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Review Paper

Immune function across generations: integrating mechanism and evolutionary process in maternal antibody transmission

Jennifer L. Grindstaff*, Edmund D. Brodie III and Ellen D. Ketterson

Department of Biology and Center for the Integrative Study of Animal Behavior, 1001 E. Third Street, Indiana University—Bloomington, Bloomington, IN 47405, USA

The past 30 years of immunological research have revealed much about the proximate mechanisms of maternal antibody transmission and utilization, but have not adequately addressed how these issues are related to evolutionary and ecological theory. Much remains to be learned about individual differences within a species in maternal antibody transmission as well as differences among species in transmission or utilization of antibodies. Similarly, maternal-effects theory has generally neglected the mechanisms by which mothers influence offspring phenotype. Although the environmental cues that generate maternal effects and the consequent effects for offspring phenotype are often well characterized, the intermediary physiological and developmental steps through which the maternal effect is transmitted are generally unknown. Integration of the proximate mechanisms of maternal antibody transmission with evolutionary theory on maternal effects affords an important opportunity to unite mechanism and process by focusing on the links between genetics, environment and physiology, with the ultimate goal of explaining differences among individuals and species in the transfer of immune function from one generation to the next.

Keywords: immunocompetence; maternal effects; egg quality; indirect genetic effects; indirect environmental effects; ecological immunology

1. INTRODUCTION

The ability of mothers to transmit antibodies to their offspring was documented in both mammals and birds over 100 years ago (Ehrlich 1892; Klemperer 1893). Since that time, elegant empirical studies have further elucidated the mechanisms of antibody transmission and the subsequent utilization of antibodies by offspring (e.g. Brambell 1970; Solomon 1971*a*; Rose *et al.* 1974; Kowalczyk *et al.* 1985). However, the potential implications of maternal antibody transmission for evolutionary processes have been largely neglected. We integrate empirical studies of maternal antibody transmission with recent theoretical developments in the evolutionary and ecological significance of maternal effects. We outline the genetic and environmental determinants of variation among mothers in antibody transmission and describe how maternally derived antibodies affect offspring phenotype and fitness. We conclude by offering new predictions about the evolution of maternal antibody transmission and suggest future directions in the evolutionary analysis of maternal antibody transmission.

Maternal antibody transmission is defined as the transfer of antibodies by an immunocompetent adult, typically a female, to an immunologically naive neonate transplacentally or through colostrum, milk, yolk, etc. Female fishes (van Loon *et al.* 1981; Bly *et al.* 1986; Fuda *et al.* 1992), reptiles (Schumacher *et al.* 1999) and birds (Klemperer 1893; Brambell 1970) transmit passive immunity[1] to offspring through the deposition of antibodies in eggs. In mammals, antibodies are transferred across the placenta prior to birth and through the colostrum and breast milk postnatally (Ehrlich 1892; Brambell 1970; table 1). There is recent evidence that invertebrates, which do not produce antibodies, also have some mechanism of maternal transmission of immunity to the next generation (Huang & Song 1999; Moret & Schmid-Hempel 2001).

Neonatal vertebrates have limited ability to synthesize antibodies endogenously (Brambell 1970; Solomon 1971*a*; Lawrence *et al.* 1981). Therefore, maternally derived antibodies provide the primary form of humoral (antibody-mediated) immune defence for offspring early in life (Brambell 1970; figure 1). The persistence of maternal antibodies in offspring circulation varies by species between 10 days (e.g. fishes) and nine months (e.g. humans) as a function of body size and metabolic rate. Maternal antibodies disappear at about the time of onset of active antibody production by offspring[1] (Solomon 1971*a*; table 1). For example, in the chicken (*Gallus domesticus*), maternal immunoglobulin G (IgG)[2] is catabolized by offspring over the first 14 days post-hatch, and by *ca*. 5 days post-hatch offspring begin to synthesize IgG independently (Patterson *et al.* 1962; Brambell 1970; Rose & Orlans 1981; Apanius 1998)[2]. As a result, after approximately two weeks the circulating IgG in young is principally of endogenous origin. Adult levels are attained between six weeks and six months of age (Patterson *et al.* 1962; Brambell 1970; Rose & Orlans 1981; Apanius 1998). Maternal antibodies may continue to affect offspring phenotype even after they are catabolized by influencing growth and developmental rates (Robison *et al.*

*Author for correspondence (jgrindst@indiana.edu).

Table 1. Routes of transmission of passive immunity across taxa.
('Duration of passive immunity' is the time-period over which maternally derived antibodies may be detected in the plasma of offspring. 'Active immunity' indicates the point at which offspring endogenously produce antibodies at the same level as adults.)

taxa/species	prenatal route	postnatal route	duration of passive immunity	development of active immunity	source
fish					
carp (*Cyprinus carpio*)	yolk sac	yolk sac	*ca.* 10 days	5–8 months	van Loon *et al.* (1981)
reptile					
desert tortoise (*Gopherus agassizii*)			< 1 year		Schumacher *et al.* (1999)
bird					
chicken (*Gallus domesticus*)	yolk sac	yolk sac (< 5 days)	2 weeks	6 weeks–6 months	Patterson *et al.* (1962), Brambell (1970), Rose & Orlans (1981), Apanius (1998)
mallard duck (*Anas platyrhynchos*)	yolk sac	yolk sac	2 weeks	< 71 days	Liu & Higgins (1990)
blue and gold macaw (*Ara ararauna*)	yolk sac	yolk sac	< 40 days	> 6 weeks	Lung *et al.* (1996)
mammal					
rat (*Rattus norvegicus*)	placenta	gut (20 days)	4–10 weeks	> 2 weeks	Brambell (1970), Arango-Jaramillo *et al.* (1988), Zhang *et al.* (1988)
mouse (*Mus musculus*)	placenta	gut (20 days)	6–10 weeks	> 2 weeks	Brambell (1970), Reuman *et al.* (1983)
guinea pig (*Cavia porcellus*)	yolk sac	none	4 months		Brambell (1970), Mylvaganam & Solomon (1981)
rabbit (*Oryctolagus cuniculus*)	yolk sac	none	1–2 months		Mushin & Schoenbaum (1980), DiGiacomo & Thouless (1986)
hedgehog (*Erinaceus europaea*)	placenta	gut (40 days)	*ca.* 2 months		Morris (1961), Brambell (1970)
human (*Homo sapiens*)	placenta	gut	9 months	1–2 years	Brambell (1970), Roitt *et al.* (1998)
horse (*Equus caballus*)	none	gut (24 h)	32–39 days		van Maanen *et al.* (1992)
pig (*Sus scrofa*)	none	gut (24–36 h)	3–4 weeks	*ca.* 6 weeks	Brambell (1970)

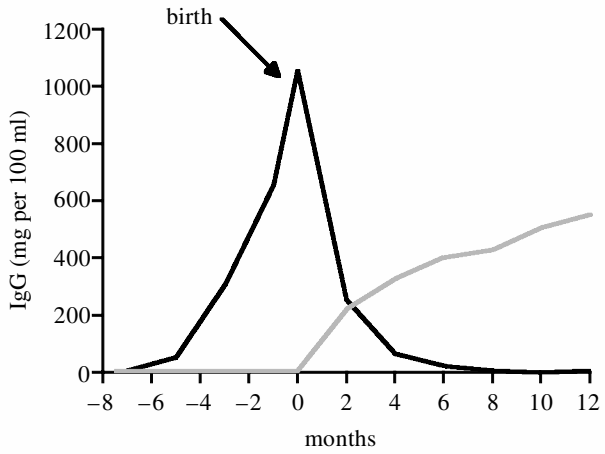

Figure 1. Ontogeny of serum IgG levels in human infants. IgG in the neonate (grey line) is solely of maternal origin. This maternal IgG (black line) is completely catabolized by the age of nine months, by which time the infant has begun to synthesize IgG endogenously. (Redrawn from Roitt *et al.* (1998) with permission from Elsevier. Copyright © 1998 Elsevier Science.)

