The Fate of Foreign Antigens in the Intestinal Tract in Infancy and Childhood

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The gastrointestinal tract encounters a greater amount of foreign antigen than any other mucosal surface of the body. It therefore must be well equipped with the means to deal appropriately with offending agents on the one hand and food protein on the other. Not only the quality of the reaction but also its magnitude must be adjusted by intrinsic controls.

Immediately after birth, the gastrointestinal tract is guarded against foreign antigens through specific antibodies, nonspecific antiinfective agents, and the cellular components found in mother’s milk. In addition, foreign antigens that enter the gastrointestinal tract may penetrate far enough into the intestinal lymphoid tissue to be recognized as such. Such contacts may start a chain reaction ultimately leading to the secretion of specific antibodies at all mucosal surfaces. Some macromolecules penetrate even into the bloodstream. In the case of immune globulins, this is obviously an advantage. Whether the absorption of other macromolecules subserves a useful function is not known.

Although IgA is the main immune globulin of the mucosal surfaces, in the form of the specially adapted dimeric secretory IgA, immunoglobulins G, M, E, and D are also produced in the lamina propria. Whereas the translocation of secretory IgA from the lamina propria to the intestinal lumen has been largely elucidated, the factors leading to the release of the other immune globulins into the intestinal lumen are less well understood. Recent evidence suggests that this release is under the control of gastrointestinal hormones as well as the parasympathetic system. In addition to what might be termed the short-term control of the secretion of antibodies, the body also possesses a subtle mechanism for controlling the nature of the immune response. This can extend on the one hand from an active total suppression of the immune response by the Peyer’s patch T cell suppressor population, a state called tolerance, to a state of hypersensitivity in which foreign antigen calls forth an exaggerated response, possibly because of an absence of appropriate suppression. In between these two extremes, we have the “normal immune response” associated with the production of
antibodies but without any clinical symptomatology. This chapter tries to deal briefly with all these aspects of immune homeostasis of the gut.

**HUMAN MILK**

There is ample evidence that human milk plays an important and effective role in the prevention of infection of the gut. Epidemiologic evidence has shown that acute gastroenteritis is less frequent in the breast-fed infant (1). Human milk has been used successfully to interrupt an epidemic of *E. coli* gastroenteritis in a neonatal ward (2). Even when used as a supplement to formula feeds, fresh colostrum or breast milk has been shown to reduce the number of infections that occurred among neonates (3). At least one specific cause of chronic diarrhea can also be prevented in some individuals by human milk: it was recently shown that gluten-sensitive enteropathy is significantly less common among infants breast fed for 3 months than among infants initially bottle fed (4). This phenomenon was not related to the age of introduction of gluten into the diet, which was the same in both groups.

**Specific Antibodies in Human Milk**

Antibodies in breast milk belong mainly to the secretory IgA class, although immunoglobulins G, M, E, and D are also represented. The repertoire of specific antibodies in breast milk is considerable and varies from mother to mother. It is determined by the bacterial, viral, and food antigens present in her gastrointestinal and respiratory tracts (5,6). These antibodies are directed against bacterial and viral as well as fungal antigens (7,8). The mechanism by which these antibodies reach the breast via the gastrointestinal or bronchial associated lymphoid tissue is discussed below in the context of immune regulation in the gastrointestinal tract.

The total amount of IgA ingested by the infant remains at the level of 1 g/day throughout lactation. The fate of ingested IgA is, however, unknown, but several possibilities exist. In rats, it has been shown that the neonatal intestine possesses specific receptors for breast milk IgA (9). Whether a similar phenomenon exists in the human infant remains to be investigated. Another possibility is that IgA becomes adsorbed onto the mucus overlying the glycocalyx, as is the case in the adult intestine (10). In either case, IgA would be anchored for prolonged periods to the wall of the intestine, where it would serve to prevent bacterial adhesion (11) and promote agglutination of bacteria (12), neutralization of viruses, and complexing of food proteins (10). All nine components of complement have been detected in breast milk (13). The function of complement within the intestinal lumen is a matter for conjecture (Tables 1 and 2).
TABLE 1. The antiinfective factors of human colostrum and milk

