Chapter 7

The Protective Properties of Milk and Colostrum in Non-Human Species

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1. Introduction

Newborn mammals emerge from the clean, stable and sterile uterus into a world where they are immediately exposed to an enormous variety of microorganisms. If they are to survive, newborns therefore must be able to control microbial invasion. The immune system, however, may not be ready for this defensive role. In mammals with a short gestation period such as the marsupials, the immune system may not have developed fully. In mammals with a long gestation period such as the domestic herbivores, although the immune system is structurally complete at birth, it cannot function fully for several weeks. The complete development of immune capability depends on antigenic stimulation. The development of adequate numbers of antigen-sensitive lymphocytes depends on clonal selection and antigen-driven cell multiplication. The first immune responses mounted by a newborn animal must be primary responses with a prolonged lag period and low concentrations of antibodies produced. Thus newborn mammals are highly vulnerable to microbial invasion for the first few weeks of life and unless immunological assistance is provided, they may be killed by microorganisms that present little threat to an adult. This "immunological assistance" is provided by antibodies and other proteins transferred from the mother to her offspring through the placenta and/or by antibodies and lymphocytes transferred through colostrum and milk.

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2. Placentation and Passive Immunity

Because of the state of their immune system, all young mammals must acquire maternal antibodies either before or immediately after birth. Whether they do so by transplacental passage or through mammary secretions depends on the structure of their placenta. In the least developed form of placenta (epitheliochorial), the fetal chorionic epithelium comes into direct contact with the intact uterine epithelium (Blüm, 1985). This form of placenta occurs in Pholidota (such as the harbor seal), in primitive primates such as lemurs and in some ungulates such as horses and pigs as well as in their close relatives, the Cetacea such as the bottle-nosed dolphin (Carter *et al.*, 1990). A more developed form of placenta is found in other ungulates such as the ruminants. They have a syndesmochorial placenta in which a uterine epithelium is not present and the chorionic epithelium is in direct contact with uterine tissues. In mammals with these types of placenta, transplacental passage of immunoglobulins cannot occur and the newborn of these species are agammaglobulinemic at birth. These animals, therefore, are totally dependent on antibodies received through mammary secretions for immediate protection. Carnivores, in contrast, have an endotheliochorial placenta in which the chorionic epithelium comes into contact with the endothelium of the maternal capillaries. In these mammals a small fraction (five to ten per cent) of the newborn's IgG may be derived by transplacental transfer but the remainder must be obtained through mammary secretions.

In lagomorphs (rabbits), hystricomorphs (guinea pigs) and rodents there is a yolk sac placenta that permits immunoglobulin transfer. In the advanced primates (including hominoids), the placenta is hemochorial so that maternal blood comes into direct contact with the placental trophoblast. In these mammals, maternal IgG can reach the fetal bloodstream by direct transfer across the chorioallantoic placenta. Because maternal IgG enters the fetal blood stream directly, mammals with this form of placentation are born with circulating IgG levels comparable to those of their mother.

3. Immunoglobulins and Cells in Colostrum and Milk

3.1. Immunoglobulins

In species with placentas that are impermeable to immunoglobulins, newborns must receive both IgG and IgA through mammary secretions. In general they receive IgG from colostrum and IgA from milk (Norcross, 1982).

Colostrum represents the accumulated secretions of the mammary gland over the last few weeks of pregnancy together with proteins actively transported

from the bloodstream. Its composition differs among species. In mammals such as the primates with placentas that permit immunoglobulin transfer, colostrum contains predominantly IgA. In mammals with impermeable placentas, IgG must accumulate in colostrum. Very high affinity immunoglobulin receptors (FcR) are expressed on bovine mammary gland acinar cells about a week prior to birth (Sasaki *et al.*, 1977). These transport IgG, and to a lesser extent IgM and IgA, into the mammary gland so that all the IgG, most of the IgM and about half of the IgA in bovine colostrum are derived from the blood. IgG may account for 65 to 90% of the total antibody content of bovine colostrum. Only 30% of the IgG1 and 10% of the IgA in bovine milk are derived from the blood; the rest is produced locally in the udder.

IgG in colostrum provides a source of antibodies that provide systemic immunity in the newborn. However as lactation proceeds, the proportion of locally synthesized IgA increases so that it becomes the predominant immunoglobulin in most milks. One exception to this pattern occurs in ruminants, in which IgG1 is the predominant immunoglobulin isotype in both milk and colostrum. The low level of IgA in ruminant milk, it has been speculated, may permit the earlier development of ruminal flora.

Thatcher and Gershwin (1989) demonstrated that colostral transfer of IgE occurs in the bovine. IgE was transferred to newborn calves, in which maximum levels were reached during the first week of lactation and declined rapidly thereafter. It was suggested that this passive transfer of maternal IgE might be important in providing early protection from intestinal parasites. Likewise, although IgD has not been considered a significant colostral immunoglobulin, it is present in rat milk in extraordinary high concentrations, approximately 100 times those found in the serum of lactating rats (Olson and Leslie, 1982).

Colostrum also contains secretory component both in the free form and bound to IgA. Secretory component may play a role in the transport of IgA within the mammary gland. For the first few weeks of life, while proteolytic digestion is poor, colostral and milk immunoglobulins can be found throughout the intestine and in the feces of young mammals. As the digestive ability of the intestine increases, eventually only secretory IgA molecules remain intact. SIgA is therefore important in protection against enteric infection.

3.2. Cells

It has been recognized for many years that mammary secretions contain many different cells, whose function has been difficult to ascertain (Head and Beer, 1978). They are a mixture of blood leukocytes and mammary epithelial cells. Their numbers and relative proportions vary among species and at different times during lactation. Milk phagocytic cells are loaded with vacuoles

containing lipid, casein or cellular debris, and as a result are poorly phagocytic (Crighton, 1984).

