ACTIVE IMMUNIZATION OF THE DAM: PASSIVE PROTECTION OF THE NEWBORN

by

PETER A. BACHMANN, WERNER EICHHORN and R. GÜNTHER HESS

Institute of Medical Microbiology, Infective and Epidemic Medicine, University of Munich

Newborns of all mammal species are dependent on passively acquired protection against infection in order to survive the change from the relatively safe intrauterine life to extrauterine life with its many risks of infection. Most infections occur during the postnatal phase, that is, the first 7–10 days of life (Bachmann 1980). Domestic animals can only acquire protection against infection through the intake of colostrum and milk which contain the necessary antibodies.

In these animals (horses, ruminants and pigs), immunoglobulins are not transported from the dam to the fetus via the placenta.

The fetus is capable of actively producing antibodies, e. g. after intrauterine infection during the third trimester of gestation (Schulz 1973a, b; Wellman and Reblin 1972; Braun et al. 1973, Bachmann et al. 1975). However, the contact with an environment full of microorganisms usually represents the first experience of the newborn's immune system with foreign antigens. It is not until a few days later that the resulting primary response leads to the formation of antibodies in the newborn. These antibodies belong either to the IgM class (low affinity) or to the IgA class (secretory antibodies in local infections). But the formation of active immunity either occurs too late to afford protection against disease or is hindered by the existence of specific antibodies in colostrum and milk. Thus, active immunization is not possible at this age.

In addition, the newborn possesses nonspecific defence mechanisms which are either transferred via maternal milk or evolve gradually in the body itself. These nonspecific antimicrobial factors form part of both the cellular and humoral immune responses. The nature and functions of these defence mechanisms *in vivo* are not yet fully known. During the neonatal phase they may perhaps play a subordinate role (Porter 1979) when compared with the

protective effect of passively acquired antibodies, since both specific and non-specific defence systems of the newborn only begin to function fully between the 8th and 16th weeks of life (Schulz 1973).

The first part of this review describes the origin, composition and physiological role of maternal antibodies. The second part – concentrating mainly on cattle and pigs – lists the possibilities of preventing neonatal infectious diseases by active immunization of pregnant dams aimed at stimulating, enhancing and prolonging the secretion of antibodies in milk.

Immunoglobulins in mammary gland secretion

Maternal antibodies can be transferred to the fetus not only by secretions of the mammary gland but also via the diaplacental route. The route of this transfer depends on the placental structure characteristic of each species. Horses, cattle, pigs and goats have a Placenta epitheliochorialis impermeable to macromolecules, i. e. immunoglobulins. These animal species supply antibodies to their offspring only via the secretions of the mammary gland. In carnivores (Placenta endotheliochorialis) most of the maternal antibodies (90–95 %) are transferred to the offspring through mammary gland secretions; 5–10 % of passive immunity is transferred diaplacentally. Carnivores, therefore, hold an intermediate position. In contrast, humans, monkeys and most rodents (Placenta haemochorialis) have a pronounced diaplacental transfer of immunity. These differences in placentation are also reflected in the composition of immunoglobulins in colostrum and milk (Table 1).

In species without diaplacental transfer of immunoglobulins, high levels of IgG and IgM are found in colostrum whereas the concentration of IgA is low. Newborns of these species absorb the immunoglobulins during the first 12 to 36 hours of life via the intestine, thus acquiring a high blood level of IgG. This provides systemic immunity to the newborn if (1) the mother itself is immune and (2) antibodies are essential for immunity against a pathogen. Colostral IgG originates mostly from serum (Bourne and Curtis 1973; Newby and Bourne 1977). This passage of IgG commences in the precolostral phase and is probably subject to hormonal control. Finally, the concentration of IgG in colostrum is higher than in serum. In cattle, it has even been possible to demonstrate a selective transport mechanism by means of a specific receptor for IgG_1 (Kemler et al. 1975). IgA and IgM derive partly from blood serum and local production in the mammary gland (Newby and Bourne 1977).

The colostrum of domestic animals is a transudate rather than a secretion as far as immunoglobulins are concerned.

The concentration of immunoglobulins in mammary gland secretions decreases drastically after a few days of lactation. The drop in immunoglobulin

concentration is primarily due to the decline of IgG which is present only in small quantities. The concentration of IgA also decreases in absolute terms, but not as much as IgG. In the pig, IgA becomes the dominant immunoglobulin of milk. At this stage, 90 % of IgA and 70 % of IgM are synthesized locally by plasma cells of the mammary gland.

In species with diaplacental transfer of immunoglobulins (primates, rodents) and in cats and dogs secretry IgA, i. e., IgA produced in the mammary gland, is the main immunoglobulin in colostrum and milk. The concentration of IgG is only low. Although the total concentration of immunoglobulins declines considerably during the post-colostral period of lactation, qualitative changes do not occur. Secretory IgA remains the main immunoglobulin (Drife et al. 1976).

Cattle and other ruminants, however, behave differently. In these species, IgA does not play a dominant role either in active or in passive maternal immunity as compared to other species (Bourne 1977). According to Mach and Pahud (1978) and Newby and Bourne (1977), IgG_1 is the predominant immunoglobulin in colostrum and milk. IgG_1 derives entirely from blood serum. Small quantities of IgG_2, IgA and IgM have also been demonstrated in colostrum and milk; a proportion of these immunoglobulins are produced in the mammary gland. Ruminants behave similarly to other species including man in that their milk immunoglobulins rapidly drop a few days post partum (Straub and Matthaeus 1978). Since more than 80 % of the immunoglobulins in colostrum and milk derive from blood serum, the local production of antibodies in the mammary gland appears to be of minor importance (Newby et al. 1982). It is unclear whether the so-called "gut-mammary link" – the migration of antigen-sensitized lymphocytes from Peyer's patches into the mammary gland – exists in ruminants (Chang et al. 1981). However, this mechanism probably also occurs in ruminants although its function is not as pronounced as in other species. This assumption is supported by recent findings that the secretion of antibodies in bovine milk can be stimulated and prolonged by parenteral immunization of cattle which have already been sensitized intestinally (Snodgrass et al. 1980; Eichhorn 1981), whereas there is only a moderate rise of antibody titers in serum. These milk antibodies mainly belong to the IgG_1 class.

