Transport of Passive Immunity to the Calf

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Acquisition of Passive Immunity.

Passive immunity according to the classical definition is the acquisition of short duration antibodies from an outside source. In the case of the calf, antibodies are transferred via the colostrum from the dam. The calf is born with only traces of antibodies or immunoglobulins in its sera. This lack of immunoglobulins is explained by the concept that immunoglobulins do not pass the placental membranes and few immunoglobulin-producing cells are present at birth. Immunoglobulins are derived from the first nursing, being secreted by the mammary gland into the colostrum, and are rapidly absorbed from the intestine of the young calf. Colostral immunoglobulins appear unchanged in the serum of the newborn calf within one to three hours after nursing colostrum and in effect are transported from the maternal sera to the calves sera confiring passive immunity. Immunoglobulins generally reach a maximum serum level in the calf by 6 to 24 hours after nursing, (1, 28, 39) however, there are considerable individual variations. Following nursing the serum immunoglobulin pattern approaches that of the dam's colostrum (1, 7, 28) and individuals may acquire levels comparable to those of their respective dam. The period of time after birth for the absorption of immunoglobulins is generally considered to be limited to 24-36 hours after birth (3, 7). Absorption of immunoglobulins occurs in the small intestine and transfer is intracellularly through the absorptive epithelial cells into the lymphatics (2, 10, 11). The acquired immunity may remain in the sera for 14 to 90 days (39, 41). Following this period the calves' serum pattern becomes virtually free of passive immunoglobulins, but then acquires the adult serum pattern by three to six months (39, 41) once the calf begins to form increasing amounts of its own immunoglobulins which may be as early as two weeks (24).

Protective Effects of Colostrum.

The protective effects of colostrum in the newborn calf has been reported by numerous investigators (42, 12, 14). Some of the earliest work reported a correlation between feeding colostrum and the absence of septicemia (42). Wood (52) indicated septicemia was more frequent in colostrum deprived calves, whereas a localized intestinal infection was more common in those receiving colostrum.

The exact role that colostrum plays in protection has not been fully defined, however, various components of colostrum have been implicated. Agglutinins to the capsular "K" antigen of *E. coli* have been suggested as a protective factor in colostrum. Briggs (4) reported that a serum containing the precipitin and the antibody against the "K" antigen was necessary to protect mice infected with *E. coli.* Ingram, et al. (23) showed that in colostrum fed calves which died, few had agglutinins against the strains of *E. coli* associated with their deaths. Evidence against the specific agglutinating antibody to the K antigen of *E. coli* involved has been reported by Gay (16). These workers feel that low serum gamma globulins levels are directly related to colisepticemia. Gay (17) further points out that calves generally don't receive K agglutinins in the colostrum and further that colostrum fed calves may be resistant to *E. coli* regardless of the presence of specific agglutinins in their sera. Ingram and Malcomson (24) have shown that agglutinins and antiglobulins can be measured by different techniques and do not represent the same antibodies. Further, both agglutinins and antiglobulins against *E. coli* "O" antigens were relatively specific, whereas those against *E. coli* "K" antigens were cross reactive (24, 25). Agglutinins against *Brucella* (32) and *E. coli* (24, 25, 26) have been shown to be absorbed into the circulation of the suckling calf, so cannot be denied a contributory role in the protective effects of colostrum. Recent work by Jacks and Glantz (26) have suggested that *E. coli* "O" antibodies or agglutinins in the colostrum are immunoglobulins of the IgG and IgA types. Immune globulins or immunoglobulins of the maternal sera, colostrum, and suckled calf sera have been found to be qualitatively similar (33). Butler (7) has recently compiled an excellent review of the bovine immunoglobulins. He defines immunoglobulins as a family of high molecular weight proteins that have common antigenic

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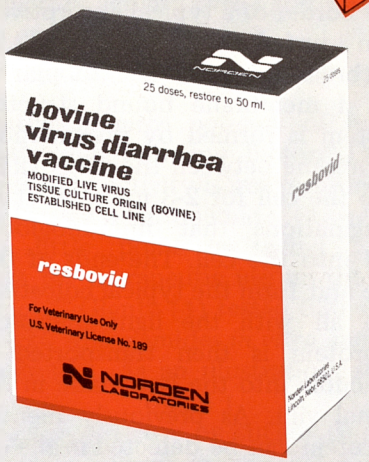

