Immunology of Breast Milk

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A most important adaptation of the gastrointestinal (GI) tract of the newborn to the extrauterine environment is the development of a mucosal barrier against the penetration of bacteria, viruses, and other environmental antigens, i.e., food proteins. The mechanisms of host defense at mucosal sites, both immunologic and nonimmunologic, are underdeveloped during the neonatal period and more so in premature and small for date neonates (1).

The intestinal epithelial cells lack a well-defined brush border and retain a primitive transport mechanism for endocytosis of large molecules (2). It has been proven that the neonatal intestine may absorb larger quantities of ingested antigenic proteins and proliferating microorganisms than the adult intestine (3).

The number of the Peyer’s patches is small in mammals during the neonatal period and although recent studies have described T-helper and T-suppressor lymphocytes, B-lymphocytes, and macrophages on their lymphoid follicles (4), the functional ability of the cells seems to be immature until about 1 month of age (5). Furthermore, plasma cells, which are normally abundant in the mucosal lamina propria, are not detected in utero or during the immediate neonatal period (6).

Taking into consideration all of these immaturities and the absence of mucosal antigenic stimulation during intrauterine life, it is no wonder that human and other mammalian neonates exhibit characteristic absence of secretory IgA (sIgA) during the early postnatal period.

Shortly after birth, however, the ingestion of food antigens and the colonization of the gut with various microorganisms provide enough antigenic stimulation to evoke a secretory immune response. By 1 month of age, approximately all infants will have some detectable sIgA (7).

The availability of immunological factors in the secretions of the mammary gland may represent an evolutionary event to compensate through breast feeding for the transient deficiency of mucosal immunity in the neonate. Indeed human colostrum and milk bear many similarities to the external body fluids bathing the mucosal surfaces of the GI and respiratory tracts. Evidence so far also suggests that the immunoglobulin-producing cells observed in the mammary tissue during lactogenesis and in the colostrum and milk are of mucosal origin (8).

Fresh human milk contains many components that provide specific as well as nonspecific defenses against infectious agents or other macromolecules (9-11).
The contribution of colostrum to neonatal immunity involves both humoral and cellular factors.

HUMAN MILK ANTIBODIES

The most important of the humoral immunological factors in human milk are its antibodies, the principal immunoglobulin being the 11S secretory IgA. The slgA exists as a dimer of two 7S IgA molecules linked together by a polypeptide chain, called J-chain, and associated with a nonimmunoglobulin protein referred to as the secretory component. The IgA dimers produced by the plasma cells of the mammary gland are transported to specialized columnar epithelial cells where they unite with the secretory component (SC) and are discharged into the alveolar space (Fig. 1) (12,13).

Linkage of SC to the IgA dimer provides most mammals with antibody molecules that can coexist with the proteolytic enzymes of intestinal secretions (14). Thus, about 70% to 75% of the ingested colostral IgA has been found to survive passage through the gut of the newborn and is excreted in the feces (15).

The slgA constitutes about 20% of the total protein content of milk (16). Apart from slgA, other immunoglobulins such as 7S IgA, IgG, IgM, IgD, and IgE have been found in human colostrum and milk but in much smaller quantities (17). The highest levels of IgA and IgM are present during the first 5 days of lactation (Fig. 2) (18) with levels of IgA ranging fourfold to fivefold higher than IgM, 20- to 30-fold higher than IgG, and sixfold higher than serum IgA. As lactation progresses slgA as well as IgM decline, whereas IgG levels do not change significantly. After their rapid decline during the first days of life, IgA levels in milk decline more slowly until 3 months postdelivery. From then on and up to 12 months, the IgA levels are maintained at a stable level (19). However, when estimating the amount of immunoglobulins a breast-fed baby receives, one should also consider the increasing amounts of milk the baby is taking when getting older. It has been estimated that the breast-fed infant receives on average about 1 g of IgA each day and approximately 10 mg of IgM and IgG (20).

Some mammals, e.g., piglets and calves, acquire all the antibodies necessary for their protection from colostrum and milk by absorption through the gut wall during the first few hours of life. When deprived of milk, they die from septicemia (21).