In all species of mammals except ruminants, the presence of a sufficient amount of IgA antibodies provides passive, local immunity in the intestinal tract of the neonate. As a rule, IgA is more resistant to proteases of the digestive tract than IgG (Tomasi and Bienenstock 1968). IgA neutralizes viruses (Bohl et al. 1972; Thouless et al. 1977) and plays a role in the bacteriostatic activity of milk (Dolby and Honour 1979). Furthermore, by attaching to intestinal epithelial cells, specific IgA prevents the adhesion of

pathogenic microorganisms to these cells. The intestinal tract is thereby coated with a protective film (Heremans 1974). In cattle this role is taken over by IgG_1; similar to IgA of other species, IgG_1 is also resistant to proteases (Bourne 1977). Following an intestinal infection, pigs (and other species) secrete in milk specific IgA antibodies for at least two weeks (Hess and Bachmann 1981) whereas in cattle, antibodies against rotavirus, for example, can be demonstrated only during a short period of lactation (Woode et al. 1975). In calves, specific colostral IgG and IgM confer protection against *E. coli* infection; IgA provides such protection only to a low extent (Logan et al. 1974).

In the immunologically mature organism IgA is formed locally by plasma cells after antigen contact in the intestine and other mucosal surfaces. During the neonatal phase, IgM-forming plasma cells are found in the Lamina propria (Allen and Porter 1973). Both Ig classes act synergistically in milk (Porter 1979).

Characterizing the antibodies in mammary gland secretions, Adinolfi et al. demonstrated already in 1966 the secretion of antibodies mainly of the IgA class specific for antigens normally present in the intestine. A short time later Bohl et al. (1972) demonstrated that mainly IgG was found in mammary gland secretions after parenteral administration of TGE virus while enteral infection resulted in the increased production of IgA. The authors postulated that the migration of antigen-sensitized lymphocytes from the intestinal wall into the mammary gland was responsible for the enhanced secretion of specific IgA antibodies. This hypothesis was confirmed by further investigations: in the pig (Bohl and Saif 1975; Hess et al. 1978; Evans et al. 1980), in man (Goldblum et al. 1975), and in some rodent species (Michalek et al. 1976; Roux et al. 1977). These results led to the development of a diagram which is generally accepted today, showing the migratory cycle of IgA-producing cells after antigen contact in all mammals except ruminants (Fig. 1).

Precursors of IgA-producing B-lymphocytes are resting in the Peyer's patches of the intestine until they are sensitized by antigens entering the intestine. After antigen contact these cells migrate into the mesenteric lymph nodes, differentiating into blast cells. The blast cells then travel through the lymph system and finally enter the blood stream via the Ductus thoracius. While precursors of IgG and IgM-producing cells mainly settle in the spleen and peripheral lymph nodes (McDermott and Bienenstock 1979), cells committed for IgA synthesis predominantly home to the Lamina propria of the mucosae and basal membranes of exocrine glands. Although this so-called "homing" appears to be independent of the presence of specific antigen in the target organ, it is greatly stimulated by antigen contact (Husband and Watson 1978). At the end of the gestation period a large proportion of blast cells

