The cover depicts a collage of photos of mucosal inductive sites. Counterclockwise from the top, a view of a lymphoid aggregate in the airway (courtesy of John Bienenstock, in the “Handbook of Mucosal Immunology” with permission); a line drawing of the Peyer’s patch from Peyer’s original manuscript, 1677; a scanning electronmicrograph of M-cells overlying a patch (courtesy of Jacques Pappo). The background is another scanning electronmicrograph of M-cells.

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Editorial

This issue addresses a number of aspects of atopy from a mucosal perspective. Cummins and Thompson review the ontogeny of mucosal allergic responses and indicate there is a lack of appropriate animal models for testing the various hypotheses and mechanisms that are purported to exist. Knippels and Penninks focus on food allergy. This paper outlines the clinical importance of food allergy, its diagnosis and possible mechanisms. The authors go on to describe a useful animal model that they have developed in the Brown Norway rat to study food allergy. The following paper by Leach and Collins demonstrate the mast cell as the effector cell in gastrointestinal hypersensitivity reactions. Sly and Holt provide a review of evidence which suggests that the failure to switch off Th2 responses in utero is a key factor in the eventual development of allergic sensitisation. In the final paper by Clancy et al, it is hypothesised that defective immune tolerance is the major mechanism for the development of hypersensitivity in the respiratory tract. The paper goes on to discuss possible intervention strategies for the re-establishment of tolerance.

Allan W. Cripps, Editor
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Ontogeny of Mucosal Allergic Responses

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The prevalence of allergic diseases has increased recently in many developed countries with rising living standards. A popular theory at the moment is that of the 'hygiene hypothesis' as applied to hay fever and asthma. This hypothesis proposes that a reduced number of infections during infancy predisposes to allergic responses. Other studies which are discussed below suggest that early childhood infections, especially viral infections promote a Th1 response and protect against development of later allergy, which has a high level Th2 response. Typical allergic diseases are seasonal conjunctivitis, rhinitis, urticarial reactions to food or drugs, house dust allergy, atopic dermatitis, asthma and cow's milk allergy. Generally these are IgE mediated diseases, but some diseases such as a subset of cow's milk allergy are also T-cell mediated with delayed-type hypersensitivity. There has been a resurgence of interest in the ontogeny of allergic responses over the last 5 to 10 years. Unfortunately, animal models of mucosal allergic responses have only helped to a certain extent in understanding ontogeny of human allergy. The challenge is to discover what is the basis of the hygiene hypothesis and to the predisposition of humans to develop allergic diseases.

The ontogeny of allergic responses is difficult to define for a number of reasons. It is worthwhile reviewing past and the present difficulties that have hindered progress. An unfortunate and long established notion has been that the human infant has an immature and presumed defective immune system. While the majority of human infants may get frequent infections during infancy, this should only be taken as evidence of repeated naive antigen exposure rather than defective immunity. These infections are handled appropriately and immunity is generated. Information obtained from the body of literature regarding the postnatal immune response would suggest that the otherwise healthy human infant has a problem with immunodeficiency with unspecified morbidity and mortality. This does not seem to be justified. This notion of an immature defective immune system during infancy has also been difficult to reconcile with evidence available for decades that congenital infections with rubella, toxoplasmosis, cytomegalovirus, and syphilis generate antibody responses in utero. In the 1970s to early 1990s, the notion of an immature immune system was reinforced by laboratory studies of cord blood which
showed that neonatal T cells have an immature CD38 phenotype, high ‘naive’ CD45RA but low CD45RO ‘memory’ expression, impaired proliferation, helper and cytotoxic effector responses and impaired production of IFN-γ and IL-4. We would argue that these data are evidence of the naivety of the systemic immune system. It is now appreciated that the mucosal immune system is compartmentalized and may have a different phenotype and activity. In fact, T-cell activity reaches a physiological peak during infancy rising within 3 to 4 days of birth. This is evidenced by elevated levels of soluble IL-2 receptors and IFN-γ with the likely source being the gut-associated lymphoid tissue and presumably other mucosal tissues. It is likely that the immune system is immunocompetent and functional early in fetal life given that the ontogeny of T and B cells is largely complete by 16 weeks gestation.

There has been continuing controversy about whether maternally inhaled/ingested antigens cross the placenta and prime the fetus for later immune responses. Certainly, it has been shown that low levels of food proteins can be detected in amniotic fluid. A number of clinical trials of feeding hypoallergenic diets to mothers have been performed in order to reduce the incidence of cow’s milk allergy with variable success. Holt and co-workers have mostly resolved this controversy by prospectively following neonates with a family history of atopy and shown that children are sensitized in utero to maternal inhaled/ingested respiratory allergens and ovalbumin (a food antigen). Their studies relate only to those with early phase allergic responses. They showed a proportion of children who later develop allergy have antibodies to allergens in cord blood and show T cell proliferative responses to these antigens. They have demonstrated that stimulated peripheral blood lymphocytes of atopic individuals have a Th2 ‘allergic’ cytokine profile which becomes reinforced during childhood whereas healthy children lose the fetal Th2 cytokine profile during the first 2 years of life.