In man, passive immunity is derived almost entirely from the intrauterine transport of maternal antibodies (2). Until recently it was believed that in human neonates immunoglobulins of breast milk could not cross the intestinal wall. However, Ogra et al. (15) have shown that small quantities of milk IgA antibodies can be absorbed immediately after birth by human neonates.

IgA immunoglobulin contains antibodies against many pathogens and potential pathogen viruses and bacteria, including several Enterobacteriaceae. Some specific antibodies discovered in human milk are listed in Table 1.

IgA antibodies found in milk possess specificity for infective agents endemic to
Intestinal Lumen

FIG. 1. Transport mechanisms for intestinal antibodies. (From Walker and Isselbacher, ref. 13.)

FIG. 2. Geometric mean levels of IgG, IgM, and IgA in colostrum and milk of 200 female subjects at various intervals after the onset of lactation. (Adapted from Ogra and Ogra, ref. 18.)
TABLE 1. Specific antibody reactivity in human colostrum and milk

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<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Other</th>
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<tr>
<td>Escherichia coli (O + K antigens and enterotoxin)</td>
<td>Rotavirus</td>
<td>Candida albicans</td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td>Polio virus types 1,2,3</td>
<td>Giardia</td>
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<tr>
<td>Clostridium tetani</td>
<td>Rubella virus</td>
<td>Chlamydia</td>
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<td>Bordetella pertussis</td>
<td>Echo viruses</td>
<td>Food proteins</td>
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<td>Salmonella</td>
<td>Coxsackie viruses A,B</td>
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<td>Shigella</td>
<td>Respiratory syncytial virus</td>
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<td>Vibrio cholerae</td>
<td>Cytomegalovirus</td>
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<td>Bacteroides fragilis</td>
<td>Influenza A virus</td>
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<td>Streptococcus Mutans type B</td>
<td>Herpes simplex</td>
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<td>Hemophilus influenzae type B</td>
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or pathogenic for the intestinal and respiratory tracts. They may be present in the milk and absent in the serum. Pregnant women, given *Escherichia coli* 083 orally, had IgA antibodies in their milk but not in their serum (22). Other investigators have observed similar responses using intrabronchial immunization in rabbits (23). Thus antibody response in the milk appears to be the characteristic feature of antigenic exposure in the gut associated lymphoid tissue or the bronchoepithelium associated lymphoid tissue, and strongly supports the concept of an enteromammary as well as a bronchomammary axis of immunologic reactivity in the breast.

The more probable explanation for the appearance of milk antibodies after antigenic exposure in various mucosal sites in humans is that specific IgA-producing cells home to the mammary gland after they have been exposed to the antigen at these sites as for example in the Peyer's patches. There are also indications that the homing to the mammary gland is dependent on hormonal factors (24). Other information indicates that homing may be further directed by glandular cell Ia-antigens coded for by the major histocompatibility complexes (25).

As breast-fed babies receive considerable amounts of sIgA antibodies directed against a variety of microorganisms that dominate in their surroundings, milk antibodies can be used as an epidemiological tool.

What Is the Functional Role of Milk Antibodies?

A number of action mechanisms have been suggested for secretory milk antibodies such as opsonization and, in particular, ability to promote phagocytosis by macrophages, complement fixation, bactericidal, antitoxic, and antiviral activities as well as aggregation of antigens (17,26). However, there is now substantial evi-
dence that a major function of intestinal antibodies is the process of immune exclusion at the mucosal surface (2), thus preventing infections and allergies.

Finally, it has been shown that immunization or vaccination of the mother improves the passive immunity transferred to the baby via breast milk as antibodies (27,28).

CELLULAR IMMUNE FACTORS

The cells of human colostrum and milk have been studied relatively little although they were discovered more than a century ago. The cells of human colostrum were apparently first observed by the pioneer biologist-microscopist-photographer Alexandre Donné who obtained their first photographic portrait in 1839 (29). He called them corpuscles and was unable to recognize their cellular nature.

The corpuscles of Donné were found to be cells 20 years later, in 1868, when Beigel examined stained preparations of colostrum microscopically (30). However, in those early days the functions of these cells were not examined and remained virtually unknown to immunologists.

