucida. Discussing the case in humans, Desoye *et al.* (1988) could not find any MHC molecules on the blastocysts which are released from the zona pellucida and are implanted into the uterus tissue.

(*f*) *Embryo growth, spontaneous abortion or resorption*

Maternal selection could also take place at a later stage during the embryo's growing, still selecting for certain offspring genotypes on loci which have a selective advantage in the host–parasite co-evolution. In humans 10–25% of clinically recognized pregnancies end in spontaneous abortion (Chen 1986). Some of these abortions seem to be caused by immunological factors. In many human populations it has recently been shown that couples who suffer from recurrent spontaneous abortion (RSA) share a higher proportion of MHC fragments compared to control families. For the U.S.A. this is discussed by Beer *et al.* (1985), for Germany by Karl *et al.* (1989), for a Chinese population in Taiwan by Ho *et al.* (1990), for Japan by Koyama *et al.* (1991) and for Finland by Laitinen (1993). Further examples are given in these studies.

Reznikoff–Etievant *et al.* (1991) found in a French population that newborn children of RSA-couples with a high incidence of MHC-sharing showed a significant lower birth weight. Correspondingly, Billington (1964) had found in mice that heterozygote foetuses have larger placentae and are considerably larger themselves than homozygous ones in mothers of two different strains. The birth weight and the size of the placenta could reveal a mother's 'decision' about her investment into the embryo. This view is supported by

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

further findings on mice, hamsters and rats (Beer *et al.* 1975). (It should be stressed that this decision is most probably no more a conscious one than is the decision to reject an allograft.) However, there are of course other possible explanations. It should be recalled that heterozygosity at the MHC is likely to correlate with heterozygosity at many other loci. It may simply be heterosis expressed at some of these (as well as, possibly, at MHC) that causes a general advantage independent of their mother's decision.

Spontaneous abortions are better understood in mice. Bruce (1959) discovered that the blocking of pregnancy can be induced by the odour of a strange male. This so-called 'Bruce effect' strongly depends on the MHC of the second male which induces the pregnancy block (Yamazaki *et al.* 1983). The incidence of the pregnancy blocking was higher if the MHC of the second male differed from the one of the father of the embryos (the authors used congenic inbred strains which only differed in their MHC type). Therefore, the pregnancy block in mice may sometimes reveal a strategic decision of the mother which is at least partly influenced by the MHC.

For an evolutionary explanation of the observed MHC-sharing in RSA couples, Verrell & McCabe (1990) suggested that the MHC could be a marker for relatedness in inbred populations, indicating the possible sharing of deleterious alleles in related mates. Females may abort in order to prevent too much investment in inbred offspring of low reproductive value. They stressed, however, that their suggestion could only explain RSAs in highly inbred populations.

In agreement with my suggested evolutionary explanation, the MHC does not seem to be the only genetic system which is both important in pathogen defence and in embryo growth (compare section 3(b)). Already Weitkamp *et al.* (1985) observed an increased frequency of transferrin *C3* in couples with recurrent spontaneous abortions. Although they did not investigate the possible role of the foetal transferrin genotype, they hypothesized that different combinations of maternal and paternal transferrin genes could affect the embryonic development differently. Correspondingly, a dense concentration of transferrin and transferrin receptors have been found at the human materno–foetal interface (Faulk & Galbraith 1979).

(*g*) *Selective killing or neglect of newborns*

Poor parental care and maternal cannibalism are well documented and common in many rodent species (Elwood 1992). Often, maternal cannibalism could be of adaptive value. By killing her weakest offspring the mother might stop investments in young that are sick and therefore unlikely to survive. Another possibility is allocation of resources to young in a selective manner. In poor environmental conditions mothers often kill and consume the smallest pups to minimize wasted investment and to provide their larger pups with sufficient milk. This is known for mice, but is even more common in hamsters, where females typically produce more pups than they can rear. Filial cannibalism has also been documented in birds of 13 different families (Stanback & Koenig 1992). In these species, too, parents normally kill the weakest chicks.

4. CONCLUSIONS AND PERSPECTIVES

One of the most substantial benefits of sexual reproduction itself could be that it allows animals to rapidly react to a continuously changing environmental selection pressure, e.g. co-evolving parasites ('Red Queen Hypothesis', e.g. Ladle 1992). This counteraction would be most efficient if the females (or their ova) were able to encourage for allele combinations in the progeny either by direct and specific favour or by favouring manifest vigour. Such selection should mainly act on loci which are crucial in the arms race in co-evolving systems, e.g. polymorphic loci which encode for parasite resistances in the host. Good candidates for which some evidence already exists may be the MHC and the transferrin locus, but many other polymorphic defense-systems loci may be implicated (Hamilton *et al.* 1990; Hamilton 1993).

