THE IMMUNE SYSTEM OF THE NEWBORN CALF

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I. Passive transfer of immunoglobulins (antibodies) in the the bovine species:

The newborn calf enters an environment which is more antigenic and pathogenic than its previously sheltered live in utero. Although the bovine fetus develops immunocompetence during gestation, full immunological reactivity is only reached during postnatal life. Thus the neonate needs to be protected by maternal antibody which he receives via the colostral-intestinal route.

II. The placental barrier in the cow:

The anatomical structure of the bovine placenta is of interest in as much as it determines the transmissibility of maternal antibody to the fetus. Morphologically, the bovine placenta is of the epitheliochorial type (according to the older classification of GROSSER (1909) 7. (New classification of AMOROSO, 1961: all higher mammals have a "chorio-allantoic placenta).

According to present knowledge, there is no transmission of maternal antibody in utero in the bovine species. This appears to be due to the multiple layers (6 layers) between foetal and maternal circulations.

In experiments involving the immunization of cows with a number of different antigens (Erythrocytes, Brucella abortus, Diphteria toxin, Trichomonas foetus, Rinderpest virus, Foot-and Mouth Disease virus), transmission of antibody to the bovine fetus has never been observed.

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It follows that the calf should receive its only significant transmission of immunity after birth via the colostral-intestinal route at suckling.

III. Postnatal transmission of antibody via the colostral-intestinal route:

Calves are born virtually in a state of agammaglobulinaemia and without a significant level of antibody. Therefore, it is essential for the newborn calf to receive passive protection by way of colostral antibodies. Antibodies present in the colostrum are derived from the cow's serum. In cattle, the mammary gland is able to concentrate immunoglobulins (much of it being of the IgG class). So, the level of immunoglobulins present in the colostrum may be 10 times the serum concentration (PIERCE and FEINSTEIN, 1965).

The immunoglobulins of the colostrum:

Protein concentration of colostrum within few hours of parturition: 15-26%, that is 3-4 times the concentration in the plasma (SMITH, 1948). The immunoglobulins constitute 50-60% of the total colostral protein (SMITH, 1948).

Immune globulin passes from the blood to the colostrum (or milk) without degradation or resynthesis (BRAMBELL,1970, ASKONAS et al. 1954). Four immunoglobulins were identified in the blood serum and the colostrum, however, in very different proportions in the two fluids (PIERCE and FEINSTEIN, 1965): IgG, IgA IgM.

The mammary gland of the cow continually incorporates serum proteins into its secretions. During colostrum formation γ-globulin is concentrated over 100 times more than serum albumin. At parturition, the γ-globulin concentration in the colostrum in 5-10 times that in serum (albumin only 5½ that

Immunoglobulin classes identified in the colostrum:

There is evidence of selective secretion and concentration of immunoglobulins in the mammary gland. Two principal varieties or subclasses of IgG are present in adult bovine serum: The electrophoretically fast IgG_1 and the slower IgG_2. It has been found that only IgG_1 is concentrated in the colostrum. Thus, IgG_1 should be the predominant (90%) source of passive immunity transferred to the calf (BRAMBELL 1970, BUTLER *et al*. 1972). IgM and IgA are also part of the colostral immunoglobulins and are equally well absorbed in the gut of the newborn calf (BRAMBELL 1970).

The immunoglobulin concentration in the colostrum and milk, respectively, changes very rapidly (KRUSE, 1970). In the first colostrum we find extremely hight values that are more than 10 times the serum concentration of the cow's serum. But the concentration decreases rapidly within the first few days.

It appears important to note differences in the immunoglobulin production in the bovine species. In a secretory organ such as the salivary gland IgA is produced locally and secreted as a major immunoglbulin. Whereas the mammary gland transports IgG selectively from serum to colostrum and synthesizes only a negligible amount of immunoglobulin (MACH *et al*. 1969; MACH and PAHUD, 1971).