In 1966 Smith, in Goldman's laboratory, examining the "debris" that were obtained after centrifuging colostrum, was surprised to find what Donné had observed 122 years before. Phase microscopy revealed that colostrum was packed with living motile cells (31).

Large numbers of leukocytes are present in human milk, particularly during the first weeks of lactation. Early colostrum contains the highest concentration of cells, about 1–3 × 10^6–8 cells/ml (17). By the end of the first week of lactation cell concentration is of the order of 10^5 cells/ml but because of the increase in the quantity of milk offered, the total number of cells available to the neonate remains large (24).

The leukocytes seen in colostrum are usually macrophages (40–50%), polymorphonuclear neutrophils (40–50%), and lymphocytes (5–10%). Numerous epithelial cells and epithelial cell-fragments are also seen in human colostrum. Later on, mature human milk cells consist of 85% to 90% macrophages, the remainder being mainly lymphocytes and very few epithelial cells or polymorphonuclear neutrophils. The proportion of the various white cell types does not change during breast feeding (32).

Morphologically, the neutrophils are similar to those seen in blood except that they contain numerous fat globules and fewer granules. Macrophages also contain many fat globules and other granular material (Fig. 3). The typical colostral corpuscle of Donné is a very large, lipid-laden macrophage. Lymphocytes appear similar to those found in peripheral blood.

Macrophages

Milk macrophages can be identified as being 20 μ to 40 μ in diameter. They are motile cells that adhere to glass. Histochemically, the milk macrophages differ
from the blood monocyte by having increased numbers of lysosomes and somehow decreased peroxidase staining. Furthermore, their cytoplasm contains significantly higher amounts of IgA (33).

The origin of milk macrophages has not been clearly defined yet. They could come from blood monocytes that begin to home to the mammary gland during the last months of pregnancy and differentiate there to activated-appearing macrophages (9).

There is little information about the function and rôle of the macrophages of breast milk. It has been suggested that macrophages in colostrum and milk are presumably involved in the defense against infections both in the breast and in the neonatal gut. In view of the extremely high proportion of macrophages in colostrum, it is tempting to postulate that these cells may be more important to the neonatal intestine than to the mammary gland.

Because their cytoplasm contains large amounts of sIgA antibodies, it has been suggested that these cells can function as a vehicle for transport or storage of immunoglobulins in breast milk (34).

In rats, Pitt et al. (35) have shown that a Klebsiella-induced necrotizing enterocolitis could be prevented by feeding rat colostral macrophages but not by feeding soluble colostral factors. These findings are in agreement with the observation that necrotizing enterocolitis is a rare disease in infants fed with untreated breast milk (36).

Milk macrophages have been shown to possess Fc and C3b receptors (35). Two recent studies performed to evaluate in vitro the ability of milk phagocytes (macrophages and polymorphonuclear neutrophils) to phagocytose and kill pathogenic organisms have shown good phagocytic activity against Staphylococcus aureus, E. coli and Candida albicans; however, their killing ability against E. coli has been found good in one (37) but quite poor in the other study (38).

Milk macrophages have also been shown to participate in antibody-dependent cell-mediated cytotoxicity of Herpes simplex type 1 virus infected tissue culture
We have also shown them in vitro to elicit antibody-dependent cytotoxicity using erythrocytes A₁ as targets. However, their cytotoxic ability was inferior when compared to that elicited from adult or neonatal peripheral blood monocytes when the same target cells were used (40). The latter could be owing to the extensive fat ingestion by these cells.

In order to further investigate their killing ability we also used the chemiluminescence assay and investigate their oxidative metabolic responsiveness during phagocytosis of opsonized zymosan particles. Human colostral phagocytes possess a definite oxidative metabolic activity that is intimately involved with the bactericidal function of these cells; however, their activity was significantly lower than that elicited by peripheral blood monocytes of healthy adults (41).

From the above we may conclude that human milk macrophages possess both phagocytic and killing abilities; however, how much they use their abilities in vivo and in what respects remains to be elucidated.