Another line of literature has suggested that antigen exposure during neonatal life causes tolerance but this has now been questioned. One possible reason for this concept in the past was methodology of using T-cell proliferation as a marker of immune response, whereas it is now appreciated that T cells can be activated to secrete cytokines but not proliferate which is particularly relevant to mucosal immune responses. Our studies have shown that physiological inflammation occurs in the small intestine that peaks at mid-weaning (2-4 months in human infants). This is associated with both mucosal mast cell in the lamina propria and T cell activation in Peyer’s patches, lamina propria and mesenteric lymph nodes. Presumably, physiological inflammation also occurs in the respiratory tract during infancy. Certainly, studies have shown that TCRab+ T-cells expand both in the small intestine and in the respiratory tract of rats during infancy which is consistent with physiological inflammation.

The recent direction of immunology has emphasized the action of cytokines as determinants of immune response. A putative allergic response is taken to be present if IL-4 and IL-13 are present as they are associated with IgE production. IgE is not detectable in serum during infancy but may be found in older children and adults with symptomatic allergy. This of course does not account for delayed-type hypersensitivity diseases. Cytokine profiles are related to the paradigm of Th2, Th1 and Th0 functions. Th2 function and cytokine profile have a close association. Holt and colleagues have extended previous studies showing that atopic infants have impaired production of IFN-γ and shown other changes in Th2 cytokines including IL-4, IL-5, IL-10 and IL-13 with the limitation being that these are all in peripheral blood cells. The assumption is made that these cells are representative of mucosal immune cells. Prescott, Holt and co-workers have demonstrated that low level Th2 cytokines are produced in neonates as a continuation of the fetal environment in both allergic prone or normal infants. They studied infants at birth, 6, 12 and 18 months of life and classified them into non-atopic or atopic retrospectively. Interestingly, non-atopic infants had low IFN-γ at birth but higher levels at 6 months, whereas atopic infants had reciprocal changes of high IL-4 and lower levels of IFN-γ at 6 months of age. Similarly, stimulated IL-13 production was high in non-atopic infants at birth and decreased at 1 and 2 years compared to atopic infants who had low IL-13 production at birth but rising levels at 1 and 2 years. Thus, atopic individuals continued to increase their Th2 responses (IL-4, IL-13) appropriately during the first 2 years of life.

What remains unexplained is the mechanism of down-regulation of mucosal immune responses to allergens during infancy in health and why this process goes wrong in allergy. This process is presumably similar to the development of tolerance to oral food antigens. This is best described using systemic unresponsiveness, generally in vitro, to food antigens and it is assumed that a similar process occurs mucosally, not only in the gastrointestinal...
tract, but also in the respiratory tract. The higher doses of food antigens versus low levels of aeroantigens are believed to induce deletion and/or anergy of reactive T cells for food antigens compared to immune deviation of T cells for aeroantigens. As far as the gastrointestinal tract goes, anergy is more likely as the predominant mechanism because of the simple reason that lymphocytes are present in significant numbers in the intestines in health and have not been deleted. Penttila and co-workers have also shown that TGFβ1 (an immunosuppressive cytokine) is expressed after mid-weaning in rats in the small intestine which could also potentially mediate immune deviation. It would be interesting to investigate the ontogeny of expression of IL-4, IL-10, IL-13 and TGFβ1 in the respiratory mucosa during infancy. It would be important to explain how some of these cytokines (IL-4, IL-13) are associated with allergy, but others are also important for down-regulation. Possibly, IL-10 and TGFβ1 are more important in mediating immune deviation.

The lack of Th1 stimulation during infancy has been proposed as a factor in development of mucosal allergic responses. It has been suggested that BCG immunization, which elicits a strong Th1 response, relatively protects against development of allergy. This shows that the ontogeny of allergic mucosal immune responses may be modulated by environmental infection/immunization. The Th2 paradigm does not explain late phase cow’s milk allergy which appears to be more of a delayed-type hypersensitivity with increased IFN-γ production by systemic blood lymphocytes after exposure to cow’s milk protein. A study by Hauer has shown IFN-γ, IL-4, IL-5 and IL-10 producing lymphocytes are present systemically and increased IFN-γ and IL-4 but not IL-5 or IL-10 producing lymphocytes in duodenal mucosa. Asthma also has features of both early and late phase allergic responses. Studies by Holgate and co-workers have emphasised that asthma is an inflammatory disease as has been evident from the clinical use of corticosteroids. While the Th2 paradigm is applicable to the early allergic response with involvement of IgE and mast cells and release of cytokines such as IL-4 and IL-13 that mediate IgE production, the picture becomes more complex with cytokines that mediate eosinophil infiltration (GM-CSF, IL-5) and with activation of T cells in the bronchial mucosa that suggest delayed-type hypersensitivity.