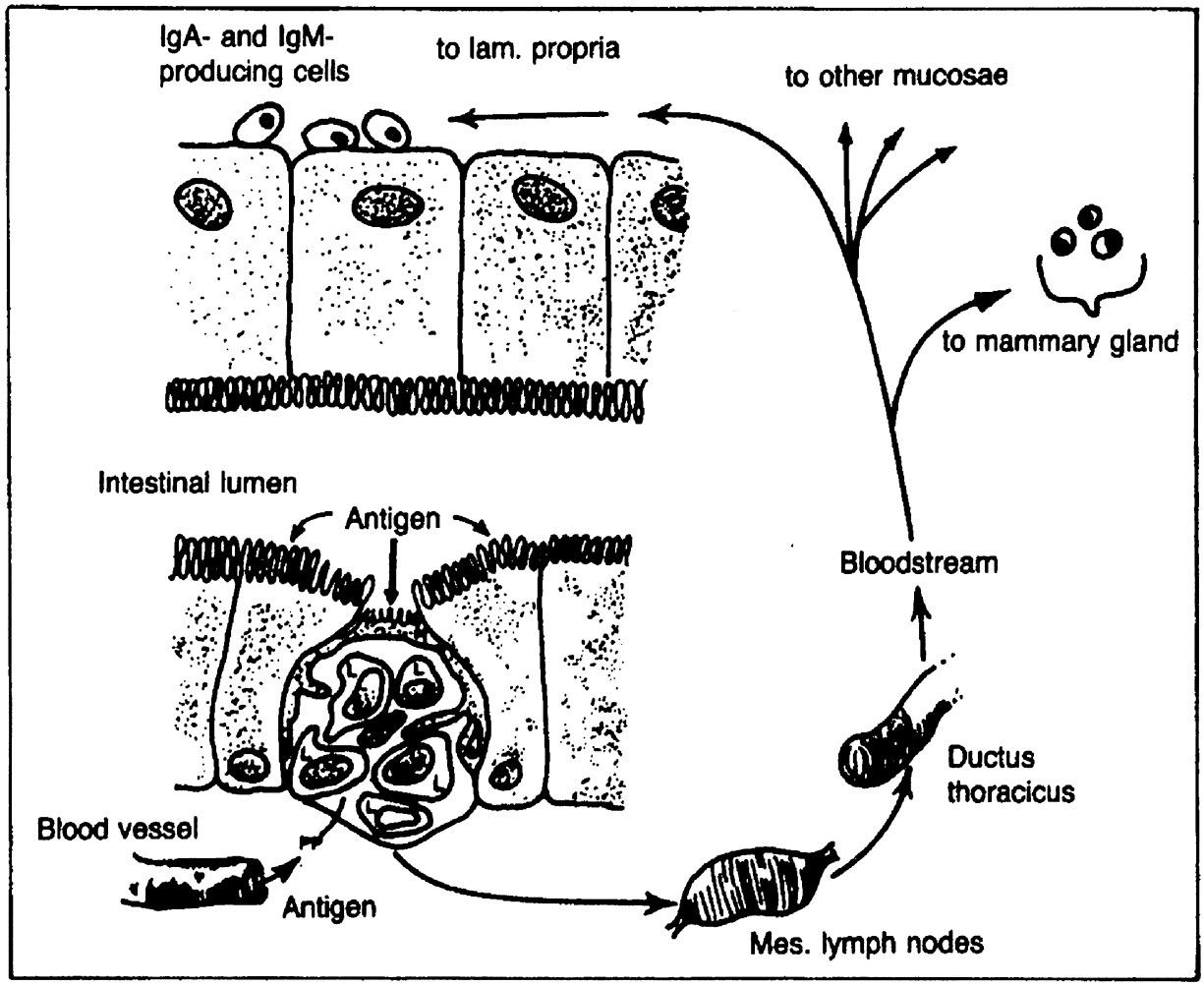

Fig. 1 – *Diagrammatic representation of the migration of IgA-producing lymphocytes from the Peyer's patches of the intestine to the mammary gland and other secretory organs (after Roux et al., 1977).*

Precursors of IgA-producing lymphocytes remain inactive in the Peyer's patches (PP), where they are sensitized by enteral antigens. They then migrate into the mesenteric lymph nodes, where they differentiate into blast cells, eventually entering the peripheral blood through the d. thoracicus. Finally, these cells home on the l. propria of the intestines (LP) and on the basal membranes of exocrine glands. The migration to the mammary gland is probably hormone-controlled.

migrate under hormonal control to the mammary gland (Weisz-Carrington et al. 1978; McDermott et al. 1981). At this stage they acquire full immunological maturity and provide the neonate with passive, immune protection through the secretion of IgA antibodies specific for enteral pathogens.

The mucosal secretory immune system may also be active in other target organs. The so-called "remote site" stimulation includes not only the lymphatic tissue associated with the intestine as well as the mammary gland, but also the bronchus-associated lymphatic tissue and immunocompetent elements in the mucosae of the genital tract, the salivary glands, the respiratory tract and the pharynx (Bienenstock et al. 1979; Ogra et al. 1982). It is assumed that primary antigen contact is followed by local production of secretory anti-

bodies (Montgomery et al. 1978; Rudzik et al. 1975). Moreover, after stimulation of the lymphatic tissue of the intestine and/or respiratory tract precursor cells can migrate to all other mucosae in the body. Thus, for example, oral immunization with a *Streptococcus mutans* vaccine in rats and man leads to the formation of specific IgA antibodies in the intestine and saliva (Arnold et al. 1976; Michalek et al. 1976; Mestecky et al. 1978; Rudzik et al. 1975). These results however, are in contrast to those obtained by Saif and Bohl (1977) after infecting the respiratory tract of gravid sows with pseudorabies virus and the virus of transmissible gastroenteritis. Secretion of specific IgA antibodies in milk could not be demonstrated in these studies. Therefore, at this stage it is not possible to make any conclusive statements concerning the function of the mucosal immune system as a whole.

Cells and nonspecific factors in mammary gland secretions

A great variety of cells are secreted with colostrum and milk. B- and T-lymphocytes, macrophages and neutrophils have so far been identified. However, considerable uncertainty exists as to their function, particularly in domestic animals (Newby et al. 1982; Keller et al. 1981). The activities mediated by the cells in mammary gland secretions include stimulation of phagocytosis, spontaneous cell-mediated cytotoxicity and the formation of interferon (Kent and Newboult, 1969; Lawton and Shortridge 1977). The phagocytic activity of colostral leukocytes, however, is lower than that of blood leukocytes (Pickering et al. 1980). Immunocompetent cells present in mammary gland secretion have specific protective functions. The lymphocytes in milk consist of 50 % T-cells, 30 % B-cells and 20 % "null" cells (Ogra and Ogra 1978). IgG, IgM and IgA have been demonstrated on the surface of B-cells, although hitherto it has only been possible to follow the course of IgA synthesis in vitro (Murello and Goldman 1970, Ahlstedt et al. 1975). In man, there are indications that IgA-producing colostral lymphocytes contribute to passive, local immunity in the digestive tract of the suckling infant (Walker 1975). Other evidence suggests that cellular immune factors are transferred to the suckling animal (Schlesinger and Covelli 1977). The successful in vitro stimulation of lymphocytes from colostrum and milk with specific antigens or mitogens demonstrates that these cells are immunologically active; their lower reactivity compared with peripheral lymphocytes suggests that there may be different types of cell populations (Smith and Schulz 1977, Parmeley et al. 1976).