Human milk macrophages are also involved in a variety of biosynthetic and excretory activities. Thus they produce lactoferrin, lysozyme (9,42), components of complement, properdin, factor B, and epithelial growth factor (17).

Finally, some data indicate that milk macrophages may be important in the regulation of T-cell function by direct cellular cooperation or by processing the antigen (33).

**Lymphocytes**

The colostral lymphocytes comprise about 10% of the total cells. Of these, in colostrum, 50% are T-lymphocytes, but as lactation progresses, along with the drop of total lymphocyte-numbers, the percentage of T-cells falls to around 28% (43).

Colostral and milk lymphocytes have been found to respond in vitro to a number of viral and microbial antigens (31,44). Several studies have shown, however, that colostral and milk lymphocytes often respond to different antigens than those to which peripheral blood lymphocytes of the same persons do (43,45).

Thus, while rubella virus stimulates T-lymphocytes in secretory sites and milk as well as in systemic sites, *E. coli K*₁ antigen stimulates only milk lymphocytes. These studies support the concept of the enteromammary and bronchomammary axis reactivity in the breast that we discussed concerning slgA. As Parmely and Beer (46) have stated, "cells in colostrum and milk do not represent a random collection of leukocytes expelled as a casual by-product of exocrine secretion but rather give every indication of being a selected population of cells accumulated by specific, active biological processes."

Milk lymphocytes display a decreased response to mitogens such as PHA (43). This decreased reactivity has been attributed to various causes such as a relative deficiency of a certain population of T-cells (45), to suppressive factors found in the milk (24), or to deficient macrophage-T-cell interactions (34).
The majority of colostral T-lymphocytes are fully mature as they stain with monoclonal antibody to OKT$_3$ cell surface markers but do not possess OKT$_6$ surface markers, which are only found on immature cells (47).

The T-lymphocyte population in human milk was also found to contain both OKT$_4$ (helper/inducer phenotype) and OKT$_8$ (suppressor/inducer phenotype) subsets. The relative ratio of OKT$_4$-to-OKT$_8$ positive T-cell subsets in milk was found to be higher when compared with that found in peripheral blood T-cells (48).

Colostral lymphocytes have been found to be as reactive in the mixed lymphocyte reaction as their blood counterparts. However, the cytotoxic potential of human colostral lymphocytes is selectively deficient and its expression is dependent on the particular stimulating or target antigens presented (49). This finding suggests that some, but not all, cytotoxic T-cell precursors reside in colostrum.

In rats leukocytes may be transmitted through the milk from the mother’s bloodstream to the suckling’s bloodstream; this may be beneficial, causing adoptive immunity, or harmful, causing graft-versus-host disease (50).

We have no evidence thus far that human milk leukocytes can cross the human intestinal wall and enter the neonatal blood circulation. However, the transfer of maternal T-cell reactivity to tuberculin protein (PPD) from the mother to the human neonate has been observed through breast feeding (51). It has also been suggested that partly digested cells or smaller molecules transported by the T-cells, such as transfer factor or migration inhibitory factor can be transferred to the breast-fed baby (52). More studies are needed to elucidate the immunological benefits for the newborn transmitted through the immunocompetent cells in human milk.

Most B-lymphocytes in colostrum or milk bear surface IgA (52). There are conflicting results regarding the production of IgA antibodies by human milk lymphocytes. Some investigators think they do (53), whereas others found no active synthesis of IgA (34). At the moment it is not clear whether IgA antibodies present in milk are only a product of cells secreting IgA in the mammary gland parenchyma or also of cells present in the milk itself. Some investigators think that the immunoglobulins in milk originate mainly from colostral macrophages that transport it passively (34).

There are also some soluble factors in human milk that promote IgA synthesis. Pittard and Bill (33) have recently shown that cell-free media from colostral cells stimulate IgA synthesis in peripheral blood cells, but IgG and IgM synthesis is not affected.

So far the role of the ingested lymphocytes in the intestine of the newborn needs much further investigation.

