Ontogeny of the Mucosal Immune System

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INTRODUCTION

Contrary to most animal species, the human fetus acquires maternal immunoglobulin G (IgG) via the placenta (1) and probably to some extent from swallowed amniotic fluid via Fcγ receptors expressed by fetal enterocytes (2). Intestinal uptake of secretory IgA (S-IgA) antibodies after breast-feeding appears to be of little or no importance in supporting systemic immunity in the neonatal period (3), except perhaps in the preterm infant (4). “Gut closure” in humans normally seems to occur mainly before birth, but the various factors involved in this process remain poorly defined (5,6).

Most babies growing up under privileged conditions show remarkably good mucosal resistance to infections if their nonspecific defense mechanisms are normally developed; this fact reflects largely a satisfactory humoral immune protection of their mucosae mediated by maternal IgG antibodies, which are distributed to the interstitial tissue fluid at a ratio of 50% to 60% of the intravascular concentration (7). Nevertheless, an optimal barrier function of mucosal membranes in the neonatal period depends on adequate supply of breast milk; this is especially apparent in relation to infectious diseases and is highlighted in a regrettable manner in developing countries (8–10).

Immediately after birth, the mucosae are bombarded by a large variety of microorganisms and protein antigens from the environment (the latter particularly in formula-fed infants); the mucosal surface area to be protected is indeed enormous, probably more than 100 times that of the skin. Therefore, after the period of passive immunity, the survival of the babies will rely on their own immune responses.

At mucosal surfaces such adaptive immunity is exerted mainly by locally produced and actively externalized S-IgA and S-IgM antibodies, which after infancy represent quantitatively by far the most important humoral immune system of the body (11,12).
The cellular basis for this is the fact that exocrine glands and secretory mucosae contain most of the body’s activated B cells, particularly the gut lamina propria where about 80% of all Ig-producing blasts and plasma cells are located (12). The majority of these immunocytes produce dimers or larger polymers of IgA that can be transported actively through the serous type of secretory glandular epithelial cells (13) to act in a first-line mucosal defense providing immune exclusion (Fig. 1). In adults, more IgA (~40 mg/kg body weight) is thus transferred to the gut lumen as S-IgA every day than the total daily production (~30 mg/kg) of IgG (14).

**FIG. 1.** Model for epithelial transport of J-chain-containing dimeric IgA by transmembrane secretory component (SC or poly-Ig receptor) expressed basolaterally on glandular cells (at the top) and for humoral immunological homeostasis in mucosal lamina propria (at the bottom). It is postulated that a critical balance is normally maintained in the mucosa between available immunoglobulins (for simplicity, only IgA and IgG are depicted). Secretory IgA acts as a first-line defense by performing immune exclusion of antigens in the mucus layer at the epithelial surface (to the right). Antigens bypassing this trapping mechanism may meet corresponding serum-derived IgG antibodies in lamina propria, where they are subjected to immune elimination. The IgG-containing immune complexes formed in this process will activate complement and engage phagocytic cells; inflammatory mediators are thus probably formed continuously in the mucosa. Some IgG also leaks out between epithelial cells (broken line) and contributes to immune exclusion, particularly in the respiratory tract. An adverse inflammatory and tissue-destructive development is normally inhibited by blocking antibody activities exerted in the mucosa by serum-derived monomeric IgA and locally produced dimeric IgA. Moreover, antigens may be returned efficiently to the lumen by the SC-mediated transport mechanism (at the top) after being bound to dimeric IgA antibodies. (For further details, see ref. 13.)
PASSIVELY ACQUIRED SPECIFIC MUCOSAL IMMUNITY