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determinants and physico-chemical properties. All proteins with antibody activity are included in this group. Antibody activity is associated with particular classes of immunoglobulins but classification is not related to antibody but rather antigenic and physico-chemical properties of proteins. Three classes of immunoglobulins have been identified in bovine serum and lacteal secretions: IgG, IgM, and IgG. IgM is present as 10% of the total immunoglobulins in serum and colostrum. The sedimentation coefficient of IgM is (19S.) and has a molecular weight of 900,000. IgM is apparently a more effective antibody than IgG particularly in agglutination, phage neutralization, complement fixation, and hemolysis. The primary response to Brucellosis, anaplasmosis and *E. coli* consists of IgM. IgG however, is the most abundant immunoglobulin in serum and colostrum making up 85-90% of the total. IgG may be further subdivided in IgG_1 and IgG_2 on the basis of antigenicity, amino acid composition, anion exchange chromatography, immunoelectrophoresis, and immunodiffusion. IgG_1 is the principal immunoglobulin in lacteal secretions. The sedimentation coefficient is (6.3S) and the molecular weight is approximately 163,000. The existance of a bovine secretory IgA has been suggested (6, 26) although apparently it is present in very low amounts. In man and other species this immunoglobulin has been partially characterized and has a sedimentation coefficient of 11S and a molecular weight of 385,000 (51). In the pig antibodies to *E. coli* 0141 and 08 have been predominantly associated with IgA (38). However IgA antibody in the pig is not absorbed as a part of the circulating passive immunity but becomes the predominant milk immunoglobulin during the first two days of lactation and persists as the major source of immunoglobulin and source of *E. coli* antibody (38). The role of secretory IgA, which is not absorbed in the pig (38) but may be absorbed in the calf (26), in providing protection is not fully understood. IgA has been shown to coat bacteria (51), but its enhancement of lysis and/or phagocytosis has not been established. Since IgA appears to be present in very low amounts in bovine colostrum, it would appear that IgG_1 is of more significance even though it is absorbed and presumably does not persist in the intestinal tract. Antibodies of the IgG, IgM, and IgA classes reactive with the "O" antigen of gram negative bacteria *(Neisseria gonorrheae, Escherichia coli,* and *Salmonella typhosa)* have been demonstrated in human adult sera (9). These immunoglobulins are selectively secreted by the mammary gland and concentrated in the colostrum (37).

Intestinal Epithelial Morphology as Related to Absorption

The ultrastructure of the intestinal epithelial cells of the calf has been described prior to feeding and following exposure to marker proteins (48). Ultrastructural studies have shown a characteristic cellular organelle in the intestinal absorptive epithelial cells of all species which absorb undigested proteins from the digestive tract, i.e. dogs (46), pigs (44), horses (47) and calves (48). This organelle is a tubular system found in the apical ends of the cell variously named, apical tubular system, apical canaliculi, or endocytic complex. This tubular system is responsible for engulfing immunoglobulins or colostral proteins from the digestive lumen. The apical tubular system has a limited life span and is present in the absorptive cell only during the postnatal period. The time of absorption as previously mentioned in calves is 24-36 hours after birth. In pigs the disappearance of the apical tubular system has been correlated with the cessation of protein absorption (45). Electron microscopic studies of the luminal border of a typical absorptive cell from a newborn unfed calf have well developed microvilli (brush border). The tubular system is present as a membrane bound structures. This tubular system is formed by invaginations of the plasma membrane between the microvilli and may extend into the cell for 2-3 microns. It is through these invaginations that immunoglobulins are transported into the cell. The ends of the tubules will enlarge and form the typical colostral vacuoles familiar to all with the light microscope. The colostral protein is then transported from the colostral vacuole into the lymphatic in the core of the intestinal villi. As previously mentioned the colostral protein can be detected in the circulation as early as one hour after suckling (13).

The Absorptive Period

The absorptive process can be envisioned as occurring in three steps, as immunoglobulins are transported from the gut lumen into the circulation. The first step involves the engulfing of immunoglobulin by the intestinal epithelial cell. The surface membrane of the intestinal epithelial cell between the microvilli is extremely active in invaginating and extending into the cytoplasm for some distance as tubules (approximate diameter 65-85 millimicrons). Immunoglobulins enter these invaginations and is thus carried into the cytoplasm. The second step involves enlargement of the tubular end-piece to form a vacuole.

Immunoglobulin or colostral protein fills and distends the vacuole, the tubular connections are lost, and the vacuole then is transported toward the basal cell membrane. Once in contact with the basal cell membrane (the third step) the vacuole opens and discharges its contents into the lamina propria where it passes the lymphatic endothelium into the circulation.