POST-NATAL DECREASE OF THE IMMUNOGLOBULIN CONTENT IN COLOSTRUM AND MILK (KRUSE, 1970):

Content	TIME OF MILKING			
mg/100 ml)	Day 1	Day 2	Day 3	4 Days
IgG	7.500	2.300	470	40
IgA	500	450	90	5
IgM	490	80	30	4

Most of the immune globulin in colostrum is certainly derived from the circulation. The problem remains as to whether there is any local production of Ig or antibody that is then secreted into the colostrum? In the normal udder there is very litle or no local formation of immuno-globulins (DIXON et al. 1961). Immunoglobulin producing plasma cells are scarce; but during colostrum formation the interstitial fluid increases greatly and the acinar cells become loaded with γ -globulins (immuno-fluorescence). During colostrum formation the acinar epithelium of the udder functions primarily as a transporter of serum protein, largely immunoglobulin; while in lactation it acts as a protein producer.

There is some evidence that after experimental injection of antigen into a quarter there is some local synthesis of antibody, but predominantly active transfer from the circulation occurs.

IV. Termination of the transmission of passive immunity:

It is important to note that the intestinal absorption of antibody only occurs for the first day, up to 36 hours, after birth! After that time, the gut of the newborn calf loses its permeability to large molecules (DEUTSCH and SMITH, 1957). It follows,that the transmission of maternal antibody must occur intensely and rapidly. Therefore,the concentration of immunoglobulins in the cow's udder is an important mechanism.

What is the mechanism that permits the orally ingested immunoglobulins to remain intact in the stomach and intestine? According to the hypothesis of HILL (1956) it appears that a changes in the pH in the stomach, that is a drop in the pH from 6.0 - 7.0 in the newborns's stomach to 3.0 - 4.0 some 36 hrs. later is an essential factor. Besides the increase in acidity of the gastric content there may be a specific mechanism for switching the gut wall from a state of permeability to immunoglobulins to a state of impermeability.

An other factor most likely is an enzyme inhibitor. It has been shown that colostrum contains a trypsin inhibitor which may facilitae that colostral immunoglobulins reach the small intestine to become absorbed there.

Still an other hypothesis suggests (EL-NAGEH, 1967): The intestinal epithelium of the newborn calf is totally renewed after 1.6 to 2 days. The renewal proceeds from the bottom (crypts) of the mucosa along the villus towards the apical end of the vilus. Absorption of Ig takes place in the first 6 hrs. in all areas of the villus, but at 53 hrs. it is limited to the apical end of the villus. The new replacement cells no longer have the function of absorbing intact Ig.

V. Mechanism of transeptithelial transport in the gut:

The transfer of maternal antibody across the epithelium of the intestinal wall involves pinocytosis: that is the uptake of small fluid droplets by the intestinal cell at its luminal aspect, which are transported as vesicles filled with maternal antibody across the epithelial cell (BAMFORD, 1966). On the other side of the epithelial cell the cell membrane opens up (reverse pinocytosis) and discharges the vesicle's content into the lymph. According to BRAMBELL (1966) the hydrolytic enzymes in the lysosomes of the epithelial cells digest all colostral proteins other than immunoglobulins. Why is that so?.

There is evidence that the Fc part of the immunoglobulin molecule combines with specific receptor sites on the epithelial cells in the villi; these are then carried into the cell during pinocytosis. The union between the immunoglobulin and the receptor protects it from subsequent degradation by lysosomal enzymes. Thus, the transepithelial transport has specificity.

Cells of the intestinal wall of calves absorb IgA, IgM and IgG immunoglobulins without discrimination of selectivity (HALLIDAY 1965; KLAUS *et al*. 1969; PORTER 1969) as weel as heterologous antibodies (OLSSON 1959).

Plasma cells in the lamina propria of the intestine produce IgA, IgG_1, IgM. But IgG_1 is the predominant Ig class in the intestinal juice (NEWBY and BOURNE, 1976).