Various confounding factors still need to be remembered. One of these is breast-feeding which is known to relatively protect against a variety of allergic and autoimmune diseases. What is almost universally overlooked in many fine research manuscripts is that the normal physiology of the human infant is to be breast-fed. The infant immune system is directly connected with the maternal mucosal immune system by immune cells, cytokines, other immune factors (lysozyme, lactoferrin) and antibodies in breast milk. It is important to acknowledge that breast-feeding affects the ontogeny of allergic mucosal responses. A second confounding factor is the role of dendritic cells that are acknowledged to be the primary antigen presenting cells. It is still being resolved whether there are particular subsets and whether these in turn direct the immune response along a Th1 or Th2 pathway. Nelson and other workers have shown that the number of dendritic cells in the respiratory airway of rats increases during infancy. Other workers have shown that dendritic cells are activated by lipopolysaccharide. This occurs during infancy in the gastrointestinal tract during weaning when the resident flora changes from predominantly Gram positive (in breast-fed infants) to a mixed Gram positive and Gram negative flora. This could potentially affect dendritic cells in other mucosal sites such as the respiratory tract. A third confounding factor is the effect of NK T cells on the ontogeny of mucosal allergic responses. NK T cells are part of the innate immune system that were probably initially effector but now seem to have an immunoregulatory role. A deficiency of these cells seems to be a permissive condition for autoimmune disease (type 1 diabetes mellitus and scleroderma) and begs the question is there also a deficiency in subjects with atopy? It has also been recently demonstrated in separate studies by Tomura and Cui and their co-workers that NK T cells can direct immune response along the Th1 or Th2 pathways. They showed that NK T cells induce IL-12 production from antigen presenting cells that in turns stimulates IFN-γ and IL-4 production from NK T cells. The effect of IL-12 and IFN-γ was epistatic to that of IL-4. They suggested that IL-12 primarily directs a Th1 response with IFN-γ regulating Th cell sensitivity to IL-12. These activated NK T cells in vitro inhibited Th2 development and IgE production.

There is still some way to go in understanding the ontogeny of mucosal allergic responses. Animal models have not been very successful to date. The new paradigm of high level Th2 versus Th1 and Th0 responses is very popular. The principal finding to date is that a systemic Th2 cytokine profile to allergen stimulation, as seen in vitro, is rapidly suppressed during the first year of life in...
healthy infants but is augmented during this same period in atopic prone infants. Cytokine profiles in human infants still need to be determined in the nasal, respiratory and gut mucosa but are ethically difficult. It remains to be explained why cytokine profiles change in the first 2 years of life— that is, why down-regulation occurs and how this process fails and thereby generates allergic responses in pre-disposed individuals. These studies are important because the mucosal immune system is compartmentalised. Both breast-fed and bottle-fed infants will need to be compared as cytokine profiles may differ. The notion that neonatal/infant immune system is defective needs to change and account needs to be taken of physiological inflammation during infancy that certainly occurs in the gastrointestinal tract and probably the respiratory tract. Various other aspects of immunology still need to be integrated into the ontogeny of mucosal allergic response. These include the role of dendritic cells and of NK T-cells in directing Th2 responses.

References

Food Allergy; An increasing clinical problem and the need for new animal models for mechanistic research

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Prevalence of IgE mediated food allergy

Only IgE-mediated (type I) allergic reactions are for certain known to play a major role in food allergy. IgE-mediated (food) allergy often occurs as a part of the so called atopic syndrome. People with atopy are considered to have a hereditary trait (the atopic constitution) associated with a greater risk of development of IgE-mediated allergies. However, up to 10% of the children of healthy, non-atopic parents were also calculated to develop atopic diseases. Although, genetic factors play a major role in the development of allergic diseases, other factors, like the introduction of new allergens and air pollution, are also thought to be responsible for the recent increase in the prevalence of allergic diseases.