ADDITIONAL PROTECTIVE FACTORS

In addition to human milk antibodies and its cellular immunological factors, several other substances have been demonstrated to provide additional protection against systemic and gastrointestinal infection in newborn infants.
Human colostrum and milk contain all the components of the complement system. Active C₃ production has been reported in vitro in breast milk cell cultures (54).

Lactoferrin and other iron-binding proteins have been shown to possess inhibiting effects on the growth of *E. coli*, *S. aureus*, and *C. albicans* by withdrawing the iron that these organisms need for their metabolism (55).

Lysozyme is found in human milk in amounts 300 times greater than in cow’s milk. Lysozyme is known to possess powerful bacteriolytic properties (56).

Interferon, migration inhibiting factor, alpha-fetoprotein, and a number of other substances are also present although their roles have not yet been fully determined (9).

Antistaphylococcal factors appear to be active against experimental staphylococcal infections and may be important for local mammary gland protection (57).

Growth factors that promote the growth of *Lactobacillus bifidus* are valuable because they inhibit growth of enteric gram-negative bacilli (9).

Antiviral factors have also been demonstrated in lipid and aqueous phases of human and animal milk in vitro; their in vivo roles remain to be elucidated (10).

Recent studies have also demonstrated the presence of other substances in human milk that promote growth and maturation of intestinal epithelial tissue (58). The acceleration of the maturation of epithelial cells will shorten the period of vulnerability in the neonate and lessen the susceptibility to disease.

However, in discussing antibacterial factors in human milk one should not forget the interactions between them: Although complement lysis of *E. coli* did not occur in the presence of secretory IgA alone, it occurred when, in addition to complement and IgA, lysozyme was present as well (56).

As pointed out by Welsch and May (10), although it is often difficult to assign a precise clinical significance to each factor, it is hard to avoid the conclusion that the sum of the factors is responsible, at least partially, for the differences in the morbidity and mortality of breast-fed versus non-breast-fed infants.

Finally, HLA antigens and other antigens that have been associated with cell-to-cell recognition events have recently been found in fat globules and epithelial cells of human milk (59). Their role in cellular homing mechanisms or immune responsiveness remains to be clarified.

**HUMAN MILK AND NEONATAL MORBIDITY AND MORTALITY**

There is now growing information documenting that human breast milk is superior to cow’s milk in minimizing both the morbidity and mortality caused by a number of infective and noninfective disorders.

Many epidemiologic studies support the idea that breast feeding can protect the infant against infections and death from diarrheal disease particularly in underdeveloped countries and disadvantaged communities (60-63). One should nonetheless bear in mind that this is in part owing to lack of contamination of human milk. However, breast milk is also able to prevent the development of induced necrotiz-
ing enterocolitis in a rat model (35). Largua et al. (64) report from Argentina that only small doses of colostrum (5 mg/kg daily) reduce the incidence of endemic neonatal *E. coli* diarrhea in the nursery. However, even in well-developed countries investigators have not uniformly supported the belief that breast-fed babies have diarrhea less often than formula-fed ones (64,65). With respect to necrotizing enterocolitis it seems that frozen human milk does not protect premature from developing the disease (67), whereas untreated human milk with living cells does (36).

The protective effect of human milk has been shown by some investigators to extend to other extraintestinal infections such as those caused by respiratory syncytial virus (68) and Rotavirus (69).

Finally, although Chandra (70) has suggested a lower incidence of allergy in breast-fed infants, more studies are required to define the antiallergic role of breast feeding.

From the data available thus far regarding the effect of human breast milk on the incidence and severity of neonatal infections, we can come to the following conclusion. Newborns and more so prematures are born with various immaturities, some of which concern mucosal immunity. However, they cope quite well provided they are not challenged with conditions of stress. However, when increased activity of their host-defense mechanisms is demanded, they are unable to overcome difficulties and severe generalized and often overwhelming infections may develop.

Human milk with its many valuable immunological factors helps to increase neonatal resistance to infections. This is more obvious in disadvantaged communities where the babies meet with increased challenges.

It will be interesting to see what the effect of untreated human milk in sick low-birth-weight babies nursed in intensive care units in developed countries is. Babies in these units are usually colonized with pathogenic antibiotic-resistant, gram-negative organisms (71).