During the first few days after birth, only occasional traces of S-IgA and S-IgM normally appear in exocrine fluids, whereas some IgG is usually present (15,16), obviously as a result of passive external diffusion or epithelial "leakage" (Figs. 2 and 3). Its immediate source is the interstitial tissue fluid, which after 13 to 17 weeks' gestation, contains readily detectable IgG of maternal origin in most organs, particularly in the highly vascularized mucosae (17,18). Such IgG antibodies to dietary constituents and infectious agents may, in theory, adversely affect mucosal penetration by macromolecules through various biological amplification mechanisms and hence act as a two-edged sword (Fig. 1). This possibility has been suggested by in vitro and in vivo test models in which IgG antibodies to one antigen were shown to enhance mucosal penetration of bystander proteins (19,20). Mucosal integrity can apparently be damaged by lysosomal enzymes released from polymorphonuclear granulocytes

FIG. 2. Immunofluorescence staining for IgG (A) and IgA (B) in comparable fields from adjacent tissue sections of proximal small intestinal mucosa from a 26-week-old fetus. The specimen was fixed in ethanol to retain diffusible proteins. IgG abounds in the lamina propria but is absent from the crypt epithelium (C). The epithelium covering the villi (V) contains some intercellular IgG, indicating leakage of interstitial fluid to the gut lumen, where IgG is associated with the mucous layer. Note complete lack of IgA. Original magnification ×150. Reproduced with permission from Brandtzæg P, Nilssen DE, Rognum TO, Thrane PS. Gastroenterol Clin North Am 1991; 20: 397–439.
FIG. 3. Schematic representation of possible sources of mucosal antibodies in the alimentary tract in the perinatal period. The question marks indicate that the nature (degree of degradation) and source (maternal or fetal urogenital system) of amniotic S-IgA are uncertain (29); that the presence of locally produced salivary S-IgA varies among infants immediately after birth (23); and that S-IgA of local origin is quite unusual in the intestinal tract of newborns (23).
that are known to be attracted when complement-activating immune complexes are formed locally (21). Such inflammatory mechanisms of low intensity may contribute to an increased influx of dietary antigens in newborns compared with older infants, although there is no direct evidence to support this notion.

Maternal IgG within the mucosal lamina propria is unquestionably of value for protection against infections in a second-line mucosal defense affording immune elimination (Fig. 1); but breast-feeding, providing S-IgA antibodies for first-line defense, should rightly be considered an important "substitution therapy" in infancy (Fig. 4), as mentioned in the Introduction. Moreover, it seems justified to believe that the immunopathological potential of maternal IgG antibodies is of greater importance in infants who are not breast-fed. Nevertheless, regardless of age, systemically derived or locally produced IgG antibodies probably also aid protection against infections significantly in first-line defense by contributing to immune exclusion (Fig. 1), particularly in the respiratory secretions, where less proteolytic activity exists than in intestinal juice (22).

INDUCTION OF SPECIFIC MUCOSAL IMMUNITY

After the cessation of passive immunity, the chances of survival depend on the body's capacity for induction of adaptive defense mechanisms. Specific mucosal immune responses are mainly elicited in the intestinal Peyer's patches and other organized parts of gut-associated lymphoid tissue (GALT), such as the numerous solitary lymphoid follicles, although a primary role of mesenteric lymph nodes as well as oro- and nasopharyngeal lymphoid tissue (Waldeyer's ring) should also be considered (23).

Important characteristics of lymphoepithelial structures like the Peyer's patches and tonsils are the organized microcompartments containing distinct B cell, T cell, and accessory cell subpopulations, as well as restrictions in the potential for recirculation of lymphoid cells to (and from) various other tissues (11,12). Hence activation of mucosal immunity is at least partially independent of the systemic immune system. GALT mainly supports the immunological protection of gut mucosa, but to some extent also other mucosae, including those of breast-fed infants (Fig. 4). Mucosa-associated lymphoid tissue (MALT) distributed throughout the body apparently functions principally in an integrated way (the "common mucosal immune system"); but recent evidence suggests a certain regionalization, especially a dichotomy between the gut and the upper aerodigestive tract with regard to homing properties and terminal differentiation of B cells (23).