The prevalence of food allergy in children is estimated to be about 1.5-5% of the general population, corresponding to about 8-10% of the pediatric population, and around 1% in adults. Food allergy in children usually appears to be a transient phenomenon and the allergic symptoms tend to subside with age. Over 75% of food allergic children have “outgrown” their respective reactions within 5 to 9 years after the onset of clinical symptoms. However, some food allergies, like allergic reactions to peanuts, are more persistent and often do not diminish or disappear while growing up. The decreased incidence of food allergy with age suggests that immaturity of the immune system may be an important factor in the pathophysiology of the disease.

Diagnostic tests for IgE mediated food allergy

A correct diagnosis of food allergy is often difficult, although several procedures are available for the diagnosis of food allergy. Since food allergy is usually associated with atopy, a family history gives a good indication of the existence of an atopic constitution. The demonstration of sensitization to the offending food, skin prick tests (SPT), radio-allergo-sorbent tests (RAST) and enzyme-linked immunosorbent assays (ELISA) are often performed. The sensitivity and the specificity of the tests are controversial since the diagnostic concordance of skin-prick tests in suspected food allergic symptoms is only around 60-70%. However, in the diagnosis of food allergy, a combination of SPT and RAST is mostly used.

The double-blind, placebo-controlled food challenge (DBPCFC) has been labelled as the golden standard for the diagnosis of food allergy. Reproducible objective clini-
clinical reactions to the test food, but not to the placebo, constitutes a positive result. However, this method is not applicable for patients with suspected anaphylactic sensitization to the offending food. To obtain a correct food allergy diagnosis the results of multiple tests have to agree with each other. After the diagnosis of food allergy is established, an elimination diet in which the offending food is avoided is mostly recommended.

**Clinical manifestations of IgE-mediated food allergy**

The sensitization phase of a type I or immediate type hypersensitivity is characterized by the production of food allergen-specific IgE and the activation of mast cells or basophils. These IgE antibodies bind to the high affinity IgE receptors (FceRI) present on mast cells throughout the body tissues and basophils in the circulation. Upon renewed contact with the food allergen, the allergen binds to the Fab region of cell-associated IgE and subsequently crosslinks the membrane-bound IgE molecules. Crosslinking of several IgE molecules will result in an intra-cellular signal causing degranulation of the mast cells and basophils. The release of chemical mediators such as histamines, leukotrienes, prostaglandins, platelet-activating factor, and newly formed cytokines cause the allergic symptoms. These mediators induce a variety of food allergy-associated clinical symptoms involving the gastrointestinal tract, the skin, the respiratory tract, and the circulatory system (Table 1). The symptoms may occur within minutes to days after ingestion of the offending food and may sometimes result in a (fatal) anaphylactic shock.

**Food allergens**

In theory, every food (glyco)protein can potentially be a food allergen. Most food allergens are glycoproteins with a molecular weight between 10 and 60 kD. Factors that determine the allergenicity of food proteins are poorly known, but an important factor may be the digestibility of the protein in the gastrointestinal tract since it is known that food allergens are relatively stable to acid- and heat-treatment and relatively resistant to digestive breakdown. However, even small molecules are known to cause sensitization either directly or via the hapten-carrier mechanism. It is also known that carbohydrate structures on proteins in part determine or influence the allergenicity of proteins. In particular with respect to B cell epitopes, since carbohydrate structures may play an important part determine the secondary and tertiary structure of proteins and as such may strongly determine the conformational B cell epitopes. The allergenicity not only differs between proteins from different food products, but also between proteins from one product. For instance, cow’s milk contains proteins that only play a minor role in allergic reactions, while other milk proteins demonstrate strong allergic properties. Proteins for which many patients are sensitized are often referred to as “major allergens”. The most frequently observed food allergies are those observed to cow’s milk, chicken eggs, peanut, soybean, nuts, fish, seafood, and fruits.

**Mechanism of IgE-mediated allergy**

Several studies have shown that CD4+ Th2 cells play an important role in the pathophysiology of allergic diseases. T cell clones from atopic donors, specific for environmental allergens, were shown to have a Th2 phenotype with high production of IL-4 and IL-5 and little or no IFN-γ whereas T cell clones from non-atopic donors upon stimulation with antigen produced IFN-γ and no or little IL-4. These data suggest different functional subsets of CD4+ T cells in atopic and normal individuals. The Th2 cell-derived cytokine IL-4 has been shown to induce B cell switch to IgE, a phenomenon that has also been reported for IL-13. As a consequence, atopic individuals have elevated levels of IgE. In contrast, IgE synthesis is inhibited by IFN-γ, a Th1 cytokine. Moreover, most CD8+ T cells produce IFN-γ and have been suggested to suppress IgE responses. However, a subset of CD8+ T cells (Tc2) cells are known to produce a similar cytokine profile as Th2 cells, although their role in IgE-mediated reactions is not yet clear.