1988; Gustafsson *et al.* 1994) and strength and diversity of the immune response (Lemke & Lange 1999; Lundin *et al.* 1999; table 2).

These influences of maternal antibody transmission on offspring phenotype are examples of maternal effects (Mousseau & Fox 1998*b*; Wolf *et al.* 1998), whereby a trait of the mother (antibody transmission) affects variation in offspring phenotypic traits. Maternal effects occur when offspring phenotype is determined not only by its own genotype and the environment it experiences but is also determined by the maternal phenotype (Kirkpatrick & Lande 1989; Cheverud & Moore 1994; Mousseau & Fox 1998*b*; Wolf *et al.* 1998). Mothers may influence offspring phenotype in multitudinous ways beyond the genes that they transmit. For example, females may influence offspring phenotype and survival through mate choice, selection of oviposition sites and offspring provisioning (for reviews see: Bernardo 1996; Mousseau & Fox 1998*a*). Maternal effects generally have their greatest impact early in development and then decline as offspring mature (Cheverud *et al.* 1983; Price 1998; Wolf *et al.* 1998). However, because mortality and thus selection are often greatest during early development (Rossiter 1996), even maternal effects of short duration may have important evolutionary consequences.

One feature that distinguishes maternal effects from other traits is that they are shaped by selection on both parents and offspring (Kirkpatrick & Lande 1989; Mousseau & Fox 1998*b*; Wolf & Wade 2001). Because these levels of selection may frequently oppose each other, models of maternal effects synthesize selection on the maternal and offspring generations in terms of the covariance between the maternal trait and offspring phenotypes (Kirkpatrick & Lande 1989; Wolf *et al.* 1998). By applying this perspective to the study of passive immune transfer, one can simultaneously model the potential positive and negative direct fitness consequences for both mothers and offspring of selection on antibody transmission. This approach allows a more complete depiction of the interactions between generations and a more accurate prediction of the evolutionary response to selection of maternal antibody transmission.

2. GENETIC SOURCES OF VARIATION AMONG FEMALES IN ANTIBODY TRANSMISSION (INDIRECT GENETIC EFFECTS)

If there is genetically based variation among mothers in the developmental environment that they provide for offspring in terms of antibody transmission, then the maternal effect is described as an indirect genetic effect (IGE) (Wolf *et al.* 1998). Depending on the dynamics of the system, IGEs may hasten or retard the evolutionary response to selection, reverse the direction of a response or create oscillations in phenotypic expression (Kirkpatrick & Lande 1989; Wolf *et al.* 1998). When parents influence traits in their offspring through IGEs, evolutionary change in the offspring generation is partially determined by evolution that occurred in the preceding parental generation, resulting in evolutionary time-lags or momentum (Wolf *et al.* 1998). These time-lags arise because the genes for the expression of maternal traits are held in the maternal generation, but selection acts on phenotypic variation expressed in the offspring generation (Cheverud & Moore 1994). For example, any genes that determine the level of transmission of maternal antibodies are expressed in the maternal generation, but selection may act primarily on the variation in maternal antibodies received by offspring, because offspring survival is more likely than maternal survival to be affected by variation in transmission. Differential survival of offspring as a result of the level of maternal antibodies received will alter the distribution of maternal antibody transmission in the offspring generation. Therefore, changes in gene frequency due to selection on maternal antibody transmission would not be evident until offspring mature and transmit maternal antibodies to the subsequent generation.

(a) *Genetic determinants of variation in maternal antibody transmission*

Artificial selection experiments on various components of the immune response in livestock have provided some evidence that variation in maternal antibody transmission is at least partially genetically based. In cattle, levels of IgG in the colostrum of an individual female are repeatable both within years ($r = 0.20$) and across years ($r = 0.41$) (Dardillat *et al.* 1978). Because repeatability provides an upper bound on heritability (Falconer & Mackay 1996), this suggests that colostral IgG levels may be, at most, moderately heritable. Artificial selection experiments to elevate early growth provide independent evidence that colostral IgG levels may be moderately heritable. Calves from lines selected for elevated weaning weight, yearling weight or muscle development have significantly lower serum IgG levels of colostral origin than calves from randomly selected control lines (Bradley *et al.* 1979; Muggli *et al.* 1984). In other words, selection to increase early growth has led to a correlated decline in maternally derived antibody levels.

In chicken lines selected for elevated antibody responsiveness to sheep red blood cells (SRBC) at the juvenile stage, the lag between maternal antigen exposure and

Table 2. Documented effects of maternal antibodies on offspring survival, immune response and growth across taxa.

taxa/species	effect of maternal antibodies	source
bird	survival	
chicken, pigeon	offspring *survival* after disease challenge	Kissling *et al.* (1954), Reeves *et al.* (1954), Heller *et al.* (1990), Leitner *et al.* (1990), Goddard *et al.* (1994)
mammal		
mouse	offspring survival after disease challenge	Reuman *et al.* (1983)
rat	offspring survival after disease challenge	Zhang *et al.* (1988)
bird	*immune response*	
chicken	MHC class II cell numbers	Yasuda *et al.* (1998)
mammal		
mouse	B-cell repertoire diversity	Strayer *et al.* (1974), Wikler *et al.* (1980), Rubinstein *et al.* (1982), Elliott & Kearney (1992)
mouse	B-cell number	Malanchere *et al.* (1997)
rat	antibody response intensity	Okamoto *et al.* (1989), Lundin *et al.* (1999), Lemke & Lange (1999)
mammal	*growth*	
dairy cattle	offspring growth rate	Robison *et al.* (1988)
mice	offspring growth and survival	Gustafsson *et al.* (1994)

detection of antibody in the egg yolk was shortened, the antibody level in the 18 day embryo was elevated, peak maternal antibody levels persisted longer in progeny, and the rate of decline of the offspring antibody response was slower in comparison with lines selected for decreased antibody responsiveness (Boa-Amponsem *et al.* 1997). Selection line differences in levels of maternally derived antibodies and the rate of decay of maternal antibodies after challenge with infectious bursal disease virus have also been documented in chickens (Bumstead *et al.* 1993). These results suggest that selection to increase the strength of the humoral immune response has led to a concomitant increase in the quantity and quality of maternal immune transfer and therefore provides evidence that the maternal immune environment is at least partially genetically based. However, these selection lines also exhibited differences in key reproductive traits in adults. Hens in the high SRBC antibody response line were older at first egg laying, had lower egg production and fertility, and a shorter duration of fertility over their lifespan than hens in the low antibody response line (Siegel *et al.* 1982; Martin *et al.* 1990). Therefore, selection for higher immune responsiveness in hens also led to a correlated decline in general fertility and reproduction. Furthermore, selection to increase antibody formation and transmission to offspring may also have correlated effects on other aspects of the immune response. Hens in the high antibody response line have decreased thymus mass (Ubosi *et al.* 1985) and reduced activity of macrophages (Biozzi *et al.* 1982), which suggests that selection for elevated humoral immune responsiveness in hens has led to correlated declines in cell-mediated and innate immunity (Ubosi *et al.* 1985). Taken together, these artificial selection experiments demonstrate a genetic basis for antibody transfer as well as genetic correlations between the transfer of maternal antibodies to offspring and adult reproductive rate and between antibody transmission and other components of the immune response.

3. ENVIRONMENTAL SOURCES OF VARIATION AMONG FEMALES IN ANTIBODY TRANSMISSION (INDIRECT ENVIRONMENTAL EFFECTS)

If variation among mothers in the developmental environment they provide is non-genetically based, the maternal effect is described as an indirect environmental effect (IEE) (Wolf *et al.* 1998). Although IEEs may influence the environment in which selection occurs (Rossiter 1996), and thus the outcome of selection, they differ from IGEs because they do not contribute directly to the evolutionary response to selection. Variation in maternal antibody transmission is most probably a result not only of genetic differences among mothers but also of variation in the environment experienced by mothers prior to antibody transmission. Maternal antibody transmission may induce phenotypic variation in offspring (i.e. generate transgenerational phenotypic plasticity; Fox & Mousseau (1998); Agrawal *et al.* (1999)) by priming offspring for the disease environment experienced by mothers. For example, if maternal exposure to a particular pathogen induces antibody production in the mother, the antibodies are transmitted to her offspring, and those offspring mount a more efficient antibody response when challenged with the same pathogen, this could be described as an IEE or transgenerational phenotypic plasticity.