Although a primary inductive role of the mucosal lamina propria cannot fully be discounted, antigen priming of B and T cells belonging to the mucosal immune system mainly seems to take place in the organized parts of MALT, at least against infectious agents. Particulate antigens from the mucosal surfaces are preferentially taken up at these sites through specialized areas of the follicle-associated epithelium containing M ("membrane") cells and are then transported into the underlying lymphoid tissue,
FIG. 4. Schematic representation of the integrated mucosal immune system, with particular emphasis on the migration of primed B cells from Peyer's patches via lymph and peripheral blood to lactating mammary glands. Such distribution of precursors for IgA plasma cells beyond the gut is an important basis for local production and subsequent occurrence of S-IgA antibodies (→) specific for enteric antigens (*) not only in breast milk but also in other exocrine secretions such as saliva, tears, and respiratory fluids. By this mechanism, the breast-fed baby will receive S-IgA antibodies (→) directed against the microbiota colonizing its mucosae (initially reflecting the microflora of the mother) and thereby be better protected both in the gut and upper airways.
which contains lymphoid cells as well as macrophages and other antigen-presenting cells (APCs) of the dendritic variety (11,12). Less is known about the preferential port of entry for soluble antigens.

After antigen-induced proliferation and partial differentiation in MALT, both B and T cells migrate rapidly to regional lymph nodes; after further differentiation, the antigen-primed cells proceed via lymph into the peripheral circulation. Since these cells express adhesion molecules or "homing receptors" that are specific for determinants on endothelial cells present in mucosal and glandular tissues, they will extravasate preferentially into these tissues (Fig. 4). Thus most of the B and T cells stimulated in GALT migrate to distant intestinal lamina propria, and certain T cell subsets prefer the intestinal epithelium and become intraepithelial lymphocytes, particularly those bearing CD8 (12).

Human Peyer's patches are well developed early in fetal life but B cell activation, as reflected by germinal centers, is not apparent until shortly after birth (24,25). Such dependency on antigenic and mitogenic stimulation is supported by the delayed appearance of circulating IgA-producing cells after birth (26). Also, animal studies have demonstrated lack of activated B cell follicles in Peyer's patches of germ-free mice (27). In addition to the increasing microbial load, food antigens probably contribute to the early stimulation of GALT as suggested by the appearance of S-IgA antibodies to β-lactoglobulin in neonatal breast milk ("witch's milk") from babies fed cow's milk formula (28).

IgG and S-IgA from amniotic fluid (29) may be taken up by the fetus, and maternal anti-idiotypic antibodies of these classes could constitute a low-grade antigenic stimulus of MALT before birth. In addition, S-IgA from breast milk, either as anti-idiotypic antibodies or bound to luminal antigen, might represent a stimulus in the suckling baby as there appears to be some sort of Fc receptors on M cells of Peyer's patches (30). It may be theorized that antibodies from the mother in various ways exert a guidance function in early priming of the newborn's mucosal immune system, but the importance of this possibility is unknown.

Intrauterine infection results in early activation of MALT-derived, Ig-producing immunocytes, particularly of the IgM class (26). Furthermore, T cells in fetal intestinal lamina propria can be activated by mitogens or superantigen in vitro (25). Such observations suggest that the mucosal immune system is immunologically competent, at least during the final trimester. It may seem paradoxical, therefore, that several weeks normally elapse after birth before MALT responds to antigenic exposure. However, stimulated neonatal T cells are relatively deficient in secretion of interleukin-2 (IL-2), IL-4, IL-6, and interferon-γ (IFN-γ)—cytokines that are most likely to be important to the immunological responsiveness of MALT and to the immune system in general (reviewed in ref. 25). Other proposed explanations for the postnatal delay in overt immunostimulation are immaturity of APCs, immunosuppressive effects of maternal IgG, and hormonal influences. Anyhow, the neonate has to pass through a vulnerable period in terms of susceptibility to infections.
Scattered B and T lymphocytes are seen in the human fetal gut lamina propria from 14 weeks' gestation (24,25). A few IgM- and IgG-producing plasma cells have been reported to appear somewhat later and remain in small numbers until birth, whereas IgA-producing cells are either absent or extremely rare (reviewed in ref. 23). By contrast, human fetal salivary glands sometimes contain a few additional IgA-producing cells, especially after 30 weeks' gestation (Fig. 5); most of these immunocytes (~90%) are of the IgA1 subclass and virtually all express J chain. This apparent difference between salivary glands and gut mucosa with regard to low-grade fetal immune activation is intriguing (Fig. 3). Foreign protein antigens and maternal antiidiotypic antibodies may be present in amniotic fluid, to which the oral cavity is continuously exposed during fetal life. Perhaps the salivary glands, particularly the minor ones, may be stimulated locally by retrograde passage of antigens or maternal antibodies (32) through the ducts. It is also possible that tonsillar stimulation is of special importance for salivary gland immunity in the fetal and perinatal period.