Macrophages, neutrophils, and lymphocytes are present in the colostrum and milk of the tammar wallaby (*Macropus eugenii*) (Young *et al.*, 1997). Neutrophils are the predominant cell type in early secretions while macrophages become common later when the young are no longer attached to the teat.

Around two million leukocytes/ml are found in rat, human, pig and cow's milk with lower numbers (8000/ml in mares and water buffalo (Head, 1977; Head and Beer, 1978; Lee *et al.*, 1983). The predominant cell type in humans, rats, cows, sheep and quokkas is the macrophage. Neutrophils may be present in greater numbers in early lactation and in mastitis (Cockson and McNeice, 1980; Outteridge and Lee, 1988).

In the pig, neutrophils predominate in colostrum whereas epithelial cells predominate in milk, although macrophages, eosinophils and lymphocytes are present throughout lactation (Lee *et al.*, 1983). Sow's colostrum contains about $1–2.5 \times 10^6$ cells/ml. Ten to 25 percent of these are lymphocytes and 70–90 percent of the lymphocytes are T cells. Their CD4/CD8 ratio is approximately 0.57 which is somewhat lower than their ratio in blood (0.8).

Bovine colostrum contains up to 1×10^6 lymphocytes/ml, about half of which are T cells (Chabaudie *et al.*, 1993). While some milk lymphocytes migrate from the bloodstream others may be derived from the mammary gland itself. They tend to be located close to the alveolar epithelium and in cattle are a mixture of CD4+ and CD8+ T cells as well as IgA+ B cells (Chabaudie *et al.*, 1993).

The functional significance of the cells found in colostrum and milk has been difficult to determine. Nevertheless, the lymphocytes found in mammary secretions are functional and probably play a role in the development of immunity in the newborn. Thus bovine colostral lymphocytes collected in the first two days after calving are responsive to concanavalin A (Con A) (Archambault *et al.*, 1988a). Lymphocytes from the colostrum of cows immunized with a rotavirus vaccine during pregnancy also showed a significant blastogenic response to bovine rotavirus. Colostral lymphocytes showed a higher response than blood lymphocytes, and the response lasted for at least 21 days after parturition (Archambault *et al.*, 1988b).

Riedel-Caspari and Schmidt (1990, 1991a) examined the influence of colostral cells on the concentration of immunoglobulins against *E. coli* in the sera of newborn calves. The calves received either complete colostrum or cell-free colostrum during the first three days of life. The sera of the calves fed complete colostrum had significantly higher concentrations of IgG1 antibodies against *E. coli* than the sera of the calves fed cell-free colostrum. The sera of the calves receiving cells also contained significantly more IgM and slightly more IgA during the first week of life. The groups had equal concentrations of serum IgG. The investigators therefore suggested that the colostral leukocytes enhanced

passive immunity in the neonatal calf. They also compared cell-containing and cell-free colostrum for their ability to protect calves against enteropathic *E. coli*. The calves receiving complete colostrum excreted significantly fewer bacteria than the animals receiving cell-free colostrum. The concentration of IgA and IgM-specific antibodies against *E. coli* in the serum of neonatal calves was higher in those that received cells in their colostrum than in those that did not. The calves that received colostrum containing cells had a better response to Con A and an enhanced responsiveness to sheep erythrocytes. Riedel-Caspari and Schmidt (1991b) also examined the effect of ingesting colostral cells on lymphocyte responses in neonatal calves. They found that animals fed cell-free colostrum or a milk substitute showed an enhanced lymphocyte response to mitogens relative to that of calves fed colostrum containing cells. Thus colostral cells may exert immunoregulatory actions as well as immunostimulatory influences.

Leukocytes ingested in mammary secretions can survive within the intestine and migrate to the bloodstream of newborns. Colostral lymphocytes may survive for up 36 hours in the intestine of newborn calves; some penetrate the intestinal wall and reach the lacteal ducts and the mesenteric lymph nodes (Kmetz *et al.*, 1970). Within two hours after receiving colostrum containing labeled cells piglets had maternal lymphocytes in their bloodstream. The cells apparently penetrated between epithelial cells in the duodenum and ileum. Piglets that had received these colostral cells showed enhanced responses to Con A, pokeweed mitogen (PWM) and phytohemagglutinin (PHA) compared to that of control piglets that had been fed a suspension of peripheral blood mononuclear leukocytes. Viable maternal milk lymphocytes can also reach the mesenteric lymph nodes in rats and lambs (Sheldrake and Husband, 1985). In the rat, graft-versus-host disease may result (Head, 1977) but this has not been reported in other species.

4. Absorption of Colostral Immunoglobulins

Young mammals that suckle soon after birth take a large volume of colostrum into their intestinal tract. Naturally suckled calves ingest an average of two liters of colostrum, but individual calves can ingest as much as six liters (Norcross, 1982). In these young mammals, the level of proteolytic activity in the intestine is low and it is further reduced by protease inhibitors in colostrum. Therefore colostral proteins are not degraded and used as a food source but instead remain for long periods within the small intestine. Once within the intestine, colostral IgG probably binds to specialized Fc receptors on the intestinal epithelial cells of newborns (FcRn). Eventually the colostral immunoglobulin reaches the systemic circulation and newborn mammals thus obtain a massive transfusion of maternal IgG. The first detectable IgG in the thoracic duct appears

60–120 minutes after the initial intake of colostrum (Comline *et al.*, 1951; Balfour and Comline, 1962) or in the blood after 180 minutes (Logan *et al.*, 1978, Stott *et al.*, 1979a,b).

