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Immunological Functions of the Mammary Gland and Its Secretion—Comparative Review

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Abstract

The mammary gland performs vitally important immunological roles, both in providing passive immune protection to the suckling infant and in immunological defence of its own tissues against infection with microorganisms. These immunological functions differ greatly between species of mammals in both nature and magnitude. In ungulates the mammary gland is singularly responsible for transfer of immunoglobulin (IgG) from mother to young. This process is dependent on a highly selective mechanism which results in the transport of blood-borne IgG molecules across secretory epithelial cells of the colostrum-forming mammary gland and into secretion. Upon ingestion of colostrum by the young ungulate this immunoglobulin is absorbed across the wall of the small intestine and thence into the bloodstream.

In other species, including rodents and primates, there is a well-developed local IgA system operating in the mammary gland. In this situation, plasma cells located near the basal membranes of secretory epithelial cells secrete IgA which passes through the epithelial cells and into colostrum or milk. In these species the IgA in mammary secretions is not absorbed into the circulation of the suckling infant; because of its unique property of resisting proteolytic degradation, it may mediate a local protective role in the lumen of the intestine of the suckling infant.

Specific immunological protection of mammary tissue may be mediated through blood-derived antibody (particularly IgG), locally synthesized antibody (particularly IgA) or phagocytic cells. Neutrophils arrive in mammary tissue and secretions in very large numbers following bacterial invasion of the gland. It has been established recently that these cells carry cytophilic antibody on their cell membrane. This cytophilic antibody can play an important functional role in enhancing the phagocytic capacity of neutrophils in the mammary gland.

Introduction

In recent years there has been a revival of interest in the immunological roles of the mammary gland and its secretion, and this has been reflected by the appearance in the literature of several excellent reviews on particular aspects of the subject (Beer *et al.* 1974; Reiter 1978; Lascelles 1979). In this paper the topic is reviewed in a broad way with particular emphasis on differences between species. Differences between species of mammals in immunological functions are at least as pronounced in the mammary gland (and its secretions) as in any other organ. These differences are worth highlighting for two main reasons. Firstly, they represent basic physiological disparity between species in the overall reproductive process and accentuate the re-allocation (in an evolutionary sense) of vital functions to different organs (e.g. selective transport of IgG by mammary tissue in ruminants or placental tissue in primates). Secondly, the differences between species in certain areas of mammary gland immunity are so great that extrapolations from one species to another are

unsatisfactory. An example of this is the difference in local IgA production in the mammary glands of rodents and ruminants. It is hoped that by drawing attention to such differences this paper may encourage research on immunological functions of the mammary gland of individual species without investigators having preconceived ideas of what ought to be expected of mammals in general.

The immunological functions of mammary secretion may be considered in relation to protection of the suckling infant or protection of the mammary gland itself. Naturally, there is a considerable overlap of interests between the two. In addition to species differences, the physiological and pathological state of the gland has a considerable bearing on its protective functions. The effector mechanisms of mammary gland immunity include leucocytes, immunoglobulins, and a number of other proteins. Some of the relationships between these various factors are shown in Fig. 1.

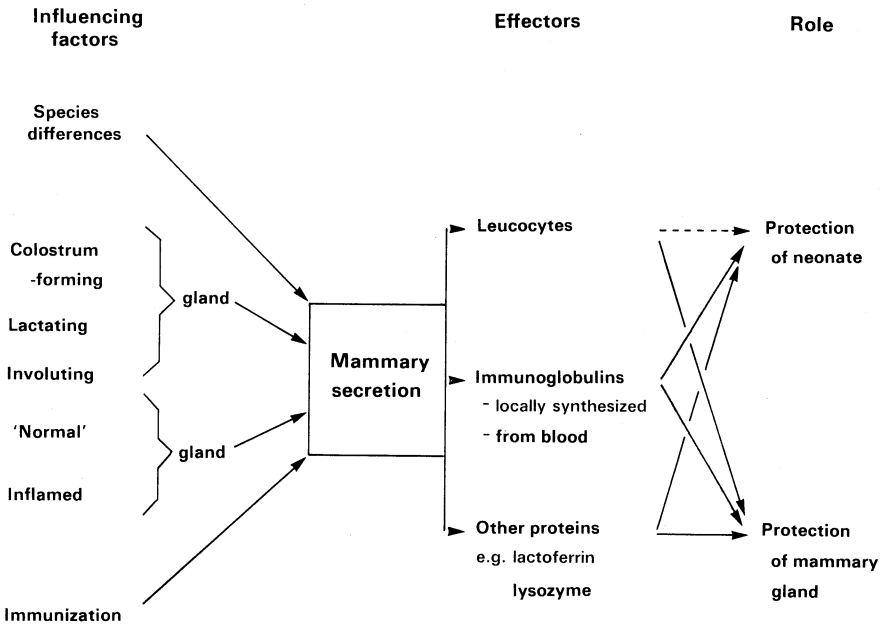

Fig. 1. Diagrammatic representation of relationships between various factors concerned with the immunological roles of the mammary gland.

Mammary Secretion as a Source of Circulating, Passively Acquired Antibody

In the neonatal period the young animal requires immunological protection until its own immune mechanisms amplify under the influence of environmental antigens and it becomes immunologically independent. In mammals and birds biological mechanisms have evolved to provide the neonate with this immunological protection in the period after birth or hatching. In birds transmission of antibody from mother to young occurs via the egg yolk. Antibodies are transferred from mother to young in mammals either before or immediately after birth, and the mode of this transmission is related to the species involved and its type of placentation (Table 1). Two species, humans and cattle, can be selected to illustrate the differences and similarities in transfer of passive immunity from mother to young.

In the pregnant woman, during the last trimester of pregnancy, IgG is transported from maternal to foetal circulation across the placenta (Morphis and Gitlin 1970). This transport of immunoglobulin is achieved by an active process which is selective in favour of IgG and effectively excludes antibody of the other immunoglobulin classes (i.e. IgM, IgA, IgE and IgD). Furthermore there is selectivity even within the IgG immunoglobulin subclasses—the selective mechanism favours the transport of IgG_1 and IgG_3 at the expense of IgG_2 and IgG_4 (Bernier *et al.* 1967; Virella *et al.* 1972).

The situation in the pregnant cow is quite different. The placenta in the cow is syndesmochorial and the uterine epithelium is maintained throughout pregnancy. Consequently, there is effectively no prenatal transfer of antibody (or other large proteins) from mother to foetus. Thus the calf is born agammaglobulinaemic or markedly hypogammaglobulinaemic (Brambell 1970; Husband *et al.* 1972). In the cow, however, the colostrum-forming mammary gland has assumed the role of

Table 1. Differences between species in transmission of circulating, passively acquired antibody

Values in brackets represent the duration after birth of absorption of immunoglobulin from mammary secretion. For more detail see Brambell (1970)

Species	Placentation	Mode of transmission	
		Prenatal	Postnatal
Ruminant	Syndesmochorial	0	+++ (36 h)
Pig	Epitheliochorial	0	+++ (36 h)
Horse	Epitheliochorial	0	+++ (36 h)
Dog	Endotheliochorial	+	++ (10 days)
Mouse	Haemoendothelial	+	++ (16 days)
Rat	Haemoendothelial	+	++ (20 days)
Guinea pig	Haemoendothelial	+++	0
Rabbit	Haemoendothelial	+++	0
Man	Haemochorial	+++	0

transporting immunoglobulin from mother to young and in the pre-parturient period this organ is responsible for accumulating antibody-rich colostrum, which is available for ingestion by the calf immediately after it is born. The transport process in the colostrum-forming mammary gland is both active and highly selective in favour of one of the IgG subclasses, namely IgG_1 (Murphy *et al.* 1964; Pierce and Feinstein 1965). When the newborn calf ingests colostrum the immunoglobulins are absorbed into its blood (see later). Because of the preceding selection which has taken place in the mammary gland, the concentration of IgG_1 in the calf's circulation far exceeds that of IgG_2, IgA and IgM (Brandon and Lascelles 1971).

It is worth emphasizing, therefore, that in both species the newborn animal is provided with a repertoire of maternal antibodies belonging to a particular subclass of IgG. In both species this immunoglobulin exerts its protective influence from the blood circulation of the neonate. The major difference is the organ/tissue which carries out this highly selective transport process. Thus the mammary gland through its secretion of IgG-rich colostrum serves an essential function in species such as ruminants, pigs and horses (Jeffcott 1972; Simpson-Morgan and Smeaton 1972; Campbell *et al.* 1977). The quantitative importance of IgG in the colostrum of these

species is illustrated by the data in Table 2. This situation contrasts with those for man and the rabbit in which species colostral immunoglobulin levels in general, and concentrations of IgG in particular, are much lower.