The postnatal numbers of IgA- and IgM-producing immunocytes in the intestinal lamina propria and salivary glands start to rise rapidly after 2 to 4 weeks, with the IgA class becoming predominant after 1 to 2 months (Figs. 5 and 6). For the first 6 months, however, there is a striking admixture of IgD-producing cells in the parotid

![Image](image_url)
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IgA-producing immunocytes are normally undetectable in human intestinal mucosa (including the appendix) before 10 days of age (reviewed in ref. 23). Thereafter a rapid increase takes place, apparently somewhat earlier than in the salivary glands, but IgM immunocytes usually dominate up to 1 month (Figs. 6 and 7). Prominent development of IgM cells in the early phase of gut immune responses has been shown also in animal experiments. No significant increase of intestinal IgA-producing cells has been reported after 1 year, but IgM-producing cells seem to decrease (23).

These observations have been made in industrialized countries, while a much faster development of the mucosal IgA immune system is seen in healthy children from developing countries (reviewed in ref. 23). This shows that mucosal immunity is...
FIG. 7. Immunofluorescence staining for IgA in ethanol-fixed normal adult colonic mucosa (A) compared with staining for IgA (B) and IgM (C) in adjacent tissue sections of mucosa from a 2-month-old girl (gut lumen at the top). Note the relatively small number of Ig-producing cells in the latter specimen; the ratio of IgA to IgM immunocytes is about 2.5:1 compared to the adult colonic isotype ratio of 15:1. Despite the few immunocytes, large amounts of IgA and IgM have been taken up by columnar crypt cells (signifying external transport). Virtual absence of interstitial IgA staining (B) reflects low serum level of IgA, contrasting the background staining seen especially in the basal parts of the adult lamina propria (A). Original magnification ×150. Reproduced with permission from Brandtzaeg P, Nilssen DE, Rognum TO, Thrane PS. Gastroenterol Clin North Am 1991; 20: 397–439.
highly adaptable to the antigenic load of the environment. However, at least in the first 6 months of life, there is no apparent difference in salivary S-IgA antibody levels between breast-fed and bottle-fed infants (31).

**EPITHELIAL TRANSPORT AND DEVELOPMENT OF SECRETORY ANTIBODIES**

The epithelial poly-Ig receptor, or transmembrane secretory component (SC), is imperative for the active external transport of S-IgA and S-IgM (13). Its constitutive intestinal expression is quite weak in the crypt epithelium before the 29th week in utero; thereafter, it increases up to 32 weeks' gestation. An adult SC level is reached in the crypts 1 to 2 weeks after birth (Fig. 6). A comparable development is seen in fetal salivary glands, where SC first appears in a few acini and small ducts and increases between 20 and 30 weeks' gestation (Fig. 5). In addition, there is a remarkable temporary enhancement of SC expression shortly after birth (see later).