Jochims *et al.* (1994) used protein A-gold to investigate the transfer of colostral IgG from the gut lumen to the circulation in newborn calves and found that intracellular micropinocytotic transport was the prime mechanism of transfer throughout the small intestine. Colostral IgG binds to the apical plasma membrane and is taken up in noncoated pits and invaginations, pinocytosed, transported in endocytotic vesicles and accumulated in granules in the apical cytoplasm (Komuves and Heath, 1992). It eventually reaches the lacteals and possibly the intestinal capillaries.

Mammals differ in the selectivity and duration of their intestinal permeability to proteins (Norcross, 1982). For example, in the horse and pig, immunoglobulin absorption is highly selective, so that IgG and IgM are preferentially absorbed while IgA remains mainly in the intestine. In ruminants, however, the intestine is unselectively permeable and all immunoglobulin isotypes are absorbed, although IgA is gradually re-excreted. The lactating mammary gland produces secretory component and secretory IgA (Lejan 1993). As a result, young pigs and probably other young mammals possess large amounts of free secretory component within their intestinal tract. This may inhibit the absorption of both IgM and IgA.

The period for which the intestine is permeable to immunoglobulins also varies among species and among immunoglobulin isotypes. In the ungulates, passage of immunoglobulins across the intestinal wall has largely terminated by 24 hours after birth. In contrast, in suckling rats and mice transfer continues for up to 16–21 days, and in the hedgehog, an insectivore, it lasts for up to 40 days (Manning and Turner, 1976). As discussed below, in marsupials absorption of immunoglobulins occurs for as long as the newborn remains attached to the teat, perhaps for as long as six months. The eventual cessation of immunoglobulin absorption results from the replacement of neonatal Fc receptor (FcRn)-expressing fetal intestinal epithelial cells by more mature cell populations which lack these receptors. In addition, there is an increase in intracellular proteolytic activity by lysosomes. In species such as cattle, pigs and horses, which absorb immunoglobulins immediately after birth, intestinal permeability is highest immediately after birth and begins to decline after six hours. As a rule, absorption of all immunoglobulin isotypes drops to a relatively low level after approximately 24 hours, a phenomenon termed "closure". Feeding colostrum tends to hasten closure whereas a delay in feeding results in a slight delay of closure. The presence of the mother may be associated with increased immunoglobulin absorption. In controlled laboratory studies in which measured amounts of colostrum were fed, there was great variation (±25–35%) in the quantity of immunoglobulin absorbed (Norcross, 1982).

Unsuckled mammals of species with impermeable placentas are effectively lacking in blood immunoglobulins (Halliday, 1978). The absorption of colostral IgG immediately supplies them with blood IgG at a level approaching that found in adults. Peak serum IgG levels are normally reached between 12 and 24 hours after birth. After absorption ceases, these passively acquired antibodies decline through normal catabolic processes. The rate of decline differs among immunoglobulin isotypes, the time taken to decline to unprotective levels depending upon their initial concentration. As intestinal absorption is taking place, a simultaneous proteinuria may occur. This is due to the absorption from the intestine of proteins such as β-lactoglobulin and polypeptides that are sufficiently small to be excreted in the urine. In addition, the glomeruli of newborn mammals are permeable to macromolecules. Thus the urine of neonatal ruminants also contains intact immunoglobulin molecules. This proteinuria ceases spontaneously with the termination of intestinal absorption.

4.1. Fc Receptors

In order to be transported across epithelial barriers, immunoglobulins must first bind to specific receptors. The best characterized of these is the neonatal Fc receptor (FcRn), which has been examined mainly in laboratory rodents. Intestinal epithelial cells of the neonatal rat and mouse express FcRn (Jakoi *et al.*, 1985; Kandil *et al.*, 1995; Raghavan and Bjorkman, 1996; Simister *et al.*, 1997). Although directly involved in immunoglobulin transfer across the intestine, this same receptor is also employed to transfer IgG across the rodent and human placenta.

FcRn is a member of the nonpolymorphic MHC class Ib family. It has an alpha-chain similar to the MHC alpha chain and beta 2-microglobulin (β2M) (Ahouse *et al.*, 1993). The overall exon-intron organization of the FcRn gene is similar to that of classical MHC class I genes. However, regulatory elements normally found in classical MHC class I genes are absent. Sequence analysis of the FcRn gene isolated from eight mouse strains showed that the membrane-distal domain of FcRn has at least three amino acid variants which might be of functional significance. The fact that FcRn is a single copy gene indicates that the same molecule is expressed in both the neonatal intestine and the fetal yolk sac. Phylogenetic analysis suggests that the FcRn gene diverged from MHC class I genes after the emergence of amphibians but before the split of placental and marsupial mammals.

FcRn binds to IgG through a site at the CH2-CH3 domain interface (Medesan *et al.*, 1996). It binds this IgG at the pH of milk in the proximal intestine (pH 6.0–6.5) and releases it at the pH of blood (pH 7.5). Exchange is more than 10 times slower at pH 6.1 than at pH 7.8. These observations imply a pH-dependent conformational change in the FcRn heterodimer that may be

related to its physiological function (Raghavan *et al.*, 1993). Like rat and mouse FcRn, human placental FcRn also binds IgG preferentially at low pH, which may imply that IgG binds hFcRn in an acidic intracellular compartment during transport across the placenta (Story *et al.*, 1994).