CD8+ T cells were found to be active early in the induction phase of the immune response, suggesting an ideal position to skew the immune response into a Th1
response. Moreover, IL-12, which is obligatory in the generation of Th1 cells, plays an important role in developing human cytotoxic CD8+ T cells. In addition, it has been demonstrated that TCRab+ cells produce type 1 or type 2 cytokines. This is of critical importance as TCRab+ cells produce these cytokines with rapid kinetics and upon first encounter with the antigen, and thus may be one of the sources for the cytokine that influence CD4+ and CD8+ polarization.

As described above, our knowledge on the pathophysiological mechanisms involved in the development of food allergy as well as the development of immune mediated effects upon challenge has greatly increased over the past decades. Nevertheless, many questions have still remained unanswered. Because tools for research into these issues are rather lacking, new models suitable for mechanistic studies will be of great value.

The role of the gastrointestinal tract physiology in food allergy

Many elements of the gastrointestinal tract physiology influence the ultimate allergenicity of food proteins. These include the pH, digestive enzymes, bile, peristalsis, transit time, bacterial fermentation, and the intestinal barrier function, permeability, and absorption. It should be recognized that primary, secondary, and tertiary structures of (glyco)proteins are affected to different degrees by digestion, indicating that B and T cell epitopes will be affected by digestion to different degrees. In addition, it should be recognized that digestion of food proteins is part of the normal sequence of events following consumption of food and that food allergic patients may well have become sensitized to digested allergens. Indeed, in vitro enzymatic digestion of food allergens does not necessarily diminish patient IgE binding, yet may even increase the IgE binding. Based on human clinical observations, an important role of digestion with respect to the allergenicity of food proteins is often suggested, yet this role is still poorly investigated and documented. Evidence for an important role of digestion with respect to food protein allergenicity also comes from animal studies. Prefeeding of an endopeptidase inhibitor (aprotinin) to mice results in an inhibition of oral tolerance induction by protein feeding, while feeding of protein antigens to mice is known to induce substantial systemic tolerance for specific antibody and cell mediated immune responses under normal circumstances.

Animal models in food allergy research

Because of the restrictions of the limited possibilities for human research, animal models suitable for food allergy research would be of real value. Several attempts to develop animal models for food allergy research have been conducted in the past. Although some of the attempts to develop enteral sensitization and/or challenge protocols for laboratory animals were rather successful or at least promising, these efforts hardly resulted in structured approaches aimed at the development of well validated enteral allergenicity models.

For food allergy research, 3 rodent species have frequently been used: the mouse, the guinea pig, and the rat, although occasionally other animals were used. Many studies have been conducted using parenteral sensitization and enteral challenges. In addition, effects of challenges have also frequently been investigated in in vitro studies with intestinal tissue or with, for instance, ligated gut. Although effects upon oral challenge in these models of IgE mediated hypersensitivity were successfully investigated, the natural route of feeding during the sensitization period was not taken into account. Natural barriers such as the gastrointestinal acid denaturation and digestion and the mucosal/epithelial layers, which are all known to prevent, reduce, or in any other way influence the contact between food antigens and the local and systemic immune system, are not modelled or taken into account in such assays. The ideal model would include the possibility for oral sensitization.

In mice, immune priming or sensitization may occur after enteral protein administration if adjuvants are used or if enteral exposure is performed at early stages of life. However, under normal conditions, oral protein feeding of mice both through gavage as well as via the drinking water or diet most easily results in tolerance induction. Particularly, repeated exposure was demonstrated to result in systemic tolerance rather than priming of humoral and cellular responses. The easy induction of an immunological tolerance upon enteral protein exposure of mice indicates that the mouse is not a most suitable species for studying oral sensitization. However, this preferential response makes the mouse most useful in oral tolerance induction research.

For the guinea pig, several studies with oral sensitization to food proteins have been described. Oral guinea pig sensitization assays are quite sensitive and proved of value in studies on differences in sensitizing properties of
“classical” infant formulas and formulas based on modified protein products (hypoallergenic formulas). However, a significant difference in immunophysiology in guinea pigs when compared to other species, the limited knowledge on the guinea pig immune system, and the lack of tools for studying the guinea pig immune system are major drawbacks for the use of this species in food allergy research.

For the rat, oral sensitization to food proteins administered through the diet or by intra-gastric dosing, often in combination with an adjuvant to facilitate the immune response, was also reported. Although tolerance induction may also occur in rats, it was not observed to be the general response upon oral antigen feeding.