Apical staining for IgA in epithelial elements has been noted in salivary glands after 30 weeks' gestation, suggesting external transport of S-IgA (reviewed in ref. 23). This accords with the presence of J-chain-positive IgA immunocytes (see above). The J chain peptide has to be incorporated into the poly-Ig structure of dimeric IgA and pentameric IgM to make these polymers reactive with SC (Fig. 1). We have been unable to see similar signs of an active S-IgA system in fetal intestinal mucosa. The S-IgA that has been reported to occur in the fetal gut lumen may therefore be derived both from amniotic fluid (29) and saliva (Fig. 3). In fact, S-IgA and S-IgM antibodies to poliovirus as well as to Escherichia coli have been detected by sensitive immunoassay in both meconium and saliva of some neonates on the first day of life (32).

**REGULATION OF EPITHELIAL IMMUNE FACTORS AND INVOLVEMENT OF CYTOKINES**

SC shows strikingly increased expression in salivary gland epithelium after the second postnatal week; it subsequently decreases to the perinatal level around the sixth month (Fig. 5). In the intestinal crypts, an adult level of SC expression is reached at 1 to 2 weeks. In salivary glands, a remarkably decreased epithelial expression of amylase, lysozyme, and lactoferrin is observed shortly after birth (Fig. 8), perhaps because the cellular stores are emptied by postnatal increase in secretory activity resulting from suckling. The subsequently raised expression of these defense factors parallels that seen for SC and might be ascribed to activation of the immune system with release of cytokines. Experiments with the HT-29 human epithelial cell line have suggested that T cell- and macrophage-derived immunoregulatory peptides such as IFN-γ, tumor necrosis factor-α (TNF-α), and IL-4 can upregulate SC expression and act in various additive or synergistic ways (33). The parallel enhancement of SC and epithelial human leukocyte antigen (HLA) class II expression seen in inflammatory diseases of exocrine tissues may likewise have an immunoregulatory basis (33).
From a teleological point of view, enhanced production of nonspecific defense factors such as lysozyme and lactoferrin during the first 6 postnatal months (Fig. 8) might aid the protection of the infant’s mucosal surfaces until specific secretory immunity has been better developed. There seems to be no significant increase in the salivary levels of lysozyme subsequent to 6 months of age (23).

OVERSTIMULATION OF MUCOSAL IMMUNITY IN SIDS

It has been claimed that sudden infant death syndrome (SIDS) is often associated with mild upper respiratory tract infection caused by various viruses shortly before death. In keeping with this, we found a significantly increased number of all three major immunocyte classes in salivary glands of such victims, on an absolute basis, in the order IgA > IgM > IgG (34). Furthermore, intensified local immunostimulation with release of cytokines was strongly supported by the fact that salivary glands from the same SIDS cases showed significantly raised numbers of interstitial leukocytes and enhanced epithelial HLA class II and SC expression (33). It is possible that increased cytokine levels affecting the central nervous system could contribute to SIDS in vulnerable infants.
CONCLUSION

Despite being structurally mature at birth, the human mucosae and exocrine glands show a postnatal delay in immune responsiveness for several weeks; thus, babies have to pass through a vulnerable period in terms of susceptibility to infections. In this period, the specific adaptive immune defense at mucosal surfaces relies heavily on passive humoral immunity transferred from the mother—serum-derived IgG reaching interstitial tissue fluid as well as S-IgA provided by breast milk feeding. Although the healthy baby’s own S-IgA system is remarkably adaptable to the environmental antigenic load, several months elapse before the levels of secretory antibodies are fully developed. However, glandular epithelia express high levels of non-specific defense factors at birth, and antimicrobial proteins such as lysozyme and lactoferrin may be of particular value in infancy by aiding the protection of mucosal surfaces.

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REFERENCES


**DISCUSSION**

*Dr. Guesry:* People caring for premature babies all make the same observation, that they don't see the manifestations of allergy in such infants. But when you follow them up to 6
months or 1 year of age, the manifestations of allergy may appear. It is as if the premature baby were able to recognize allergens but not express the clinical manifestations of allergy. Do you have an explanation for this?