Neonatal mice homozygous for a targeted disruption of the β2M gene have reduced FcRn expression on their intestinal cells. These mice had much lower serum IgG levels during the first month after birth than littermates with functional FcRn. By fostering mice on mothers with different IgG allotypes, it was shown that none of the IgG in the sera of β2M –/– mice was derived from milk. Thus FcRn is the only transporter of IgG from mother to young in the mouse. There were no differences between the IgG concentrations in the milk of β2M –/– and β2M +/– mice, indicating that FcRn is not involved in the secretion of IgG into milk (Israel *et al.*, 1995).

In addition to transferring immunoglobulins across the intestinal epithelium in rodents, FcRn may be involved in the transmission of IgG from mother to fetus: rat fetal yolk sac, mouse fetal yolk sac and human placental syncytiotrophoblast (Ghetie and Ward, 1997). In addition to being present in these tissues it is also expressed on the surface of mouse hepatocytes (Blumberg *et al.*, 1995). IgG has a much longer half-life in blood than other immunoglobulin isotypes. This selective protection from catabolism is lost in mice that lack a functional FcRn (Junghans and Anderson, 1996). It is likely, therefore, that one function of FcRn is to protect circulating IgG from degradation (Israel *et al.*, 1996).

FcRn has not been characterized in mammals other than laboratory rodents and humans. Nevertheless, it is likely to be equally important in other species. Uncharacterised FcR for IgG1 has been identified on cells in bovine mammary tissues (Barrington *et al.*, 1997).

5. Interference with Active Immunity

The presence of high titered maternal antibodies interferes with the response of newborn mammals to vaccination. Antibodies exert a negative feedback on responding B cells by cross-linking the B cell receptor to a FcR and so sending an inhibitory signal to the B cell (Anderson and Sinclair, 1998). Brar *et al.* (1978) and Bradshaw and Edwards (1996) found that calves could not respond to an infectious bovine rhinotracheitis (IBR) vaccine until maternal antibodies had decreased to undetectable levels. They also showed that, although maternal antibodies inhibited the response to IBR vaccination, priming for a secondary response occurred. Thus, on subsequent vaccination, after maternal antibodies had disappeared, calves responded anamnestically to IBR vaccination. Kitching and Salt (1995) showed that maternally-derived antibody provided immediate protection against infection with foot-and-mouth disease virus, but

interfered with the development of active immunity following vaccination. This interference has also been reported in calves for antibody responses to bovine coronavirus (Heckert *et al.*, 1991) and bovine virus diarrhea (Menanteau-Horta *et al.*, 1985). A similar negative feedback is well recognized in companion animals, in which it represents the major cause of vaccination failure in young puppies and kittens. In general this resistance to immunization lasts for eight to twelve weeks after birth. However, for some viral antigens such as canine parvovirus it may persist for as long as 20 weeks (Carmichael, 1983).

6. Specific Mammalian Species

6.1. Marsupials

The marsupials diverged from the eutherian mammals during the Cretaceous period about 145–165 million years ago. Metatheria, the subclass that contains the marsupials, are distinguishable from the Eutheria or placental mammals by differences in their reproductive tract, such as the development of a functional, noninvasive yolk sac placenta. Thus they do not develop a trophoblast or form intimate connections between fetal and maternal tissues. At birth the marsupial, although altricial, has well developed arms and can transport itself to the teat, which in many female marsupials is enclosed in a pouch. It locks onto the teat and suckles for a prolonged period. Marsupial pouches have a diverse bacterial flora and the young therefore require immediate immune protection. Nevertheless, in most marsupials examined, maternal antibodies are not transported across the placenta and immunoglobulins cannot be detected in the embryonic fluids or in the blood of the newborn at birth. Newborn opossums (*Didelphis virginiana* and *Monodelphis domestica*) and the quokka (*Setonyx brachyurus*) do not acquire serum immunoglobulins until they suckle (Yadav *et al.*, 1971, 1973; Hindes and Mizell, 1976; Samples *et al.*, 1986). It is possible that in the tammar wallaby (*Macropus eugenii*) a limited quantity of IgG crosses the placenta since some IgG is detectable two days before birth in fetal serum (Renfree, 1973). Deane *et al.* (1990) also found that IgG increases in concentration in the fetal serum, neonatal serum and colostrum of tammar wallabies. They suggested that both transplacental and intestinal transfer of IgG takes place in this species.

Thus, marsupials secrete colostrum that provides immunoglobulins to the young. Yadav (1971) found that antibodies appeared in the blood of 90-day-old *S. brachyurus* within 15 to 60 minutes of feeding immune serum by stomach tube. In addition, when *S. brachyurus* nursing mothers were immunized with bacteriophage ϕX174 or Salmonella flagellar antigens, specific antibodies could be detected in their colostrum and milk as well as in the serum of pouch young

(Yadav, 1971). Samples *et al.* (1986) immunized lactating *M. domestica* with sheep erythrocytes and found specific antibodies in suckled young 9–10 days later. Antibodies to sheep cells were not found in newborn opossums that had not suckled.

Deane and Cooper (1984) found that pouch young *Macropus robustus* had relatively low levels of serum IgG (20 to 50 mg/dl) up to day 95. However, a steep rise occurred between days 95 and 110 so that concentrations eventually reached 700 mg/dl. This rise coincided with the time that the newborn kangaroo first released from the teat, a time when it is much more likely to ingest harmful microorganisms. The authors suggest that in the first 90–100 days the pouch young are protected largely by passive immunity from the mother, and after this time increasingly mount their own responses (Deane and Cooper, 1984).