**Brown Norway rat food allergy model**

As the rat was observed to be (the most) promising rodent model, we developed an oral feeding protocol to sensitize Brown Norway (BN) rats to food proteins. BN rats were used since this is a high-immunoglobulin (particularly IgE) responder strain and thus, to a certain degree, resembles atopic humans in their genetic predisposition to react with an overproduction of IgE to antigens. After daily intra-gastric dosing of the BN rats with 1 mg ovalbumin (OVA), a well defined chicken egg white allergen, during 42 days without the use of an adjuvant, we were able to induce OVA-specific IgE responses in these animals. Using this feeding protocol we also exposed the animals to a total hen’s egg white protein extract and cow’s milk proteins and compared the specificities of induced antibody responses with the specificities of antibodies in sera from egg and milk allergic patients. The results of these studies showed that orally exposed BN rats and young patients demonstrate IgE antibody responses to a comparable selection of proteins in the tested hen’s egg white and cow’s milk [Knippels et al, Allergy in press]. This indicates that the BN rat reacts to relevant proteins after oral exposure if compared to human patients. When performing these kinds of studies it is of major importance to control the diet of the animals and their parenteral generations. Exposure of the parenteral generation via its diet to the protein under investigation can result in non-responsiveness of the test animals. As allergic humans suffer from more or less severe clinical symptoms after renewed contact with the food proteins (Table 1), we investigated whether comparable symptoms occurred in our orally sensitized animals after renewed contact with the allergen. Therefore we investigated, after an oral challenge in previously sensitized rats, the effects on the respiratory system, blood pressure, and permeability of the gastro-intestinal barrier, in order to further validate our model. An increased gastro-intestinal permeability was observed in most animals and some animals showed a drop in blood pressure or breathing frequency. These results are in accordance with observations made in allergic humans.

All together, the oral BN rat model shows sufficient similarities with human observations to be considered a valuable research tool. It may provide an important possibility for research on mechanisms and factors involved in oral sensitization and elicitation of clinical effects. In addition, it may be of value in studies on the relative allergenicity of new food proteins (hypoallergenic or biotechnologically derived new food proteins) and in research with respect to prophylactic and therapeutic interventions in food allergy. Since the rat is commonly used in routine toxicity testing, knowledge on the oral sensitizing properties of food proteins in the rat would enable the evaluation of such properties in a perspective to the total of information on the potential health effects of a food product.

**References**

Mast cells and gastrointestinal hypersensitivity reactions

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Deteriorious reactions to food include intolerances such as lactose intolerance, and sensitivities of both immunological and non-immunological etiology. There is a public perception that such reactions are a widespread problem. In fact, the problem is nowhere near as common as is believed. Careful investigation by double-blind, placebo controlled food challenge suggests the prevalence is only around 1.5%1,2. Amongst children less than three years of age, however, prevalence rates of around 6% have been reported3.

Adverse immunological reactions to food may be a consequence of both IgE and non-IgE-mediated mechanisms. Although clinical testing can reliably identify the presence of a food hypersensitivity, such testing is frequently unable to determine the nature of the responsible mechanism. A recent study by Bengtsson and colleagues failed to identify specific IgE in any one of a cohort of adult patients defined by double blind, placebo controlled food challenge4. This may reflect the fact that IgE-mediated reactions to food are particularly seen in childhood. It may alternatively highlight the possibility that neither serum IgE (RAST), nor sensitization of mast cells in the skin (skin prick test) reflect events at the mucosal surface5. Certainly the release of tissue histamine, upon intragastric provocation under endoscopic control, has been reported in adult patients with negative SPT and RAST for the tested allergens9,10.

This review will focus upon the effector phase of IgE-mediated gastrointestinal hypersensitivity, with an emphasis on recent developments in our knowledge of the mast cell proteases, and on the possible role of extraintestinal mast cells in gastrointestinal hypersensitivity.

Pathogenesis

In keeping with the general uncertainty that surrounds the phenomenon of food hypersensitivity, even the symptoms are extremely varied. No signs or symptoms are considered pathognomic for the condition. Symptoms include oropharyngeal reactions such as pruritis, urticaria and angioedema, intestinal symptoms such as nausea, diarrhoea, vomiting, colic, and flatulence, and extraintestinal symptoms ranging from headaches to shortness of breath4,7,9. The time of onset of symptoms has been shown to range from several minutes to several hours, and the duration to range from hours to more than a day5.

The inaccessibility of the gastrointestinal tract has made it difficult to obtain objective measures of human gastrointestinal hypersensitivity. This in turn has limited progress in our understanding of disease pathogenesis. Advances in endoscopy have begun to change this situation. In 1989, Knutson and colleagues reported the development of a technique for the isolation of intestinal segments between two balloons. Infusion of antigen, delivery of marker substances and the aspiration of perfusate is made via a multichannel tube10. A number of groups have since used this technique. Knutson was able to show release of mast cell mediators into the lumen in response to specific antigen. She used patients allergic to milk, birch and psyllium powder. Each antigen produced an intestinal response, however, milk atopic patients responded with the release of different mediators to those seen in birch or psyllium powder sensitive patients8. In addition to mast cell-derived histamine, activation of eosinophils was indicated by the detection of eosinophil cationic protein in the perfusate of some patients.