<table>
<thead>
<tr>
<th>Soluble</th>
<th>Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulins (secretory IgA, IgG, IgM, IgD, and IgE)</td>
<td>Macrophages</td>
</tr>
<tr>
<td>Components of complement (9)</td>
<td>B lymphocytes</td>
</tr>
<tr>
<td>Antistaphylococcal factor</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td>Chemotactic factors</td>
<td>Plasma cells</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
</tr>
<tr>
<td>Lysozyme</td>
<td></td>
</tr>
<tr>
<td>Lactoperoxidase</td>
<td></td>
</tr>
<tr>
<td>Bifidus factor</td>
<td></td>
</tr>
<tr>
<td>Interferon (?)</td>
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</tr>
</tbody>
</table>

Nonspecific Antibacterial Factors in Human Milk

Unsaturated lactoferrin, the iron-binding protein of milk, has bacteriostatic activity. This was originally described in vitro (14) but has subsequently been confirmed in an in vivo model (15). It is active against *E. coli* and against *C. albicans*. Lysozyme, an antibacterial substance present in many tissues, can also be found in human milk. Human milk lysozyme is active, among others, against *Pseudomonas aeruginosa*, *Streptococcus fecalis*, and *Staphylococcus aureus* (16). It is believed that lactoferrin and lysozyme form a complex that potentiates their antibacterial activity (17). Lactoperoxidase is another antibacterial substance present in human milk (18).

Nonspecific Antiviral Factors in Human Milk

It has been shown that some free fatty acids and monoglycerides have the capacity to attack the envelopes of certain viruses (19). Other nonlipid fractions, which have not been isolated, have been shown to be active against herpes simplex virus as well as against rotavirus, one of the most common if not the

TABLE 2. Antibody activity in human colostrum and milk

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>Enteroviruses</td>
<td>Candida</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>Polio 1, 2, 3</td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Coxsackie A, B</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Echo 6, 9</td>
<td></td>
</tr>
<tr>
<td>Enterobacteria</td>
<td>Rotavirus</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Respiratory syncitial virus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herpes virus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td></td>
</tr>
</tbody>
</table>

* Antibody activity is variable and determined by the antigenic experience of the mother. This is to be seen merely as a representative sample.
most common cause of infantile gastroenteritis (20). Free interferon has not been detected in human milk, but milk lymphocytes can be stimulated to produce it (21). Whether such response to stimulation does in fact take place \textit{in vivo} is still unknown.

The Cells of Human Breast Milk

Numerically the most important cells in human milk are the macrophages. These large and metabolically active phagocytes are capable of synthesizing many of the antibacterial substances present in breast milk, such as complement components $C_3$ and $C_4$, lysozyme, and lactoferrin (22). In addition, macrophages seem to exert a helper function on IgA-producing plasma cells \textit{in vitro}; in the presence of macrophages, more IgA is released, and activation persists for longer periods. The phagocytic function of macrophages and neutrophils has been shown to be directed against staphylococci, \textit{E. coli}, and \textit{C. albicans} (23). It is likely that these cells have an important role in the first 2 weeks, as their concentration in colostrum is high. However, by 6 weeks, their numbers decrease to 1/100 of that at 2 weeks (24).

T and B lymphocytes are present in breast milk in the same proportion to each other as are found in the maternal circulation. B lymphocytes secrete immunoglobulins G, A, M, E, and D. Little is known about the function of T lymphocytes in breast milk. It has been shown that tuberculin-reactive T cells in breast milk can confer this reactivity to the infant’s peripheral lymphocytes, but only for a brief period (25). The mechanism by which this transfer of cellular immunity from mother’s milk to the infant’s peripheral blood is achieved is not known, nor do we know whether the antiviral and antifungal activity of these T cells can be transferred to the infant.

From the above it is apparent that there is a considerable array of antiinfective factors in breast milk. Assays of individual factors may be misleading, as two or three factors may act in concert. For example, it has been shown that secretory IgA binds complement in the presence of lysozyme in order to kill susceptible strains of \textit{E. coli} (26,27). Studies on total antibacterial activity of raw human milk have shown clearly that it is effective in inhibiting the growth of bacteria (28). Pasteurization of human milk destroys this effect.