Table 2. Levels of immunoglobulins (mg/ml) in colostrum of several species

For more detail see Lascelles and McDowell (1974)

Species	IgG	IgA	IgM
Sheep	60·0	2·0	4·1
Cow	50·0–90·0	4·5	6·0
Pig	57·0	10·0	2·7
Rabbit	2·4	4·5	0·1
Man	0·2	18·0	0·8

Mechanism of Selective Transport of Immunoglobulin in the Mammary Gland

Until the early 1970s it was generally accepted that selective transport of 'fast IgG' (as IgG_1 was then known) was effected by a mechanism similar to that proposed by Brambell (1966). Brambell had developed his hypothesis from data obtained on selective transport of immunoglobulin in the yolk sac endoderm of rabbits and guinea pigs, the primate placenta, and the gut of the rat. This hypothesis, stated briefly, maintained that IgG, together with other proteins, was taken up in pinocytotic vesicles by the transporting cell. IgG then became attached to specific receptors and when the transport vesicle fused with lysosomes containing proteolytic enzymes, the IgG was protected from degradation by virtue of its attachment to the receptors, whereas other (unattached) proteins within the vesicle were enzymatically degraded.

In 1971 evidence was published which indicated that the hypothesis put forward by Brambell did not explain the selective transport of IgG_1 into the colostrum-forming mammary gland of the cow, and an alternative hypothesis was proposed to explain the mechanism of this phenomenon (Brandon *et al.* 1971). This alternative hypothesis is shown diagrammatically in Fig. 2. In this model IgG_1 molecules attach to specific receptors on the basal or intercellular membrane of the acinar epithelial cells. Thus membrane-bound vesicles forming at these sites would contain more IgG_1 than IgG_2 or other proteins. The transport vesicle would then travel across the cytoplasm of the cell and discharge its contents into the lumen of the alveolus by reverse pinocytosis, resulting in greater levels of IgG_1 than IgG_2 in colostrum (Table 3). This model avoids the necessity to postulate a destructive and biologically inefficient process (enzymatic degradation) to explain selectivity of transport. Subsequent evidence has supported the conservative hypothesis outlined above for selective transport of IgG_1 in the ruminant mammary gland (Cripps *et al.* 1976; Sasaki *et al.* 1976), and there is also data which suggest that the Brambell hypothesis may not apply even in the species on which it was originally based (Rodewald 1970; Jones and Waldmann 1972; Jones 1978).

On this basis, the degree of selectivity of transport of IgG_1 over IgG_2 must depend on the number of IgG_1-specific receptors on the cell membrane, as well as the frequency of vesicle formation and transport. Although transport activity is at a maximum during the colostrum-forming period a slight selectivity of transport is sustained during the ensuing lactation in ruminants, although at a very greatly reduced

rate (Mackenzie and Lascelles 1968; Table 3). It is clear, therefore, that during lactation either the number of IgG_1 receptors or transport activity, or both, must be

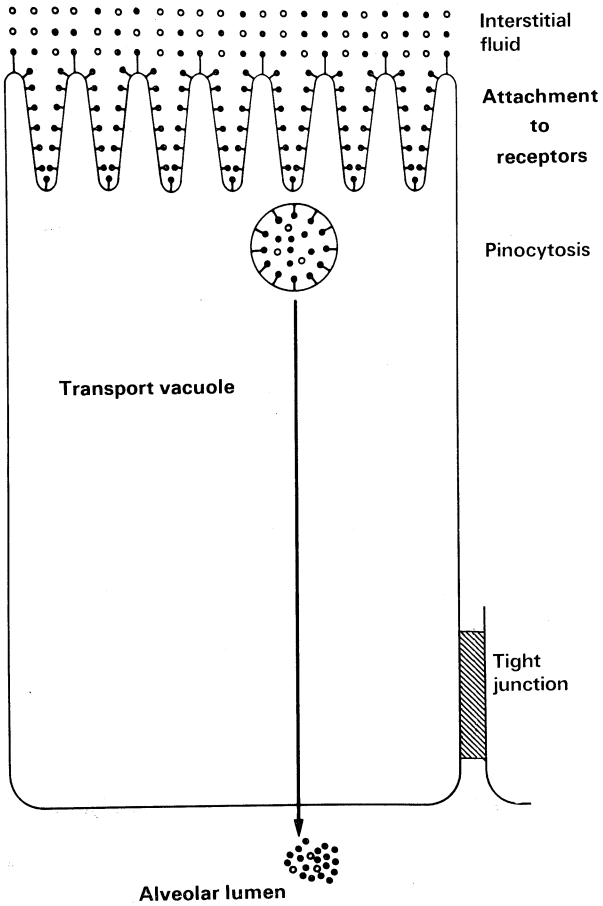

Fig. 2. Model for selective transport of IgG_1 across the glandular epithelium of the ruminant mammary gland (after Lascelles 1979). ● IgG_1 molecules. ○ IgG_2 molecules. Reproduced with the permission of the Editor of the Journal of Dairy Science

reduced compared with the colostrum-forming period. In this connection it has been noted that an inverse relationship exists between selective transport of IgG_1 and *de novo* synthesis of proteins and lactose by the mammary gland (Lascelles 1969;

Table 3. Levels of immunoglobulins (mg/ml) in body fluids of the cow

Fluid	IgG_1	IgG_2	IgA	IgM
Blood serum	14·0	13·0	0·4	3·8
Colostral whey	40·0–80·0	2·5	4·5	6·0
Milk whey	0·4	0·06	0·1	0·09

Watson *et al.* 1972). It would appear that, during peak lactation, the 'metabolic attention' of the cell is diverted from its selective transport function to its anabolic role.

Acquisition and Role of Colostral Immunoglobulin in the Neonatal Ungulate

The newborn ungulate is generally on its feet and suckling within 2 h after birth. IgG-rich colostral whey passes quickly through the stomach and into the small intestine, and it is in this organ that absorption into the circulation occurs (Simpson-Morgan and Smeaton 1972). For the first 24–36 h after birth the small intestine is lined with highly vacuolated, immature mucosal epithelial cells which are capable of absorbing macromolecules (Moon 1972). The colostral immunoglobulin is thus transported from the lumen of the intestine, via the absorptive epithelial cells and intestinal lymphatic system, to the blood (Sibalin and Bjorkman 1966; Yoffey and Courtice 1970). This absorptive process is non-selective in nature but because of the selectivity in favour of IgG which has occurred beforehand in the mammary tissue, the young animal acquires much more IgG (IgG_1 in the case of ruminants) than immunoglobulin of other classes (Brandon and Lascelles 1971). Absorption of immunoglobulin ceases when the immature absorptive cells lining the intestine are replaced with mature cells which are incapable of absorbing macromolecules. This process, known as 'gut closure', is usually completed by 36 h after birth (Clark and Hardy 1969; Smeaton 1969).

Passage of functionally intact IgG molecules into the circulation of the infant ungulate is facilitated by several factors. Firstly, colostrum has a high buffering capacity which tends to minimize denaturation of immunoglobulin due to gastric proteases or extremes of pH (Mason 1962; Mylrea 1966). Secondly, colostral IgG_1, in the cow at least, is more resistant to proteolysis by chymotrypsin than are other immunoglobulin classes (Brock *et al.* 1977*a*, 1977*b*). Thirdly, colostrum contains a substance known as 'trypsin inhibitor' which prevents trypsin-mediated proteolysis of the immunoglobulin (Laskowski and Laskowski 1951; Balfour and Comline 1962). Additional absorption-enhancing factors must be involved, however, since the absorption of polyvinyl pyrollidone, which is not susceptible to enzymatic digestion, is enhanced if it is fed together with colostrum (Hardy 1964). This combination of factors ensures that when the IgG molecule reaches the infant's circulation it is still capable of mediating immunological functions such as complement fixation, toxin neutralization and opsonization.

There is ample evidence to show that colostral antibody absorbed by the neonatal calf, lamb, piglet or foal exerts an extremely important protective function. Indeed it is generally accepted that the young of these species, if completely deprived of colostrum and not otherwise protected from infection, stand very little chance of survival (Brambell 1970). This vital protective role of colostral immunoglobulin in the neonate has been demonstrated most commonly with regard to bacterial (Cameron and Fuls 1970; Logan and Penhale 1971; Brandenburg and Wilson 1973; Piercy 1974) and viral (Williams *et al.* 1975; Smith *et al.* 1976) infections.