Although free interferon is not demonstrable in milk, it is possible to stimulate its production in milk lymphocytes (Lawton and Shortridge 1977, Keller et al. 1981). A number of factors, which have been found in milk and

colostrum, are capable of reinforcing the effect of maternal antibodies in their protective capacity (Sabin and Fieldsteel 1962, Matthews et al. 1977, Welsh and May 1979). For example, trypsin inhibitors and other still undefined factors facilitate the adsorption of immunoglobulins in cattle and man (Balfour and Comlin 1962). The proliferation of numerous viral and bacterial infectious agents is inhibited in vitro by lipids in milk, lysozyme, lymphokines and other undefined macromolecules (Falker et al. 1975, Welsch et al. 1978, Matthews et al. 1981, Toluhisa et al. 1981). For instance, lysozyme, which splits peptidoglycans of bacterial cell walls, exhibits a bacteriolytic effect in combination with specific antibodies. Lactoferrin, on the other hand, has a bacteriostatic effect, partly by withholding iron from microorganisms. In addition, the so-called lactobacillus factor promotes the growth of *L. bifidus* in the intestine of the newborn. This agent produces acetic and lactic acid, which inhibit the proliferation of *E. coli* (Ballabriga et al. 1975). In the pig, the membrane of the milk-fat globules possesses a receptor for the *E. coli* antigen K 88, which may, in combination with specific antibodies, effectively inhibit the adsorption of K 88-positive strains (Porter 1979). In human colostrum, substances other than immunoglobulins have been shown to exhibit an inhibitory effect on infections with rotavirus, *E. coli* enterotoxin, influenza and syncytial viruses (Otnaess and Orstavik 1981, Shortridge and Wong 1976, Toms et al. 1980).

Farm animal studies of this kind of activity are only beginning. Increasing knowledge of these factors will promote future understanding of the effects of non-specific antimicrobial activities in maternal milk.

Stimulation of antibodies in the mammary gland

Experiments in stimulating or prolonging antibody secretion in milk have been conducted in several species. In principle, two methods of antigen administration are possible: parenteral (subcutaneous or intramuscular) and local application. The second method focuses on oral and intramammary administration of the antigen.

Oral administration – except in cattle – offers the best prospects of practical use. The basis for this is represented by the gut-mammary link whereby infection of the intestinal tract leads to local stimulation of precursor cells. At the onset of lactation, these cells (under hormonal control) produce antibodies in the mammary gland. Experiments with pathogens, which usually infect the digestive tract, were highly successful in pigs, rats, mice and man (Bohl et al. 1972, Bohl and Saif 1975, Hess et al. 1980, Goldblum et al. 1975, Michalek et al. 1976, Roux et al. 1977). Antigen replication in the intestinal tract is important since inactivated antigens show hardly any effect (Evans et al. 1980). This type of immunization is well suited to induce high antibody titers in the

colostrum and during the postcolostral phase. The newborn thus attains systemic and local immune protection. As already mentioned, local immunization via the respiratory tract does not lead to stimulation of secretory antibodies against Aujeszky viruses and TGE viruses in the mammary gland (Saif and Bohl 1977).

Following intramammary application of antigens, the formation of both specific IgA and IgG was demonstrated in rabbits (Genco and Taubman 1969), guinea pigs (McDowell 1973), pigs (Bohl et al. 1972, Djurickovic and Thorsen 1970, Bourne et al. 1975, Chidlow and Porter 1977), cattle (Kerr et al. 1959, Hilpert et al. 1974) and sheep (Lascelles and McDowell 1970). These results lead to the conclusion that the synthesis of antibodies stimulated by intramammary administration occurs mostly in the mammary gland. Onset of antibody production is quite rapid (Sarwar et al. 1964) in the gland's vaccinated and nonvaccinated sections and in the serum (Sarwar et al. 1964, Djurickovic and Thorsen 1977).

Intramammary vaccination is rarely employed despite its obvious advantages and successful results. It also does not play an important role in more recent developments of maternal vaccines. Although the reasons for this disinterest are numerous, intramammary vaccination is not employed mainly because of the high risk of infections associated with it and the large amount of work entailed. At present, it would not be feasible to put intramammary vaccination into practical operation.

Parenteral administration generally results in the production and stimulation of serum antibodies. The origin of antibodies in colostrum and milk makes it clear that this type of immunization leads to the stimulation or boostering of antibodies secreted in colostrum. Colostral antibodies in farm animals derive mainly from blood serum, and recent experiments with specific antigens resulted in the stimulation of IgG antibody secretion in colostrum and milk (Bohl et al. 1975, Wells et al. 1978, Chidlow and Porter 1977). The amount of antibodies secreted decreases rapidly during the postcolostral phase. This type of immunization induces passive, systemic protection in the newborn provided that there is a sufficient amount of colostrum intake and antibody adsorption. However, results of previous studies have shown that parenteral immunization not only induces systemic immune protection, but also promotes the production of secretory antibodies under certain conditions. Svennerholm et al. (1977) observed that parenteral (subcutaneous) immunization of women who had antibodies against *Vibrio cholerae* after natural infection, led to a rise in specific IgA antibodies in their milk and saliva. Seronegative women were observed having no specific IgA antibodies even after receiving two subcutaneous vaccinations; however, there was a significant increase in the amount of serum antibodies (Svennerholm et al. 1980).

These results clearly indicate the possibility of a combined local/parenteral vaccination or parenteral booster vaccination after natural infection or enhancing the antibody secretion in milk.