A more recent study re-examined the question of eosinophil involvement in hypersensitivity reactions, using skin prick test positive patients allergic to prawns, lobster, peanuts or hazelnuts. It was shown that mast cell mediators, but not eosinophil mediators, were released in response to these antigen11.

Most insights into the nature of mast cells within the gastrointestinal tract still come from animal studies, although clear differences between human and animal sensitization should be noted. In humans, the sensitization process usually involves repeated oral exposure to antigen. Sensitization in animal models has generally been achieved with systemic priming, either by passive injection of antibodies12,13 or active sensitization involving intra-peritoneal injection of an antigen and adjuvant14. The hypersensitivity response is then initiated by peroral antigen challenge. A model that more closely mimics the human situation has recently been reported. Knippels and colleagues sensitise rats by repeated oral administration of antigen. Subsequently, local gastrointestinal symptoms are exhibited upon oral antigen challenge5. Systemic symptom also sometimes occur but at a frequency similar to the human situation16.
Despite the shortcomings of some animal studies, the mast cell has been clearly identified as the key effector cell in gastrointestinal hypersensitivity reactions. It is therefore critical to better characterise the mast cells of the intestinal mucosa. Many years ago, the pioneering work of Lennart Enerback led to the description of two types of rodent mast cell: the connective tissue mast cell (CTMC) and the mucosal mast cell (MMC). The differentiation was initially based upon the staining characteristics that resulted from the different granular glycosaminoglycans expressed in the two cell types. The anatomical separation of the CTMC and MMC appeared to be almost absolute. It was later shown that rat CTMC express a specific neutral serine protease Rat Mast Cell Protease I (RMCPI), while MMC express a second protease Rat Mast Cell Protease II (RMCPII). In recent years, the number of identified mast cell proteases has expanded enormously. This has led to a fresh appraisal of the function of these molecules, and to a new appreciation of mast cell heterogeneity.

The neutral proteases can be divided into three general classes. The chymases have similarities to chymotrypsin and the tryptases have similarities to trypsin. The third group is represented by the exopeptidase carboxypeptidase A. Only proteases with chymase activity are expressed by intestinal mast cells in rodents. In the rat intestine, RMCPII is by far the major protease expressed, though low levels of the chymases RMCPI-3 and RMCPI-4 have been identified in the mucosa during helminth infections. In the mouse, MMC generally express mMCP-1 and mMCP-2, though gastric intraepithelial mast cells express mMCP-2 but not mMCP-1. In contrast, mouse CTMC express the chymases mMCP-4 and mMCP-5, the tryptase mMCP-6 as well as carboxypeptidase A (mM C-CPA). Surprisingly, Helicobacter felis infection of mice induces the expression of connective tissue-associated mMCP-5 in gastric intraepithelial mast cells (J. Chen, A. Collins, A. Lee and J. Hunt, unpublished data). Further, such surprises no doubt await us as investigators focus upon protease expression in different inflammatory conditions.

Some of the cytokines responsible for the differential expression of the murine proteases are now known. Mouse bone marrow-derived mast cells grown in the presence of IL-3 contain high steady state mRNA levels of mMCP-5 and mMCP-6. Later culture in the presence of Stem Cell Factor, IL-4, IL-9 or IL-10 will induce the expression of mMCP-1, mMCP-2, mMCP-4 and mMCP-7. It now appears though that some or all of these effects may be indirect. A recent report of the role of TGF-b in the regulation of mMCP-1 production and release has shown that anti-TGF-b antibodies can abrogate the IL-9-mediated upregulation of mMCP-1 expression.

Just as has been described in the rodent, two human mast cell populations have been recognized for sometime. One cell type (MC T) expresses both tryptase and chymase activity, and the other (MC C) expresses tryptase alone. The existence of a third population (MC C) that only expresses chymase remains controversial. In the human, the anatomical compartmentalization of phenotypically distinct subpopulations is not complete. Both MC C and MC C are found throughout the intestinal mucosa and submucosa, though MC C are predominant. A further striking difference between the situation in rodents and that in humans is that only a single chymase gene has been identified in humans. The four closely related human tryptase genes were recently shown to be functionally distinct. The expression of these genes at different anatomical sites has not yet been reported.