Transfer of Cellular Immunity via Mammary Secretions

Recently there has been some interest expressed in the possibility that cell-mediated immune phenomena, as well as antibody, may be transferred from mother to young via colostrum or milk (Beer *et al.* 1974). Since B and T lymphocytes, macrophages and neutrophils are commonly found in mammary secretion (Smith and Goldman 1968; Mohr *et al.* 1970; Diaz-Jouanen and Williams 1974), a possible protective role for them in the suckling infant has been sought. There is evidence from studies in

both humans and rodents that cell-mediated hypersensitivity (Mohr 1973) and cell-mediated skin graft reactions (Beer *et al.* 1974) are transferred from mother to young via mammary secretion. Although there is no doubt that a proportion of these cells are immunologically competent whilst in mammary secretion (Parmely *et al.* 1976), there is no crucial evidence in favour of their ability to survive the relatively hostile environment of the stomach and intestine and gain access to the circulation of the infant. Thus, the possibility remains that cell-mediated immune phenomena which are transferred from mother to young result from the passage of soluble factors produced by lymphocytes, such as transfer factor (Lawrence 1969; Klesius and Fudenberg 1977), rather than transfer of the cells themselves. Indeed, the most recent evidence available from *in vitro* studies suggests that soluble factors released by breast milk leucocytes may play an important role in immunoregulation in the suckling infant (Pittard and Bill 1979).

Adverse Effects of Transfer of Passive Immunity to the Young via Mammary Secretion

Despite the overwhelming benefits to the newborn animal arising from ingestion of antibody-rich colostrum, this transmission of passive immunity (like many other biological processes) can have undesirable side-effects (Beer *et al.* 1974). Haemolytic disease of the young animal may occur if the absorbed colostral immunoglobulin has antibody activity directed against isoantigens on erythrocytes of the neonate (Brambell 1970). This problem is not uncommon in horses (Roberts and Archer 1966) and pigs (Buxton and Brooksbank 1953). In this disease jaundice and death usually rapidly follow ingestion of colostrum unless therapy is effected immediately. Of wider implication is the well-known specific inhibitory effect of circulating, maternally derived antibody on the development of an autologous, humoral immune response in the neonate (Hoerlein 1957; Sharpe 1966; Husband and Lascelles 1975; Muscoplat *et al.* 1977). Acquisition of passive immunity also may result in antibody-mediated suppression of specific, local immune responses in the small intestine (Horsfall *et al.* 1979; Watson *et al.* 1979).

In recent years evidence has been presented which indicated that specific immunological tolerance could be transmitted from mother to young via ingested colostrum or milk (Auerbach and Clark 1975). Other work has indicated however, that this phenomenon is due to neither transmission of immunocompetent lymphocytes nor transfer factor (see above). Rather, the tolerant state was reportedly induced by transmission of the tolerogen itself through the mammary secretion and its subsequent ingestion and absorption by the suckling infant (Halsey and Benjamin 1976).

Notwithstanding the above examples, it should be emphasized that for most young ungulates the ingestion of colostrum and absorption of antibody is a beneficial rather than disadvantageous process.

Local Production of Immunoglobulin in Mammary Tissue

In the early 1950s Petersen and his colleagues in the United States published several papers and articles which were based on the notion that the immunoglobulin in colostrum and milk of dairy cows was synthesized locally in the mammary gland (Campbell *et al.* 1950; Petersen and Campbell 1955). This concept was discredited in the early 1960s by critical evaluation of the data (Lascelles 1963) and by further experimentation (Dixon *et al.* 1961). Indeed the first authenticated studies of any

magnitude on local immunity in the ruminant mammary gland were carried out in Australia by Lascelles and his colleagues. These workers showed that infusion of particulate or soluble sterile antigen into the mammary gland of the ruminant during the dry period resulted in the development of a local antibody response which persisted during the following lactation (Outteridge *et al.* 1965, 1968; Lascelles *et al.* 1966). By means of immunofluorescent techniques, Lee and Lascelles (1970) established the cellular basis for local immunity in the ruminant mammary gland.

It is pertinent, at this point, to draw attention to the disparity between species in local production of antibody by plasma cells in mammary tissue. In the physiologically 'normal' lactating mammary gland of a ewe or cow there is very little local production of antibody and only trivial numbers of immunoglobulin-containing cells are found in the mammary tissue (Dixon *et al.* 1961; Lee and Lascelles 1970). This picture can be changed by locally immunizing the gland *pre-partum*, a procedure which results in sequestration of immunocytes into mammary tissue and a substantial increase in secretion of antibody, mainly IgA, but with some IgM (McDowell and Lascelles 1969; Lee and Lascelles 1970; Watson and Lascelles 1973). In contrast, in primates and rodents the local IgA system in the mammary gland is naturally activated and does not require artificial immunization. In these species lactating mammary tissue contains significant numbers of IgA-containing plasma cells and there is a substantial amount of IgA in colostrum and milk (Tomasi and Bienenstock 1968; Vaerman 1970; Ahlstedt *et al.* 1975). Thus there appears to be an inverse relationship (at least to some degree) between the selective transport of IgG into mammary secretion and the natural activity of the local IgA system in the mammary gland. The sow provides an interesting link between the two extremes. In the porcine mammary gland there is active transport of IgG from blood into colostrum and a reasonably well-developed local IgA system which assumes quantitative ascendancy 1–2 days *post partum* (Fig. 3; Porter and Noakes 1969; Curtis and Bourne 1971). Notwithstanding, the local IgA system in the mammary gland of the sow can be augmented by local infusion of antigen during late pregnancy (Bennell and Watson 1979*a*).

These differences between species in terms of the degree of natural development of the local immune system in the mammary gland are now well established (Lascelles and McDowell 1974; Table 2).

Factors Influencing Local Synthesis of Antibody in the Gland

Although antigenic stimulation at the local level is clearly the major (if not the only) factor influencing an immune response in the mammary glands of ruminants, the same cannot be said of local immune responses in those species in which precursors of IgA-secreting plasma cells sequester to the mammary gland naturally. For instance it is now known for both the mouse (Weisz-Carrington *et al.* 1977) and rat (Lee *et al.* 1978) that the numbers of immunoglobulin-containing cells (mostly of IgA specificity) in mammary tissue fluctuate with the reproductive/lactational status of the animal. In rodents, both virgin females and those in the early stages of pregnancy have very few plasma cells in mammary tissue. There is a dramatic increase in numbers of these cells during late pregnancy to reach a peak during early lactation; these high numbers are sustained during early lactation but begin to decrease when weaning takes place and mammary involution begins. Recent work has shown that sequestration of IgA-containing cells to the mammary gland is under hormonal control (Weisz-Carrington *et al.* 1978), but since the hormones involved (progesterone,