From preliminary studies by our group and other investigators (72), it seems that human milk—pasteurized, frozen, or untreated—does not quantitatively alter the bacterial flora. However, Gothefors et al. (72) found decreased virulence of the bacteria present in stools and speculate that this may be one of the ways in which breast feeding prevents infections. This fascinating field is still widely open for research.

REFERENCES


IMMUNOLOGY OF BREAST MILK


**DISCUSSION**

*Dr. Rubaltelli:* It is well known that necrotizing enterocolitis (NEC) is a multifactor disease and in many nurseries it is apparently related to the use of umbilical catheters and to microbiological ecology, among many other things. Human milk, for instance, is not available in our unit, and we use a special preterm formula; however, since we substituted transcutaneous pCO₂ and pO₂ measurements for umbilical arterial catheterisms, we do not see NEC anymore, whereas in other nurseries where they are using raw human milk they still see the disease. I do not think I can support the affirmation that human milk prevents NEC. The incidence of NEC in a neonatal unit will depend on many different things, among which the microbiological ecology and the way the sick newborn is approached are probably the most important.

*Dr. Xanthou:* You are right, there is a great debate regarding: (a) the etiology of NEC, and (b) the effect of human milk. As you mentioned, different etiologies have been proposed. For instance, a substantial proportion of investigators have found it to be associated with epidemics of *Klebsiella* or *Clostridium*, and they believe that infective microorganisms at least contribute to the development of the disease. Now regarding the second argument, it seems that in all the studies that came to the conclusion that human milk has no effect on NEC, either frozen or pasteurized human milk, which does not contain any living cells, was used. It seems that the living cells are really active. Eric Burnard in Australia did a very careful study with fresh human milk containing living cells and was able to reduce the incidence of NEC in his neonatal unit to almost nil (1).
Dr. Stern: Dr. Rubaltelli, your suggestion is that the disease is always a phenomenon of vascular compromise from the catheter. Pathologically it looks like an ischemic enteropathy that could be catheter related or attributed to hypoxia. However, there is also concern that the solute load of the formula, rather than the nature of the formula, may be responsible because a partially compromised bowel just can not deal with a high solute load and gives way quicker. It may therefore not be so much the constituent of the milk but the actual solute concentration.

Dr. Lozano: I wonder if you have any precise information regarding how the humoral and the cellular response will be modified by previous infections in the mother or by labor and delivery.

Dr. Xanthou: We do not have a lot of information about the milk of sick mothers because in those circumstances they usually do not breast-feed. Infections will clearly cause a rise in antibody titers in the milk. When the mother has mastitis, then increased numbers of polymorphonuclearphils may appear in the milk due to the local infection. I do not think information is available on milk from mothers with, let us say, neoplastic diseases of the breast. Furthermore, I am not aware of studies regarding the influence of the mode of delivery and so on, on the composition of the milk.

Dr. Goyens: Which mechanism could explain the antiallergic activity of human milk? Could it be that human milk has an antiallergic potential by itself, or is the incidence of allergy lower in breast-fed infants because the first contact with allergens is delayed, allowing the biological clock to go on turning and the immune system to mature? I do not know if there are any data with regard to this in humans. Ann Fergusson showed that when mice are exposed perinatally to ovalbumin, they develop a very heavy allergic reaction, whereas when they are exposed for the first time 24 hr later, they become tolerant.

Dr. Xanthou: There is still much work to be done in order to make sure that breast milk has an antiallergic activity. One of the mechanisms that is proposed depends on the presence of sIgA in human milk. These sIgA prevent the entrance of allergenic substances, e.g., cow’s milk proteins, into the intestinal wall and from these into the systemic circulation, which triggers the allergic reaction in the newborn (2). This sort of immune exclusion is very important during the neonatal period owing to the immaturity of the intestinal tract. The intestinal wall is much more permeable at that time than later in life.

Dr. Heim: Could you tell us how allergy would be if you give an infant breast milk from another mother. How dangerous is that in respect to later immunological reactions, allergy, and so forth?