**Dr. Brandtzaeg:** It is possible that the immature period of immune responsiveness is extended in these infants. It is quite likely that uptake of colostral IgA occurs if such babies are fed on breast milk, in contrast to full-term babies, and this may also influence the immune system.

**Dr. Marini:** You said that maternal IgG may influence IgA synthesis in the infant gut. Very low birthweight babies tend to have rather low maternal IgG in their circulations, and there are interesting observations showing that if you give immunoglobulin iv to preterm babies they have a reduced risk of developing allergy in the future (1). So there may be some link between the level of IgG in the blood in the neonatal period and the later development of allergy.

**Dr. Chandra:** There is preliminary evidence to suggest that there is an altered distribution of T cells in the peripheral blood of infants who express atopic disease very early in life. Is there any information about the distribution of CD8 vs. CD4 cells in the intestinal mucosae of those infants who have a strong family history of atopic disease and in some cases develop symptoms themselves?

**Dr. Brandtzaeg:** I am not aware of any T cell studies in the gut in subjects at genetic risk but there are some studies showing that such individuals (with one or both parents atopic) have slow development of the IgA system. This has been shown both in the salivary IgA profiles, which take longer to reach their normal mature level, and also with regard to the number and density of IgA-producing cells in the gut. Soothill was keen on this slow development of the IgA system 15 to 20 years ago, and the new evidence appears to give some backing to his concept that the IgA system is retarded in those who develop atopy.

**Dr. Hamburger:** When Conner examined the question of IgA in allergy-prone babies some years ago, he found that if you corrected for breast-feeding there was no difference in gut IgA between those infants with an allergic family history and those without. Breast-fed babies tended to have low gut IgA.

**Dr. Brandtzaeg:** This is a very difficult field and the relation to breast-feeding has not perhaps been well enough controlled in some studies. However, there is a good Australian study (2) that followed salivary IgA in babies very carefully and showed that where one or both parents were atopic the salivary IgA was much lower than normal.

**Dr. Chapoy:** We know that secretory IgA is a very powerful anti-adherent system. Could you explain how bacteria can transmit messages to the immune system?

**Dr. Brandtzaeg:** The focus is on the M cells in the follicle-associated epithelium which covers the domes of Peyer's patches. This epithelium does not secrete IgA, so there is a gap in the IgA barrier at this point. There are also few goblet cells and little mucus secretion in this area, as well as a very leaky basement membrane. Therefore antigens are able to contact M cells by receptor-mediated and nonreceptor-mediated mechanisms. Thus, despite an ongoing secretory IgA response, there is at these sites a good possibility for microbial penetration.

**Dr. El Gamal:** You spoke about the sudden infant death syndrome (SIDS) in relation to food allergy. What is the underlying allergic or immunologic mechanism of SIDS?

**Dr. Brandtzaeg:** The focus at present is on upper respiratory tract infections rather than on food allergens. There are epidemiologic studies showing that there is a relationship between respiratory tract infections and SIDS incidence. SIDS is also more common in cold climates, and there are upregulated IgA and IgM systems in the salivary glands and in the bronchial mucosae in children dying from SIDS. However, it is not enough just to have an infection.
There must be a predisposition, perhaps some sensitivity of the central nervous system to cytokines from an activated local immune system that is able to penetrate the blood–brain barrier and activate the immune system in the brain. I have no good information to support the view that food allergy is important in these cases, although there is some indication that breast-feeding protects against SIDS.

Dr. Strobel: Could you tell us about the memory of the IgA system? Do you need continual stimulation to have a memory?

Dr. Brandtzaeg: Most people now agree that there is a memory but that it is fairly short-lived. For a gut immune system mainly aimed at the microflora and potential pathogens, there is probably no need for a long-term memory since the antigenic profile of the microflora in the gut is constantly changing. This is something that needs to be taken into account when designing enteric vaccines: you need some sort of persistent stimulation to have a good and long-lasting response.

Dr. Duchateau: What is the role of IgD?