Maternal antibody transmission is not only a maternal effect but is also an example of a cross-generational inducible defence (Agrawal *et al.* 1999; Tollrian & Harvell 1999). Inducible defences are phenotypic changes induced by cues associated with biotic agents, which diminish the effects of subsequent attacks by these agents (Tollrian & Harvell 1999). The vertebrate immune response is one example of an inducible defence (Frost 1999). A characteristic of inducible defences is that they are costly to maintain and are therefore induced only when the risk of encountering the biotic agent is high enough to balance the cost, i.e. inducible defences involve trade-offs

(Frost 1999). Therefore, we would expect that elevated maternal antibody transmission would necessitate reproductive trade-offs for females (Heeb *et al.* 1998; J. L. Grindstaff, D. Hasselquist, J.-Å. Nilsson, M. Sandell and M. Stjernman, unpublished data).

(a) *Environmental determinants of variation in maternal antibody transmission*

The diversity and quantity of specific antibodies transmitted to offspring have been shown to reflect differences in the local disease environment experienced by females prior to antibody transmission (Lemke & Lange 1999; Lundin *et al.* 1999; Gasparini *et al.* 2001). Females not exposed to particular pathogens prior to transmission will not transfer antibodies to those pathogens, leaving their offspring susceptible to infection (Heller *et al.* 1990; Leitner *et al.* 1990). In several avian species (i.e. white ibis (*Eudocimus albus*), rock doves (*Columba livia*), house sparrows (*Passer domesticus*), great blue herons (*Ardea herodias*), house finches (*Carpodacus mexicanus*) and mourning doves (*Zenaida macroura*)) females naturally exposed to encephalitis viruses transmit antibodies to offspring, causing them to be resistant to infection with encephalitis (Kissling *et al.* 1954; Reeves *et al.* 1954; Sooter *et al.* 1954). In kittiwakes (*Rissa tridactyla*), the prevalence of antibodies against the Lyme disease agent, *Borrelia burgdorferi sensu lato*, is higher in eggs from breeding areas with a high prevalence and abundance of ticks than in areas with a low abundance of ticks (Gasparini *et al.* 2001).

Resource limitation has also been suggested as one potential mediator of variation among individuals in immune function because nearly every defensive mechanism in the vertebrate immune response is reliant upon significant supplies of proteins and amino acids (Klasing 1998). During an immune response, animals often experience negative nitrogen balance that persists for at least several days (Klasing 1998) and may experience an increase in metabolic rate (Demas *et al.* 1997; Martin *et al.* 2003; Schmid-Hempel 2003; but see Svensson *et al.* 1998). Because females dramatically upregulate antibody production during gestation/lactation or egg production[2], maternal antibody transmission may be particularly sensitive to the availability of specific nutrients or minerals required as precursors in an antibody response. Rat (*Rattus norvegicus*) dams fed low-protein diets produce colostrum with twofold lower levels of IgG than in control dams (Michalek *et al.* 1975). In mammals, protein restriction in mothers may decrease both antibody production by mothers (Roulin & Heeb 1999) and absorption of antibodies by offspring. Maternal protein restriction impairs antibody absorption by offspring in rats (Loh *et al.* 1971), cattle (Blecha *et al.* 1981) and peccaries (*Pecari tajacu*) (Lochmiller & Dabbert 1993). Maternal dietary status may also influence transmission of antibodies via the yolk sac in birds. Maternal dietary vitamin E restriction decreases antibody transmission to eggs in chickens (Jackson *et al.* 1978) and in serins (*Serinus serinus*), food availability around the nest site is significantly positively correlated with offspring antibody response to SRBCs (Hoi-Leitner *et al.* 2001).

Finally, several non-nutritional factors are known to affect antibody transfer including age of the mother, time in the season and quality of the mate. At the cellular level, young laying hens (*ca.* 180 days old) have over twofold higher levels of IgG-containing cells in the ovary than either immature hens (*ca.* 50 days) or old laying hens (*ca.* 450 days old) (Barua *et al.* 1998). In cattle, offspring of mothers 3 years old have significantly higher serum IgG levels than offspring of either 2-year-old mothers or mothers older than 3 years (Dardillat *et al.* 1978; Muggli *et al.* 1984). Young cows may not produce a sufficient volume of colostrum to maximize intestinal absorption by the calf (Muggli *et al.* 1984). Maternal antibody transmission may vary within a season as has been found for other immune compounds (Saino *et al.* 2002*b*) and antibody transmission may even be influenced by attractiveness of the social mate (Saino *et al.* 2002*a*,*c*).

4. CONSEQUENCES OF VARIATION IN MATERNAL ANTIBODY TRANSMISSION FOR OFFSPRING IMMUNE FUNCTION, GROWTH AND SURVIVAL

Both the concentration of IgG and the diversity of the antibody population transferred are correlated between mothers and their offspring (Stott & Fellah 1983; Brown *et al.* 1989; Bumstead *et al.* 1993; Graczyk *et al.* 1994; Bollen & Hau 1997; Gasparini *et al.* 2002; Saino *et al.* 2002*c*). The amount and types of maternal antibodies transmitted may partially determine the survival probability of offspring (Heller *et al.* 1990; Leitner *et al.* 1990). For example, when chicks are exposed to *Escherichia coli* or infectious bursal disease virus soon after hatching, the percentage of progeny surviving is positively correlated with the hen's antibody titre (Heller *et al.* 1990; Goddard *et al.* 1994). Similarly, in dairy cattle, mortality rates are lower among calves with high levels of serum IgG than in offspring with low circulating IgG levels (Dardillat *et al.* 1978; Muggli *et al.* 1984; Robison *et al.* 1988). In mice (*Mus musculus*), offspring nursed by immunoglobulin-deficient mothers (due to gene knockout) also exhibit high mortality (Gustafsson *et al.* 1994; Roulin & Heeb 1999).

(a) *Consequences for offspring immune function*

Many of the effects of maternal antibodies on offspring are inducible only during early development and lead to nearly irreversible alterations of the offspring immune repertoire. Thus, the duration of these maternal effects may far outreach the presence of maternally derived antibodies in offspring. Antibodies administered during the neonatal period of mammals influence the B-cell repertoire expressed after antigenic challenge later in life (mice: Strayer *et al.* 1974; Wikler *et al.* 1980; Rubinstein *et al.* 1982; Elliott & Kearney 1992; rats: Lundin *et al.* 1999). In some cases, maternal antibodies may even affect immune function across multiple generations. In one study (Lundin *et al.* 1999), antibody response to intestinal colonization with *E. coli* did not differ between control rat pups and experimental pups that had been orally immunized with a mouse antibody directed against an *E. coli* capsular polysaccharide. However, in the second generation, the offspring of rats from the manipulated generation given *E. coli* antibodies had an enhanced antibody response to *E. coli* as well as to other structurally similar antigens as compared with the offspring of non-immunized mothers (Lundin *et al.* 1999). The only exposure of pups

in the second generation to the *E. coli* antigen had been through the immune network of the mother. Although the mechanism for this shaping of the immune network is not yet fully understood, it is known that neonatal treatment with monoclonal antibody can cause selection and expansion of both the B-cell and T-cell repertoire (Cerny *et al.* 1983; Martinez-A. *et al.* 1985; Coutinho *et al.* 1987). Because the effects on immune differentiation are primarily a result of the disease environment experienced by the mother, this is one example of an IEE with persistent consequences for subsequent generations of offspring.