MORPHOLOGY OF THE GASTROINTESTINAL TRACT AT BIRTH

The intestinal mucosa of the infant at birth appears to be mature by light microscopy as well as by some enzymatic markers. The enterocytes are indistinguishable from those of adults (29). Peyer’s patches, which form the afferent limb of the immune response in the gastrointestinal tract, are also present at birth, albeit in reduced numbers, which increase, reaching a maximum at puberty (30). Plasma cells, the efferent limb of the humoral immune response, are absent; they appear shortly after birth as a result of antigenic stimuli to the intestine.
Mucin-producing goblet cells are present in early fetal life (29), and a coat of mucus covers the epithelial cells early in intestinal development. This mucous coat plays an important role in gastrointestinal defense against pathogens and other foreign antigens. The function of mast cells in the human gastrointestinal tract is not known. Their number in the lamina propria at birth appears to be similar to that of the adult intestine (32).

THE ROLE OF THE STOMACH IN HOST DEFENSE

From the third to the 30th day of life, secretion of gastric acid is well below that of the adult (33) and does not respond to secretagogues (34). Gastric acid secretion has a major influence on the intestinal flora, and it has been clearly shown that both achlorhydria and hypochlorhydria are associated with increased numbers of bacteria in the proximal small bowel (35–37). It appears, therefore, that in the first month of life an important nonspecific antibacterial factor is absent and that this may predispose the infant to gastrointestinal infections early in life. Gastric pH also has an effect on subsequent uptake of food antigens by the intestine. The addition of bicarbonate to bovine serum albumin enhances macromolecular transport (38). It is possible that by neutralizing gastric pH the digestion of protein by pepsin is inhibited, and increased amounts of intact antigen come into contact with the intestinal mucosa.

MACROMOLECULAR TRANSPORT

In those species of animals that are born without immunoglobulins, macromolecular absorption serves an obviously important function. The immunoglobulins of the mother’s milk attach to specific receptors on the intestinal epithelium (39). These protect the immunoglobulins from extracellular degradation and set in motion the absorption of these proteins into the bloodstream (40,41). This absorption continues as long as suckling proceeds and is discontinued at weaning. The cow, goat, pig, and horse belong to the species manifesting such a mechanism of absorption. In the human, more definitive studies are still required. Although man is born with a full complement of maternal IgG, there is some evidence that further absorption of immunoglobulins may take place (42,43).

In the healthy adult, macromolecular transport from the intestine to the breast has been demonstrated in lactating mothers (44). In disease states in the human, macromolecular transport has been studied in conditions associated with partial or total villous atrophy (45). It was shown that in those states that are associated with mucosal damage, there was increased absorption of l-rhamnose and lactulose—sugars that are only minimally absorbed by the healthy small intestine. Of greater significance were studies of the absorption of polyethylene glycol (PEG) in patients with eczema with or without demonstrable food allergy (46).
These studies showed increased absorption of the large molecular forms of PEG (600–4,000 daltons) in all cases of eczema.

In the newborn rabbit, macromolecular transport of foreign antigen is closely related to the type of feed. Breast-fed animals absorb less foreign antigen than do bottle-fed animals (47). Breast milk, therefore, presumably has a specific protective effect in reducing the uptake of foreign protein. Macromolecular transport in the rabbit decreases with age (48). This decrease is accompanied by changes in the composition of the cell membrane of enterocytes (48).

THE GUT-ASSOCIATED LYMPHOID TISSUE

The gut is rich in lymphoid tissue. It includes the aggregates of lymphoid cells found in Peyer's patches, the plasma cells found in the lamina propria, and the interepithelial lymphocytes as well as the mesenteric lymph nodes. Peyer's patches represent the afferent limb of the immune response.