Dr. Brandtzaeg: We don’t know very much about the function of IgD antibodies, but they are apparently not complement activating. The only place where you have a substantial local production of IgD is in the upper respiratory tract, mainly as a compensatory phenomenon in IgA-deficient patients. It appears from a study we have performed together with Karlsson et al. in Göteborg (3) that those patients with IgA deficiency who compensate with local IgD production have more upper respiratory tract infections than those who compensate with IgM. IgD may therefore be a bad antibody locally, and it may even block the defense mechanisms exerted by IgG because it is not secreted and it is not complement activating. Hence, it mostly stays around in the tissues and may compete with IgG, as well as with IgM antibodies of the same specificity.

Dr. Aalberse: Is food allergy really a gut problem? In other words, is the antigen triggering the immune system in the gut or somewhere else?

Dr. Brandtzaeg: I don’t think the point of contact with the immune system is necessarily in the gut. Antigen is rapidly delivered to the liver and gets into the circulation. Husby showed that you can find cow’s milk antigen circulating 1 to 2 hours after a meal, so it is obviously well distributed and the whole immune system will be engaged.

Dr. Hill: Food allergy has been our major interest. In our studies, we have identified three statistically separate groups of patients who had cow’s milk allergy. The first was an IgE-sensitized group; the second had a much higher incidence of IgA deficiency than one would expect; and the third group had multisystem disease with eczema, diarrheal problems, and some respiratory symptoms. They had markers of enhanced T cell reactivity, in vivo inhibition of leukocyte production, and enhanced production of interferon-γ in vitro. How much do you think these systemic markers reflect mucosal events?

Dr. Brandtzaeg: Of course, the IgA system in the gut is part of the whole body’s immune system. We should not think of it as something segregated from the rest. There is compartmentalization and there are various local cytokine profiles, but even the J chain, which is such an important marker of IgA cells in the gut, is found to be produced in other sites. I believe it to be a marker of a particular stage of maturation or differentiation of the B cell system. Thus, the immune system in the gut is the same system as elsewhere but with local possibilities for differentiation. You can measure IgA in the blood and take the result to some extent as an indication of the activation state of the IgA system in the gut. In most situations, I should say that this is a reasonable indicator but not perfect. There will always be local variations in response that are not mirrored systemically. For these, you have to be able to investigate the local site specifically.
Dr. de Week: You have indicated that IgG transmitted from mother to child may have a regulatory action on the child's immunological development and gut responses, possibly through an anti-idiotypic type of regulation. One thing we should be aware of now is that there is also an anti-isotypic regulation by anti-isotypic autoantibodies; for example, there is accumulating evidence that IgG anti-IgE transmitted to the child from the mother may modulate the child's IgE production and expression.

Dr. Chandra: If maternal IgG plays a role in immunoregulation in the infant, then one would expect that infants born of mothers with hypogammaglobulinemia would have different immunological development from infants of normal mothers, but this is not the case. I feel that the role of maternal IgG is likely to be minimal.

Dr. Brandtzaeg: But such mothers would be treated with immunoglobulin so they should have normal or near-normal systemic IgG, would you not agree?

Dr. Chandra: But what I said also holds true for infants of mothers mildly affected with common variable immune deficiency who do not require treatment.

Dr. Brandtzaeg: It is a difficult question. They all have some IgG, whether their own or through supplementation.

Dr. Chapoy: Could you comment briefly on the role of the intraepithelial lymphocyte?

Dr. Brandtzaeg: Intraepithelial lymphocytes are present to some extent before birth and they are mainly of the CD8 phenotype. They are able to gain access to the gut epithelium without any apparent antigenic stimulation. However, after birth the T cell αβTCR+ CD8 population increases enormously because of antigenic stimulation. We can see this in celiac disease where the numbers of such intraepithelial T lymphocytes will fluctuate with the amount of exposure to gluten. However, not much is known about the role of epithelial T cells in relation to food allergy.

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