Dr. Xanthou: Most human milk banks take milk from various mothers and usually mix all samples together, so that the babies are not receiving milk from their own mothers. It would be preferable to have the baby taking his/her own mother’s milk because it contains antibodies against microorganisms that are present in her environment and her gastrointestinal tract, which are clearly more useful for the baby. However, if that is impossible, the next best thing to do is to give another mother’s milk. I am not worried about graft-versus-host disease (GVHD) at all; it has not been shown to occur in humans. Although we do a lot of exchange transfusions, even intrauterine transfusions very early in gestation (3), very rarely do cases of GVHD occur, and my suspicion is that these only probably occur in extremely immunodeficient babies.

Dr. Heim: I am very happy to hear this because on the North American continent, especially in the United States, the idea is growing among people that we have to avoid giving foster mothers’ milk or wet nurses’ milk to premature infants. We have been doing it in
Toronto for many years, giving fresh premature breast milk to premature infants, within 24 hr after collection, not pasteurized, and no reaction has been observed.

Dr. Xanthou: Human milk banks have been working very successfully in Europe for the last 10 years. So far no complications such as GVHD have been reported. Many of these human milk banks try to give untreated human milk, kept at 4°C not only for 24 hr, but even for 72 hr. This storage does not increase the number of pathogenic microorganisms. The number of living cells in human milk decreases slightly but their function remains intact, even after 72 hr (4).

Dr. Heim: I wonder if other colleagues from the United States could comment on it.

Dr. Xanthou: There is a long experience with that. In fact in the United States alone, there were 80,000 prematures raised in Martin Cooney's incubator exhibitions by a series of wet nurses who breast-fed all the infants. That began in 1900 and went on until the late 1930s. The interesting thing is that Cooney insisted that the same nurse always wetnurse the same infant. These were not the natural mothers, but women who were brought in to breast-feed. It is interesting that nobody ever studied that population. As far as I know, nobody ever suggested that there was anything wrong with any of this. I do not know that it is such a new phenomenon; it was quite common in Germany, too, at the turn of the century.

Dr. Xanthou: It is certainly better to have the baby breast-fed by the same person than given banked human milk. Indeed, it has been shown that when the sucking baby is colonized this may induce production by the foster mother of antibodies that the baby gets back through the milk. The milk contains the antibodies that defend the baby against the potential pathogenic organisms that colonize him.

Dr. Stern: There is a long experience with that. In fact in the United States alone, there were 80,000 prematures raised in Martin Cooney's incubator exhibitions by a series of wet nurses who breast-fed all the infants. That began in 1900 and went on until the late 1930s.

Dr. Heim: I wonder if other colleagues from the United States could comment on it.

Dr. Xanthou: When we give raw human milk in the neonatal intensive care unit, we are faced with a dilemma. On the one hand, we know that in some way we may prevent infection, and on the other, we know that many viruses are transferred to the baby through human milk: CMV, for example, and, in southern Europe, hepatitis B. We have had cases of CMV pneumonia in babies receiving raw human milk from other mothers. I suggest that we always encourage mothers to give their babies their own milk. I am not really in favor of giving raw human milk to all preterm babies, because of the risk of CMV infection.

Dr. Xanthou: This is true. However, in Alabama, Stagno (5) studied this particular problem and found that indeed babies do get CMV through breast milk but at the same time, they get a lot of antibodies. About 50% excreted the virus in the urine, but the morbidity was almost nil. He followed them until the age of 6 or 7 years, and observed that their growth and psychomotor development was normal. He therefore came to the conclusion that this was a very good way to immunize these babies against CMV.

Dr. Marini: Of course, not all the babies receiving CMV will develop the infection but when you deal with very small preterm babies, they will suffer a severe infection and some will die. I am well acquainted with Stagno's studies (6) concerning excretion of CMV but others have reported contradictory findings. Of course, the problem is not only restricted to the milk; blood transfusions and so on also need to be considered. So, my conclusion is that there is a risk. I think, however, that hepatitis B represents a greater risk in the south of Europe. When we know that the mother is B positive, newborn transmission can be prevented by giving immunoglobulins and then vaccinating the baby. We do not have the serology of all the mothers who give milk; consequently, we have to vaccinate all the infants against hepatitis B, otherwise we run the risk of rapid dissemination of the disease.