Experiences with dam immunization in practice

As discussed above, the newborn can acquire immune protection after intake of antibodies in mammary gland secretion in two ways. First, systemic immunity to generalized infections is transferred through high antibody titers in colostrum if the latter is absorbed in sufficient quantities. However, circulating antibodies have no effect on pathogens of strictly localized infections such as enteropathogenic viruses or bacteria. Therefore, in order to provide the newborn with immunity continuous oral intake of antibodies is necessary during the period in which the newborn is most susceptible to infection, i. e. 14–21 days post partum. The enhanced secretion of specific antibodies must be prolonged into the postcolostral phase. Experiments with *E. coli* infections in the calf depict the situation described above very well. Logan and Penhale (1979a, b) administered colostral antibodies to calves intravenously and were thus able to provide protection against the septicemic form of *E. coli* enteropathy, but not against the enterotoxic form involving *E. coli.* However, continuous feeding of colostral or milk antibodies beyond the stage of mucosal permeability resulted in immunity to enteric infections of *E. coli* (Logan et al. 1974) and also to rotavirus (Woode et al. 1975). Similar observations were made in man (Hanson and Winberg 1972), swine (Haelterman 1965, Svendsen and Wilson 1971, Nagy et al. 1976) and sheep (Fahey et al. 1981) after intake of antibody-containing colostrum and milk followed by intestinal infections with various pathogens.

With respect to active immunization of the dam, most results available concern local, passive immunization against infections caused by enteropathogens. This type of immunization is aimed against pathogens with a ubiquitous occurrence and against which a large percentage of the population already possesses antibodies from a natural infection, e. g., *E. coli* and rotaviruses in cattle, swine and sheep, or coronaviruses in cattle. Immunization against infections caused by such pathogens must therefore be regarded as a booster immunization. Such results were obtained by Svennerholm et al. (1977, 1980), who demonstrated that parenteral immunization can stimulate secretion of antibodies in colostrum and milk if the organism has already been naturally infected via the intestinal tract. A combined oral and parenteral vaccination may be successful in cases where the animal to be vaccinated has not yet had any antigen contact. For an efficient parenteral immunization, the vaccine must contain a sufficient amount of antigen and must be administered with

adjuvants (Myers 1980, Hess et al. 1981, Snodgrass et al. 1980). Subcutaneous and intramuscular administration are both effective (Bagley and Call 1979). Recent results claiming that merely the administration of adjuvant enhances the secretion of specific rotavirus antibodies in colostrum and milk could thus far not be substantiated (Eichhorn 1981).

Passive, local immunization against infections of the intestinal tract

The first attempts to control diarrhea in newborn animals by immunization of the dam were carried out with enterotoxigenic *Escherichia coli* (ETEC) infections. Since ETEC-monoinfections lead to severe illness only during the first few days of life (Moon et al. 1976, Smith and Halls 1967) and passively transferred antibodies inhibit the adsorption of the bacteria in the small intestine (Morris et al. 1980), the stimulation of antibody secretion in colostrum and milk only provides effective immune protection for a few days (Moon 1981, Acres et al. 1982). In cattle, immunization of the dam via the oral route plays a minor role because of the omasum system and the resultant dilution of the antigen. Earlier, parenteral immunization was carried out with herd-specific vaccines (Myers, 1976) because of the considerable number of subtypes. Since Guinee et al. (1976) and Moon et al. (1976) demonstrated that most of the ETEC bacteria isolated from calves carry the pilus antigen K 99 on their surface, vaccines now used contain K 99 antigens. The efficacy of this product has been demonstrated in various experiments. Calves of cows which have been immunized with vaccines containing K 99 were immune to orally administered doses of K 99 + ETEC, whereas calves of non-immunized cows regularly became ill. To stimulate antibodies to K 99 various vaccine preparations were used, e. g. highly or partially purified K 99 antigen (Acres et al. 1979, Contrepois et al. 1978, Nagy 1980), K 99-bearing enucleated whole ETEC (Acres et al. 1979) and bacterins derived from inactivated whole bacteria (Acres et al. 1979, 1982; Bagley and Call 1979, Myers 1980, Contrepois et al. 1978). Usually these vaccines were administered either subcutaneously or intramuscularly. Two immunizations during the last trimester of gestation are recommended at an interval of 20–28 days. Optimal results were obtained when the second immunization was made between 7 and 40 days before term (Acres et al. 1982). The main aim of these immunizations is to achieve control of ETEC infections shortly after birth.

After the demonstration that specific antibodies locally present in the intestine protect lambs and calves against viral diarrhea (Woode et al. 1975, Snodgrass and Wells 1976, 1978), experiments on the prophylaxis of such diseases by immunization of dams were initiated. Most of these experiments were performed with rotaviruses. Gravid animals (cattle and sheep) were given

intramuscular or subcutaneous vaccinations with inactivated or live bovine rotavirus and adjuvants which resulted in enhancing and prolonging the secretion of specific rotavirus antibodies in milk (Snodgrass et al. 1980, Bachmann 1980, Eichhorn 1981, Hess et al. 1981) and sheep (Wells et al. 1978). Snodgrass et al. (1980) conducted experimental rotavirus infections in calves of vaccinated dams and non-vaccinated control dams. They observed prolonged incubation and prepatent periods whereas clinical features were identical to controls.

The first clinical results of a commercial, combined vaccine (rota- and coronavirus) were recently published (Kunz 1982). The vaccine was tested at five farms on a total of 119 animals of which 40 developed diarrhea. In four herds vaccination lowered the incidence of diarrhea from 84–100 % to 15–36 %, but only to 70 % in the fifth herd. In three herds, mortality was still 8 %.