Beyond guiding the diversity of the immune repertoire of offspring, maternal antibodies may also improve the strength of the offspring immune response. For example, B-cell-deficient mice (due to gene knockout) that do not transmit maternal antibodies produce progeny with two-to-threefold lower numbers of bone marrow pre-B and B cells and splenic B cells than the progeny of phenotypically normal females (Malanchere *et al.* 1997). In the absence of maternal IgG in chickens (due to surgical bursectomy of the mother during her own embryogenesis), the frequency of MHC class II cells in the spleen of offspring is depressed (Yasuda *et al.* 1998). These cells are responsible for the presentation of antigen to helper T cells (Roitt *et al.* 1998). In the absence of maternal antibodies, the immune responsiveness of offspring is depressed, which could lower the survival of offspring particularly in harsh disease environments (Yasuda *et al.* 1998).

Mouse pups, challenged for the first time with the same antigen that their mother had been exposed to, mount the equivalent of a secondary immune response (a stronger and faster response to the antigen) (Okamoto *et al.* 1989). This effect has been observed to persist over two generations, so that in mice the F_2 progeny of immunized females sometimes produce antibody titres after primary immunization that are normally observed only in the course of a secondary immune response (Lemke & Lange 1999). Therefore, maternal antibodies not only shape the antigen-inducible B-cell repertoire but also influence the developing immune system by enhancing the strength of the antibody response to initial challenge (Lemke & Lange 1999). Again, these effects of maternal antibodies on the offspring immune repertoire are most probably a product of the disease environment experienced by the mother and provide another example of the potentially persistent effects on offspring of an IEE.

(b) *Consequences for offspring growth*

In dairy calves, the concentration of serum IgG from the mother is positively correlated with offspring growth rate during the first 180 days postpartum (Robison *et al.* 1988). Additionally, mouse pups nursed by immunoglobulin-deficient mothers exhibit retarded growth (Gustafsson *et al.* 1994). Two mechanisms may be proposed regarding how maternal antibodies influence offspring growth. First, maternal antibodies may influence offspring growth rates by non-specifically stimulating cell surface receptors involved in the regulation of neonatal growth (Gustafsson *et al.* 1994; Lozano & Ydenberg 2002). Second, it has been suggested that the physiological expense of an immune response by offspring (in any vertebrate taxa) competes with the nutrients required for growth and other functions (Sheldon & Verhulst 1996; Lochmiller & Deerenberg 2000). This hypothesis is based upon the well-established link between stimulation of the immune system and decreased growth rates, whether or not the stimulus induces illness (e.g. Klasing & Johnstone 1991; Roura *et al.* 1992; Heeb *et al.* 1998; Wright *et al.* 2000). Therefore, young with high levels of maternal antibodies might be expected to have higher growth rates than young with low maternal antibody levels (Buechler *et al.* 2002) because maternal antibodies allow offspring to resist infection without the physiological and growth-retarding expense of an immune response. Through either mechanism, elevated early growth rates may positively influence offspring fitness because weight at independence is, commonly, positively correlated with survival probability (Keller & van Noordwijk 1993; Gebhardt-Henrich & Richner 1998).

(c) *Negative fitness effects of maternal antibodies*

Although maternal antibodies may predominantly enhance offspring disease resistance, at very high levels they may block stimulation of neonatal immune mechanisms (Lancaster 1964), thus suppressing the ability of offspring to develop active immunity against later infections with the same antigen (Solomon 1971*b*). For instance, maternal antibodies that bind parasite antigens in offspring are able to cross-link receptors on the surface of offspring B cells for antibody and antigen receptors. This effect, obtained with low doses of antibodies, permits sensitization of B cells (priming) but inhibits subsequent antibody synthesis (Carlier & Truyens 1995).

With higher levels of maternal antibodies, all parasite epitopes (parts of the antigen that contact the antigen-binding site of the antibody) may be bound. This binding prevents specific B cells from recognizing parasite antigens and inhibits immune priming by the young (Carlier & Truyens 1995). Finally, the deposition of maternal antibodies on parasites may promote parasite adhesion and internalization by inactivated macrophages, which may enhance intracellular infection (Carlier & Truyens 1995). Consequently, increased maternal antibody transmission may entail both positive and negative fitness effects for offspring. Despite the potential costs, maternal antibodies are generally believed to provide net benefits to offspring (Solomon 1971*b*; Lemke & Lange 1999), however, very little is known about the protective effects of maternal antibodies in natural systems (Heeb *et al.* 1998).

5. INTERACTIONS ACROSS GENERATIONS: MATERNAL–OFFSPRING CO-ADAPTATION

Maternally derived antibody levels may differ among young within a family, despite stable IgG levels in the mother during egg production or gestation (Pardue *et al.* 1990; Bumstead *et al.* 1993; Graczyk *et al.* 1994). This effect may either be due to variation in antibody transmission to individual eggs or be a result of variation in the ability of offspring to absorb IgG (Pardue *et al.* 1990; Bumstead *et al.* 1993). The level of maternally derived antibodies absorbed by young may be determined by interactions between the maternal genome (antibody level transferred) and the offspring genome (antibody concentration absorbed). Offspring within a family may vary in their ability to absorb maternal antibodies due to factors

such as receptor density on epithelial cells, receptor binding affinity for IgG, metabolic rates and length of the incubation or gestation period (Muggli *et al.* 1984; Linder *et al.* 2000). If there is a genetic basis to antibody deposition and absorption, the interaction between the maternal and offspring genomes may create the potential for genotype-by-genotype ($G \times G$) epistasis and consequent co-adaptation of offspring and maternal traits (Wolf 2000; Kölliker & Richner 2001; Hager & Johnstone 2003). Offspring ability to absorb maternal antibodies would be predicted to be co-adapted with the level of antibodies transferred by the mother such that manipulation of either maternal antibody levels or offspring uptake would disrupt the co-adaptation and would produce a non-optimal immune environment for offspring (e.g. Wolf & Brodie 1998).

In contrast to many models of intergenerational conflict (e.g. Godfray 1995), parent–offspring co-adaptation theory currently addresses the evolutionary process rather than supplying predictions about evolutionary endpoints. The equilibrium state predicted by parent–offspring conflict theory might differ among populations and species, depending on environment or life history. For example, upregulation of the maternal immune system to supply elevated antibody levels for offspring may be more strongly favoured in short-lived species than in long-lived species, or in high-condition as opposed to low-condition individuals, if elevated immune function comes at a cost to future reproduction. However, if maternal antibody transmission is influenced by genes expressed in both females and offspring, it will be necessary to understand the underlying genetic correlations between mothers and offspring in order to accurately predict the evolutionary outcome to selection (Cheverud & Moore 1994).

6. IMPLICATIONS AND FUTURE DIRECTIONS

If there is a genetic basis to variation among females in antibody transmission, then maternal antibody transmission is an indirect genetic effect. As an indirect genetic effect, maternal antibody transmission has the potential to generate counterintuitive outcomes to short-term evolution because the response to selection is dependent on the sign of the covariance between direct additive genetic effects and maternal additive genetic effects (Kirkpatrick & Lande 1989; Wolf *et al.* 1998). A negative direct-maternal genetic covariance indicates that genes in offspring that increase the value of a character are counteracted by genes that decrease the value of the maternal trait. The genetic covariance may be due either to negative linkage disequilibrium or to pleiotropic effects of the same gene. If this covariance is highly negative, short-term evolution can proceed in a direction opposite to that of selection. For example, in mammals, maternal performance (quantity or quality of milk) generally has a negative genetic correlation with offspring weight at weaning. Genes that result in an elevated growth rate in offspring also have a negative effect on maternal performance characters that influence offspring weight (e.g. volume of milk production; Cheverud & Moore (1994)). Consequently, selection to increase milk production leads to a reduction in offspring body weight. Artificial selection experiments in chickens and cattle predict that a similar process may occur in maternal antibody transmission. Lines of chickens selected for improved immune responsiveness also exhibit a decreased juvenile growth rate (Siegel *et al.* 1982; Martin *et al.* 1990) and calves from lines selected for increased yearling weight exhibit a lower concentration of maternally derived antibodies than calves from control lines (Bradley *et al.* 1979). Thus, selection to increase maternal immune competence will probably also lead to a decline in offspring body weight. With an appreciation of the dynamics of maternal effect systems, these counterintuitive outcomes to selection can be better understood.