The absorptive period in the newborn calf as reported by various sources is: 24-30 hours (12, 43), 1-2 days (29), 36 hours (3), 24 hours (31). Smith et al. (43) reported that no absorption of gamma globulin occurred in fetuses *in utero* during the 6th through 8th month of gestation, however, calves cesarian derived at 7-8 months of gestation did absorb gamma globulin. No explaination is presented as to why comparable age calves did not absorb *in utero*. If 7-8-month-old fetuses were fed colostrum 38 hours after delivery no absorption occurred. It would therefore appear that the immature intestine will absorb at an early age after birth, whereas following termination of gestation immaturely the absorption period is limited to a time comparable to that which occurs following normal gestation and delivery. It is generally accepted that in ruminants very little absorption occurs more than 24-36 hours after birth, and is reduced to 50% at 16 hours after birth (39). When unfed newborn and day old colostrum fed calves were given a standard human serum protein on a per gram body weight basis and the concentrations of human serum, human gamma globulin, and human albumin absorbed were determined, twenty-four-hour old calves absorbed 56% less than newborn calves (48). Aguilera (1) has shown that peak serum concentrations occur at 24 hours post parturition when colostrum is fed on a body weight basis. In some calves absorption ceases as early as 4-6 hours after birth (17). There is also good evidence that in some calves absorption does not occur at all and they remain totally agammaglobulinemic (1, 27, 28). As a consequence of malabsorption, agammaglobulinemia and increased susceptibility to colisepticemia has been reported (14, 36).

The mechanism whereby intestinal protein absorption ceases has been referred to as, "closure" (30). The mechanisms of closure are not well elucidated, however, they appear to vary somewhat with species, intraluminal environment, length of postnatal life, and to some degree circulating hormones. Closure can be initiated by exposure of the intestinal epithelial cells to colostrum or milk, which occurs during the first nursing. However, in pigs even exposure to bovine colostral whey, boiled bovine colostral whey, glucose, or dialysates of colostral whey or milk will induce closure (30). When pigs are starved after birth, more than 36-48 hours, that is in excess of the normal time required for closure, then fed gamma globulin, absorption takes place but at a reduced level, as though the first nursing had occurred (30, 49). Ultrastructural changes in the absorptive epithelial cells of the pig intestine have been found accompanying closure (45). The calf apparently does not respond in the same manner as the pig, for closure occurs spontaneously whether or not nursing of colostrum has occurred (15). In attempts to maintain calves for 48 hours without feeding by blood transfusions, gamma globulin was absorbed at 24 hours, but not at 36 hours (13). The process of closure apparently occurs in a retrograde fashion, that is, the basal cell membrane ceases to release the envacuolated product. Transport ceases and eventually uptake by the tubule system ceases. It is of interest to note that apparently uptake into the cell of a non-protein substance such as polyvinylpyrrolidone can occur for up to 16 days in the goat, whereas transport to the circulation ceases by 24-48 hours (8). However it also has been shown that *E. coli* antigens can be absorbed by older animals (18) supposedly after closure has occurred. In addition, the passage of IgM through the intestinal wall into the circulation of 4-6 day old pigs has been demonstrated (50). It is then apparent that closure may only occur to a degree dependent on the absorbable material. A factor to consider is in the presence of invading bacteria, antigens may be carried along with the microorganism as they enter the cirulation. Secondly, lack of continuity of the intestinal epithelium is of obvious consequence, in that antigens brought into contact with the denuded capillary endothelium can readily pass into the circulation.

Influence of Solvent Factors on Absorption

Means of enhancing globulin absorption would appear to be a key in insuring adequate levels of circulating immunoglobulins. Factors in colostral whey appear to demonstrate this effect in controlled laboratory experiments. The influence of the solvent on the rate of absorption was first demonstrated by Balfour & Comline (2). They showed that gamma globulin when administered in aqueous solvents, with similar ionic constituents to colostrum, is extremely slow, however, when dissolved in boiled colostral whey the rate is accelerated. Further several components of colostral whey will, either singly or in combination, accelerate the absorption of globulins.

Particular attention has been directed toward a small protein fraction remaining after removal of the heat coagulable protein, however, the greatest effect on absorption was observed when protein, inorganic phosphate, and glucose-6-phosphate were present. These factors were only effective during the restricted period following birth when absorption normally occurs, and apparently did not prolong absorption. Hardy (20) extended these observations and has shown that when globulins are administered in solutions containing sodium lactate, or sodium pyruvate increased rates of absorption can be produced. The hypothesis is proposed that solvent factors act on the transfer of macromolecular material (bovine serum globulin) from the epithelial cell into the core of the villus. Solvent factors may influence transfer by providing a source of metabolic energy for the epithelial cell and may have their action on transfer of macromolecular materials into the core of the villus. However, glucose and citrate were not effective in accelerating transfer. Hardy (20) concludes that lactate and pyruvate are not present in sufficient amounts in colostral whey to contribute to absorption in the suckling animal. It is apparent however that studies of this nature are basic in understanding the mechanisms of immunoglobulin absorption. As a contrast, and an example of species variation, in the pig colostral factors which accelerated absorption were inactivated by heat. Similarly, neither phosphate, lactate, nor pyruvate accelerated absorption in the pig (21).