The results of recent experiments indicate that the rapidly developing age resistance against infections by ETEC K 99+ can be broken with the simultaneous infection of ETEC K 99+ and rotaviruses. Combined ETEC K 99+ and rotavirus infections cause severe diarrhea even in older calves (Snodgrass et al. 1982, Tzpipori et al. 1981, Gouet et al. 1978, Hess et al. 1982). Rotavirus infections in calves aged between 5 and 14 days are often associated with ETEC infections (Baljer and Bachmann 1980, Moon et al. 1978). Since it is possible that rotavirus infections are also associated with other pathogens such as bovine corona- and parvoviruses (Stair et al. 1978, Storz and Bates 1973, Bachmann and Hess 1982) combined vaccines should be used for immunization of the dam to protect calves from diarrhea. First steps towards this goal were done by our group with the development of a combined *E. coli* K 99+/ rotavirus vaccine. The vaccine consists of partially purified K 99 antigen and rotavirus immune complexes, which are absorbed on aluminium hydroxide and mixed with adjuvants. This preparation is administered subcutaneously twice at 4-week intervals during the last trimester of gravidity; after inoculation the presence of rotavirus antibodies (Eichhorn 1981, Hess et al. 1981) and K 99 antibodies (Bachmann et al., unpublished results) can be demonstrated in milk for at least 21 days. In a recent field study with 170 animals the incidence of diarrhea was reduced from 50–60 % (in the years before vaccination) to approximately 15–20 %; the mortality rate declined from 10 % to 0.6 % (Eichhorn et al. 1982). At present, a modification of this vaccine additionally containing bovine parvo- and coronaviruses is used in a larger study.

There are a number of publications on immunization of sows for passive local protection against diarrhea. The first successful experiments were carried out with oral immunization of gravid sows, using live *Escherichia coli* (ETEC) bacteria (Rutter and Jones 1974, Kohler 1975). On the basis of these studies,

oral ETEC vaccinations with live bacteria were put into general practice. Although the efficacy of such vaccines is good (Kohler 1978), they cannot be recommended because of the excretion of pathogens. A further disadvantage is that only herd-specific vaccines can be used. Oral immunization of dams using inactivated ETEC strains does not contribute to the spread of pathogens. However, large doses of bacteria, which must be administered over a fairly long period of time, are required to achieve effective passive immunity. Thus, for example, the administration of 10^{13} inactivated ETEC bacteria was ineffective, whereas the administration of 10^{11} live bacteria resulted in high antibody titers; both the inactivated and live bacteria were administered over a period of three days (Moon 1981). Porter and Chidlow (1979) administered 2×10^9 heat-inactivated *E. coli* daily from the 50th day of gestation until parturition. Their observations, however, showed only slightly higher antibody titers in colostrum compared with those of control animals. Piglets were not immune to experimental infections. Nevertheless an additional parental injection of 4×10^{10} heat-inactivated bacteria led to a marked rise in O antibody titers; specific activity was found in the IgM class. The mortality rate of infected pigs was 2 % compared with 76 % of the control animals. The precise mechanism for the passive immune effect after oral immunization with ETEC is not known.

More recent investigations ascribe the passive effect to the inhibition of adhesion by fimbria- (pilus) antigen-specific antibodies (Moon 1981). Three adhesion factors (similar to that of the calf) designated as K 88, K 99 and 987 P, are known in the pig. Additionally, toxins produced by ETEC have been introduced experimentally in the immunization of sows against *E. coli*. The toxins used are a thermolabile (LT) and a thermostable (ST) enterotoxin.

In pigs, immunization of the dam today is normally carried out with vaccines containing pilus antigens. The efficacy of these pilus vaccines has been demonstrated in various studies (Rutter and Jones 1973, Nagy et al. 1976, 1978; Rutter et al. 1976; Morgan et al. 1978; Moon 1981). However, this passive protective effect is entirely restricted to the pilus antigen used in each case (Morgan et al. 1978). This fact must be taken into account when employing the K 88 vaccines available commercially even if these vaccines cover a high percentage of the ETEC strains occurring in suckling pigs. Unfortunately, there are still no studies available on bi- or trivalent pilus vaccines, which could cover virtually all relevant ETEC strains in swine (Moon 1981). However, this is where future possibilities lie.

E. coli toxoid vaccines, which are manufactured from inactivated LT, are administered together with oil adjuvants twice via the intramammary and/or intramuscular route (Dobrescu and Huygelen 1976, Dorner et al. 1980). Morbidity after experimental infection was thereafter reduced from 94 % in

the control animals to 48–61 % in the piglets of vaccinated sows; mortality was reduced from 51 % to 5 %. Similar results were obtained after parenteral vaccination of sows with cholera toxin, which is antigenically related to LT (Dorner et al. 1980). Fuerer et al. (1982) used procholeragenoid (a derivative of cholera toxin) for immunization of gravid sows. In a field study, morbidity was thus reduced from 73 % to 11 % and mortality declined from 4.7 % to 0.77 %. After use of this vaccine, the specific activity of antibodies in colostrum is thought to be mainly associated with the IgA class as in the case with toxoid vaccines. However, the general use of toxoid vaccines is not recommended until further studies are available, since a number of ETEC strains in piglets only produce ST and not LT and conflicting reports exist on cross immunity between LT and ST (Smith and Gyles 1970, Dobrescu and Huygelen 1976).