As an indirect environmental effect, maternal antibodies may prime offspring to the current disease environment and therefore provide one means of transgenerational phenotypic plasticity (Fox & Mousseau 1998; Agrawal *et al.* 1999). Offspring raised in the same disease environment as that experienced by their mother would be predicted to have higher survival, an immune repertoire that is prepared for endemic pathogens, and higher growth rates than offspring raised in disease environments divergent from their mother's (Heeb *et al.* 1998; Buechler *et al.* 2002). Furthermore, there is currently growing interest in the natural ecology of infectious diseases, and maternal antibody transmission may be relevant for several important theoretical issues. For example, young birds typically disperse at independence and may carry diseases that are prevalent in their home range. These diseases may then infect other conspecifics at breeding sites. However, if juveniles also carry maternal antibodies that make them less susceptible to disease, the dynamics of infection may be altered in ways that current models of disease transmission do not incorporate (Grenfell & Dobson 1995). Lower susceptibility might, for example, enhance the spread of disease because maternally protected infected individuals would be more likely to survive to dispersal age than they otherwise would be. By contrast, lower susceptibility may reduce the severity of a disease, decreasing the likelihood that an individual will spread infection. Depending on how long antibodies persist in the maternal circulation, females of migratory species may even be able to transmit protection to offspring from tropical pathogens that the offspring will not encounter until they migrate to the wintering grounds for the first time.

In the presence of maternal effects, offspring fitness is likely to be affected by the combination of offspring genotype and maternal environment (Wolf & Brodie 1998; Wolf 2000; Agrawal *et al.* 2001). Particular combinations of offspring genotypes and maternal effects (both IEE and IGE) will generally result in high or low offspring fitness. Specifically in relation to antibody transmission, because offspring genotype may influence antibody absorption, and maternal antibody transmission is at least partly genetically based, development of the offspring immune system may become adapted to the maternal immune environment. In addition, evidence that maternal antibodies may have both positive and negative effects on offspring immunity provides the nonlinear effects on offspring phenotype and fitness that are required for co-adaptation to occur (Wolf & Brodie 1998). Maternal–offspring co-adaptation may be especially evident in mammals owing to the diversity in placental structure and timing of antibody transmission and absorption in this class.

In sum, immunologists have revealed many of the proximate mechanisms of maternal antibody transmission and utilization in the past 30 years, but their research has not addressed the environmental and evolutionary forces underlying differences among individuals within a species in maternal antibody transmission and, generally, has not attempted to explain differences among species in transmission or utilization of antibodies. Similarly, maternal effects theory has generally neglected the mechanisms by which mothers influence offspring phenotype (Mousseau & Fox 1998*b*). Although the environmental cues that generate maternal effects and the consequent effects for offspring phenotype are often well characterized, the intermediary physiological and developmental steps through which the maternal effect is transmitted are generally unknown. Integration of the proximate mechanisms of maternal antibody transmission with evolutionary theory on maternal effects affords an opportunity to characterize a maternal effect from the level of genetic differences to physiology, and ultimately to differences among individuals and species.

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ENDNOTES

[1]*Active versus passive immunity.* Immunity to an antigen may be characterized as either active (induced) or passive. An animal is actively immune to an antigen once it has produced antibodies (or immunoglobulins) in response to exposure to the antigen (Roitt *et aI.* 1998). By contrast, the transfer of antibodies from an immune individual to a non-immune individual confers passive immunity on the recipient (Brambell 1970). Passive immunity is transient, whereas active immunity stimulates the synthesis of memory cells that confer long-term immunity. Passive immunity may have long-term effects on the differentiation of the immune repertoire, however, if it occurs during a sensitive period (Lundin *et al.* 1999). Passively transmitted antibodies provide immediate resistance, whereas a primary active immune response involves an initial lag phase before antibodies can be detected in circulation (Roitt *et al.* 1998).

[2]*Mechanisms of maternal antibody transmission.* Although most research has been conducted on birds, especially chickens, the mechanisms of maternal antibody transmission are thought to be similar among oviparous vertebrates. Antibodies are deposited in eggs during yolk formation through the deposition of immunoglobulins, primarily IgG, in the yolk (Brambell 1970; Dohms *et al.* 1978). IgG is the most prevalent circulating antibody and enhances the phagocytic response as well as opsonization of bacteria and viruses (Roitt *et al.* 1998). IgG transferred from females to eggs or offspring is sometimes referred to as maternally derived or maternal IgG. Adult female birds have only one active ovary, which contains numerous small oocytes, each enclosed in a follicle (Brambell 1970). In laying galliforms (fowl-like birds), one oocyte begins a two-phase maturation process each day. The first phase of relatively slow growth lasts *ca*. 15 days. Rapid growth and intake of serum proteins characterize the second phase. The rapid growth lasts *ca*. 6 days and results in a 30–50-fold increase in mass. In their analysis of the kinetics of maternal antibody transfer in chickens, Kowalczyk *et al.* (1985) found that maximum rates of IgG deposition in the egg occur during the second, rapid growth phase. The transmission of antibodies to eggs may represent a significant immunological and resource drain for ovulating females because up to 45 mg d^{-1} of IgG may be accumulated in the yolk of hens' eggs during days −3 and −2 (day 0 = day of laying). Once mature, hen oocytes contain 100–200 mg of maternal IgG or 10–20% of the hen's steady-state level. This loss to the hen is in addition to the daily catabolism of 30–40% of the circulating lgG. During egg laying, a healthy female hen increases IgG synthesis from 58 mg kg^{-1} d^{-1}, which is required for baseline maintenance of immune function in non-laying hens, to 94 mg kg^{-1} d^{-1}, apparently to provide immunoglobulins for eggs (Klasing 1998).

The principal route of transfer of maternal IgG stored in yolks to the embryonic circulation occurs through receptor-mediated endocytosis across the yolk sac epithelial cells (Kowalczyk *et al.* 1985). In chickens, IgG begins to be transported into the embryonic circulation by embryonic day 7, with low levels of transmission initially. IgG concentration in embryonic plasma increases slowly until embryonic day 14, when transport accelerates. A high, sustained rate of IgG transport is achieved during days 19–21 (Kowalczyk *et al.* 1985). The IgG in embryonic circulation and in newly hatched young is, almost certainly, maternally derived because IgG-secreting cells are not detectable in neonates until 6 days after hatching (Lawrence *et al.* 1981).

REFERENCES

Agrawal, A. A., Laforsch, C. & Tollrian, R. 1999 Transgenerational induction of defences in animals and plants. *Nature* **401**, 60–63.

Agrawal, A. F., Brodie III, E. D. & Brown, J. 2001 Parent–offspring coadaptation and the dual genetic control of maternal care. *Science* **292**, 1710–1712.

Apanius, V. 1998 Ontogeny of immune function. In *Avian growth and development: evolution within the altricial–precocial spectrum* (ed. J. M. Starck & R. E. Ricklefs), pp. 203–222. New York: Oxford University Press.

Arango-Jaramillo, S., Wisseman Jr, C. L. & Azad, A. F. 1988 Newborn rats in the murine typhus enzootic infection cycle: studies on transplacental infection and passively acquired maternal antirickettsial antibodies. *Am. J. Trop. Med. Hyg.* **39**, 391–397.

Barua, A., Yoshimura, Y. & Tamura, T. 1998 Effects of ageing and oestrogen on the localization of immunoglobulin-containing cells in the chicken ovary. *J. Reprod. Fertil.* **114**, 11–16.

Bernardo, J. 1996 Maternal effects in animal ecology. *Am. Zool.* **36**, 83–105.

Biozzi, G., Mouton, D., Heumannand, A. & Bouthillier, Y. 1982 Genetic regulation of immunoresponsiveness in relation to resistance against infectious diseases. In *Proc. 2nd World Congr. Genetic Applications to Livestock Production, Madrid, 4–8 October 1982*, vol. 5, pp. 150–163.