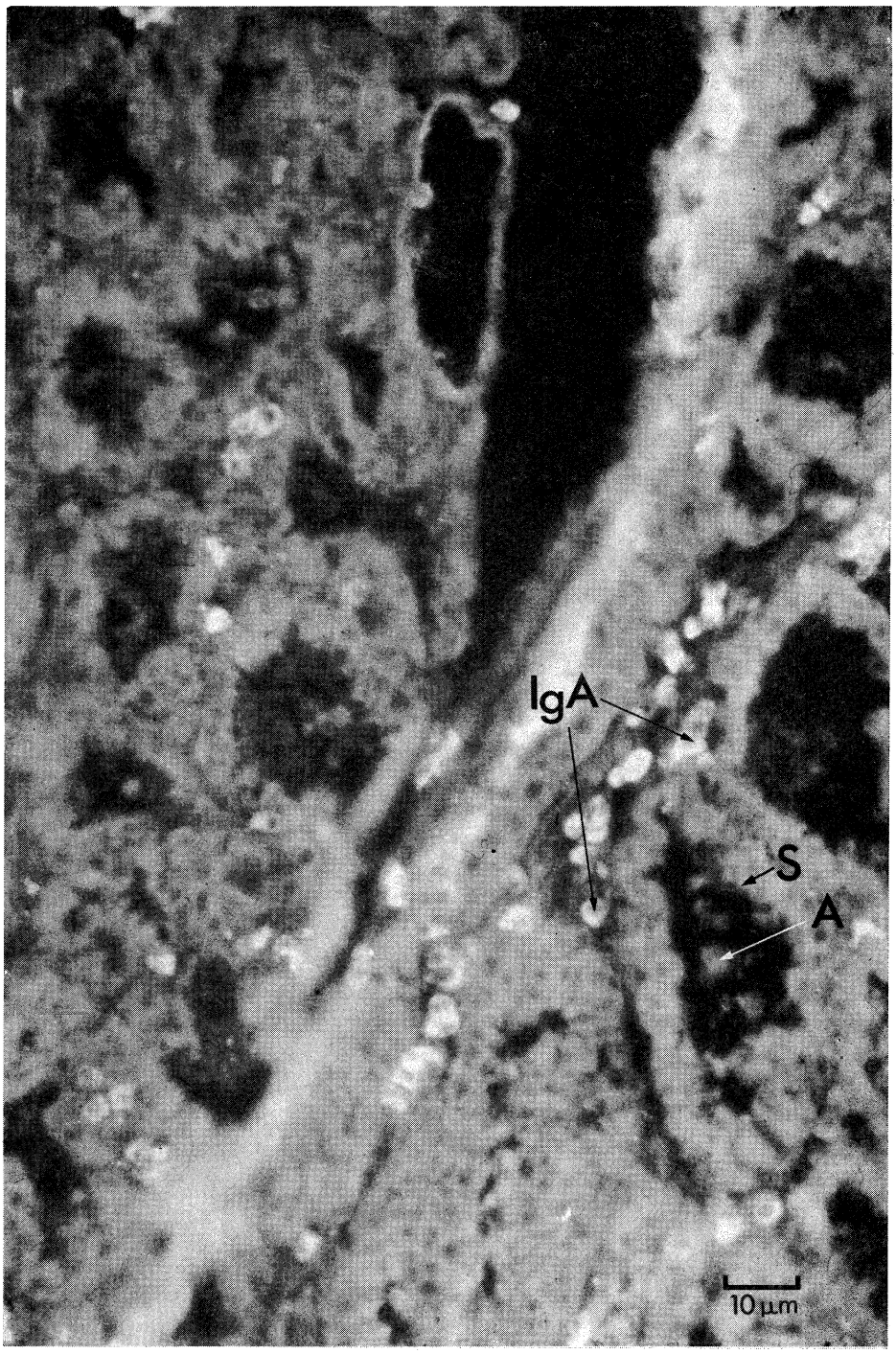

Fig. 3. Photomicrograph of a section of mammary gland tissue from a lactating sow. The section has been stained with FITC-conjugated monospecific anti-porcine IgA. There are large numbers of IgA-containing plasma cells (*IgA*) adjacent to the basal membrane of secretory epithelial cells (*S*). *A*, alveolus.

oestrogen and prolactin) also interact to initiate mammogenesis and maintain lactation, it is unclear whether their effects on the development of the local immune system in the mammary gland are direct or indirect. It has been speculated that the effects of these hormones are to increase the number of receptors on secretory epithelial cells in mammary tissue. These putative receptors would 'trap' the circulating lymphocyte precursors of IgA-secreting plasma cells and retain them in mammary tissue (Weisz-Carrington *et al.* 1978). This is an attractive theory to explain events in the rodent/primate mammary gland, but it offers no explanation for failure of the same mechanism to apply in ruminants.

In those species in which the colonization of mammary tissue with IgA-secreting plasma cells occurs naturally, it has been observed that much of the IgA in milk has antibody activity against enteric antigens (Holmgren *et al.* 1976; Stoliar *et al.* 1976). In humans, it has been demonstrated that oral immunization with enteric bacteria during pregnancy results in the appearance in colostrum of IgA plasma cells containing specific antibody directed against the immunizing organisms (Ahlstedt *et al.* 1975; Goldblum *et al.* 1975). Previous studies had shown that Peyer's patches were an enriched source of lymphoid cells which were destined to become IgA-secreting plasma cells in intestinal lamina propria (Craig and Cebra 1971), and this led to the notion that Peyer's patches also may be the source of lymphoid cells (sensitized to enteric antigen) which colonized the breast. Indeed, it has been established that lymphoid cells, collected from mesenteric lymph nodes and committed to IgA synthesis, do colonize the mammary gland of the mouse at the appropriate stages of pregnancy and lactation (Roux *et al.* 1977). Additional data suggest that these cells originate in Peyer's patches and have only temporary association with mesenteric nodes during the course of a physiologically normal migration pathway (Beh 1977).

The evidence in favour of the intestine as the organ of origin of IgA-containing plasma cells in mammary tissue suggests evolutionary development of an efficient protective mechanism. In such a system the suckling infant is ingesting antibody which would assist in protection of the intestinal lumen from infection—this antibody is likely to be of appropriate antigenic specificity for intestinal protection since the cells which manufacture it were sensitized by antigens in the small bowel of the mother.

While the above evidence is limited to B lymphocytes which subsequently become antibody producers in the mammary gland, the possibility cannot be excluded that T lymphocytes also may derive from intestinal tissue and localize in the gland. Indeed there is evidence that T lymphocytes harvested from human milk are sensitized to enteric antigens (Parmely *et al.* 1976) and since it is well established that the secretory IgA system is dependent on T cell cooperation (Clough *et al.* 1971; van Muiswinkel and van Soest 1975; Elson *et al.* 1979) the possible importance of these cells should not be discounted.

Local infusion of sterile antigen during late pregnancy has been the most successful method of inducing local IgA responses in the mammary glands of the economically important domestic animals (Mitchell *et al.* 1954; Derbyshire and Smith 1969; McDowell and Lascelles 1969, 1971; Bennell and Watson 1979*a*). In contrast to the IgA response induced by infusion of antigen, injection of antigen into mammary parenchyma results in granuloma formation (Lascelles and McDowell 1974) and an IgG response (Bourne *et al.* 1975; Chidlow and Porter 1977).

In pigs at least, oral immunization of pregnant animals with viable *E. coli* (Kohler *et al.* 1975; Kohler 1976) or transmissible gastroenteritis virus (Bohl and Saif 1975)

results in a specific local IgA response in the mammary gland. Other work with pregnant cows showed that systemic immunization with bacterial antigen in adjuvant at the time of mammary involution can lead to substantial levels of IgA and IgM antibody in milk in the subsequent lactation (Watson and Lascelles 1975). However, the mechanism by which such an immunization regimen results in a local antibody response remains obscure. Intraperitoneal administration of antigen with adjuvant is a successful method for initiating local IgA responses in the intestine of the sheep and 'priming' the rodent intestine, presumably by stimulating lymphoid cells in Peyer's patches or lamina propria (Pierce and Gowans 1975; Husband *et al.* 1979). However, injection of antigen intraperitoneally, without adjuvant, in pregnant sows failed to stimulate a local antibody response in the mammary gland (Bennell and Watson 1979*b*).

Secretion of Locally Synthesized Antibody

The independent nature of the secretory immune system of the mammary gland is obvious not only from quantitative relationships of the immunoglobulin classes in secretion and their parent plasma cells in mammary tissue, but also in qualitative differences between the IgA molecules in mammary secretion and those found in blood. Secretory IgA is an 11 S dimeric molecule with molecular weight of approximately 400 000. The two IgA monomers are held together by J chain, a property which dimeric IgA shares with pentameric IgM (Halpern and Koshland 1970). Although it was formerly believed that dimeric IgA was secreted from the plasma cell as a monomer and then dimerized extracellularly on a random basis (Costea *et al.* 1968), there is now compelling evidence that mammary gland plasma cells secrete the molecule in the dimeric form with J chain as an integral component (Lawton and Mage 1969; Lawton *et al.* 1970).

Secretory IgA contains an additional glycoprotein moiety named 'secretory component'. Secretory component is manufactured in secretory epithelial cells (Martinez-Tello *et al.* 1968; O'Daly and Cebra 1968; Tourville *et al.* 1970) and is bound to dimeric IgA by covalent and disulfide bonds during passage of the immunoglobulin across the epithelial cell (Heremans and Vaerman 1971). There have been numerous suggestions that secretory component serves a receptor and transport function in collecting IgA and ferrying it from the basal membrane of the epithelial cell to the lumen. Evidence for and against these ideas has been reviewed in detail in a recent publication (Husband and Watson 1978) and will not be repeated here. However, data obtained on local production of IgA and IgM in the mammary gland of the ewe indicated that transport of these immunoglobulins into milk was directly related to the activity of the local immune system (Watson and Lascelles 1973). It was suggested that local production of IgA and IgM, by plasma cells located in close association with the glandular epithelium, created a concentration gradient with the highest concentration immediately adjacent to the basal membrane of the epithelial cell. In this situation, preferential transfer of locally produced IgA and IgM across the glandular epithelium would occur without the necessity for a specific transport mechanism involving secretory component or any other molecule.

Protective Role of Milk IgA

Irrespective of the putative transport role of secretory component (described above), there is no doubt that secretory component confers protection from proteolytic

degradation to the secretory IgA molecule (Cederblad *et al.* 1966; Tomasi and Czerwinski 1968; Shim *et al.* 1969; Brown *et al.* 1970; Tax and Korngold 1971). Thus, secretory IgA in milk is better equipped than other immunoglobulins to withstand enzymatic attack in the stomach and intestine and to carry out a protective role in the alimentary tract of the suckling infant. The precise nature of this protective role in the lumen of the intestine is not clearly understood. It is generally accepted that IgA does not fix complement (Heddle *et al.* 1975), although there are at least two reports of IgA possessing complement-dependent bactericidal properties against *E. coli* in the presence of lysozyme (Adinolfi *et al.* 1966; Hill and Porter 1974). There is evidence from studies in the pig that the frequency of suckling and quantities of IgA in milk are both sufficiently high to maintain detectable levels of milk IgA throughout the length of the small intestine of the piglet (Porter *et al.* 1970), and there is little doubt that ingested milk IgA antibody can confer to the piglet considerable resistance against *E. coli* enteritis (Wilson and Svendsen 1971). It has been established that the initial step in the pathogenesis of several important bacterial (Jones and Rutter 1972) and viral (Holland 1964) diseases of the intestine involves adhesion of the pathogen to the luminal membrane of the intestinal epithelial cell. Therefore, if there were sufficient milk IgA with appropriate antibody specificity in the mucous blanket lining the intestine, the initiation of the disease process might be blocked. Evidence in favour of such a mechanism has been obtained recently (Rutter *et al.* 1976). Alternatively, milk IgA in the intestine may neutralize enterotoxins which are the effector molecules of several enteritis syndromes of bacterial aetiology. Finally, there is evidence that neutrophils emigrate into the intestinal lumen (Bellamy and Nielsen 1974; Bellamy and Hamilton 1976) and other data suggest that secretory IgA has a powerful opsonizing capacity (Wernet *et al.* 1971). It is possible, therefore, that phagocytosis of bacteria could occur in the mucous blanket of the intestine of the suckling neonate, and that such phagocytosis could be potentiated by IgA antibody in ingested milk. It should be mentioned, however, that workers in other laboratories believe the data on opsonizing activity of IgA (Wernet *et al.* 1971) to be unsound (Porter 1977; Soothill 1977).