Sexual selection for parasite resistances need not depend on display and the handicap principle. Under certain circumstances, cheap signals showing detailed information about the identity of resistances could be reliable. Furthermore, selection on these loci could take place at many different levels and times, both before mating ('mate choice'), and afterwards, with the afterwards itself including events before, during or after the formation of the zygote ('maternal selection'). Regarding some of the possible selection levels I have listed there is already suggestive evidence that maternal selection takes place on the MHC and the transferrin locus. However, much effort is still necessary to understand the described phenomena. Several important question are largely unsolved, e.g. whether females just select for heterozygosity on certain loci in the offspring or whether they actively seek allele combinations which might be beneficial under the current conditions. To progress it is necessary to understand better the specific allele combinations advantageous under given environmental conditions. Such understanding will clarify whether, for example, MHC-induced mate preferences in mice are simply to avoid inbreeding or are better treated as part of the rubric of good-genes sexual selection (see, e.g., the discussion in Potts & Wakeland 1993).

I very much thank Manfred Milinski, William D. Hamilton, Thomas Rülicke, Michel Chapuisat, Markus Frischknecht, Erwin Macas, Laurent Keller and Beda Stadler for stimulating discussions and comments on the manuscript.

REFERENCES

Arnaiz–Villena, A. & Festenstein, H. 1976 HLA genotyping by using spermatozoa: evidence for haploid gene expression. *Lancet* 707–709.

Ashton, G.C. & Dennis, M.N. 1971 Selection at the transferrin locus in mice. *Genetics* **67**, 253–265.

Bakker T.C.M. 1990 Genetic variation in female mating preference. *Neth. J. Zool.* **40**, 617–642.

Bakker, T.C.M. 1993 Positive genetic correlation between female preference and preferred male ornament in sticklebacks. *Nature, Lond.* **363**, 255–257.

Bazer, F.W., Geisert, R.D. & Zavy, M.T. 1987 Fertilization, cleavage and implantation. In: *Reproduction in farm animals* (ed. E. S. E. Hafez), pp. 210–228. Philadelphia: Lea & Febiger.

Beauchamp, G.K., Yamazaki, K., Wysocki, C.J., Slotnick, B.M., Thomas, L. & Boyse, E.A. 1985 Chemosensory recognition of mouse major histocompatibility types by another species. *Proc. natn. Acad. Sci. U.S.A.* **82**, 4186–4188.

Beer, A.E., Scott, J.R. & Billingham, R.E 1975 Histocompatibility and maternal immunological status as determinants of fetoplacental weight and litter size in rodents. *J. exp. Med.* **142**, 180–196.

Beer, A.E., Semprini, A.E., Zhu, X.Y. & Quebbeman, J.F. 1985 Pregnancy outcome in human couples with recurrent spontaneous abortions: HLA antigen profiles, HLA antigen sharing, female serum MLR blocking factors, and paternal leukocyte immunization. *Exp. Clin. Immunogenet.* **2**, 137–153.

Bennett, D. 1975 The *t*-locus of the mouse. *Cell* **6**, 441–454.

Billington, W.D. 1964 Influence of immunological dissimilarity of mother and foetus on size of placenta in mice. *Nature, Lond.* **202**, 317–318.

Birkhead, T.R. & Møller, A.P. 1993 Female control of paternity. *Trends Ecol. Evol.* **8**, 100–104.

Birkhead, T.R., Møller, A.P. & Sutherland, W.J. 1993 Why do females make it so difficult for males to fertilize their eggs? *J. theor. Biol.* **161**, 51–60.

Blalock, J.E. 1984 The immune system as a sensory organ. *J. Immunol.* **132**, 1067–1070.

Blalock, J.E. 1994 The immune system our sixth sense. *Immunologist* **2**, 8–15.

Boyse, E.A., Beauchamp, G.K. & Yamazaki, K. 1987 The genetics of body sent. *TIG* **3**, 97–102.

Brown, R.E., Roser, B. & Singh, P.B. 1989 Class I and class II regions of the major histocompatability complex both contribute to individual odors in congenic inbred strains of rats. *Behav. Genet.* **19**, 659–674.

Bruce, H.M. 1959 An exteroceptive block to pregnancy in the mouse. *Nature, Lond.* **184**, 105.

Canham, R.P., Birdsall, D.A. & Cameron, D.G. 1970 Disturbed segregation at the transferrin locus of the deer mouse. *Microbiol. Rev.* **16**, 355–357.