There are also contradictory results from experiments on the development of vaccines for sows against transmissible gastronenteritis (TGE). TGE infections in suckling pigs cause diarrhea with a mortality rate of up to 100 %. Although adult animals may also fall ill, the course of infection is considerably more mild. The litters of sows that have suffered an infection before or during gestation are protected by the uptake of secretory antibodies in milk. In colostrum, specific antibody is found in the immunoglobulin classes IgA and IgG; in milk, such activity is almost exclusively in the IgA class (Bohl et al. 1972, Saif et al. 1972, Abou-Youssef and Ristic 1972). Oral administration of attenuated virus strains is the method chosen to induce passive oral immunization against TGE because intramuscular administration does not lead to stimulation of IgA antibodies in milk (Bohl et al. 1975).

"Immunization" using virulent pathogens by feeding gravid sows with intestinal contents of infected piglets was recommended a long time ago (Hooper and Haelterman 1966). This method was effective, but nonetheless, because of the spread of virulent pathogens it must be judged as dangerous as oral vaccination with live *E. coli* strains. Bohl and Saif (1975) and Morilla et al. (1976) used TGE virus attenuated in pig kidney cell cultures for oral immunization of sows, but they could not induce passive protection of piglets. According to Bohl and Saif (1975), specific antibody activity was found mainly in the IgG class and after a short period of lactation it falls drastically.

The TGE strain CKp, also attenuated in pig kidney cell cultures, was developed in Hungary and it produced considerably better results. After immunizing the dam with this strain, good passive immune protection developed in piglets. Unfortunately, experimental test infections were not conducted in these studies (Csontos et al. 1973, Benyeda and Moscari 1974, Moscari et al. 1975). Woods (1978) describes a TGE virus vaccine that is highly interesting as far as its biological properties are concerned. The vaccine strain

used is a small plaque variant of the Miller TGE virus strain attenuated in a leukocyte cell line. This variant is not pathogenic for 3-day-old piglets. The virus also seems to have an altered cell tropism. After infection of newborn piglets, the presence of the virus is not demonstrated in villous epithelial cells (as is the case with virulent TGE virus) but in unidentified cells of the Lamina propria (Woods et al. 1981). In two experiments, gravid sows were immunized twice with this virus. In piglets which had taken up colostrum and milk from these sows, mortality after experimental infection with a virulent TGE strain was only 14 % and 29 % respectively (Woods 1978, Woods and Pedersen 1979). Further reports are not available.

One of the vaccines developed by our research group is a TGE strain (B1–300) that has been attenuated in pig thyroid cells. This strain exhibits only weak pathogenicity for piglets (Hess et al. 1977). After administration to adult sows and young pigs, the vaccine virus can be demonstrated in the villous epithelia of the middle and distal jejunum; however, its presence cannot be demonstrated in feces or in nasal secretion (Hess et al. 1980). After two oral administrations of the virus in acid-resistant capsules, specific antibody activity was found in the IgA class (Bachmann and Hess 1978). Experimental test infections were conducted with the virulent Miller virus strain. The mortality of control animals after infection on the 3rd day of life was 100 %; among piglets which had ingested colostrum and milk of vaccinated animals mortality was only 10 % (Hess et al. 1978). Only mild or moderate diarrhea was observed in piglets from vaccinated sows. It is possible that full immunologic protection can be obtained in piglets by raising the titer of the vaccine. Studies are still pending. Up until now, this vaccine has been tested only under experimental conditions. Two problems must be solved before the vaccine can be put into general application. First, the virus vaccine has to be propagated in pig thyroid cells, which are difficult to culture. Secondly, the virus has to be administered in acid-resistant capsules, using an appropriate instrument. This form of administration is not suitable for general use, but since the vaccine virus is labile at low pH values (Hess and Bachmann 1976) it must be protected against gastric juices.

Attempts to obtain lactogenic immunity via intramuscular injection of attenuated TGE virus strains only led to a slight reduction of mortality of 90–45 % (Bohl et al. 1975, Hess et al. 1978). Kaji and Shimizu (1978) succeeded in providing 100 % protection in piglets by immunizing the dams via the intramuscular route with high doses of an attenuated TGE strain followed by intranasal boosters. Yet further studies are necessary because tests were only performed on a small number of sows. Leopoldt et al. (1975) also used an attenuated TGE vaccine administered intramuscularly. It was possible to reduce mortality to 13 % after administering the so-called Riems TGE

vaccine in herds that had suffered TGE infections. However, virtually all the animals already had TGE antibodies in serum before immunization. Thus, these conditions are fundamentally different compared to the experiments already described for which only seronegative animals were used. The value of such parenteral immunizations lies in the fact that they control clinical morbidity in herds that had already been infected (Bohl and Saif 1981). When TGE infections are freshly introduced into a herd, parenteral vaccinations have hardly any effect.

Unlike vaccinations of sows with ETEC to provide oral passive immunization of piglets, TGE immunization of the dam has not yet advanced to the point where it can be put into general use. Further research in this field is necessary, particularly in view of the multiple etiology of viral diarrhea in swine. Other viruses, e. g. another coronavirus – the causative agent of epizootic virus diarrhea (EVD) (Chasey and Cartwright 1976, 1978; Pensaert and DeBouck 1978), rotaviruses (Woode et al. 1976, Bachmann et al. 1979) and pararotaviruses (Bohl et al. 1982, Bridger et al. 1982) can cause diarrhea in mono- and mixed infections. Thus, immunization against TGE alone would not bring about the desired success and attempts must be made to develop combined vaccines. Further studies should be encouraged by the fact that – similar to the situation in cattle – antibody secretion in milk can be enhanced by intramuscular administration of virus antigens in animals that have already been naturally infected with rotavirus via the intestinal tract.