Blecha, F., Bull, R. C., Olson, D. P., Ross, R. H. & Curtis, S. 1981 Effects of prepartum protein restriction in the beef cow on immunoglobin content in blood and colostral whey and subsequent immunoglobin absorption by the neonatal calf. *J. Anim. Sci.* **53**, 1174–1180.

Bly, J. E., Grimm, A. S. & Morris, I. G. 1986 Transfer of passive immunity from mother to young in a teleost fish: haemagglutinating activity in the serum and eggs of plaice, *Pleuronectes platessa* L. *Comp. Biochem. Physiol.* A **84**, 309–313.

Boa-Amponsem, K., Dunnington, E. A. & Siegel, P. B. 1997 Antibody transmitting ability of hens from lines of chickens differing in response to SRBC antigen. *Br. Poultry Sci.* **38**, 480–484.

Bollen, L. S. & Hau, J. 1997 Immunoglobulin G in the developing oocytes of the domestic hen and immunospecific antibody response in serum and corresponding egg yolk. *In Vivo* **11**, 395–398.

Bradley, J. A., Niilo, L. & Dorward, W. J. 1979 Some observations on serum gammaglobulin concentrations in suckled beef calves. *Can. Vet. J.* **20**, 227–232.

Brambell, F. W. R. 1970 Transmission of immunity in birds. In *The transmission of passive immunity from mother to young*, vol. 18 (ed. A. Neuberger & E. L. Tatum), pp. 20–41. New York: Elsevier.

Brown, J., Resurreccion, R. S., Dickson, T. G. & Home, A. 1989 The relationship of egg yolk and serum antibody. I. Infectious bursal disease virus. *Avian Dis.* **33**, 654–656.

Buechler, K., Fitze, P. S., Gottstein, B., Jacot, A. & Richner, H. 2002 Parasite-induced maternal response in a natural bird population. *J. Anim. Ecol.* **71**, 247–252.

Bumstead, N., Reece, R. L. & Cook, J. K. A. 1993 Genetic differences in susceptibility of chicken lines to infection with infectious bursal disease virus. *Poultry Sci.* **72**, 403–410.

Carlier, Y. & Truyens, C. 1995 Influence of maternal infection on offspring resistance towards parasites. *Parasitol. Today* **11**, 94–99.

Cerny, J., Cronkhite, R. & Heusser, C. 1983 Antibody response of mice following neonatal treatment with a monoclonal anti-receptor antibody. Evidence for B cell tolerance and T suppressor cells specific for different idiotopic determinants. *Eur. J. Immunol.* **13**, 244–248.

Cheverud, J. M. & Moore, A. J. 1994 Quantitative genetics and the role of the environment provided by relatives in behavioral evolution. In *Quantitative genetic studies of behavioral evolution* (ed. C. R. Boake), pp. 67–100. University of Chicago Press.

Cheverud, J. M., Leamy, L. J., Atchley, W. R. & Rutledge, J. J. 1983 Quantitative genetics and the evolution of ontogeny. I. Ontogenetic changes in quantitative genetic variance components in random bred mice. *Genet. Res.* **42**, 65–75.

Coutinho, A., Marquez, C., Araujo, P. M. F., Pereira, P., Toribio, M. L., Marcos, M. A. R. & Martinez-A., C. 1987 A functional idiotypic network of T helper cells and antibodies, limited to the compartment of 'naturally' activated lymphocytes in normal mice. *Eur. J Immunol.* **17**, 821–825.

Dardillat, J., Trillat, G. & Larvor, P. 1978 Colostrum immunoglobulin concentration in cows: relationship with their calf mortality and with the colostrum quality of their female offspring. *Annls Rech. Vet.* **9**, 375–384.

Demas, G. E., Chefer, V., Talan, M. I. & Nelson, R. J. 1997 Metabolic costs of mounting an antigen-stimulated immune response in adult and aged C57BL/6J mice. *Am. J. Physiol.* **273**, R1631–R1637.

DiGiacomo, R. F. & Thouless, M. E. 1986 Epidemiology of naturally occurring rotavirus infection in rabbits. *Lab. Anim. Sci.* **36**, 153–156.

Dohms, J. E., Saif, Y. M. & Bacon, W. L. 1978 Metabolism and passive transfer of immunoglobulins in the turkey hen. *Am. J. Vet. Res.* **39**, 1472–1481.

Ehrlich, P. 1892 Ueber immunität durch vererbung und säugung. *Z. Hyg. Infectkt. Krankh.* **2**, 183–203.

Elliott, M. & Kearney, J. F. 1992 Idiotypic regulation of development of the B-cell repertoire. *Ann. NY Acad. Sci.* **651**, 336–345.

Falconer, D. & Mackay, T. F. 1996 *Introduction to quantitative genetics*. Harlow: Addison-Wesley Longman Limited.

Fox, C. W. & Mousseau, T. A. 1998 Maternal effects as adaptations for transgenerational phenotypic plasticity in insects. In *Maternal effects as adaptations* (ed. I. A. Mousseau & C. W. Fox), pp. 159–177. New York: Oxford University Press.

Frost, S. D. W. 1999 The immune system as an inducible defense. In *The ecology and evolution of inducible defenses* (ed. R. Tollrian & C. D. Harvell), pp. 104–126. Princeton University Press.

Fuda, H., Hara, A., Yamazaki, F. & Kobayashi, K. 1992 A peculiar irnmunoglobulin M (IgM) identified in eggs of chum salmon. *Devl Comp. Immunol.* **16**, 415–423.

Gasparini, J., McCoy, K. D., Haussy, C., Tveraa, T. & Boulinier, T. 2001 Induced maternal response to the Lyme disease spirochaete *Borrelia burgdorferi sensu lato* in a colonial seabird, the kittiwake *Rissa tridactyla*. *Proc. R. Soc. Lond.* B **268**, 647–650. (DOI 10.1098/rspb.2000.1411.)

Gasparini, J., McCoy, K. D., Tveraa, T. & Boulinier, T. 2002 Related concentrations of specific irnmunoglobulins against the Lyme disease agent *Borelia burgdorferi sensu lato* in eggs, young and adults of the kittiwake (*Rissa tridactyla*). *Ecol. Lett.* **5**, 519–524.

Gebhardt-Henrich, S. & Richner, H. 1998 Causes of growth variation and its consequences for fitness. In *Avian growth and development: evolution within the altricial–precocial spectrum* (ed. J. Starck & R. Ricklefs), pp. 324–339. New York: Oxford University Press.

Goddard, R. O., Wyeth, P. J. & Varney, W. C. 1994 Vaccination of commercial layer chicks against infectious bursal disease with maternally derived antibodies. *Vet. Rec.* **135**, 273–274.

Godfray, H. C. J. 1995 Evolutionary-theory of parent–offspring conflict. *Nature* **376**, 133–138.

Graczyk, T. K., Cranfield, M. R., Shaw, M. L. & Craig, L. E. 1994 Maternal antibodies against *Plasmodium* spp. in African black-footed penguin (*Spheniscus demersus*). *J. Wildl. Dis.* **30**, 365–371.

Grenfell, B. T. & Dobson, A. P. 1995 *Ecology of infectious diseases in natural populations*. Cambridge University Press.

Gustafsson, E., Mattsson, A., Holmdahl, R. & Mattsson, R. 1994 Pregnancy in B-cell-deficient mice: postpartum transfer of immunoglobulins prevents neonatal runting and death. *Biol. Reprod.* **51**, 1173–1180.

Hager, R. & Johnstone, R. A. 2003 The genetic basis of family conflict resolution in mice. *Nature* **421**, 533–535.

Heeb, P., Werner, I., Kölliker, M. & Richner, H. 1998 Benefits of induced host responses against an ectoparasite. *Proc. R. Soc. Lond.* B **265**, 51–56. (DOI 10.109/rspb.1998.0263.)

Heller, E. D., Leitner, G., Drabkin, N. & Melamed, D. 1990 Passive immunization of chicks against *Escherichia coli*. *Avian Pathol.* **19**, 345–354.