Opossum enterocytes express FcR that are detectable up to 52 days of age and can mediate transport of IgG across the intestinal wall (Wild *et al.*, 1994). The disappearance of FcR from marsupial enterocytes appears to correspond to the time of weaning: 7 to 9 weeks in *M. domestica*, 170 to 200 days in *S. brachyurus* and 98 to 145 days in the brush possum (*Trichosurus vulpecula*) (Wild *et al.*, 1994). This long period of FcR expression is in marked contrast to the situation in eutherian mammals. For example, FcRn is expressed for only 21 days in the rat (Griffin and Wild, 1987). However, this pattern of expression corresponds to the suckling period in both species and raises interesting questions regarding cause and effect.

6.2. Eutherian Mammals

The vast majority of mammals belong to the subclass Eutheria. This subclass is characterized by suppression of the yolk sac placenta during early embryonic development and by the development of chorioallantoic placentation, so permitting effective nutrient exchange within the uterus. As pointed out earlier, however, mammalian placentas vary greatly in their structure and in their permeability to IgG.

6.2.1. Primates. Placentations in the more primitive primates such as the lemurs and the Strepsorhines are epitheliochorial and it may be surmised that maternal immunoglobulins can be transferred only through mammary secretions in these species (Blum, 1985; King, 1986). In the Cercopithecidae, Hylobatidae and Pongidae and in humans, placentation is hemochorial and transplacental transfer of immunoglobulins occurs. The main immunological function of mammary secretions in these primates therefore is to protect the newborn intestine by providing IgA. Secretory IgA is present in rhesus macaque milk, though

at a lower concentration than in human milk (Kunz and Lonnerdal, 1993). In general, the levels of immunoglobulins in the sera and mammary secretions of baboons and macaques parallel the levels found in humans (Cole and Bowen, 1976). It has proved possible to stimulate an increase in milk antibodies to rotavirus in pregnant baboons by parenteral vaccination (Snodgrass *et al.*, 1995).

6.2.2. Hystricomorphs. The Hystricomorphs (guinea pigs and porcupines) appear to represent a very early branch in the evolution of Eutherian mammals. Many recent studies in rodent taxonomy have focused on the status of the Hystricomorphs, especially guinea pigs and it is clear that they constitute an order distinct from that of other rodents (Derchia *et al.*, 1996). In Hystricomorphs, maternal IgG is transferred in utero across the yolk sac to the fetus (Beer and Billingham, 1976).

6.2.3. Lagomorphs. The Lagomorphs include the hares, rabbits and picas. Rabbits and hares have a unique method of feeding their young. They use an absentee parental care system that requires nursing them only once every 24 hours. Both IgG and IgM antibodies are readily transferred across the yolk sac *in utero* (Beer and Billingham, 1976).

6.2.4. Rodents. The order Rodentia shows an enormous variety of adaptations and considerable difficulty has been experienced in developing a satisfactory phylogenetic classification. Placentation in rodents is hemochorial and it would therefore be anticipated that IgG could be transferred across the placenta. However it is clear that significant quantities of immunoglobulin are also transferred in colostrum and milk (Beer and Billingham, 1976).

In mice, a small but significant transfer of IgG to the fetus occurs by the 15th day of gestation (five days before birth) but the bulk of passively acquired immunoglobulin is derived from the milk after birth (Appleby and Catty, 1983; Barthold *et al.*, 1988). All immunoglobulin acquired *in utero* and later across the intestinal barrier is exclusively IgG, even though the milk contains predominantly IgA. A high level of maternally derived antibody is maintained in the circulation of the young mouse for 24 days or more after gut closure occurs on the 16–20th day postpartum. FcRn on enterocytes binds and transports IgG until the animals are weaned (21 days in mice and 16 days in rats). In addition, IgG binds very rapidly to FcRn on the rat yolk sac membrane and so is efficiently transferred to the fetus (Mucchielli *et al.*, 1983). Up to 60% of mouse milk IgA on the fourth day of lactation is blood derived. Its transport from blood to milk is mediated by the polymeric Ig receptor (pIgR) from which secretory component is derived. Mouse mammary epithelial cells bind IgA through the pIgR and transfer it into the lacteal secretions (Halsey *et al.*, 1980). This process does not occur in the rat

where all IgA is produced within the gland (Dahlgren *et al.*, 1981). Early in lactation most of the IgA in mouse milk is transferred via the blood to the mammary gland. However, by day 8 of lactation this transferred IgA is significantly diluted by the influx of IgA synthesized locally within the mammary gland (Halsey *et al.*, 1982).

Maternally-derived passive immunity through colostrum and milk has been shown to protect mice against colibacillosis (Duchet-Suchaux, 1983), mouse hepatitis virus (Homberger, 1992), rotavirus (Gombold and Ramig, 1989), Ross River virus (Milner and Marshall, 1984), *Mycoplasma pneumoniae* (Katsura *et al.*, 1985), *Campylobacter jejuni* (Abimiku and Dolby, 1987) and *Taenia taeniaeformis* (Musoke *et al.*, 1975).

IgD is present in rat's milk in extraordinarily high concentrations, approximately 100 times those found in the blood of lactating rats (Olson and Leslie, 1982). This suggests that IgD might be an important secretory immunoglobulin in this species. It is unclear whether the IgD exerts a protective effect within the mammary gland or within the intestine of the suckling rat. Most of this IgD is synthesized locally within the mammary gland in a manner similar to IgA. Since serum IgD levels do not climb in suckling rats it appears not to be absorbed from the rat intestine. This immunoglobulin may serve several functions, including protection of the mammary gland against bacterial or viral infection, passive transfer of immunity to the intestine of the suckling rat, or as a regulatory signal that influences the normal maturation of the neonatal immune system (Steele and Leslie, 1985).