Passive systemic immunization against general infections

Another possibility for immunization of the dam is to provide the offspring with passive, systemic immunization against general infections. Until now not much attention has been given to this method as far as large animals are concerned. However, passive systemic immunization has been quite successful among poultry: chicks are passively immunized via the egg-yolk against infectious bronchitis, Gumboro disease and avian encephalomyelitis (Siegmann 1979). For cattle, no results are available. Yet the method might well be suitable for immunizations against the septicemic form of *E. coli* enteropathy, IBR-IPV infection and bovine viral diarrhea (BVD). However, the availability of inactivated vaccines would be necessary since live vaccines could cause fetal damage. In swine, immunization of the dam is carried out against pseudorabies in piglets. After infection of susceptible newborn piglets mortality is 100 %. The mortality rate declines continuously with progressing age: infection during the 10th week of life only leads to 2 % mortality and efficient active immunity is not expected before the 14th day of life when antibodies of the IgG class are demonstrable (Browne and Bourne 1976). Sows immune to pseudorabies virus (Aujeszky's disease) secrete antibodies in the colostrum.

These antibodies protect piglets against infection if they ingest sufficient quantities of colostrum in time. This holds true regardless of whether the sows were naturally infected (McFerran and Dow 1973) or vaccinated. In general, vaccines from inactivated pathogens are just as suitable as those containing attenuated virus (Zuffa 1964, Andries et al. 1978, Wittmann and Jakubik 1979), although the latter is preferred.

Immunization of the dam is also carried out against bacterial infections of piglets. Bergeland (1975) describes immunization of sows against necrotic piglet enteritis caused by *Clostridium perfringens* Type C. Endemic outbreaks of the disease occurred in pig populations. Therefore, sows were vaccinated twice 5 and 2 weeks before term with *C. perfringens* Type C toxoid in order to stimulate high colostral antibody titers for effective passive immunization. Amtsberg (1978) recommends immunization of the dam also against exudative epidermatitis in piglets caused by *Staphylococcus hyicus*. The vaccine used is a formalin-inactivated suspension of bacteria, and it is administered twice at an interval of 17 days, approx. four weeks and one week before term. All the piglets of immunized sows were protected against subsequent infection. Immunization of the dam is also employed against erysipelas – a rare disease in piglets. Results, however, vary.

Conclusions and prospects

Immunization of the dam is recommended for protection against both local intestinal and systemic infections which occur in young animals during the first weeks of life. The advantage is that under normal conditions, when colostrum and milk are ingested, immune protection commences almost immediately. Our present experience indicates that this type of passive immunization is of greater practical importance for the complex of local intestinal infections than for protection against general infections. Future developments, however, may lead to the routine use of immunization of the dam for general infections as well. This possibility has been shown by studies on swine with vaccinations against pseudorabies, necrotic enteritis and exsudative epidermatitis *(Staph. hyicus)*. It is possible that such measures may be suitable also for other diseases.

Disadvantages of immunization of the dam may be that antibodies trans ferred from the dam may influence the formation of active immunity in the newborn animal. Hitherto it has been postulated that passively supplied antibodies as a rule interfere with the active synthesis of antibodies (Uhr and Baumann 1961). Although this view has become somewhat differentiated today, it is certain that passively transferred antibodies generally do interfere with the formation of effective active immunity after initial vaccination. Corthier and Charley (1978) demonstrated that colostral antibodies inhibit the

primary response after immunization of piglets after swine fever. After test infections, however, a booster effect was observed, so that the initial vaccination did have some effect. There are similar observations in piglets which had passive antibodies against pseudorabies virus and had been actively immunized (Andries et al. 1978). According to Wittman and Jakubik (1979), vaccinations of piglets passively immune against pseudorabies are successful as early as the second week of life, although at this age the animals show high serum antibody titers.

In calves with passive immunity to IBR-IPV virus and BVD virus, Brar et al. (1978) showed that an active immunization against BVD is possible even if serum antibody titers between 1:20 and 1:96 can still be demonstrated. Following immunization with IBR-IPV virus, on the other hand, no active antibody formation was observed in passively immune animals. In revaccinations, however, it was demonstrated that the vaccinated animal had become sensitized, i. e. previously vaccinated animals developed higher antibody titers than those with only one vaccination.

It has also been stated that maternal antibodies present locally in the intestinal tract exert an inhibitory effect on the formation of an active immunity. This effect is probably responsible for the low efficacy of oral vaccination against rotaviruses and coronaviruses in the calf (Buerki et al. 1982, De Leeuw et al. 1980). Lambs fed with antibody-containing colostrum remained healthy after oral infection with rotavirus, but showed a serological reaction (Snodgrass and Wells 1978). Piglets fed with bovine colostrum also seroconverted after oral infection with rotavirus without showing any signs of sickness. From this it supposed that a subclinical infection occurs despite the protective effect of milk antibodies, and active immunity is built up (Bridger and Brown 1981). There is also a report from tests in piglets that local antibodies do not interfere with the active formation of antibodies against *E. coli* O antigens (Porter 1973). Similarly, serum antibodies do not appear to have an inhibitory effect in such cases (Watson et al. 1979).

Clearly, these few examples do not allow any fundamental recommendations to be made. Also, there may be differences between species. Nonetheless, in the application of immunizations of the dam it must be taken into consideration that during active immunization of the newborn the development of active immunity may be inhibited.

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Author's address: Prof. Dr. P. A. Bachmann, Institut für Med. Mikrobiologie, Infektions- und Seuchenmedizin, Veterinärstrasse 13, 8000 München 22.