Dr. Xanthou: The ideal situation would be to test all mothers who donate milk for hepatitis B, but unfortunately this cannot be done in all nurseries.
Dr. Räihä: In Sweden, first of all, we screen all the mothers in order to find out which mothers are CMV negative and which are CMV positive. We also screen all the donors and collect milk from CMV positive and negative donors in separate pools. All the preterm infants of CMV negative mothers primarily get their own mother's milk, but if they need substitution, then they only receive fresh, CMV negative milk.

Dr. Stern: What do you do with CMV positive milk?

Dr. Räihä: CMV positive milk is usually pasteurized or it is also used for making human milk protein and human milk fat for fortification of pooled milk.

Dr. Xanthou: I would prefer the second solution because pasteurization does not really kill viruses.

Dr. Rubaltelli: Suspension of breast feeding will not prevent the transmission of hepatitis B virus from the mother to the infant, because we know that transmission does not occur only through breast milk. I agree therefore that we need to be careful in giving banked human milk to premature infants, and that we should look for CMV and hepatitis B virus, give immunoglobulins, and vaccinate. I do not think, however, that one should discourage a hepatitis B positive mother from breast-feeding her own infant, certainly not in those countries where we suspect hepatitis B virus infection to be fairly common.

Dr. Businco: First of all, I would like to mention some recent data from Sweden (7), that shows that breast milk in vitro can prevent the attachment of some bacteria such as pneumococcus and hemophilus influenzae to the epithelial cells of the mucosa of the throat. I think this is very important because it can explain the lower morbidity due to otitis media in breast-fed infants. With regard to the risk of graft-versus-host reactions in breast milk, we are used to feeding infants who have severe combined immune deficiencies and severe T-cell defects with fresh untreated breast milk and have never seen graft-versus-host reactions in these babies. The controversy in the literature concerning the protective effect of breast-feeding newborns at risk for atopy, I mean newborns of atopic parents, can be partly explained by the fact that the different studies were not planned in the same way. Some were conducted prospectively and others retrospectively. We always need to be very cautious in interpreting the latter results. Since 1978, we have been conducting a program of atopy prevention in at-risk newborns; prolonged breast feeding is advised for all these babies. Our study (8) totally confirms the results of other authors, demonstrating the prophylactic effect of prolonged breast feeding. However, one should insist that it is absolutely necessary to control the diet of the nursing mothers because some antigens clearly pass into the milk and can consequently sensitize the baby. Large quantities of milk or eggs, for example, should be excluded from the mother's diet. Furthermore, it appears that the prophylactic effect of breast feeding is nonspecific because, as we all know, breast-fed babies experience fewer infections than nonbreast-fed; there is also a strict correlation between viral infections, enteritis, bronchiolitis, and atopic sensitization; several years ago Oscar Frick (9) demonstrated that the atopic sensitization in children is triggered by viral infections. Maybe one of the prophylactic effects of breast milk could be owing to the lower morbidity from infections in the breast-fed infants.

Dr. Shmerling: Further to what has just been said on the prophylactic effect of breast milk against the development of gastrointestinal allergy to cow's milk, a few years ago we published an analysis of cases of pure gastrointestinal cow's milk allergy (10). We observed that those children who had been breast-fed for at least 3 to 4 weeks had a much milder course of the disease than those who had never been breast-fed. Another important observation (unpublished) was that children of atopic parents who developed allergies, not only gastrointestinal cow's milk protein induced allergy but also severe generalized anaphylactic
shock reactions, after 3, 4, or 6 months of full breast feeding had all received a bottle of cow’s milk during the first day of life. Now, this situation may be the clinical correlate of the experimental situation described by Fergusson and Strobel from Edinburgh, to which Dr. Goyens referred. The early progressive transfer of antigens through breast milk may be necessary to establish immunotolerance; whereas the massive ingestion of antigens, during the first or second day of life in these newborns at risk for atopy, may cause a breakthrough into the system of immunotolerance and trigger the mechanisms leading to immunointolerance.

REFERENCES