In addition to the normal enterocytes, which overly Peyer's patches, there are microfold or "M" cells. These cells have no microvilli and only a thin layer of cytoplasm. They do not appear to have the features usually associated with the degradation and digestion of food. They are therefore believed to facilitate macromolecular transport into the underlying tissue, which is composed of macrophages, B lymphocytes, and thymus-dependent T lymphocytes (49). As regards the other cell types, most of the B cells bear surface IgA, whereas others bear IgM, IgG, IgE, and IgD. Some cells bear more than one immunoglobulin on their surface. Presumably, the environmental conditions obtaining in the bowel ultimately decide whether a cell bearing both IgA and IgE will go on to produce one or the other of these immunoglobulins (50). The helper T cells play an essential part in stimulating sensitized precursor plasma cells to proliferate and mature, whereas suppressor cells can damp the immune response of these cells (51). As an indispensable maturation process, precursor plasma cells of all immunoglobulin classes proceed from Peyer's patches to the mesenteric lymph nodes. These cells then proceed to the lamina propria of the gut, to the bronchi, the bladder, the lacrimal glands, and the breast tissue (6,50).

IMMUNE GLOBULINS IN THE GASTROINTESTINAL TRACT

Antibodies belonging to each of the immunoglobulin classes are produced by plasma cells in the lamina propria. The most important of the antibodies in the intestine is IgA. Plasma cells of the lamina propria produce mainly dimeric IgA joined together by a third protein, the J (joining) chain (52). Dimeric IgA is believed to move towards the base of the enterocytes where another protein, the secretory piece, provides a receptor for dimeric IgA (52). The complex of secretory piece–dimeric IgA, the secretory IgA (sIgA), now traverses the enterocyte in order to leave it at the luminal border. Once outside the cell, sIgA...
is believed to become adsorbed onto the mucous coat of the intestine and is believed to assist in the exclusion of foreign antigen (10). In this position, IgA could agglutinate bacteria, detoxify enterotoxins, neutralize viruses, and complex food protein. The complexing of IgA with food protein antigen in the mucous coat has been reported to enhance degradation of the antigen (10). In this way, the immune response of the intestine could be part of a physiological mechanism assisting the immobilization and digestion of food at the luminal border.

Secretory IgA is the only immunoglobulin the production and translocation of which have been elucidated to a certain extent. In addition to the intestinal mucosa, slgA and IgM also originate from the liver (53), the pancreas (54), the gastric mucosa (55), and the gallbladder (56). It is likely that the gallbladder provides most of the IgA class antibodies in the duodenal aspirate. In the rat, it has been estimated that 90% of the slgA recovered from the upper intestinal lumen is derived from bile (53). Hepatocytes in the rat have receptors for secretory IgA (57–59). The IgA is taken up by the liver from the bloodstream and excreted into the bile. This is believed to be one mechanism for the removal of noxious IgA complexes from the systemic circulation (57). In humans, the gallbladder has been shown to contain IgA and IgM (60,61) and to discharge about 500 mg of slgA into the gastrointestinal tract daily (53). The specificities of the antibodies are directed against bacterial, viral, fungal, and food antibodies. Their full range has not been elucidated and is dependent on the antigenic experience of the individual (Table 3). There can be no doubt that local intestinal secretory antibody plays a significant role in protection from diseases such as poliomyelitis and salmonella gastroenteritis (62,63).

**HUMORAL CONTROL OF ANTIBODY SECRETION**

Until recently little was known about the factors controlling and stimulating the discharge of antibodies in the gastrointestinal tract. We recently demonstrated that following intravenous administration of pancreozymin–cholecystokinin, IgA and IgM antibody activities in the duodenal fluid directed against the cow’s

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>Gluten</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Gliadin</td>
</tr>
<tr>
<td>Serratia</td>
<td>α-Casein</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>β-Lactoglobulin</td>
</tr>
<tr>
<td>Shigella</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>Polio virus</td>
<td></td>
</tr>
<tr>
<td>Echo virus</td>
<td></td>
</tr>
<tr>
<td>Coxsackie virus</td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
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</tbody>
</table>
milk proteins $\alpha$-casein and $\beta$-lactoglobulin B rose 5 to 10 min after the injection of the secretagogue (64). In parallel with this phenomenon, there was a rise in protein content and proteolytic enzyme activities. Secretin, in spite of its dilutional effect on duodenal fluid enzyme concentration, also produced a rise in IgM and IgA antibodies against the same antigens. Levels of IgG were not affected. In a subsequent series of investigations, we found that pancreozymin–cholecystokinin led to an increase in duodenal contents of IgE and IgD antibodies specific to cow’s milk and soy protein (65). In addition, we also showed that healthy adults usually had no such antibodies in their resting fluid, whereas eight out of 13 children with a variety of gastrointestinal diseases had IgE antibodies, and five out of 13 had IgD antibodies.