VI. When does it become possible to detect antibody/immunoglobulins in the calf's blood?.

Calves of cows immune to *Brucella* abortus had detectable antibody in their blood as early as 2 hours after taking colostrum; the agglutinating titer continued to rise untill 18 to 24 hr. Antibodies to the antigens mentioned earlier are all transmitted by way of the colostrum.

When colostrum (2.5 L) was fed to newborn calves, an increase during the first 12 hours from 4.5 to 5.5% of the total serum protein, was observed; this was mainly due to 6.5 γ γ-Globulins which increased from 0 to 20% of the total serum proteins (BRAMBELL, 1970,). With the method of immunoelectrophoresis it was shown that calves are born with no detectable γ-globulins in their sera; but γ-globulin was present in the serum 2 hr. after they ingested colostrum (BRAMBELL 1970).

Using the more sensitive method of radial immunodiffusion (MANCINI *et al*. 1965), it is possible to demonstrate low levels of IgG (1.4 $\pm$0.5 mg/ml) and IgM (0.1 $\pm$ 0.0 mg/ml) in the sera of presuckling calves. After ingestion of colostrum a rapid increase of these immunoglobulins occurred within 24 hrs. The peak was reached within 48 hrs: 31.6$\pm$13.6 mg/ml IgG; 1.6$\pm$0.8 mg/ml IgM. Subsequently the serum concentrations fell again.

Persistence of maternal antibody in the circulation of the newborn calf:

It is of practical imortance to know for how long maternal antibody will persist in the foetal circulation; since persistence of maternal antibody will determine how long the newborn calf is passibely protected against incection. It will also indicate the optimal time for immunisation of the calf. The decrease of maternal antibody in the circulation depends on several factors:

a) the catabolic rate.
b) increase of blood volume in the growing young animal.
c) changes in distribution of Ig between the blood compartment and the tissue or interstitial compartment during postnatal development.

In calves, the maximum titer of maternal antibody is reached at 24 hours after birth when the colostral absorption ceases. The catabolism of antibody occurs at a constant rate! (The decline of maternal antibody proceeds logarithmically). It has been found that f.e. the persistence of agglutinins to Brucella abortus may very considerably: from a few days to 18 weeks; and the decline depended on the original titer. Thus, the peak level of maternal antibody will determine the duration of persistence of the antibody.

There is an interesting relationship between the half-life of immunoglobulins and the size of the species (SOLOMON, 1971; DIXON et al. 1952). In a large species, such as the bovine, the half-lif of immunoglobulin has been determined with 14-20 days with the half-life in adults (21d) insignificantly higher than in the newborn. (For comparison, in the mouse it is only 4 days).

In Rinderpest it has been found that the mean half-life of maternally derived antibodies was 36.7 days and the extinction point 10.9 months. (BRAMBELL, 1970,). Rabies antibody (colostral) persists for 12-14 weeks after birth. And the estimated protection by maternal antibody in viral diseases such as PI-3, IBR, VD-MD is 4 months.

However,if the colostrum does not contain specific antibody against a certain bacterial antigen, it still mediates increased phagocytosis; i.e. of Brucella or Salmonalla:in other words, colostrum and also gammaglobulin preparations show general opsonizing effects.

Practical experience of investigators has shown that passive immunity may protect the young calf against IBR(KAHRSK, 1966),Parainfluenza virus (BOGEL and LIEBELT,1963),Adenovirus (BURKI,1971) for up to four months. Passive immunity may last upt to 6-10 months against BVD (KAHRSK,1966; MALMQUIST, 1968) PHILLIP, 1973, 1975).

VII. The protective effects of maternal antibody to the newborn calf:

The primary purpose of maternal antibody is to provide instant protection against micro-organisms. The presence of maternal antibody in sufficiently high titer will prevent the initial invasion and the spread of the pathogen. Such humoral antibody protects mainly by opsonisation; this favors phagocytosis by macrophages and thus the elimination of pathogenic micro-organisms.