With regard to the low levels of secretory IgA in milk of ruminants compared with other species, Porter (1971) has maintained that this was a physiological adaptation of immunological processes to allow for normal rumen development and function in the suckling calf, lamb or kid.

It must be recognized, of course, that although the nursing mammal acquires considerable protection from intestinal pathogens from ingested milk, not all of the protection is attributable to secretory IgA or other components of specific immunity (Gyorgy *et al.* 1962; Mata and Wyatt 1971; Goldman 1973). Many other non-specific factors in milk such as lysozyme, lactoferrin and mucins play important roles in protection from disease, but these have been described in considerable detail elsewhere (Bullen *et al.* 1972; Goudswaard *et al.* 1978; Reiter 1978; Carroll 1979).

Immunological Protection of the Mammary Gland Itself

Most of the protective factors in colostrum and milk which have been mentioned already in relation to welfare of the suckling infant may also play a role in protection of the mammary gland itself from infection. In this connection non-specific factors such as lysozyme, lactoferrin and the lactoperoxidase–thiocyanate–hydrogen peroxide

system may be important but they have been reviewed recently (Reiter 1978) and will not be dealt with again here. It should be pointed out, however, that considerable differences may occur between species for these factors in the same way as for specific immune mechanisms. An example of this is the great disparity in concentration of lysozyme between bovine (0·01 μg/ml) and human milk (400 μg/ml) (Vakil *et al.* 1969).

In ungulates, immunoglobulin derived from blood could play a role in protection of the mammary gland, but because overall levels are relatively low during peak lactation the greatest potential benefit would be during colostrum formation or the early stages of mammary involution. The mammary gland epithelium is exquisitely sensitive to injury (Jain 1976) and if inflammation of the gland occurs the result is an increase in the concentration of serum proteins in secretion but an inhibition of selective transfer of IgG_1 from blood to secretion (Mackenzie and Lascelles 1968). In other words an antigenic insult results in impairment of the selective transport mechanism, breaching of the epithelial barrier (which would otherwise discriminate in the transfer of protein into secretion) and allows leakage of interstitial fluid into the mammary secretion. It has been observed that following antigenic insult, when signs of acute inflammation have disappeared, but when milk production is still depressed, there appears to be an increase in the magnitude of the selective transfer of IgG_1 into milk (Lascelles 1969; Harmon *et al.* 1976). This appears to be another example of the inverse relationship between selective transport of IgG_1 and *de novo* synthesis of milk constituents in the gland (Watson *et al.* 1972).

Local infusion of killed *Staphylococcus aureus* vaccines into the preparturient gland is known to induce considerable protection from challenge with virulent staphylococci in the subsequent lactation (Outteridge and Lascelles 1967; Derbyshire and Smith 1969; McDowell and Lascelles 1971; McDowell and Watson 1974). The precise nature of the protection conferred by local immunization of the gland is not well understood, but since this procedure results in significant levels of locally synthesized IgA in milk at least two mechanisms might be involved. The first of these involves the inhibition of adhesion of the invading organism to glandular epithelial cells. There is evidence both for (Frost 1975; Frost *et al.* 1977) and against (Anderson 1978) epithelial adhesion by bacterial pathogens of the mammary gland as a critical first step in pathogenesis of mastitis. If adhesion is important then locally synthesized IgA could play a role in protection by interacting with the bacterium and obstructing this process. Alternatively, at least two studies have shown that mammary secretion from locally immunized glands has enhanced opsonizing capabilities (McDowell and Lascelles 1971; Guidry *et al.* 1977). Locally synthesized IgA may be involved in such a mechanism although, as already mentioned, its activity as opsonizing antibody is open to question. Finally, locally produced immunoglobulin could assist in protection of the mammary gland from infection by neutralization of toxins—it is recognized that bacterial toxins play an important part in diseases of the gland, particularly in staphylococcal mastitis (Anderson 1976).

The role of the neutrophil in protection of the mammary gland is well established (Jain 1976). Neutrophils arrive in mammary secretion in very large numbers in response to an inflammatory insult and are generally considered to be mediators of non-specific immunity. Recent work has shown, however, that ovine neutrophils carry cytophilic (IgG_2) antibody on their cell membrane (Watson 1975). Furthermore, appropriate methods of immunization with staphylococcal vaccines result in the

production of cytophilic IgG_2 antibody which confers upon the neutrophil an enhanced capacity to phagocytose and kill *S. aureus* organisms (Watson 1976). Thus, the synergy between cytophilic antibody and the neutrophil results in the latter participating as an effector cell in an arm of specific (rather than non-specific) immunity. It is considered that this mechanism could be exploited for practical purposes in formulating suitable vaccines and vaccination procedures for protection of the mammary gland from infection.

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References

Adinolfi, M., Glynn, A. A., Lindsay, M., and Milne, C. M. (1966). Serological properties of γA antibodies to *Escherichia coli* present in human colostrum. *Immunology* **10**, 517–26.

Ahlstedt, S., Carlsson, B., Hanson, L. A., and Goldblum, R. M. (1975). Antibody production by human colostral cells. I. Immunoglobulin class, specificity and quantity. *Scand. J. Immunol.* **4**, 535–9.

Anderson, J. C. (1976). Mechanisms of staphylococcal virulence in relation to bovine mastitis. *Brit. Vet. J.* **132**, 229–45.

Anderson, J. C. (1978). Absence of bacterial adherence in the establishment of experimental mastitis in mice. *Vet. Pathol.* **15**, 770–5.

Auerbach, R., and Clark, S. (1975). Immunological tolerance: transmission from mother to offspring. *Science* **189**, 811–13.

Balfour, W. E., and Comline, R. S. (1962). Acceleration of the absorption of unchanged globulin in the newborn calf by factors in colostrum. *J. Physiol. (Lond.)* **160**, 234–57.

Beer, A. E., Billingham, R. E., and Head, J. (1974). The immunologic significance of the mammary gland. *J. Invest. Dermatol.* **63**, 65–74.

Beh, K. J. (1977). The origin of IgA-containing cells in intestinal lymph of sheep. *Aust. J. Exp. Biol. Med. Sci.* **55**, 263–74.

Bellamy, J. E. C., and Hamilton, D. L. (1976). Effects of immune-mediated enteroluminal neutrophil emigration on intestinal function in pigs. *Can. J. Comp. Med.* **41**, 36–40.

Bellamy, J. E. C., and Nielsen, N. O. (1974). Immune-mediated emigration of neutrophils into the lumen of the small intestine. *Infect. Immun.* **9**, 615–19.

Bennell, M. A., and Watson, D. L. (1979*a*). The local immune response in the mammary gland of the sow following infusion of a protein antigen. *Microbiol. Immunol.* **23**, 1225–31.

Bennell, M. A., and Watson, D. L. (1979*b*). Failure to stimulate a local immune response in the mammary gland of the sow using intra-peritoneal "priming". *Vet. Immunol. Immunopathol.* (In press.)

Bernier, G. M., Ballieux, R. E., Tominaga, K. T., and Putnam, F. W. (1967). Heavy chain subclasses of human γG globulin-serum distribution and cellular localization. *J. Exp. Med.* **125**, 303–18.

Bohl, E. H., and Saif, L. J. (1975). Passive immunity in transmissible gastroenteritis of swine: immunoglobulin characteristics of antibodies in milk after inoculating by different routes. *Infect. Immun.* **11**, 23–32.

Bourne, F. J., Newby, T. J., and Chidlow, J. W. (1975). The influence of route of vaccination on the systemic and local immune response in the pig. *Res. Vet. Sci.* **18**, 244–8.

Brambell, F. W. R. (1966). The transfer of immunity from mother to young and the catabolism of immunoglobulins. *Lancet* **ii**, 1087–93.