In cotton rats (*Sigmodon hispidus*), passive maternal immunity protects against respiratory syncytial virus (Prince *et al.*, 1983, 1985). Immune females confer antibody to their young prenatally and postnatally, most of the antibody being transferred via colostrum and milk. Maternally transmitted immunity was found to be more effective in the lungs than in the nose and to betransient in both organs.

6.2.5. Carnivores. Carnivores have an endotheliochorial placentation (Blum, 1985) which is not totally impermeable to immunoglobulins. For all practical purposes, however, young carnivores must ingest colostrum and absorb maternal IgG in order to survive.

Canine colostrum is rich in IgG whereas the predominant immunoglobulin in canine milk is IgA with small quantities of IgM and IgG (Heddle and Rowley, 1975). Maternal antibody is protective against canine parvoviruses (CPV) (Macartney *et al.*, 1988), canine distemper (Krakowka *et al.*, 1978) and canine adenovirus (Carmichael *et al.*, 1962). Antibodies to CPV are transferred from an immune mother to her pups through both placenta and colostrum (Pollock and Carmichael, 1982). Colostral transfer accounts for approximately 90% of the maternally-derived CPV antibody. Likewise, neonatal ferrets (*Mustela erminea*)

can be passively immunized following maternal vaccination with killed influenza A vaccine although the relative importance of colostrum and milk in this species has not been examined (Sweet *et al.*, 1987).

Because some maternal immunoglobulins can cross the cat placenta, IgG or IgM can be detected in some fetal and pre colostral kitten sera (Yamada *et al.*, 1991). However, the largest proportion of blood IgG, IgA and IgM is transferred to kittens through colostrum. Casal *et al.* (1996) found that the mean concentration of IgG was higher in colostrum than in maternal serum, implying that there is active transport. Intestinal closure apparently occurs before 16 hours postpartum in kittens since maternal IgG given at or after 16 hours could not be found in any kitten serum.

Passive transfer of immunity has been demonstrated against many different pathogens including feline leukemia virus (Hoover *et al.*, 1977) and *Toxoplasma gondii* (Omata *et al.*, 1994).

In seals (*Phoca vitulina*) the importance of maternal transfer of immunoglobulins through milk is unclear. Neonatal seal pups have a relatively high concentration of some IgG subclasses at birth, suggesting that they either synthesize IgG *in utero* or that it can cross the seal placenta (King, 1986). Ross *et al.* (1994) found that seal pup lymphocytes responded more strongly to mitogens than do the lymphocytes of their mothers. In contrast to newborn cats and dogs, newborn seal pups develop high specific antibody responses after immunization with an inactivated rabies vaccine. Circulating levels of total IgG in newborn seal pups increase rapidly after colostrum intake to 65% of maternal levels after 15 days. Serum IgM levels rise to adult levels by 14 days of age (King, 1986). A similar increase was observed for phocine distemper virus-specific antibodies. The relative immunocompetence of the harbor seal pup at birth may reflect an adaptation to its relatively short nursing period and limited maternal care. In agreement with this view, the IgA concentration in southern elephant seal milk (*Mirounga leonina*) is lower than in other mammals and IgG could not be detected (Marquez *et al.*, 1995).

6.2.6. Ungulata. Since all ungulates appear to have either an epitheliochorial or a syndesmochorial placenta, no significant amount of immunoglobulins can reach the fetus via this route.

Horses have an impermeable epitheliochorial placenta. As a result, foals must obtain their IgG from mare's colostrum. IgG and IgG(T), the latter an immunoglobulin subclass unique to equids, are the predominant immunoglobulins in equine colostrum (MacDougall, 1975) although their concentration varies among breeds. In Arabian mares the concentration of colostral IgG is significantly higher than in thoroughbred mares (Pearson *et al.*, 1984). In suckling foals, immunoglobulin levels climb rapidly for the first 24 hours of life and then fall over the next four weeks to less than half their original values. Maternal

antibodies usually disappear completely by six months (Jeffcott, 1975). The presence or absence of maternal IgG significantly affects a foal's chances of developing septicemia but, as might be expected, does not appear to directly affect resistance to surface infections such as diarrheal disease or *Rhodococcus equi* pneumonia (Haas *et al.*, 1996; Raidal, 1996). Robinson *et al.* (1993) found that seven out of eight colostrum deprived foals developed sepsis. Organisms isolated included *Actinobacillus equuli*, *Escherichia coli*, *Pseudomonas* spp. and *Actinomyces pyogenes*. In contrast, none of the colostrum-fed foals became septicemic. The proportion of foals reported to exhibit failure of passive transport (FPT) depends upon the diagnostic criteria used. Perryman and McGuire (1980) and McGuire *et al.* (1977) examined foals with evidence of immunodeficiency (increased susceptibility to bacterial and viral infections) and found that full or partial FPT occurred in 20% of the foals at risk. They suggested that about 10% of foals have FPT as defined by a circulating IgG concentration of <800 mg/dl.

Kohn *et al.* (1989) found that IgG concentrations in foal serum correlated poorly with IgG concentrations in colostrum. This raises the interesting possibility that the high incidence of FPT in foals might indicate a problem with expression of FcRn. Galan *et al.* (1986) examined the passive transfer of immunoglobulins to *Streptococcus equi* in young foals. Shortly after colostral intake, IgG and IgA antibodies were found not only in sera but also in nasal secretions. Intragastrically administered labeled IgA was transported to the nasal mucosa of a newborn foal within a few hours of colostrum uptake. They suggested therefore that passive protection of the foal respiratory tract was derived not only by immunoglobulins directly coating the upper respiratory and oral mucosa but also by secretion of immunoglobulins directly onto the nasopharyngeal mucosa. Passively acquired maternal antibodies have also been shown to protect foals against experimental equine herpesvirus-1 challenge (Kendrick and Stevenson, 1979).