Hormones and Closure

Cortisone acetate is known to stimulate the maturation of immature intestinal epithelial cells and induce closure. When administered to starved pigs, closure was established by 48 hours (35). However, in the calf neither cortisone or ACTH had any effect on permeability of the intestine or closure. Also diethylstilbesterol, progesterone (13) or somatotrophin (43) had no observable effect on permeability in the intestine.

Proteolytic Enzymes and Closure

The appearance of proteolytic enzymes and in general the ontogeny of the intestinal enzyme systems have been considered to have some role in the cessation of protein absorption. The unsuckled calf gut contents average pH 4.4. However, colostrum has considerable buffering activity and neutralizes the hydrochloric acid of the stomach and thereby raises the pH to 6-7 (34). In addition, gamma globulin or polyvinylprolidone is not degraded to any significant degree prior to absorption, hence few proteolytic enzymes are present. Also there was little change in proteolytic activity between 3-hour and 21-hour-old calves. There is some slight hydrolysis in the abomasum (19). The pancreas is also relatively inactive at this early age and therefore is not of significance in protein digestion (22). It therefore appears that proteolytic activity of the intestine in the calf has little to contribute to intestinal closure.

Efficiency of Immunoglobulin Absorption by the Calf

Klaus, et al., (28) reported that when calves were allowed to nurse *ad libitum* for the first 19½ hours, and then fed 4 liters of colostrum per day by bucket, colostral IgM and IgG were absorbed with equal facility. This type of absorption is non-selective in nature. However, the resulting average peak serum levels of IgM in the calf were lower than either the average level in the dam's sera or colostrum (62.9% of the sera & 53.1% of the colostrum). The average IgG level in calves sera was 84.1% of the average sera level of the dam and 60.7% of the colostrum level. There was, however, a considerable variation in serum immunoglobulin concentration between calves, and the authors conclude that there was a complete lack of correlation between immunoglobulins in calf serum and colostral immunoglobulin levels. The shortcomings of this study, as pointed out by the authors, was the total intake of colostrum and immunoglobulin was not known. In a subsequent study by Aguilera (1), calves were fed known amounts of colostrum at the rate of 2.5% and 3.75% of the calves body weight during the 1st and 2nd days respectively. The total immunoglobulin (IG) transported is much clearer. The peak concentration of IG in calf sera occurred at 24 hours after birth. However, the average IG level was significantly lower than the average dam's sera or initial colostral IG concentration. There was a positive linear correlation between colostral IG consumption per unit of body weight and serum IG concentration attained in calves. Aguilera maintains that the variations in blood IG levels were attributable to differences in the amount of IG consumed but also could be due to differences in absorptive efficiency or other factors. McCoy, et al., (31) has reported that gamma globulin levels were significantly higher, by 7 hours after birth, in calves fed pooled colostrum than in calves which nursed their dams. However, serum gamma globulin levels in nursing calves were higher by 24-31 hours after birth than calves fed pooled colostrum. The factor responsible for this

discrepancy would appear to be related to intake of IG whether due to deficient intake, deficient absorption, or deficient IG in colostrum. Selman et al., (40) reported that no significant relationship was found between total suckling time during the first 8 hours and the 48 hour serum immune globulin concentration. However, they point out that such things as suckling intensity, milking out rate, and IG concentration of colostrum are obvious variables in an evaluation of this nature.

Summary

The protective effects of colostrum in the newborn calf appear to be directly associated with the immunoglobulins IgG, IgM, and IgA. The exact role which these colostral components play in protection is still in debate.

The transport of intact immunoglobulins from the intestine into the circulation of the calf is dependent on the lining intestinal epithelial cells. These cells are characterized by the capacity to engulf large molecular weight proteins, maintain them within a vacuole during transport, and release them at the basal cell membrane into the lamina propria. The ability of the intestinal epithelium to transport proteins is decreased approximately 56% during the first 24 hours after birth. This process referred to as "closure" does not appear to be absolute, since bacterial antigens may be absorbed throughout the life of the animal.

Enhancing immunoglobulin absorption or prolonging neonatal permeability of the intestine would appear to be an approach in insuring adequate levels of passive immunity.

The efficiency of absorption of immunoglobulins is due largely to the amount of immunoglobulin consumed, however, other factors such as deficient absorption and/or immunoglobulin in colostrum also must be considered.

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(Continued on page 46)

- All sulfonamides have the same mode of action. The differences are mainly due to pharmacological activity.
- Blood level patterns are the best single criteria to judge potential activity.
- Water administration is widely accepted, effective and economical.

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