Brambell, F. W. R. (1970). The transfer of passive immunity from mother to young. In 'Frontiers of Biology'. Vol. 18. (Eds A. Neuberger and E. L. Tatum.) (North Holland: Amsterdam.)

Brandenburg, A. C., and Wilson, M. R. (1973). Immunity to *Escherichia coli* in pigs: IgG immunoglobulin in passive immunity to *E. coli* enteritis. *Immunology* **24**, 119–27.

Brandon, M. R., and Lascelles, A. K. (1971). Relative efficiency of absorption of IgG_1, IgG_2, IgA and IgM in the newborn calf. *Aust. J. Exp. Biol. Med. Sci.* **49**, 629–33.

Brandon, M. R., Watson, D. L., and Lascelles, A. K. (1971). The mechanism of transfer of immunoglobulin into mammary secretion of cows. *Aust. J. Exp. Biol. Med. Sci.* **49**, 613–23.

Brock, J. H., Arzabe, F. R., Ortega, F., and Pineiro, A. (1977*a*). The effect of limited proteolysis by trypsin and chymotrypsin on bovine colostral IgG_1. *Immunology* **32**, 215–19.

Brock, J. H., Arzabe, F. R., Pineiro, G., and Olivito, A. M. (1977*b*). The effect of trypsin and chymotrypsin on the bactericidal activity and specific antibody activity of bovine colostrum. *Immunology* **32**, 207–13.

Brown, W. R., Newcomb, R. W., and Ishizaka, K. (1970). Proteolytic degradation of exocrine and serum immunoglobulins. *J. Clin. Invest.* **49**, 1374–80.

Bullen, J. J., Rogers, H. J., and Leigh, L. (1972). Iron-binding proteins in milk and resistance to *Escherichia coli* infection in infants. *Brit. Med. J.* **1**, 69–75.

Buxton, J. C., and Brooksbank, N. H. (1953). Haemolytic disease of newborn pigs caused by iso-immunization of pregnancy. *Nature* (*London*) **172**, 355.

Cameron, C. M., and Fuls, W. J. P. (1970). Immune response to dead and live *Escherichia coli* vaccines and colostral transfer of immunity to calves and lambs. *Onderstepoort J. Vet. Res.* **37**, 157–64.

Campbell, B., Porter, R. M., and Petersen, W. E. (1950). Plasmacytosis of the bovine udder during colostrum secretion and experimental cessation of milking. *Nature* (*London*) **166**, 913.

Campbell, S. G., Siegel, M. J., and Knowlton, B. J. (1977). Sheep immunoglobulins and their transmission to the neonatal lamb. *N.Z. Vet. J.* **25**, 361–5.

Carroll, E. J. (1979). The role of lysozyme in killing and lysis of coliform bacteria in the bovine animal. 1. Serum and milk concentrations of lysozyme and susceptibility of coliform strains to its action. *Vet. Microbiol.* **4**, 61–72.

Cederblad, G., Johannson, B. G., and Rymo, L. (1966). Reduction and proteolytic degradation of immunoglobulin A from human colostrum. *Acta Chem. Scand.* **20**, 2349–57.

Chidlow, J. W., and Porter, P. (1977). Uptake of maternal antibody by the neonatal pig following intramuscular and intramammary vaccination of the preparturient sow. *Res. Vet. Sci.* **23**, 185–90.

Clarke, R. M., and Hardy, R. N. (1969). An analysis of the mechanism of cessation of uptake of macromolecular substances by the intestine of the young rat ("closure"). *J. Physiol.* (*Lond.*) **204**, 127–34.

Clough, J. D., Mims, L. H., and Strober, W. (1971). Deficient IgA antibody responses to arsanalic acid bovine serum albumin (BSA) in neonatally thymectomized rabbits. *J. Immunol.* **106**, 1624–9.

Costea, N., Yakulis, V., Schmale, J., and Heller, P. (1968). Light chain determinants of exocrine isoagglutinins. *J. Immunol.* **101**, 1248–52.

Craig, S. W., and Cebra, J. J. (1971). Peyer's patches: an enriched source of precursors for IgA-producing immunocytes in the rabbit. *J. Exp. Med.* **134**, 188–200.

Cripps, A. W., Fulkerson, W. J., Griffiths, D. A., McDowell, G. H., and Lascelles, A. K. (1976). The relationship between the transfer of immunoglobulins, sodium and potassium into mammary secretion of the parturient ewe. *Aust. J. Exp. Biol. Med. Sci.* **54**, 337–48.

Curtis, J., and Bourne, F. J. (1971). Immunoglobulin quantitation in sow serum, colostrum and milk and the serum of young pigs. *Biochim. Biophys. Acta* **236**, 319–32.

Derbyshire, J. B., and Smith, G. S. (1969). Immunization against staphylococcal mastitis in the goat by intramammary infusion of cell toxoid vaccine. *Res. Vet. Sci.* **10**, 559–64.

Diaz-Jouanen, E. P., and Williams, R. C. (1974). T and B lymphocytes in human colostrum. *Clin. Immunol. Immunopathol.* **3**, 248–55.

Dixon, F. J., Weigle, W. O., and Vasquez, J. J. (1961). Metabolism and mammary secretion of serum proteins in the cow. *Lab. Invest.* **10**, 216–37.

Elson, C. O., Heck, J. A., and Strober, W. (1979). T-cell regulation of murine IgA synthesis. *J. Exp. Med.* **149**, 632–43.

Frost, A. J. (1975). Selective adhesion of microorganisms to the ductular epithelium of the bovine mammary gland. *Infect. Immun.* **12**, 1154–6.

Frost, A. J., Wanasinghe, D. D., and Woolcock, J. B. (1977). Some factors affecting selective adherence of microorganisms in the bovine mammary gland. *Infect. Immun.* **15**, 245–53.

Goldblum, R. M., Ahlstedt, S., Carlsson, B., Hanson, L. A., Jodal, U., Lidin-Janson, G., and Sohl-Akerlund, R. (1975). Antibody forming cells in human colostrum after oral immunization. *Nature (London)* **257**, 797–9.

Goldman, A. S. (1973). Host resistance factors in human milk. *J. Pediat.* **82**, 1082–90.

Goudswaard, J., Bakker-De Koff, E. C., and Van Ravenswaaijkraan, H. P. M. (1978). Lysozyme and its presence in bovine milk and serum. *Tijdschr. Diegeneesk.* **103**, 445–50.

Guidry, A. J., Paape, M. J., and Pearson, R. E. (1977). The effect of local immunization of the mammary gland on phagocytosis and intracellular kill of *Staphylococcus aureus*. *J. Dairy Sci.* (Suppl. 1), 135.

Gyorgy, P., Dhanamitta, S., and Steers, E. (1962). Protective effects of human milk in experimental *Staphylococcus* infection. *Science* **137**, 338–40.

Halpern, M. S., and Kosland, M. E. (1970). Novel subunit in secretory IgA. *Nature (London)* **228**, 1276–8.

Halsey, J. F., and Benjamin, D. C. (1976). Induction of immunologic tolerance in nursing neonates by absorption of tolerogen from colostrum. *J. Immunol.* **116**, 1204–7.

Hardy, R. N. (1964). Intestinal absorption of macromolecules in the newborn pig. *J. Physiol. (Lond.)* **176**, 19p–20p.

Harmon, R. J., Schanbacher, F. L., and Smith, K. L. (1976). Changes in lactoferrin, immunoglobulin G, bovine serum albumin and α-lactalbumin during acute experimental and natural coliform mastitis in cows. *Infect. Immun.* **13**, 533–42.

Heddle, R. J., Knop, J., Steele, E. J., and Rowley, D. (1975). The effect of lysozyme on the complement-dependent bactericidal action of different antibody classes. *Immunology* **28**, 1061–6.

Heremans, J. F., and Vaerman, J. P. (1971). Biological significance of IgA antibodies in serum and secretions. In 'Progress in Immunology'. (Ed. B. Amos.) pp. 875–90. (Academic Press: New York.)

Hill, I. R., and Porter, P. (1974). Studies of bacterial activity to *Escherichia coli* of porcine serum and colostral immunoglobulins and the role of lysozyme with secretory IgA. *Immunology* **26**, 1239–50.

Hoerlein, A. (1957). The influence of colostrum on antibody response in baby pigs. *J. Immunol.* **78**, 112–17.

Holland, J. J. (1964). Enterovirus entrance into specific host cells, and subsequent alterations of cell protein and nucleic acid synthesis. *Bact. Rev.* **28**, 3–13.

Holmgren, J., Hanson, L. A., Carlsson, B., Lindblad, B. S., and Rahimtoola, J. (1976). Neutralizing antibodies against *Escherichia coli* and *Vibrio cholerae* enterotoxins in human milk from a developing country. *Scand. J. Immunol.* **5**, 867–71.