It is clear that the neonate enters an environment which is more antigenic and pathogenic than its previously sheltered live in utero. Neonates are therefor not sensitized to react rapidly to pathogenic organisms. Although the calf becomes immunocompetent long before birth, it needs the protection by maternal antibody which is acquired as suckling commences.

However, the quality and quantity of antibody transmitted from the cow to the newborn will depend upon the antigenic stimulation which the mother has received from pathogens in her environment or by vaccination during the later stages of gestation. Thus, the newborn calf will passively acquire antibody specific for those micro-organisms in the mother's environment.

These basic immunological facts have long been recognized in calves. i.e. feeding of colostrum is important to protect newborn calves from scours, that is E.coli infection. (Experiments of INGRAM *et al.*, 1956: in agroup of 103 colostrum-deprived calves 94 died; whereas in a group of 161 calves receiving colostrum, 118 survived and 43 died).

VIII. The decline of passive immunity and development of active immunity:

At a certain postnatal period the decline of passively acquired immunoglbulin overlaps the rise in autogenous Ig. The practical point is: (1) The duration of protection from disease provided by passive immunity and (2) The stage at which active immunity can be induced effectively (DANGER: induction of a state of partial or complete tolerance resulting from very early exposure to antigen).

Studies were performed in calves raised without colostrum:

Serum proteins reach their normal values at 8 weeks of age; gradual increase in γ -globulins and concurrent decrease in a-glbulins. Autogenous production of γ -globulins by the calf begins soon after birth (but at this stage calves connot be actively immunized to most antigens). By the 10 th day it is possible to distinguish autogenous IgG_1 and IgG_2 ($IgG_1 > IgG_2$). By the 30 th day the IgG_2 exceeded the IgG_1.

Circulating B lymphocyes in neonatal calves:

The development of active immunity in the young calf is reflected in changes of the nubmer of circulating B lymphocytes, the precursor cells of humoral immunity.

Neonatal calves have in the peripheral blood low levels of B-lymphocytes, that is lymphocytes bearing surface immunoglobulins as revealed by fluorescent antibody technique (MUSCOPLAT et al.1974). In a study of SENOGLES and co-workers (1978) the percentage of B-lymphocytes in the new born and young calf (colostrum-fed) was determined from one day to 140 days old.

Onset of specific antibody formation in the newborn calf:

In principale, the young calf is capable to respond to antigens with a primary reaction, which is relatively weak. On the other hand, maternal antibody has an immunosuppressive effect on the immune system of the neonate.

1) When calves were repeatedly immunised with Salmonella the H antigens at 6 days of age (ROBERTS et al. 1954). Colostrum deprivation did not affect the onset of antibody formation.

2) Calves born from non-immune dams were immunized with Rinderpest vaccine beginning at one day of life up to 2 months. At 21 days of life the neutralising antibody titer in their sera was as high as that produced by adult cattle (BROWN, 1958). However, in calves of dams which had previously been immunized to Rinderpest the transmission of maternal antibody at suckling interfered with the active antibody response of the calves.

3) It appears important to use strong immunogens to elicit immune responses in the bovine fetus and newborn calf:

a) When one-day-old calves were injected with HSA in incomplete Freund's adjuvant they produced high levels of antibody one week after immunization.

b) HSA alone failed to stimulate antibody production even in 3-6 month-old calves. (SMITH and INGRAM, 1965).

c) No response to other antigens , Klebsiella pneumoniae polysaccharide occurred in calves inoculated while less than one month of age.

4) Parasites:

a) When newborn calves were infected with eggs of Taenia saginata they produced little complement-fixing antibody; they could not destroy the eggs.

b) If older animals were infected, they eradicated the worms,no living cysts were found and they became immune to re-infection (SOULSBY, 1963).

These few examples show that calves should be actively immunized at a time when most of the maternal antibody has been degraded.

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