Hoi-Leitner, M., Romero-Pujante, M., Hoi, H. & Pavlova, A. 2001 Food availability and immune capactiy in serin (*Serinus serinus*) nestlings. *Behav. Ecol. Sociobiol.* **49**, 333–339.

Huang, C. & Song, Y. 1999 Maternal transmission of immunity to white-spot syndrome associated virus (WSSV) in shrimp (*Penaeus monodon*). *Devl Comp. Immunol.* **23**, 545–552.

Jackson, D. W., Law, G. R. & Nockels, C. F. 1978 Maternal vitamin E alters passively acquired immunity of chicks. *Poultry Sci.* **57**, 70–73.

Keller, L. F. & van Noordwijk, A. J. 1993 A method to isolate environmental effects on nestling growth, illustrated with examples from the great tit (*Parus major*). *Funct. Ecol.* **7**, 493–502.

Kirkpatrick, M. & Lande, R. 1989 The evolution of maternal characters. *Evolution* **43**, 485–503.

Kissling, R. E., Eidson, M. E. & Stamm, D. D. 1954 Transfer of maternal neutralizing antibodies against eastern equine encephalomyelitis virus in birds. *J. Infect. Dis.* **95**, 179–181.

Klasing, K. C. 1998 Nutritional modulation of resistance to infectious diseases. *Poultry Sci.* **77**, 1119–1125.

Klasing, K. C. & Johnstone, B. J. 1991 Monokines in growth and development. *Poultry Sci.* **70**, 1781–1789.

Klemperer, F. 1893 Über natürliche immunität und ihre verwerthung für die immunisierungstherapie. *Arch. Exp. Path. Pharmak.* **31**, 356–382.

Kölliker, M. & Richner, H. 2001 Parent–offspring conflict and the genetics of offspring solicitation and parental response. *Anim. Behav.* **62**, 395–407.

Kowalczyk, K., Daiss, J., Halpern, J. & Roth, T. F. 1985 Quantitation of maternal–fetal IgG transport in the chicken. *Immunology* **54**, 755–762.

Lancaster, J. 1964 Newcastle disease-control by vaccination. *Vet. Bull.* **34**, 57–58.

Lawrence, E. C., Arnaud-Battandier, F., Grayson, J., Koski, I. R., Dooley, N. J., Muchmore, A. V. & Blaese, R. M. 1981 Ontogeny of humoral immune function in normal chickens: a comparison of immunoglobulin-secreting cells in bone marrow, spleen, lungs and intestine. *Clin. Exp. Immunol.* **43**, 450–457.

Leitner, G., Melamed, D., Drabkin, N. & Heller, E. D. 1990 An enzyme-linked immunoabsorbent assay for detection of antibodies against *Escherichia coli*: association between hemagglutination test and survival. *Avian Dis.* **34**, 58–62.

Lemke, H. & Lange, H. 1999 Is there a maternally induced immunological imprinting phase a la Konrad Lorenz? *Scand. J. Immunol.* **50**, 348–354.

Linder, N., Waintraub, I., Smetana, Z., Barzilai, A., Lubin, D., Mendelson, E. & Sirota, L. 2000 Placental transfer and decay of varicella-zoster virus antibodies in preterm infants. *J. Pediatrics* **137**, 85–89.

Liu, S. S. & Higgins, D. A. 1990 Yolk-sac transmission and post-hatching ontogeny of serum immunoglobulins in the duck (*Anas platyrhynchos*). *Comp. Biochem. Physiol.* B **97**, 637–644.

Lochmiller, R. L. & Dabbert, C. B. 1993 Immunocompetence, environmental stress, and the regulation of animal populations. *Trends Comp. Biochem. Physiol.* **1**, 823–855.

Lochmiller, R. L. & Deerenberg, C. 2000 Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos* **88**, 87–98.

Loh, K. R., Shrader, R. E. & Zeman, F. J. 1971 Effect of maternal protein deprivation on neonatal intestinal absorption in rats. *J. Nutr.* **101**, 1663–1671.

Lozano, G. A. & Ydenberg, R. C. 2002 Transgenerational effects of maternal immune challenge in tree swallows (*Tachycineta bicolor*). *Can. J. Zool.* **80**, 918–925.

Lundin, B. S., Dahlman-Hoglund, A., Pettersson, I., Dahlgren, U. I. H., Hanson, L. A. & Telemo, E. 1999 Antibodies given orally in the neonatal period can affect the immune response for two generations: evidence for active maternal influence on the newborn's immune system. *Scand. J. Immunol.* **50**, 651–656.

Lung, N. P., Thompson, J. P., Kollias, G. V., Olsen, J. H., Zdziarski, J. & Klein, P. A. 1996 Maternal immunoglobulin G antibody transfer and development of immunoglobulin G antibody responses in blue and gold macaw (*Ara ararauna*) chicks. *Am. J. Vet. Res.* **57**, 1162–1167.

Malanchere, E., Huetz, F. & Coutinho, A. 1997 Maternal IgG stimulates B lineage cell development in the progeny. *Eur. J. Immunol.* **27**, 788–793.

Martin, A., Dunnington, E. A., Gross, W. B., Briles, W. E., Briles, R. W. & Siegel, P. B. 1990 Production traits and alloantigen systems in lines of chickens selected for high or low antibody-responses to sheep erythrocytes. *Poultry Sci.* **69**, 871–878.

Martin, L. B., Scheuerlein, A. & Wikelski, M. 2003 Immune activity elevates energy expenditure of house sparrows: a link between direct and indirect costs? *Proc. R. Soc. Lond.* B **270**, 153–158. (DOI 10.1098/rspb.2002.2185.)

Martinez-A., C., Bernabe, R. R., de la Hera, A., Pereira, P., Cazenave, P. A. & Coutinho, A. 1985 Establishment of idiotypic helper T-cell repertoires early in life. *Nature* **317**, 721–723.

Michalek, S. M., Rahman, A. F. & McGhee, J. R. 1975 Rat immunoglobulins in serum and secretions: comparison of IgM, IgA and IgG in serum, colostrum, milk and saliva of protein malnourished and normal rats. *Proc. Soc. Exp. Biol. Med.* **148**, 1114–1118.

Moret, Y. & Schmid-Hempel, P. 2001 Immune defence in bumble-bee offspring. *Nature* **414**, 506.

Morris, B. 1961 The transmission of anti-*Salmonella* agglutinins from the mother to the young in *Erinaceus europaea*, with some observations on the active immunization of suckling hedgehogs. *Proc. R. Soc. Lond.* B **154**, 369–376.

Mousseau, T. A. & Fox, C. W. 1998*a* The adaptive significance of maternal effects. *Trends Ecol. Evol.* **13**, 403–407.

Mousseau, T. A. & Fox, C. W. 1998*b* *Maternal effects as adaptations*. New York: Oxford University Press.

Muggli, N. E., Hohenboken, W. D., Cundiff, L. V. & Kelley, K. W. 1984 Inheritance of maternal immunoglobulin G1 concentration by the bovine neonate. *J. Anim. Sci.* **59**, 39–48.

Mushin, R. & Schoenbaum, M. 1980 A strain of *Pasteurella multocida* associated with infections in rabbit colonies. *Lab. Anim.* **14**, 353–356.

Mylvaganam, R. & Solomon, J. 1981 Transfer of ^{125}I-insulin in immunised pregnant guinea pigs. In *Aspects of developmental and comparative immunology* (ed. J. Solomon), pp. 341–346. New York: Pergamon Press.

Okamoto, Y., Tsutsumi, H., Kumar, N. S. & Ogra, P. L. 1989 Effect of breast feeding on the development of anti-idiotype antibody response to F glycoprotein of respiratory syncytial virus in infant mice after post-partum maternal immunization. *J. Immunol.* **142**, 2507–2512.

Pardue, S. L., Ring, N. M. & Smyth Jr, J. R. 1990 Autosomal albinism affects immunocompetence in the chicken. *Devl Comp. Immunol.* **14**, 105–112.