Horsfall, D. J., Brown, M. A., and Rowley, D. (1979). The suppressive effect of circulating specific antibody on the response to oral immunisation with *Vibrio cholerae*. *Aust. J. Exp. Biol. Med. Sci.* **57**, 271–8.

Husband, A. J., Beh, K. J., and Lascelles, A. K. (1979). IgA-containing cells in the ruminant intestine following interperitoneal and local immunization. *Immunology* **37**, 597–601.

Husband, A. J., Brandon, M. R., and Lascelles, A. K. (1972). Absorption and endogenous production of immunoglobulins in calves. *Aust. J. Exp. Biol. Med. Sci.* **50**, 491–8.

Husband, A. J., and Lascelles, A. K. (1975). Antibody responses to neonatal immunisation in calves. *Res. Vet. Sci.* **18**, 201–7.

Husband, A. J., and Watson, D. L. (1978). Immunity in the intestine. *Vet. Bull.* **48**, 911–24.

Jain, N. C. (1976). Neutrophil leukocytes and inflammation of the bovine mammary gland. *Theriogenology* **6**, 153–73.

Jeffcott, L. B. (1972). Passive immunity and its transfer with special reference to the horse. *Biol. Rev.* **47**, 439–64.

Jones, E. A., and Waldmann, T. A. (1972). The mechanism of intestinal uptake and transcellular transport of IgG in the neonatal rat. *J. Clin. Invest.* **51**, 2916–27.

Jones, G. W., and Rutter, J. M. (1972). Role of the K88 antigen in the pathogenesis of neonatal diarrhoea caused by *Escherichia coli* in piglets. *Infect. Immun.* **6**, 918–27.

Jones, R. E. (1978). Degradation of radio-actively labelled protein in the small intestine of the suckling rat. *Biol. Neonate* **34**, 286–94.

Klesius, P. H., and Fudenberg, H. H. (1977). Bovine transfer factor: *in vivo* transfer of cell-mediated immunity to cattle with alcohol precipitates. *Clin. Immunol. Immunopathol.* **8**, 238–46.

Kohler, E. M. (1976). Oral vaccine helps prevent *E. coli* scours in baby pigs. *Ohio Rep. Res. Dev. Agric.* **61**, 44–6.

Kohler, E. M., Cross, R. F., and Bohl, E. H. (1975). Protection against neonatal enteric colibacillosis in pigs suckling orally vaccinated sows. *Am. J. Vet. Res.* **36**, 757–64.

Lascelles, A. K. (1963). A review of the literature on some aspects of immune milk. *Dairy Sci. Abstr.* **25**, 359–64.

Lascelles, A. K. (1969). Immunoglobulin secretion into ruminant colostrum. In 'Lactogenesis: The Initiation of Milk Secretion at Parturition'. (Eds M. Reynolds, and S. J. Folley.) p. 131. (University of Pennsylvania Press: Philadelphia.)

Lascelles, A. K. (1979). The immune system of the ruminant mammary gland and its role in the control of mastitis. *J. Dairy Sci.* **62**, 154–60.

Lascelles, A. K., and McDowell, G. H. (1974). Localized humoral immunity with particular reference to ruminants. *Transplant Rev.* **19**, 170–208.

Lascelles, A. K., Outteridge, P. M., and Mackenzie, D. D. S. (1966). Local production of antibody by the lactating mammary gland following antigenic stimulation. *Aust. J. Exp. Biol. Med. Sci.* **44**, 169–80.

Laskowski, M., and Laskowski, M. (1951). Crystalline trypsin inhibitor from colostrum. *J. Biol. Chem.* **190**, 563–73.

Lawrence, H. S. (1969). Transfer factor. *Adv. Immun.* **11**, 195–266.

Lawton, A. R., Asofsky, R., and Mage, R. G. (1970). Synthesis of secretory IgA in the rabbit. II. Production of alpha, light and T chains by *in vitro* cultures of mammary tissue. *J. Immunol.* **104**, 388–96.

Lawton, A. R., and Mage, R. G. (1969). The synthesis of secretory IgA in the rabbit. I. Evidence for synthesis as an 11S dimer. *J. Immunol.* **102**, 693–7.

Lee, C. G., Ladds, P. W., and Watson, D. L. (1978). Immunocyte populations in the mammary gland of the rat at different stages of pregnancy and lactation. *Res. Vet. Sci.* **24**, 322–7.

Lee, C. S., and Lascelles, A. K. (1970). Antibody-producing cells in antigenically stimulated mammary glands and in the gastrointestinal tract of sheep. *Aust. J. Exp. Biol. Med. Sci.* **48**, 525–35.

Logan, E. F., and Penhale, W. J. (1971). Studies on immunity of the calf to colibacillosis. I. The influence of colostral whey and immunoglobulin fractions on experimental colisepticaemia. *Vet. Rec.* **88**, 222–8.

Mackenzie, D. D. S., and Lascelles, A. K. (1968). The transfer of [^{131}I]-labelled immunoglobulins and serum albumin from blood into milk of lactating ewes. *Aust. J. Exp. Biol. Med. Sci.* **46**, 285–94.

Martinez-Tello, F. J., Braun, D. G., and Blanc, W. A. (1968). Immunoglobulin production in bronchial mucosa and bronchial lymph nodes particularly in cystic fibrosis of the pancreas. *J. Immunol.* **101**, 989–1003.

Mason, S. (1962). Gastric function in the newborn. *Arch. Dis. Childh.* **37**, 387–91.

Mata, L. J., and Wyatt, R. G. (1971). The uniqueness of human milk: host resistance to infection. *Am. J. Clin. Nutr.* **24**, 976–86.

McDowell, G. H., and Lascelles, A. K. (1969). Local production of antibody by ovine mammary glands infused with *Salmonella* flagellar antigens. *Aust. J. Exp. Biol. Med. Sci.* **47**, 669–78.

McDowell, G. H., and Lascelles, A. K. (1971). Local immunization of ewes with staphylococcal cell and cell-toxoid vaccines. *Res. Vet. Sci.* **12**, 258–64.

McDowell, G. H., and Watson, D. L. (1974). Immunity to experimental staphylococcal mastitis: comparison of local and systemic immunisation. *Aust. Vet. J.* **50**, 533–6.

Mitchell, C. A., Walker, R. V. L., and Bannister, G. L. (1954). Persistence of neutralizing antibody in milk and blood of cows and goats following the instillation of virus into the mammary gland. *Can. J. Comp. Med.* **18**, 426–30.

Mohr, J. A. (1973). The possible induction and/or acquisition of cellular hypersensitivity associated with ingestion of colostrum. *J. Pediatrics* **82**, 1062–4.

Mohr, J. A., Leu, R., and Mabry, W. (1970). Colostral leukocytes. *J. Surg. Oncol.* **2**, 163–7.

Moon, H. W. (1972). Vacuolated villous epithelium of the small intestine of young pigs. *Vet. Path.* **9**, 3–21.

Morphis, L. G., and Gitlin, D. (1970). Maturation of the materno-foetal transport system for human γ-globulin in the mouse. *Nature (London)* **228**, 573.

Murphy, F. A., Aalund, O., Osebold, J. W., and Carroll, E. J. (1964). Gamma globulins of bovine lacteal secretions. *Arch. Biochim. Biophys.* **108**, 230–9.

Muscoplat, C. C., Setcavage, T. M., and Kim, Y. B. (1977). Regulation of the immune response in neonatal piglets by maternal antibody. *Int. Arch. Allergy Appl. Immunol.* **54**, 165–70.

Muiswinkel, W. B. van, and Soest, P. L. van (1975). Thymus dependence of the IgA response to sheep erythrocytes. *Immunology* **28**, 287–91.

Mylrea, P. J. (1966). Digestion of milk in young calves. I. Flow and acidity of the contents of the small intestine. *Res. Vet. Sci.* **7**, 333–41.

O'Daly, J. A., and Cebra, J. J. (1968). Structure and cellular localization of secretory IgA. In 'Protides of the Biological Fluids'. 16th Colloquium, Bruges 1968. (Ed. H. Peeters.) pp. 205–19. (Pergamon: Oxford.)

Outteridge, P. M., and Lascelles, A. K. (1967). Local immunity in the lactating mammary gland following the infusion of staphylococcal toxoids. *Res. Vet. Sci.* **8**, 313–20.

Outteridge, P. M., Mackenzie, D. D. S., and Lascelles, A. K. (1968). The distribution of specific antibody among the immunoglobulins in whey from the locally immunized gland. *Arch. Biochem. Biophys.* **126**, 105–10.

Outteridge, P. M., Rock, J. D., and Lascelles, A. K. (1965). The immune response of the mammary gland and regional lymph node following antigenic stimulation. *Aust. J. Exp. Biol. Med. Sci.* **43**, 265–74.

Parmely, M. J., Beer, A. E., and Billingham, R. E. (1976). *In vitro* studies on the T lymphocyte population of human milk. *J. Exp. Med.* **144**, 358–70.