Chen, C. 1986 Early reproductive loss. *Aust. N.Z. J. Obstet. Gynaecol.* **26**, 215–218.

Clutton-Brock, T.H. & Parker, G.A. 1993 Potential reproductive rates and the operation of sexual selection. *Q. Rev. Biol.* **67**, 437–456.

Desoye, G., Dohr, G.A., Motter, W. *et al.* 1988 Lack of HLA class I and class II antigens on human preimplantation embryos. *J. Immunol.* **140**, 4157–4159.

Doherty, P.C. & Zinkernagel, R.M. 1975 Enhanced immunological surveillance in mice heterozygous at the *H-2* gene complex *Nature, Lond.* **256**, 50–52.

Dunbar, B.S. 1983 Morphological, biochemical, and immunochemical characterization of the mammalian zonae pellucida. In: *Mechanism and control of animal fertilization* (ed. J. F. Hartmann), pp. 139–175. New York, London: Academic Press.

Eddy, E.M., Welch, J.E. & O'Brien, D.A. 1993 Gene expression during spermatogenesis. In: *Molecular biology of the male reproductive system* (ed. D. de Kretser), pp. 181–232. New York, London: Academic Press.

Egid, K. & Brown, J.L. 1989 The major histocompatibility complex and female mating preferences in mice. *Anim. Behav.* **38**, 548–550.

Elwood, R. 1992 Pup-cannibalism in rodents: causes and consequences. In: *Cannibalism. Ecology and evolution among diverse taxa* (ed. M. A. Elgar & B. J. Crespi), pp. 299–322. Oxford: Oxford University Press.

Faulk, W.P. & Galbraith, M.P. 1979 Trophoblast transferrin and transferrin receptors in the host-parasite relationship of human pregnancy. *Proc. R. Soc. Lond. B* **204**, 83–97.

Fellous, M. & Dausset, J. 1970 Probable haploid expression of HL-A antigens on human spermatozoon. *Nature, Lond.* **225**, 191–193.

Ferstl, R. Pause, B., Schüler, M. *et al.* 1990 Immune system signalling to the brain: MHC-specific odors in human. In: *Psychiatry: a world perspective (volume 2)* (ed. C. N. Stefanis *et al.*), pp. 751–755. London: Elsevier Science Publishers.

Fisher, R.A. 1958 *The genetical theory of natural selection (2nd ed.)*. New York: Dover Publications.

Folstad, I. & Karter, A.K. 1992 Parasites, bright males and the immunocompetence handicap. *Am. Nat.* **139**, 603–622.

Gilbert, A.N., Yamazaki, K., Beauchamp, G.K. & Thomas, L. 1986 Olfactory discrimination of mouse strains (*Mus. musculus*) and major histocompatibility types by humans (*Homo sapiens*). *J. comp. Psych.* **100**, 262–265.

Giphart, M.J. & D'Amaro, J. 1983 HLA and reproduction? *J. Immunogenet.* **10**, 25–29.

Goldberg, E.H., Aoki, T., Boyse, E.A. & Bennett, D. 1970 Detection of *H-2* antigens on mouse spermatozoa by the cytotoxicity test *Nature, Lond.* **228**, 570–572.

Grafen A. 1990*a* Sexual selection unhandicapped by the Fisher process. *J. theor. Biol.* **144**, 473–516.

Grafen A. 1990*b* Biological signals as handicaps. *J. theor. Biol.* **144**, 517–546.

Grossman, C.J. 1985 Interactions between the gonadal steroids and the immune system. *Science* **227**, 257–261.

Haas, G.G. Jr. & Nahhas, F. 1986 Failure to identify HLA ABC and Dr antigens on human sperm. *Am. J. Reprod. Immunol. Microbiol.* **10**, 39–46.

Hafez, E.S.E. 1987 Transport and survival of gametes. In: *Reproduction in farm animals* (ed. E. S. E. Hafez), pp. 168–188. Philadelphia: Lea & Febiger.

Haig, D. 1993 Genetic conflicts in human pregnancy. *Q. Rev. Biol.* **68**, 495–532.

Halim, K. & Festenstein, H. 1975 HLA-D on sperm is haploid, enabling use of sperm for HLA-D typing. *Lancet* 1255–1256.

Halim, K., Wong, D.M. & Mittal, K.K. 1982 The HLA typing of human spermatozoa by two color fluorescence. *Tissue Antigens* **19**, 90–91.

Hamilton, W.D. 1993 Haploid dynamic polymorphism in a host with matching parasites: effects of mutation/subdivision, linkage, and patterns of selection. *J. Hered.* **84**, 328–338.

Hamilton, W.D. & Zuk, M. 1982 Heritable true fitness and bright birds: a role for parasites? *Science* **218**, 384–387.