The pig has an impermeable epitheliochorial placenta and newborns are therefore dependent on colostral IgG for immediate protection. Two of the three pig subisotypes (IgGA and IgGB but not IgGC) are preferentially stored in the mammary glands of full-term sows and secreted into colostrum after farrowing (Huang *et al.*, 1992).

The ability of enterocytes of the small intestine of piglets to transport IgG has been assessed by Leary and Lecce (1979). Transport occurred mainly through the enterocytes in the proximal part of the small intestine. When bovine albumin or porcine IgG was presented separately to the piglet's gut, they were transported at about the same low level. However, when mixtures of these proteins were presented IgG was preferentially transported, i.e., albumin enhanced IgG transport. Mature milk is the main source of IgA to the piglet intestine. For instance, a three-week-old piglet may receive 1.6 g/day of IgA from sow's milk (Klobasa *et al.*, 1987).

Passive maternal immunity either in the form of maternal IgG from colostrum or IgA from milk has been shown to protect piglets against transmissible gastroenteritis virus (TGEV) (Stone *et al.*, 1977; Woods and Wesley, 1986; Fu *et al.*, 1990; Lanza *et al.*, 1995; Sestak *et al.*, 1996; Shoup *et al.*, 1997), pseudorabies (McFerran, 1975; Vannier *et al.*, 1995), colibacillosis (Rutter *et al.* 1976; Contrepois *et al.*, 1978; Chidlow and Porter, 1979; Isaacson *et al.*, 1980; Moon, 1981; Furer *et al.*, 1982, 1983; Rijke *et al.*, 1983; Nagy *et al.* 1985), porcine parvovirus (Paul *et al.*, 1980, 1982), *Hemophilus parahaemolyticus* (Nielsen, 1975), eastern equine encephalitis (Elvinger *et al.*, 1996), *Bordetella bronchiseptica* (Smith *et al.*, 1982), and *Pasteurella multocida* toxin (Foged *et al.*, 1989). In general the IgG tends to protect against systemic infections while the prolonged intake of milk IgA protects against enteric disease.

The route by which an antigen enters the body of the sow influences the isotype of immunoglobulin found in colostrum or milk. For example the presence of IgA anti-TGEV antibodies in sow's milk is associated with intestinal infection, whereas IgG antibodies resulted from parenteral antigenic stimulation of the sow (Bohl and Saif, 1975; Bohl *et al.*, 1975; Moxley *et al.*, 1989).

As in cattle, IgG is the predominant immunoglobulin in the milk of the dromedary *Camelus dromedarius* (Azwai *et al.*, 1996). IgM and IgA have also been identified in camel colostrum. Their protective significance has not been ascertained.

Alpacas (*Lama pacos*) lack blood immunoglobulins at birth, but show a 70% increase in total serum proteins within 24 hours because of absorption of gamma globulins from colostrum (Garmendia and McGuire, 1987). IgG is the isotype in highest concentration in colostrum and in serum from 24-hour-old crias. IgM is also absorbed from colostrum but IgG accounts for greater than 85% of the passively transferred protein. Failure of passive transfer of immunoglobulin (IgG $\leq$ 900 mg/dl) is a major risk factor for mortality in newborn alpacas (Garmendia *et al.*, 1987).

6.2.7. Ruminantia. In view of the importance of passive maternal immunity, it is not surprising that in mule deer fawns (*Odocoileus hemionus*) serum gamma globulin concentrations directly affect morbidity and mortality. Parkinson *et al.* (1982) showed that all fawns with serum total protein concentrations of 5 g/dl or less during the first week of life developed diarrhea and died before 17 days of age. Only one of 14 fawns with a serum protein concentration above this level became sick and died (Parkinson *et al.*, 1982). Sams *et al.* (1996) examined a herd of white-tailed deer (*Odocoileus virginianus*) and also showed that increased mortality was associated with lower serum gamma globulin concentrations. This suggests that inadequate absorption of colostrum and partial failure in passive immunity predisposes suckling fawns to increased mortality.

Cattle have a syndesmochorial placenta so that no IgG crosses the bovine placenta. Thus, calves are born agammaglobulinemic and depend on absorption of maternal colostral IgG for survival. There is an inverse correlation between passively acquired serum IgG levels and calf mortality. If failure of passive transport (FPT) occurs then increased neonatal morbidity and mortality occurs. (It may be useful to point out here that the causes of FPT are numerous. They can be classified as; production failure, where insufficient colostrum is produced by the mother—a common feature in multiple births; ingestion failure, where the newborn fails to suckle properly; and absorption failure, where the newborn fails to absorb sufficient immunoglobulin). The prevalence and severity of FPT depends on the definition of the condition. Mortality was significantly increased in calves with serum IgG1 levels <500 mg/dl as a result of FPT (Rea *et al.*, 1996). Calves classified as having FPT had a 9.5 times greater risk of developing infections prior to weaning than calves classified as exhibting sufficient passive transfer of immunoglobulin (Perino *et al.*, 1993). Calves with less than 1000 mg/dl of IgG in their serum by 24–48 hours of age die at more than twice the rate of calves with higher IgG levels. McGuire *et al.* (1976) found that serum IgG1 concentrations in calves less than three weeks old, and dying from infectious disease, were significantly lower than those of clinically normal calves. These low IgG1 concentrations were attributed to FPT. They concluded that "In view of the large numbers of calves that die from neonatal infection each year, it may be assumed that failure in passive transfer, as reflected by low serum immunoglobulin concentrations, is one of the most important factors influencing neonatal calf mortality".