The origin of the IgE and IgD antibodies following stimulation with pancreozymin–cholecystokinin is not known. One possible source is the liver or gallbladder, but no IgE has been reported in bile to date. Nor has it been reported in pancreatic fluid. Another possibility is that these hormones have an effect on translocation of IgE and IgD antibodies through the epithelium. As yet, no specific transport mechanisms for IgE and IgD from the lamina propria to the intestinal lumen have been described (66). Against this mechanism is the fact that neither IgE nor IgD is regarded as a true secretory immunoglobulin. Plasma cells containing IgE and IgD are found in lamina propria (67), but IgE does not combine with secretory component, the glycoprotein that endows IgA with its resistance to proteolysis. In children with gastrointestinal disease the presence of IgE and IgD is probably part of the inflammatory response (68).

As pancreozymin–cholecystokinin is believed to be released during normal digestion, the antibodies that appear as a result of this hormonal stimulation may have a physiological role in the digestion of food proteins. In the case of IgA, we have already discussed the likelihood that food antigen–antibody complexes (IgA) in the mucous layer would facilitate the process of digestion. As far as IgE is concerned, this immunoglobulin lacks a demonstrable function in the healthy human gastrointestinal tract. In view of the known effects of IgE elsewhere in the body, it is possible that it induces localized histamine release through mast cell degranulation. This would enlarge the adjacent intestinal vascular bed and increase vascular permeability. Such a mechanism, if it exists, may also be operative to a greater degree in pathological states, as the duodenal fluid content of total IgE in food allergy has been found to be raised (69).

In animal models, intestinal reaginic antibodies equivalent to human IgE have been studied more intensively than in the human. In the rat, reaginic antibodies to egg albumin have been found to correlate with gastrointestinal hypersensitivity to this protein (70). The local hypersensitivity response in the intestine is accompanied by enhanced mucus secretion and by an increase in vascular permeability (70). Mucus may then protect the mucosal surface against penetration by microorganisms and by toxins and limits the access of soluble antigens to the absorptive surface of intestinal cells.
NEURAL CONTROL OF SECRETORY IMMUNOGLOBULIN SECRETION

It has recently been shown that the secretion of IgA in the gastrointestinal tract may also be under the control of the parasympathetic nervous system. The injection of pilocarpine, muscarine, or bethanechol into rats significantly increased secretion of sIgA into the intestine (71). Atropine blocked the effect of pilocarpine and inhibited basal intestinal IgA secretion for 40 min after injection. These results further emphasize the fact that the secretion of sIgA is not a continuous process but is coordinated with the digestive activity of the gastrointestinal tract.

The Normal Immune Response

Under normal circumstances, the ingestion of food in infancy gives rise to the appearance of appropriate antibodies in the serum. Thus, cow's milk administered to infants at birth will result in the appearance of antibodies in the serum that reach a peak at 3 months and thereafter decline gradually. They are composed mainly of IgA antibodies, with lower titers of IgG and IgM antibodies (72). If cow's milk is started only at 3 months of age, the immune response is smaller (73) for reasons that are not known. A number of factors may be operative. Firstly, macromolecular absorption of milk antigen may have decreased in view of the presence of IgA milk antibodies coating the intestinal mucosa in the older infants (74). Secondly, the production of antibodies in the intestine is subject to immune regulation by populations of T suppressor and helper cells. Finally, it is not known if some other age-dependent factor, as is believed to occur in rabbits, may also affect antigen uptake and indirectly the antibody response (75).