Hamilton, W.D., Axelrod, R. & Tanese, R. 1990 Sexual reproduction as an adaptation to resist parasites (a review). *Proc. natn. Acad. Sci. U.S.A.* **87**, 3566–3573.

Haring, V., Gray, J.E., McClure, B.A., Anderson, M.A. & Clarke, A.E. 1990 Self-incompatibility: a self-recognition system in plants. *Science* **250**, 937–941.

Ho, H.N., Gill, T.J., Nsieh, R.P., Hsieh, H.J. & Lee, T.Y. 1990 Sharing of human leukocyte antigens in primary and secondary recurrent spontaneous abortions. *Am. J. Obstet. Gynec.* **163**, 178–188.

Karl, A., Metzner, G., Seewald, H.J., Karl, M., Born, U. & Tilch, G. 1989 HLA compatibility and susceptibility to habitual abortion. Results of histocompatibility testing of

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

couples with frequent miscarriages. *Allerg. Immunol. (Leipz)* **35**, 133–140.
Klein, J. 1986 *Natural history of the major histocompatibility complex*. New York: John Wiley & Sons.
Koyama, M., Saji, F., Takahashi, S. *et al.* 1991 Probabilistic assessment of the HLA sharing of recurrent spontaneous abortion couples in the Japanese population. *Tissue Antigens* **37**, 211–217.
Kurpisz, M., Fernandez, N., Witt, M., Kowalik, I., Szymczynski, G.A. & Festenstein, H. 1987 HLA expression on human germinal cells. *J. Immunogenet.* **14**, 23–32.
Ladle, R. J. 1992 Parasites and sex: catching the Red Queen. *Trends Ecol. Evol.* **7**, 405–408.
Laitinen, T. 1993 A set of MHC haplotypes found among Finnish couples suffering from recurrent spontaneous abortions. *Am. J. Reprod. Immunol.* **29**, 148–154.
Lande, M. 1981 Models of speciation by sexual selection on polygenic traits. *Proc. natn. Acad. Sci. U.S.A.* **78**, 3721–3725.
Lenington, S., Coopersmith, C.B. & Williams, J. 1992 Genetic basis of mating preferences in wild house mice. *Am. Zool.* **32**, 40–47.
Lopo, A.C. 1983 Sperm-egg interaction in invertebrates. In: *Mechanism and control of animal fertilization* (ed. J. F. Hartmann), pp. 269–324. New York, London: Academic Press.
Møller, A.P. 1990*a* Parasites and sexual selection: Current status of the Hamilton and Zuk hypothesis. *J. evol. Biol.* **3**, 319–328.
Møller, A.P. 1990*b* Effect of a haematophagous mite on the barn swallow (*Hirundo rustica*): a test of the Hamilton and Zuk Hypothesis. *Evolution* **44**, 771–784.
Moore, H.D.M. & Bedford, J.M. 1983 The interaction of mammalian gametes in the female. In: *Mechanism and control of animal fertilization* (ed. J. F. Hartmann), pp. 453–497. New York, London: Academic Press.
Mortimer, D. 1983 Sperm transport in the human female reproductive tract. In: *Oxford reviews of reproductive biology* (ed. C. A. Finn), pp. 30–61. Oxford: Clarendon Press.
Nicol, A. & McLaren, A. 1974 An effect of the female genotype on sperm transport in mice. *J. Reprod. Fert.* **39**, 421–424.
Nordlander, C., Hammarström, L., Lindblom, B. & Smith, C.I.E.E. 1983 No role of HLA in mate selection. *Immunogenetics* **18**, 429–431.
Overstreet, J.W. 1983 Transport of gametes in the reproductive tract of the female mammal. In: *Mechanism and control of animal fertilization* (ed. J. F. Hartmann), pp. 499–543. New York, London: Academic Press.
Pagel, M. 1993 Honest signalling among gametes. *Nature, Lond.* **363**, 539–541.
Potts, W.K., Manning, C.J. & Wakeland, E.K. 1991 Mating patterns in seminatural populations of mice influenced by MHC genotyp. *Nature, Lond.* **352**, 619–621.
Potts, W.K. & Wakeland, E.K. 1993 Evolution of mhc genetic diversity: a tale of incest, pestilence and sexual preference. *TIG* **9**, 408–412.
Read, A.F. 1990 Parasites and the evolution of host behaviour. In: *Parasitism and host behaviour* (ed. C. J. Barnard & J. M. Behnke), pp. 117–157. London: Taylor and Francis.