Productivity in calves, as expressed by weight gain, is also affected by FPT (Robison *et al.*, 1988; Virtala *et al.*, 1996). Calves fed colostrum with high immunoglobulin content gained weight from birth to day four while those fed colostrum with low concentrations of immunoglobulins lost weight (Nocek *et al.*, 1984).

Given that mammals transfer IgG to their newborn either through colostrum or via the placenta, it makes sense to enhance resistance to disease by vaccinating pregnant animals. Consequently, antibodies made by the mother will confer immunity on their offspring. Preparturient vaccination of dairy cows induces increases in passive antibody titers in their calves to antigens of *Pasteurella haemolytica* (Hodgkins and Shewen, 1994, 1996), *Salmonella typhimurium* (Jones *et al.*, 1988), rotaviruses (Snodgrass, *et al.*, 1980; Castrucci *et al.*, 1988; Tsunemitsu, *et al.*, 1989) and *E. coli* (Wilson and Jutila, 1976a,b; Valente *et al.*, 1988). Protection by maternal passive immunity has been shown against bovine respiratory syncytial virus (Belknap *et al.*, 1991), bovine rotavirus (Saif *et al.*, 1983; Saif and Smith 1985; Besser *et al.*, 1988), enterotoxigenic *Escherichia coli* (Snodgrass *et al.*, 1982), septicemic *E. coli* (Johnston *et al.*, 1977), infectious bovine rhinotracheitis virus (Mechor *et al.*, 1987), bovine diarrhea virus (Howard

et al., 1989; Bolin and Ridpath, 1995), *Salmonella typhimurium* (Staak and Luge, 1995), cryptosporidium (Fayer *et al.*, 1989) *Taenia saginata* (Rickard *et al.*, 1977) and bovine leukemia virus (Lassauzet *et al.*, 1989). There is no doubt that the passive transfer of immunoglobulins through milk and colostrum is absolutely essential for resistance to disease and neonatal health during the first months of life in the major domestic species.

Besser *et al.* (1985) found a negative correlation between the efficiency of absorption and the total amount of immunoglobulin fed to calves. They suggested that there was a physiologic limitation to the amount of immunoglobulin that can be absorbed from a given volume of colostrum. In calves receiving colostrum at six hours after birth, 65.8% of the ingested IgG appeared in the plasma (Matte *et al.*, 1982).

Stott and Menefee (1978) examined the efficiency of absorption of different immunoglobulin isotypes in the colostrum fed to calves. They found that IgG absorption varied from 10 to 46% and IgA absorption from 5 to 50%. The percent of IgM absorbed increased as the amount ingested decreased, whereas, the efficiency of IgA and IgG absorption did not change with intake. Selective transport of IgM, they speculated, may be important for its role as the primary protective immunoglobulin during the first few days of life. Clover and Zarkower (1980) examined the influence of colostrum on calf lymphocyte reactivity. They found that peripheral blood lymphocytes from calves deprived of colostrum during the first 24 hours after delivery were significantly more responsive to mitogens than leukocytes from colostrum-fed calves.

Sheep, like cattle, have a syndesmochorial placenta and lambs consequently require colostral immunoglobulins to survive. Colostrum from ewes contains significantly higher concentrations of immunoglobulins than does their serum, IgG being selectively concentrated over IgM (Sawyer *et al.*, 1977). As in cattle, IgG is the predominant immunoglobulin in sheep milk (Smith *et al.*, 1975).

Absorption of immunoglobulins through the intestinal tract of the lamb appears to be a non-selective process. Concentrations of IgG1 were measured in 590 lambs, among which FPT (less than 600 mg/dl) occurred in twenty (McGuire *et al.*, 1983). Of these, 45% died before three weeks of age, whereas only 5% of the 570 lambs with adequate passive transfer died. Sawyer *et al.* (1977) found that 14% of clinically normal lambs demonstrated some FPT. Protection of lambs through passive transfer of antibodies from colostrum has has been reported for contagious pustular dermatitis (Lejan *et al.*, 1978), K99 colibacillosis (Sojka *et al.*, 1978; Morris *et al.*, 1980; Pugh and Wells, 1985), rotavirus (Snodgrass and Wells, 1978), *Echinococcus granulosus* (Dempster and Harrison, 1995), *Taenia ovis* (Sutton, 1979) and *Taenia hydatigena* (Jacobs *et al.*, 1994).

The IgG concentration in goat colostrum is about 2.5 times greater than in the maternal serum, and 95–98% is IgG1 (Micusan and Borduas, 1977). Given

the structure of the goat placenta it is clear that kids are dependent on colostral immunoglobulin for survival.

7. Conclusions

The diversity observed in placental structures testifies to the remarkable nature of mammalian evolution. There appears to be no obvious phylogenetic pattern to placental structure except that less phylogenetically advanced species appear to have less permeable placentas. It can be argued teleologically that continued evolution of the means by which mammals regulate immune responses against fetal antigens permit the evolution of placentas with more efficient transport functions. However, other factors clearly come into play. Less permeable placentas may limit the supply of nutrients to the fetus and so necessitate a longer gestation period. It is also clear that passive transfer of immunoglobulins, and possibly cells, from the mother to the newborn by way of colostrum and milk was an essential step in mammalian evolution. Mammals with impermeable placentas must acquire their immunoglobulins in some other way and milk is the obvious source. It is likely, therefore, that mammalian viviparity and the secretion of milk immunoglobulins evolved at the same time. Once immunoglobulin-permeable placentas evolved, the role of colostrum became less important. On the other hand, placental structure has little bearing on the defense of the newborn's intestine by the continued intake of milk IgA. That seems to be a constant role for milk irrespective of the phylogenetic status of the species.

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