TOLERANCE TO FOOD ANTIGENS

Tolerance, in the immunological field, signifies the absence of clinical symptoms, as well as any demonstrable immune response following contact, ingestion, injection, or inhalation of foreign antigen. The first observations on tolerance were made 70 years ago. It was known that the intravenous injection of a foreign protein such as zein—the protein of corn—would cause death from anaphylactic shock in guinea pigs (76). This phenomenon could be prevented by giving zein by mouth for several weeks. The present concept of tolerance envisages the active suppression of the immune response by a specific subpopulation of T lymphocytes. One of the sites of regulation of the immune response is the Peyer's patches. These aggregates of lymphocytes contain T helper and suppressor cells in addition to plasma cell precursor "B" lymphocytes (77). "T" suppressor cells can depress the production of immunoglobulins G, A, M, and E. When
this occurs, a state of tolerance has been induced. This suppression is specific for individual immunoglobulins. Thus, in the experimental model, a state has been described in which, as a result of regulatory T cell activity, the production of IgA was enhanced, whereas that of IgG and IgM was decreased (78). In the context of hypersensitivity, the regulation of the IgE response in the gastrointestinal tract would, of course, be relevant. This was shown by elegant experiments in which mice were fed ovalbumin for prolonged periods (79). Thereafter, Peyer's patches were transferred from these presumably tolerant animals to recipient mice. It was shown that the transferred Peyer's patches were capable of suppressing an IgE response in the recipients. This is evidence that tolerance is not a passive process, an absence of an immune response, but rather the active suppression of such a response. These observations suggest that Peyer's patches play an important role in regulating the immune response of the gastrointestinal tract; it is here that the immune response to ingested antigen is determined as a result of such factors as type and quantity of antigen, age of animal, type of species, and strain of the animal within the species, or the genetic endowment of the human being.

Food Hypersensitivity in the Experimental Animal

With the rat used as a model, it was found that certain strains are more efficient IgE producers than others (80). The high IgE producers are more suitable for the induction of gastrointestinal hypersensitivity. We have already described that the oral administration of antigens can be a means of producing tolerance. The same antigens, however, can produce a state of hypersensitivity if they are administered simultaneously with adjuvants. Some microorganisms such as E. coli and B. pertussis act as adjuvants. Their effect on the immune status of infants has not as yet been investigated. Other adjuvants, Freund's adjuvant, concanavalin A, and aluminum hydroxide, have been used in the experimental situation. Adjuvants are effective orally as well as by injection. Thus, the administration of bovine serum albumin together with adjuvant by stomach tube to mice sensitized those animals so that subsequent oral challenge with bovine serum albumin produced anaphylactic shock (81). This observation was an important step in developing the experimental animal model for food hypersensitivity.

Further refinements allowed the objective measurement of this response. These include the use of radioactively labeled proteins injected into the bloodstream (82) or perfused through the intestine (83). These techniques have made it possible to follow macromolecular uptake from the bloodstream into the intestinal lumen and vice versa and thus provide objective parameters of the local intestinal hypersensitivity reaction. Using this model, Bloch and Walker (83) have sensitized rats to egg albumin. At the time of challenge with this protein, a local intestinal anaphylactic response was produced. At the time of
this response, bovine serum albumin (BSA) was introduced into the intestine. It could be shown subsequently that increased amounts of BSA entered the bloodstream following local intestinal anaphylaxis. This observation may be pertinent to conditions obtaining in the intestine of human infants with cow’s milk protein hypersensitivity (CMPH). In this context, it is relevant that we have observed in the past that if infants allergic to cow’s milk are given soy milk as part of their dietary management, 30% of them will develop soy protein hypersensitivity within 15 days (84).

COW’S MILK PROTEIN HYPERSENSITIVITY

Effect of Heredity

A number of etiological factors have been invoked in the causation of CMPH. As far as heredity is concerned, we have shown that the incidence of atopic disease is more common in first-degree relatives of children with CMPH. We therefore believe that a family history of atopy predisposes the development of CMPH (85). As in other allergies, we could find no association between CMPH and the HLA type of the individual (86).