Petersen, W. E., and Campbell, B. (1955). Use of protective principles in milk and colostrum in prevention of disease in man and animals. *Lancet (Minneapolis)* **75**, 494–6.

Pierce, A. E., and Feinstein, A. (1965). Biophysical and immunological studies on bovine immune globulins with evidence for selective transport within the mammary gland from maternal plasma to colostrum. *Immunology* **8**, 106–23.

Pierce, N. F., and Gowans, J. L. (1975). Cellular kinetics of the intestinal immune response to cholera toxoid in rats. *J. Exp. Med.* **142**, 1550–63.

Piercy, D. W. (1974). Natural resistance to infection in the neonatal sheep: comparison of the ability of colostrum-deprived, normally suckled and passively-immunized lambs to localize *Erysipelothrix rhusiopathiae*. *Res. Vet. Sci.* **17**, 210–14.

Pittard, W. B., and Bill, K. (1979). Immunoregulation by breast milk cells. *Cell. Immunol.* **42**, 437–41.

Porter, P. (1971). Immunoglobulin IgA in bovine mammary secretions and serum of the neonatal calf. *Biochim. Biophys. Acta* **236**, 664–74.

Porter, P. (1977). In 'Immunology of the Gut'. Ciba Foundation Symposium 46 (New Ser.) p. 72. (Elsevier: London.)

Porter, P., and Noakes, D. E. (1969). Immunoglobulins in sow mammary secretions throughout lactation and their significance as anti-(*Escherichia coli*) antibodies to the young pig. *Biochem. J.* **113**, 6p–7p.

Porter, P., Noakes, D. W., and Allen, W. D. (1970). Secretory IgA and antibodies to *Escherichia coli* in porcine colostrum and milk and their significance in the alimentary tract of the young pig. *Immunology* **18**, 245–57.

Reiter, B. (1978). Review of the progress of dairy science: antimicrobial systems in milk. *J. Dairy Res.* **45**, 131–47.

Roberts, E. J., and Archer, R. K. (1966). Current methods for the diagnosis and treatment of haemolytic disease in the foal. *Vet. Rec.* **79**, 61–7.

Rodewald, R. (1970). Selective antibody transport in the proximal small intestine of the neonatal rat. *J. Cell. Biol.* **45**, 635–40.

Roux, M. E., McWilliams, M., Phillips-Quagliata, J. M., Weisz-Carrington, P., and Lamm, M. E. (1977). Origin of IgA-secreting plasma cells in the mammary gland. *J. Exp. Med.* **146**, 1311–22.

Rutter, J. M., Jones, G. W., Brown, G. T. H., Burrows, M. R., and Luther, P. D. (1976). Antibacterial activity in colostrum and milk associated with protection of piglets against enteric disease caused by K88-positive *Escherichia coli*. *Infect. Immun.* **13**, 667–76.

Sasaki, M., Davis, C. L., and Larson, B. L. (1976). Production and turnover of IgG_1 and IgG_2 immunoglobulins in the bovine around parturition. *J. Dairy Sci.* **59**, 2046–55.

Sharpe, H. B. A. (1966). The effect of partial deprivation of colostrum, or weaning at two weeks of age, on serum antibody levels to *Escherichia coli* in the young pig. *Res. Vet. Sci.* **7**, 74–80.

Shim, B. S., Kang, Y. S., Kim, W. J., Cho, S. H., and Lee, D. B. (1969). Self-protective activity of colostral IgA against tryptic digestion. *Nature (London)* **222**, 787–8.

Sibalin, M., and Bjorkman, N. (1966). On the fine structure and absorptive function of the porcine jejunal villi during the early suckling period. *Exp. Cell. Res.* **44**, 165–74.

Simpson-Morgan, M. W., and Smeaton, T. C. (1972). The transfer of antibodies by neonates and adults. *Adv. Vet. Sci. Comp. Med.* **16**, 355–86.

Smeaton, T. C. (1969). Studies of gamma-globulin metabolism in the foetal and neonatal lamb. Ph.D. Thesis, Australian National University, Canberra.

Smith, C. W., and Goldman, A. S. (1968). The cells of human colostrum. I. *In vitro* studies of morphology and function. *Pediatr. Res.* **2**, 103–9.

Smith, W. D., Wells, P. W., Burrells, C., and Dawson, A. McL. (1976). Maternal immunoglobulins and parainfluenza 3 virus inhibitors in the nasal and lachrymal secretion and serum of new born lambs. *Clin. Exp. Immun.* **23**, 544–53.

Soothill, J. F. (1977). In 'Immunology of the Gut'. Ciba Foundation Symposium 46 (New Ser.). p. 72. (Elsevier: London.)

Stoliar, O. A., Kaniecki-Green, E., Pelley, R. P., Klaus, M. H., and Carpenter, C. C. J. (1976). Secretory IgA against enterotoxins in breast milk. *Lancet* **i**, 1258–61.

Tax, A., and Korngold, L. (1971). Comparison of the effect of elastase on human secretory IgA and serum IgA. *J. Immunol.* **107**, 1189–91.

Tomasi, T. B., and Bienenstock, J. (1968). Secretory immunoglobulins. *Adv. Immun.* **9**, 1–96.

Tomasi, T. B., and Czerwinski, D. S. (1968). The secretory IgA system. In 'Birth Defects'. Vol. 4. The immunologic deficiency diseases in man. (Ed. D. Bergsma.) pp. 270–5. (The National Foundation—March of Dimes: New York.) [*Orig. Art. Ser.* **4**,]

Tourville, D. R., Ogra, S. S., Lippes, J., and Tomasi, T. B. (1970). The human female reproductive trace: immunohistological localization of γA, γG, γM, secretory "piece" and lactoferrin. *Am. J. Obstet. Gynec.* **108**, 1102–8.

Vaerman, J. P. (1970). Studies on IgA immunoglobulins in man and animals. Thesis, Université Catholique. (Sintal-Louvain: Belgium.)

Vakil, J. R., Chandan, R. C., Parry, R. M., and Shahani, K. M. (1969). Susceptibility of several microorganisms to milk lysozymes. *J. Dairy Sci.* **52**, 1192–7.

Virella, G., Silveira-Nunes, M. A., and Tomagnini, G. (1972). Placental transfer of human IgG subclasses. *Clin. Exp. Immun.* **10**, 475–8.

Watson, D. L. (1975). Cytophilic attachment of ovine IgG_2 to autologous polymorphonuclear leucocytes. *Aust. J. Exp. Biol. Med. Sci.* **53**, 527–9.

Watson, D. L. (1976). The effect of cytophilic IgG_2 on phagocytosis by ovine polymorphonuclear leucocytes. *Immunology* **31**, 159–65.

Watson, D. L., Bennell, M. A., and Chaniago, T. D. (1979). Effect of circulating, maternally-derived antibody on the development of a local immune response in the intestine of the neonatal pig. *Am. J. Vet. Res.* **40**, 61–5.

Watson, D. L., Brandon, M. R., and Lascelles, A. K. (1972). Concentrations of immunoglobulin in mammary secretion of ruminants during involution with particular reference to selective transfer of IgG_1. *Aust. J. Exp. Biol. Med. Sci.* **50**, 535–9.

Watson, D. L., and Lascelles, A. K. (1973). Mechanisms of transfer of immunoglobulins into mammary secretion of ewes. *Aust. J. Exp. Biol. Med. Sci.* **51**, 247–54.

Watson, D. L., and Lascelles, A. K. (1975). The influence of systemic immunization during mammary involution on subsequent antibody production in the mammary gland. *Res. Vet. Sci.* **18**, 182–5.

Weisz-Carrington, P., Roux, M. E., and Lamm, M. E. (1977). Plasma cells and epithelial immunoglobulins in the mouse mammary gland during pregnancy and lactation. *J. Immunol.* **119**, 1306–9.

Weisz-Carrington, P., Roux, M. E., McWilliams, M., Phillips-Quagliata, J. M., and Lamm, M. E. (1978). Hormonal induction of the secretory immune system in the mammary gland. *Proc. Natl Acad. Sci., U.S.A.* **75**, 2928–32.

Wernet, P., Breu, H., Knop, J., and Rowley, D. (1971). Antibacterial action of specific IgA and transport of IgM, IgA and IgG from serum into the small intestine. *J. Infect. Dis.* **124**, 223–6.

Williams, M. R., Spooner, R. L., and Thomas, L. H. (1975). Quantitative studies on bovine immunoglobulins. *Vet. Rec.* **96**, 81–4.

Wilson, M. R., and Svendsen, J. (1971). Immunity to *Escherichia coli* in pigs. The role of milk in protective immunity to *E. coli* enteritis. *Can. J. Comp. Med.* **35**, 239–43.
Yoffey, J. M., and Courtice, F. C. (1970). 'Lymphatics, Lymph and the Lymphomyeloid Complex.' (Academic Press: London.)

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