Patterson, R., Youngner, J. S., Weigle, W. O. & Dixon, F. J. 1962 Antibody production and transfer to egg yolk in chickens. *J. Immunol.* **89**, 272–278.

Price, T. 1998 Maternal and paternal effects in birds: effects on offspring fitness. In *Maternal effects as adaptations* (ed. T. A. Mousseau & C. W. Fox), pp. 202–226. New York: Oxford University Press.

Reeves, W. C., Sturgeon, J. M., French, E. M. & Brookman, B. 1954 Transovarian transmission of neutralizing substances to western equine and St. Louis encephalitis viruses by avian hosts. *J. Infect. Dis.* **95**, 168–178.

Reuman, P. D., Paganini, C. M., Ayoub, E. M. & Small Jr, P. A. 1983 Maternal–infant transfer of influenza-specific immunity in the mouse. *J. Immunol.* **130**, 932–936.

Robison, J. D., Stott, G. H. & DeNise, S. K. 1988 Effects of passive immunity on growth and survival in the dairy heifer. *J. Dairy Sci.* **71**, 1283–1287.

Roitt, I., Brostoff, J. & Male, D. K. 1998 *Immunology*, 5th edn. London: Mosby.

Rose, M. E. & Orlans, E. 1981 Immunoglobulins in the egg, embryo, and young chick. *Devl Comp. Immunol.* **5**, 15–20.

Rose, M. E., Orlans, E. & Buttress, N. 1974 Immunoglobulin classes in the hen's egg: their segregation in yolk and white. *Eur. J. Immunol.* **4**, 521–523.

Roulin, A. & Heeb, P. 1999 The immunological function of allosuckling. *Ecol. Lett.* **2**, 319–324.

Roura, E., Homedes, J. & Klasing, K. C. 1992 Prevention of immunologic stress contributes to the growth-permitting ability of dietary antibiotics in chicks. *J. Nutr.* **122**, 2383–2390.

Rossiter, M. C. 1996 Incidence and consequencs of inherited environmental effects. *A. Rev. Ecol. Syst.* **27**, 451–476.

Rubinstein, L. J., Yeh, M. & Bona, C. A. 1982 Idiotype–anti-idiotype network: II. Activation of silent clones by treatment at birth with idiotypes is associated with the expansion of idiotype-specific helper T cells. *J. Exp. Med.* **156**, 506–521.

Saino, N., Bertacche, V., Ferrari, R. P., Martinelli, R., Moller, A. P. & Stradi, R. 2002*a* Carotenoid concentration in barn swallow eggs is influenced by laying order, maternal infection and paternal ornamentation. *Proc. R. Soc. Lond.* B **269**, 1729–1733. (DOI 10.1098/rspb.2002.2088.)

Saino, N., Dall'ara, P., Martinelli, R. & Moller, A. P. 2002*b* Early maternal effects and antibacterial immune factors in the eggs, nestlings and adults of the barn swallow. *J. Evol. Biol.* **15**, 735–743.

Saino, N., Ferrari, R. P., Martinelli, R., Romano, M., Rubolini, D. & Moller, A. P. 2002*c* Early maternal effects mediated by immunity depend on sexual ornamentation of the male partner. *Proc. R. Soc. Lond.* B **269**, 1005–1009. (DOI 10.1098/rspb.2002.1992.)

Schmid-Hempel, P. 2003 Variation in immune defence as a question of evolutionary ecology. *Proc. R. Soc. Lond.* B **270**, 357–366. (DOI 10.1098/rspb.2002.2265.)

Schumacher, I. M., Rostal, D. C., Yates, R. A., Brown, D. R., Jacobson, E. R. & Klein, P. A. 1999 Persistence of maternal antibodies against *Mycoplasma agassizii* in desert tortoise hatchlings. *Am. J. Vet. Res.* **60**, 826–831.

Sheldon, B. C. & Verhulst, S. 1996 Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. *Trends Ecol. Evol.* **11**, 317–321.

Siegel, P. B., Gross, W. B. & Cherry, J. A. 1982 Correlated responses of chickens to selection for production of antibodies to sheep erythrocytes. *Anim. Blood Groups Biochem. Genet.* **13**, 291–297.

Solomon, J. B. 1971*a* Maternal antibody I: routes and specificity of transmission. In *Foetal and neonatal immunology*, vol. 20 (ed. A. Neuberger & E. L. Tatum), pp. 96–114. London: North Holland Publishing Company.

Solomon, J. B. 1971*b* Maternal antibody II: protective effects and immunological hazards. In *Foetal and neonatal immunology*, vol. 20 (ed. A. Neuberger & E. L. Tatum), pp. 115–138. London: North Holland Publishing Company.

Sooter, C. A., Schaeffer, M., Gorrie, R. & Cockburn, T. A. 1954 Transovarian passage of antibodies following naturally acquired encephalitis infection in birds. *J. Infect. Dis.* **95**, 165–167.

Stott, G. H. & Fellah, A. 1983 Colostral immunoglobulin absorption linearly related to concentration for calves. *J. Dairy Sci.* **66**, 1319–1328.

Strayer, D. S., Cosenza, H., Lee, W. M. F., Rowley, D. A. & Kohler, H. 1974 Neonatal tolerance induced by antibody against antigen-specific receptor. *Science* **186**, 640–642.

Svensson, E., Råberg, L., Koch, C. & Hasselquist, D. 1998 Energetic stress, immunosuppression and the costs of an antibody response. *Funct. Ecol.* **12**, 912–919.

Tollrian, R. & Harvell, C. D. 1999 *The ecology and evolution of inducible defenses*. Princeton University Press.

Ubosi, C., Gross, W. & Siegel, P. 1985 Divergent selection of chickens for antibody production to sheep erythrocytes: age effect in parental lines and their crosses. *Avian Dis.* **29**, 150.

van Loon, J. J. A., van Oosteron, R. & van Muiswinkel, W. B. 1981 Development of the immune system of the carp (*Cyprinus carpio*). In *Aspects of developmental and comparative immunology I* (ed. J. B. Solomon), pp. 469–470. Oxford: Pergamon Press.

van Maanen, C., Bruin, G., de Boer-Luijtze, E., Smolders, G. & de Boer, G. F. 1992 Interference of maternal antibodies with the immune response of foals after vaccination against equine influenza. *Vet. Q.* **14**, 13–17.

Wikler, M., Demeur, C., Dewasme, G. & Urbain, J. 1980 Immunoregulatory role of maternal idiotypes: ontogeny of immune networks. *J. Exp. Med.* **152**, 1024–1035.

Wolf, J. B. 2000 Gene interactions from maternal effects. *Evolution* **54**, 1882–1898.

Wolf, J. B. & Brodie III, E. D. 1998 The coadaptation of parental and offspring characters. *Evolution* **52**, 299–308.

Wolf, J. & Wade, M. 2001 On the assignment of fitness to parents and offspring: whose fitness is it and when does it matter? *J. Evol. Biol.* **14**, 347–356.

Wolf, J. B., Brodie III, E. D., Cheverud, J. M., Moore, A. J. & Wade, M. J. 1998 Evolutionary consequences of indirect genetic effects. *Trends Ecol. Evol.* **13**, 64–69.

Wright, K., Balaji, R., Hill, C., Dritz, S., Knoppel, E. & Minton, J. 2000 Integrated adrenal, somatotropic, and immune responses of growing pigs to treatment with lipopolysaccharide. *J. Anim. Sci.* **78**, 1892–1899.

Yasuda, M., Furusawa, S., Matsuda, H., Taura, Y., Urano, T., Yokomizo, Y. & Ekino, S. 1998 Development of maternal IgG-free chick obtained from surgically bursectomized hen. *Comp. Immunol. Microbiol. Infect. Dis.* **21**, 191–200.

Zhang, X. K., Takashima, I. & Hashimoto, N. 1988 Role of maternal antibody in protection from hemorrhagic-fever with renal syndrome virus-infection in rats. *Arch. Virol.* **103**, 253–265.