Effect of Age

Clinical support for the concept that the infant’s intestine is particularly prone to the development of hypersensitivity was revealed by Iyngkaran et al. (87). They showed that infants under 3 months of age in Indonesia invariably developed CMPH following acute infectious gastroenteritis. This hypersensitivity was proven by the clinical features as well as by the morphologic and enzymatic changes of the intestinal mucosa following challenge with cow’s milk. Infants over 6 months did not manifest this phenomenon. It appears, therefore, that certain characteristics of the mucosa too subtle to be seen by light or electron microscopy predispose young infants to mucosal injury and to secondary hypersensitivity phenomena in the gastrointestinal tract. Similarly, recent studies in children showed that following a mucosal injury, significantly more enterocytes became passively permeable to horseradish peroxidase than in the normal mucosa (88).

What sets the neonatal intestine apart from that of adults? We can only speculate at the moment. Increase in the absorption of macromolecules may be an important factor. The rate of epithelial cell turnover and renewal may be slower in the human neonate than in the adult—a condition that would delay repair of damaged tissue and allow more antigens to be absorbed. The relative unavailability of secretory IgA in the neonate might be another factor. Unfortunately, none of these has been critically evaluated.
 IMMUNE REGULATION AND COW'S MILK PROTEIN-SENSITIVE ENTEROPATHY

Although various immunological aberrations in CMPH have been described, there is still uncertainty as regards its pathophysiology. In view of current concepts regarding defects in immune regulation as related to disease processes, we recently investigated the activity of nonspecific suppressor cells of peripheral blood lymphocytes in 22 patients with CMPH and compared the results with 26 age-matched controls (90). The patients' suppressor cell activity on donor cell proliferation was measured following concanavalin A stimulation. We found significantly \((p < 0.05)\) reduced suppressor cell activity in patients with CMPH. This activity progressively improved over the course of the first 20 months of life and ultimately reached normal levels. Infants not suffering from CMPH had normal suppressor cell activity, similar to that of an adult population. These observations require further clarification.

Disruption of Nonspecific Defense Mechanisms as Possible Causes of Food Hypersensitivity

The major nonspecific defense mechanisms by which the body can limit the absorption of macromolecules include gastric acidity, pepsin concentrations, water and electrolytes, peristalsis, mucin, and the glycocalyx composition. Low levels of gastric acid and pepsin, such as are found in the neonatal stomach, limit gastric proteolysis. Water acts as a diluent in reducing the concentration of antigen. Absence of peristalsis, as in stasis, allows bacterial overgrowth with its harmful effects on mucosal integrity. Decreased mucin secretion, as occurs in malnutrition, reduces the physical barrier that normally minimizes direct contact between food materials and the mucosal surface. Destruction of the glycocalyx can be mediated by certain bacteria, thus exposing new sites for the adhesion of pathogens that normally would not attack the mucosa (91). Thus, mucosal injury may initiate a vicious cycle of further damage by increased antigen absorption and thus provide a link between infection and the development of hypersensitivity.

Mucosal damage also reduces the levels of lactase in the gastrointestinal mucosa, particularly in prematures (92). Similarly, during intractable diarrhea of infancy, there is usually partial or severe disaccharidase deficiency and disaccharide intolerance requiring a long term of rehabilitation (93). These infants present with symptoms of vomiting and diarrhea after the introduction of milk, and it is likely that both milk protein hypersensitivity and lactase deficiency occur at the same time.

SUMMARY

Immune homeostasis of the gut represents an interplay of numerous factors, all of which are concerned with the proper recognition by the body of foreign
antigens and subsequently with their proper exclusion from the mucosal surface. Immediately after birth the intestine is mature morphologically, but functionally and immunologically it is immature. At this time of life breast milk serves to overcome these deficiencies.

As far as foreign antigens are concerned, various bacterial factors such as adhesion and production of enterotoxin may tip the balance in favor of the microbial invader. Food antigens are liable to be problematic if they resist proteolysis, if they are absorbed excessively, or if by nature of their physico-chemical properties they become “allergenic.” On the infant’s side, malnutrition and an impaired immune response are detrimental. Similarly, an “atopic” genetic disposition may predispose to hypersensitivity. Finally, a defect in regulation of the immune response may be responsible for an excessive gastrointestinal response. All of these factors must be considered in order to understand the pathophysiology of chronic diarrhea and to design appropriate therapeutic measures.

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