Reznikoff Etievant, M.F., Bonneau, J.C., Alcalay, D. *et al.* 1991 HLA antigen-sharing in couples with repeated spontaneous abortions and the birthweight of babies in successful pregnancies. *Am. J. Reprod. Immunol.* **25**, 25–27.
Rosenberg, L.T., Cooperman, D. & Payne, R. 1983 HLA and mate selection. *Immunogenetics* **17**, 89–93.
Scofield, V.L., Schlumpberger, J.M, West, L.A. & Weissman, I.L. 1982 Protochordate allorecognition is controlled by a MHC-like gene system. *Nature, Lond.* **295**, 499–502.
Singh, P.B., Brown, R.E. & Roser, B. 1987 MHC antigens in urine as olfactory recognition cues. *Nature, Lond.* **327**, 161–164.
Stanback, M.T. & Koenig, W.D. 1992 Cannibalism in birds. In: *Cannibalism. Ecology and evolution among diverse taxa* (ed. M. A. Elgar & B. J. Crespi), pp. 277–298. Oxford: Oxford University Press.
Tiwari J.L. & Terasaki, P.I. 1985 *HLA and disease associations*. New York, Berlin: Springer-Verlag.
Verrell, P.A. & McCabe, N.R. 1990 Major histocompatibility antigens and spontaneous abortion: an evolutionary perspective. *Med. Hypoth.* **32**, 235–238.
Vodinelich, L., Sutherland, R., Schneider, C., Newman, R. & Greaves, M. 1983 Receptor for transferrin may be a 'target' structure for natural killer cells. *Proc. natn. Acad. Sci. U.S.A.* **80**, 835–839.
Wedekind, C. 1992 Detailed information about parasites revealed by sexual ornamentation. *Proc. R. Soc. Lond. B* **247**, 169–174.
Wedekind, C. 1994 Handicaps not obligatory in sexual selection for resistance genes *J. theor. Biol.* (Submitted.)
Wedekind, C. & Folstad, I. 1994 Adaptive or non-adaptive immunosuppression by sex hormones? *Am. Nat.* **143**, 936–938.
Weinberg, E.D. 1978 Iron and infection. *Microbiol. Rev.* **42**, 45–66.
Weitkamp, L.R. & Schacter, B.Z. 1985 Transferrin and HLA: spontaneous abortion, neural tube defects, and natural selection. *New Engl. J. Med.* **313**, 925–932.
Wiley, M.L. & Colette, B.B. 1970 Breeding tubercles and contact organ in fishes: their occurrence, structure, and significance. *Bull. Am. Mus. nat. Hist.* **143**, 145–216.
Wolgemuth, D.J. 1983 Synthetic activities of the mammalian early embryo: molecular and genetic alterations following fertilization. In: *Mechanism and control of animal fertilization* (ed. J. F. Hartmann), pp. 415–452. New York, London: Academic Press.
Yamazaki, K., Boyse, E.A., Miké, V. *et al.* 1976 Control of mating preference in mice by genes in the major histocompatibility complex. *J. exp. Med.* **144**, 1324–1335.
Yamazaki, K., Yamaguchi, M., Baranoski, L., Bard, J., Boyse, E.A. & Thomas, L. 1979 Recognition among mice. Evidence from the use of a Y-maze differentially scented by congenic mice of different major histocompatibility types. *J. exp. Med.* **150**, 755–760.
Yamazaki, K., Beauchamp, G.K., Wysocki, C.J., Bard, J., Thomas, L. & Boyse, E.A. 1983 Recognition of *H-2* types in relation to the blocking of pregnancy in mice. *Science* **221**, 186–188.
Yamazaki, K., Beauchamp, G.K., Kupniewski, D., Bard, J., Thomas, L. & Boyse, E.A., 1988 Familial imprinting determines *H-2* selective mating preferences. *Science* **240**, 1331–1332.
Yanagisawa, K., Pollard, D.R., Bennett, D., Dunn, L. C. & Boyse, E.A. 1974 Transmission ration distortion at the *T*-locus, identification of two antigenically different populations of sperm in *t*-heterozygotes. *Immunogenetics* **1**, 91–96.
Zahavi, A. 1975 Mate selection – a selection for a handicap. *J. theor. Biol.* **53**, 205–214.
Zahavi, A. 1977 The costs of honesty (further remarks on the handicap principle). *J. theor. Biol.* **67**, 603–605.
Zinkernagel, R.M. & Doherty, P.C. 1974 Immunological surveillance against altered self components by sensitised *T* lymphocytes in lymphocytic choriomeningitis. *Nature, Lond.* **251**, 547–548.
Zuk, M. 1984 A charming resistance to parasites. *Natur. Hist.* **4**, 28–34.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES