ABSTRACT

Passive immunity to some infectious agents is transferred from the cow to calf via colostrum. Transfer is by an apical tubular system in the intestinal absorptive cells for a limited time after birth. Uptake of macromolecules into the cells appears to be nonselective; however, some substances are not transferred to the blood. Cessation of transfer of material from the epithelial cells to blood occurs spontaneously at a progressively increased rate after 12 h of age with mean closure time at approximately 24 h. Proportions of the different classes of immunoglobulins in serum of calves after ingestion of colostrum reflect the proportions in colostrum when absorption is completed.

Variation among calves in serum concentration of immune globulins is wide. Amount of total \( \gamma \)-globulin or IgG ingested per unit of body weight soon after birth is the most important factor determining concentration of these in serum. In contrast, efficiency of absorption of IgM decreases as intake increases, so that ingestion of a larger amount of IgM does not increase the absolute amount absorbed. Absorption efficiency is decreased when ingestion of first colostrum is delayed, indicating the importance of colostrum intake soon after birth. Even more important is that transmigration of pathogenic bacteria can be prevented by colostrum in the intestinal lumen.

The transfer of maternal antibodies to the newborn animals through the colostrum was noted by Ehrlich in 1892 (15) but apparently not examined in detail prior to the work of Howe (24) who showed that in the newborn animal colostral globulins were absorbed without change in amounts sufficiently large to alter the composition of blood plasma. The importance of colostrum consumption by calves soon after birth in relation to disease resistance was recognized by others during the same decade (72, 73). In reviews on passive immunity of young animals, Brambell (5) and Simpson-Morgan and Smeaton (69) noted marked species differences relative to time of transmission of passive immunity, with the bovine being one of the species in which this occurs largely after birth via intake of colostrum. Other reviews of the subject are by Logan (43), Lustermann and Günther (49), Oudar et al. (56), Patt (58), and Selman (66). The mechanism by which this transfer occurs and the effect of certain factors on the amount of immune globulin reaching the blood are discussed in this paper.

Mechanism of Absorption

The ultrastructural morphology of the jejunal and ileal cells of newborn calves was described by Staley et al. (80). The microvilli are developed better in the jejunal cell than in the ileal cell; however, the polysaccharide layer (glycocalyx) is relatively sparse on both types of cells. Apical tubules are present with the trilaminar membrane of the tubules being continuous with that of the microvilli. In the jejunal cell the tubules extend to the area around the nucleus located in the apical cytoplasm. In the ileal cell the nuclei tend to be at the extreme basal portion of the cell, and tubules are midway through the cell. A similar apical tubular system is in the intestinal absorptive cells in other neonatal domesticated
mammals (69, 78, 81, 82). Histological evidence was presented that colostral protein is absorbed in the pig via this tubular system with possible involvement of the Golgi apparatus (81, 82). Absorption is defined as movement of substances from the lumen of the intestine to the blood. Pierce and Feinstein (63) observed that the intestine of the newborn calf had no selectivity in absorptive capacity with regard to electrophoretic mobility of immune globulins. All of the colostral whey proteins were absorbed, and those of low molecular weight were cleared from the blood by the kidneys over 24 to 36 h (3, 14). Dextran with a molecular weight (MW) of either 40,000 or 100,000 was absorbed (1), and human albumin with 68,000 MW and human gamma globulin with 163,000 MW were absorbed equally in relation to total dose (80), indicating that molecular weight was not an important factor in the process. Also, Corley et al. (12) observed that cells of Escherichia coli were transported through the ileal cells of the intestine in calves deprived of colostrum.

Ferritin-IgG was taken up by the apical tubular complex of the jejunal cell in calves but not transported past the apical end of the cell (80). In the ileal cell ferritin solutions were transported into the base of the cell but not observed in transit out of the cell. It was concluded that the intestinal epithelium exerts a degree of selectivity in transfer of proteins to the blood. Intestinal epithelia of other species, i.e., guinea pig, hamster, and rabbit, non-selectively took up macromolecules, but differed in transport of these into blood (40).

Brambell (5) suggested that there are intracellular specific receptor or recognition units that account for selective transmission of proteins into circulation.

In some experiments (6, 21, 34, 60, 65), IgG with 163,000 MW and IgM with 10^6 MW were absorbed with equal efficiency as judged by comparison of ratios in colostrum and in serum of calves. However, Husband et al. (26) and Penhale et al. (61) calculated different absorption efficiencies for the different classes of immunoglobulins, IgG, IgM, and IgA. Lower apparent efficiencies of absorption of IgG1 and of IgG2 compared to IgM were attributed to movement of the lower molecular weight immunoglobulins into the interstitial fluid (26).

Stott and Menefee (85) reported that the percentage of IgM ingested which was in the serum at 48 h depended upon the quantity ingested. Relative absorption efficiency for IgM was correlated negatively with amount consumed whereas no such relationship existed for IgG and IgA.

Logan et al. (45) noted a different time course for changes in concentrations of immune globulins in plasma of six newborn calves. Maximum concentration of IgG occurred earlier than it did for IgM or IgA. Similarly, Stott et al. (84) noted that IgM appears to be absorbed more slowly than IgG and IgA.

Comline et al. (11) demonstrated that absorption of antibody takes place entirely in the small intestine and transport to the circulation is by way of the lymphatics. Antibodies appeared in the lymph within 1 to 2 h of the introduction of colostral whey into the duodenum, providing this occurred within 27 h of birth. Uptake of 125Iγ-globulin in in vivo segments of small intestine of calves was substantially greater in the distal portion, increasing progressively at 30, 50, 70, and 90% of intestine length (31).

Closure of Intestine to Absorption

The term closure was defined by Lecce and Morgan (41) as “cessation of absorption of macromolecules from gut to blood in neonates.” This concept of closure is used in this paper rather than a later definition (40) as “cessation of uptake or internalization via pinocytosis into intestinal epithelium.” The biological significance of uptake of macromolecules into intestinal cells independent of transfer to blood has not been determined.

Deutsch and Smith (14) observed that the gut of newborn calves lost its permeability to large molecules during the first 24 to 30 h of postpartum life. Various hormone injections, gastric activity inhibition, or withholding of feed did not extend the period of permeability to 48 h. The experiments were not designed to test whether time before closure was reduced. Kruse and Buus (38) noted relatively high concentrations of corticosteroids in a calf 2 h after birth and suggested that cortisol “shock” may induce changes in the intestinal epithelium leading to a loss of ability to absorb immunoglobulin. Corticosteroid treatment of cows in the last 2 mo of gestation reduced intestinal absorption of immunoglobulin by their
calves to half that of calves from untreated cows (27). Time of onset of endogenous production of IgG1, IgG2, and IgM was similar in calves of the two groups, but increase in serum IgA concentration was delayed by treatment. Stott et al. (87) presented evidence that elevation of peripheral corticosteroids caused by stress suppressed permeability of the small intestine to colostral IgG1. However, in later work (86) there were no differences in absorption of colostral immunoglobulins in dystocial and eutocial calves, nor in absorption among blocks of calves having significant differences in cortisol concentration in serum. Moreover, Johnston and Oxender (33) reported that calves with elevated serum glucocorticoid concentration due to ACTH injections absorbed IgG to the same extent as control calves, whereas serum IgG concentration was lower in those with low glucocorticoid concentration due to injection of metyrapone. Concentration of IgG in serum peaked in 5 of 7 metyrapone-treated calves at 24 h whereas only 1 of 7 ACTH-treated calves reached its peak IgG concentration by that time.

Brambell (5) stated that duration of the capacity to absorb antibody from the gut is limited to 24 to 36 h. Smith and Erwin (74) introduced 1.5 liters of colostrum at different times into the ligated duodenum of calves previously fed milk. Those infused at 6 and 18 h of age absorbed γ-globulin whereas those at 48 to 60 h did not. Cesarean-delivered calves fed colostrum within 2 h after delivery absorbed γ-globulin whereas no absorption occurred in one fed at 38 h after delivery (75). Based on trials in which feeding of pooled colostrum to groups of 10 calves was delayed until 1, 5, or 9 h after birth, Penhale et al. (61) concluded that there is a gradual and progressive closure of the absorption mechanism for immunoglobulins which operates independently for each class of Ig. It was estimated that closure was complete by approximately 16, 22, and 27 h for IgM, IgA, and IgG. Stott et al. (83) estimated time of closure of intestinal permeability to colostral immunoglobulins by a joint point analysis on data from 210 calves. Closure was estimated near 24 h of age with a normal distribution having a standard deviation of approximately 4 h. Differences in closure time for immunoglobulin classes, IgG, IgM, and IgA, were not significant. As feeding time was delayed, the estimated time for closure also was delayed; nevertheless, closure occurred spontaneously with age at a progressively increased rate after 12 h postpartum.

McCoy et al. (51) reported that there was no difference at 31 h of life in concentration of γ-globulin in serum of calves fed glucose and those from which feed was withheld for 24 h before feeding colostrum. In contrast, consumption of food appears to have more effect on time of closure in other species. The time of closure in piglets was a function of feeding regimen (39, 41, 42) in that intake of whole colostrum or some fraction thereof initiated closure. Fed piglets had a loss in pinocytotic activity beginning at the duodenum and proceeding caudally toward the ileum to about 3 wk of age whereas starved piglets did not have diminished uptake or transport activity at 3 days of age. Transport ceased in fed piglets at 18 to 24 h (39). Similarly, the intestine of lambs denied food for 24 and 48 h were permeable to polyvinylpyrrolidone (PVP), bovine proteins, and egg proteins; lambs fed bovine colostrum soon after birth were unable to absorb PVP and egg proteins at 24 h (41). Staley (77) indicated that intestinal maturation in pigs may be influenced by hormones and initiated via the pituitary-adrenal axis. Development of enzymatic activity of intestinal epithelium to prevent absorption of undesirable antigens or microorganisms also was noted as an approach to controlling bacteremias in the neonate.

Staley (77) observed the apical tubular system in ileal cells of pigs after absorption of colostral proteins had terminated. Clarke and Hardy (9) attributed closure in pigs to cessation of release of proteins from the absorptive cell, and Lecce (39) demonstrated that transport of proteins into the blood of piglets ceased long before uptake in the entire intestinal epithelium. Martinsson and Jönsson (50) observed uptake of dextran blue in the ileum of piglets up to 18 days of age, although no macromolecules were transmitted across the intestine after 1 day of age. Similarly, uptake of PVP into the cell occurred up to 16 days in the goat, whereas transport to the circulation ceased by 24 to 48 h (10).

Absorption of significant quantities of heterologous proteins administered orally at 24 h to calves previously given colostrum at birth
and 12 h of age (80) casts doubt on the concept that pinocytic activity is exhausted after initial contact with colostrum or other matter. Feeding calves PVP in a 56.7 mM solution of sodium lactate did not prevent invasion by a septicemia-producing strain of E. coli, invalidating the concept that saturation of the macromolecular transport system would have benefit (32).

Cessation of transfer of material through the cell membrane to the intercellular or subcellular space appears to be the dominant feature of closure, rather than the inability of substances to enter the tubular and vacuolar system within the absorptive cells (79). Thus, the process of closure apparently occurs in retrograde fashion, i.e., the basal cell membrane ceases to release the evacuolated product, transport ceases, and eventually uptake by the tubular system ceases.

**Amount of Immune Globulins Absorbed**

There is wide variability among calves in concentration of immune globulins in serum (13, 16, 20, 25, 47, 52, 60). Smith et al. (70) and Klaus et al. (34) attributed low concentrations of immunoglobulins in serum of calves that received colostrum to a defect in absorption. Speculation that the low concentrations resulted from a failure in absorption was based on the lack of a positive relationship between concentration of immunoglobulins in colostrum of dams and serum of their calves. However, the amount of colostrum consumed by the calves was not measured in either study, and the amount of immunoglobulin presented to the intestine for absorption was unknown.

McEwan et al. (53) noted a significant positive correlation between amount of γ-globulin ingested by calves and amount absorbed. Kruse (36) and Bush et al. (7) utilized regression analyses to study the relationship of concentration of total immunoglobulin in serum of calves at 24 h to the quantity of immunoglobulin available for absorption. Kruse (36) calculated that the increase in immunoglobulin concentration in serum over the 24 h following colostrum feeding was primarily dependent on the mass of immunoglobulin given to the calf, with more than 50% of the variation in the increase due to this factor. Similarly, Bush et al. (7) observed that 68% of the variation in blood serum γ-globulin in calves could be attributed to differences in amount of γ-globulin consumed per unit of weight. In a later experiment, Bush et al. (8) fed calves .3 or .6 g γ-globulin per unit of metabolic size at 6-h intervals using three batches of colostrum differing in γ-globulin content. The amount of immunoglobulin consumed had a significant effect on concentration of γ-globulin and specific IgG in serum at 24 h. Concentration of γ-globulin in the colostrum as an independent factor had a negligible effect on concentration of immunoglobulin in serum. Thus, it appeared that the mass of immunoglobulin consumed, but not the total mass of colostrum, was the primary factor determining concentration in the serum of calves. In practice, concentration of immunoglobulins in colostrum would be important in determining the absolute amount of immunoglobulin consumption.

Stott and Menefee (85) observed that the efficiency of absorption of IgM, unlike IgG and IgA, decreased as intake increased. Calves receiving colostrum low in IgM absorbed approximately the same quantity of IgM as those receiving comparable amounts of colostrum with a higher concentration of IgM.

Considerable variation among cows with respect to immune globulin content of colostrum has been observed (7, 34, 35, 57, 70). Oyeniyi and Hunter (57) found that the amount of IgG in colostrum from cows beginning their first, second, or third lactation did not differ. Cows beginning their fourth through seventh lactations had more IgG in colostrum. In an experiment in which pooled colostrum was fed (83), all of 114 Holstein calves fed within 12 h after birth absorbed IgG and IgM, and all absorbed IgA except one of 24 fed at 12 h. In a similar trial by Selman et al. (68) all of 50 calves fed pooled colostrum at 1, 5, and 9 h after birth absorbed immune globulin. However, by computer simulation Kruse (37) estimated that a certain frequency of hypogammaglobulinaemia cannot be avoided under practical farm conditions due to variations in birth weight, immune globulin concentration in colostrum, dose of colostrum, age at first feeding, and probably to genetically determined ability to absorb immune globulins. James et al. (30) observed lower serum γ-globulin in calves given an inoculum of duodenal fluid with the first feeding of colostrum than in control calves, however, in later work (29) this was not confirmed. Absorption of γ-globulin was
reduced in calves given an inoculum of duodenal fluid prior to feeding of colostrum. The suggestion was made that microbial exposure of the intestinal lumen may be related to impaired absorption of colostral immunoglobulins in the newborn calf.

Kruse (36) determined that age at time of colostrum feeding was the second most important factor influencing concentration of immune globulins in serum of neonatal calves. The absorption coefficient, expressing the absorbed fraction of a given amount of immunoglobulin, was reduced linearly to about half by delaying feeding from 2 to 20 h. Similarly, Staley et al. (80) observed the concentration of heterologous proteins in serum following oral administration to calves 24 h of age was about half that resulting from administration immediately after birth. Selman et al. (67) observed a significant negative correlation between time of first suckling by calves and 48-h concentration of immune globulin in serum but no relationship between the total time spent suckling during the first 8 h of life and serum immunoglobulin.

Some workers (4, 36, 68, 88) noted breed differences in apparent ability of calves to absorb immune globulins; however, this was not evident in other studies (7, 8). Also, in the report of Tennant et al. (88) the amount of immunoglobulin consumed was not known since calves were allowed to nurse their dams.

Factors Affecting Rate of Absorption

Balfour and Comline (2) measured absorption of $^{131}$I-labeled $\gamma$-globulin administered in various media into the duodenum of newborn anesthetized calves. When administered in whey prepared by incubation of colostrum with rennin, between 12 and 25% of the $^{131}$I-labeled protein was recovered from the lymph within 5 h whereas very little was absorbed when given in a solution of sodium, potassium, magnesium, and calcium chlorides. Substances in colostral whey facilitating absorption of $\gamma$-globulin when in combination were inorganic phosphate, glucose-6-phosphate, and a low molecular weight protein fraction. Using the same technique, Hardy (23) confirmed that factors in boiled colostrum whey were necessary for rapid absorption of bovine serum $\gamma$-globulin. In the presence of boiled whey, passage of $[^{131}$I]PVP with 160,000 MW into the lymph was accelerated in a comparable manner. Labeled PVP with 40,000 MW and human serum were absorbed to some degree in the absence of solvent factors, and a large proportion passed directly into the portal capillaries. Salts of lactic, pyruvic, acetic, butyric, and isobutyric acids resembled factors in colostrum in their facilitation of absorption of both $\gamma$-globulin and PVP. Potassium isobutyrate was the most effective and at concentrations of 56.7 m mole/liter generally accelerated absorption more than colostral whey; however, lymph flow was reduced when salts of the organic acids were administered. Poly-L-arginine increased the rate of bovine IgG transport in everted sections of pig intestine (71); however, there was some question about the effect of this compound on integrity of the intestinal membrane.

In intact calves, additions of chemical compounds to colostrum did not increase the rate of immune globulin absorption (4, 59). There were no significant differences in serum $\gamma$-globulin concentration in calves that received 2 mg histamine plus 75 g $\gamma$-globulin in milk at each of three feedings and that of calves fed milk with only $\gamma$-globulin added (59). Addition of 2.83 meq potassium isobutyrate per gram of $\gamma$-globulin in colostrum given at the first feeding within 1 h after birth had a depressing effect on absorption of specific immune globulin fractions, IgG and IgM, as well as on total $\gamma$-globulin (4).

Several (17, 22, 76) observed lower serum $\gamma$-globulin concentrations in calves fed fermented colostrum than in calves fed fresh or frozen colostrum from the same batch. Adjustment of the pH of fermented colostrum to that of fresh colostrum resulted in intermediate serum concentrations (17). There was little breakdown of colostral $\gamma$-globulin and IgG during fermentation.

Vukotic and Movsesijan (89) noted a negative relationship between precolostral concentration of IgG in serum of calves and amount of absorption during 24 h after receiving colostrum.

Role of Colostrum in Preventing Colibacillosis

Logan and Penhale (46) reported that feeding calves colostral whey, prepared by the addition of rennet, after closure to immune globulin absorption, delayed the onset of scours.
providing IgM was given intravenously. Administration of the IgM fraction inhibited colisepticemia but failed to influence the incidence of enteric disease. It was concluded that two separate immunological systems are required to protect the neonatal calf against colibacillosis and that colostral whey provides both systemic immunity and a local protective function within the gastrointestinal tract. Barnum et al. (3) and Gay (19) noted that some serotypes of *E. coli* produce colisepticemia if given before colostrum feeding but do not in most cases if administered later. Barnum et al. (3) stated that there is evidence that a specific K agglutinating antibody has protective properties within the intestinal lumen, supporting the suggestion that colostrum may assist in preventing the enteric form of colibacillosis. However, Gay (19) asserted that it is most unlikely that K agglutinins are the factor in colostrum which protects calves against colisepticemia, because calves normally receive in the colostrum agglutinins against the somatic antigens of *E. coli* associated with colibacillosis but usually do not receive agglutinins against the K antigens of these strains.

Anti-*E. coli* activity attributable to IgA, comparable to that in IgM and IgG fractions, was measured in bovine colostrum and postcolostral serum of calves (64). The half life of IgA in serum was approximately 2 days whereas that of IgM was 4 days. In contrast, Logan et al. (44) observed the protection afforded by each class of immunoglobulins differed from that of the others under conditions where IgM was injected intravenously and individual classes were fed to calves. The IgA was least effective in preventing diarrhea and hemoconcentration, whereas IgG and IgM were similar in their effect on enteric disease. No class of immunoglobulin provided the full spectrum of protection obtained with colostrum. Meyers et al. (55) found that most calves receiving colostrum from dams vaccinated with *E. coli* strain B44 were protected against diarrhea following challenge with the live organism. It was postulated that antienterotoxin in the colostrum protected the intestinal epithelium against the effects of enterotoxin, although it did not cause clearance of the organism from the intestinal tract as evidenced by fecal counts. Foley and Otterby (18) noted that feeding surplus colostrum to calves during the first few weeks of life had variable effects on the incidence of diarrhea.

In a preponderance of the trials reviewed, calves fed colostrum had a lower incidence of diarrhea than calves fed whole milk or milk replacer; however, few, if any, of the trials involved a uniform challenge with pathogens.

In numerous studies (13, 16, 20, 25, 52, 54, 60) the average concentration of immune globulins in serum of calves which succumbed to infectious diarrhea was lower than in calves which survived. However, some calves which survived had relatively low immunoglobulin concentrations, indicating that other factors also are involved in resistance to colibacillosis. In a survey of market calves, Hurvell and Fey (25) observed that 16% of 3217 calves which showed no signs of illness had concentrations of gammaglobulin in serum that could be regarded as hypogammaglobulinaemic. Ingram et al. (28) emphasized the specific nature of resistance conferred by colostral immunoglobulins, noting that 45 of 59 colostrum-fed calves that died had received colostrum that was devoid of agglutinins against the strains of *E. coli* associated with their death. Logan et al. (47) reported that hypogammaglobulinaemic calves synthesized serum immunoglobulin within a week of birth whereas calves with high serum immunoglobulin did not do so until they were 4 wk of age.

Smith et al. (70) recorded low mortality in "home-bred" calves on farms even though many of them had low immune globulin in their serum. Ferris and Thomas (16) observed an interaction between herds and serum immunoglobulin concentration in that 21% of the calves with low zinc sulfate turbidity (ZST) died in herds classified as high mortality herds whereas 7% of calves with low ZST levels died in low mortality herds.

The beneficial effects of colostrum in preventing transepithelial migration of one serotype of *E. coli* 055:B5:H7, in newborn calves were demonstrated by Corley et al. (12). In calves deprived of colostrum, a large number of *E. coli* were in the ileal mucosa and in the mesenteric lymph nodes of both the jejunum and ileum. Attachment or penetration of the epithelium by *E. coli* was not observed in calves fed colostrum with *E. coli*; however, some organisms were in the mesenteric lymph nodes. No bacteria were adherent to or within the epithelial cells of calves fed colostrum prior to

exposure of E. coli, and none was in the lymph nodes.

Total leukocyte counts and neutrophil numbers were higher in colostrum-fed than in colostrum-deprived calves at 6, 12, and 24 h after birth (48). Also, there was greater oxygen uptake by neutrophils from colostrum-fed calves when bacteria were opsonized with autologous or bovine sera, indicating a direct effect of colostrum on metabolism of the cells independent of serum effects.

REFERENCES


34 Klaus, G. G. B., A. Bennett, and E. W. Jones. 1969. A quantitative study of the transfer of colostral immunoglobulins to the newborn calf. Immunology 16:293.


63 Pierce, A. E., and A. Feinstein. 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.

64 Porter, P. 1972. Immunoglobulins in bovine mammary secretions. Quantitative changes in early
lactation and absorption by the neonatal calf. Immunology 23:225.
75 Smith, V. R., R. E. Reed, and E. S. Erwin. 1964. Relation of physiological age to intestinal permeability in the bovine. J. Dairy Sci. 47:923.