The importance of the proteases to mast cell function is suggested by the fact that they account for over 50% of the cellular protein in rat and human mast cells. Their varied functions are, however, only beginning to be determined. Tryptase has been shown to stimulate the release of IL-8 and the upregulation of ICAM-1 by epithelial cells. The mouse tryptase mMCP-7 is a potent inducer of eosinophil accumulation. Of particular importance in the context of gastrointestinal hypersensitivity reactions, both tryptase and chymase can activate matrix metalloproteinases, and thereby contribute to matrix degradation. The abundant mast cell proteases are therefore likely to be important contributors to the gastrointestinal damage and altered integrity of the mucosal barrier seen during hypersensitivity reactions.

Extraintestinal mast cells: a possible involvement?

Evidence of a possible involvement of extraintestinal mast cells in food allergic reactions has come from an unexpected direction. Although there have been previous claims of the transfer of allergic sensitivity following bone marrow transplantation, a convincing report appeared recently describing the development of peanut sensitivity in a patient who had received a combined liver and kidney transplant. More recently, a similar case has occurred in Australia (Stephen Adelstein, personal communication). In the first such case, the recipient presented with symptoms of urticaria and laryngeal dyspnea after
eating peanuts. This occurred three months post-transplantation. The tissue donor had died of anaphylactic shock after the ingestion of peanuts. A number of explanations for this phenomenon have been advanced, including the migration of primed T and B cells from the donor organ to recipient tissue\(^\text{11}\). Alternatively mediators may be released by donor mast cells in the liver\(^\text{12}\).

There have been a few other reports previously of the activity of hepatic mast cells. They have, for example, been shown to be a major source of leukotrienes in rat and guinea pig models of anaphylaxis\(^\text{13}\). They also filled an interesting historical role, for it was hepatic mast cells that were the source of heparin when it was first isolated from liver extracts in 1916\(^\text{14}\).

We have developed a model of food hypersensitivity that strongly implicates hepatic mast cells in such reactions\(^\text{15}\). We have shown that when rats are passively sensitised with monoclonal IgE anti-DNP antibodies, and subsequently challenged with DNP-HSA, significant intestinal damage can be induced. The kinetics of this damage is paralleled by the anaphylactoid degranulation of hepatic mast cells. The intestinal damage is abrogated if animals are bile duct cannulated prior to antigen challenge. A formal demonstration that hepatic mast cells are solely responsible for this phenomenon has not been obtained. However we have shown that mast cells of isolated, perfused livers are capable of responding to antigen exposure, with the release of substantial quantities of RMCPII into the perfusate and bile. We have measured the release of as much as 75µg of RMCPII from a single liver (S. Leach, M. Cooley and A. Collins, unpublished data). This functionally is surprising, because various phenotypic features of hepatic mast cells suggest that they might be a population of immature cells.

We would argue that these cells are yet another example of the phenotypic diversity of mast cells. Recently we have shown by RT-PCR that hepatic mast cells in the rat produce both RMCPI and RMCPII, as well as RMCPS, RMCPS6 and RMCPS7 (A. Chan, M. Cooley and A. Collins, unpublished data). How these proteases contribute to intestinal hypersensitivity reactions remains to be determined.

To most biologists, bile continues to be viewed as a secretion of the liver with a purely digestive function. Mucosal immunologists, on the other hand, have recognised the immunological role of bile for many years. Bile was first identified as the means of delivery of sIgA to the gastrointestinal tract of rodents\(^\text{16}\). Since then, a variety of other factors have been identified in bile, although usually in the context of local pathology. We believe that the biliary system may be a means by which cell populations of the liver contribute to the maintenance of intestinal integrity. In addition to evidence from our hypersensitivity model, we have also shown that the enhanced bacterial translocation seen upon systemic exposure to lipopolysaccharide is also abrogated by bile duct cannulation\(^\text{17}\).

The liver is in a prime position to participate in immunological processes of the gut. Molecules that pass the intestinal epithelial barrier reach the blood and are then carried to the liver via the portal circulation. Portal blood is directed into the portal triad complex of the liver before being dispersed throughout the hepatic tissues. Portal triads include the portal vein, hepatic artery and bile duct. Hepatic mast cells are found adjacent to the portal triads, potentially giving them access to intestinal antigen. Similarly, mast cell mediators have ready access to the bile duct, for delivery to the intestine. In recent years, and after decades of debate, there has finally been recognition of the protective effector functions of mast cells against microorganisms\(^\text{18,19}\). Hepatic mast cells appear to have a role in the intestinal hypersensitivity response. Whether hepatic mast cells also contribute to the normal physiological processes in the gastrointestinal tract, or whether they play a role in the anti-microbial defences of the gut, remains to be determined.

References
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Etiological Factors of Atopic Disease in the Respiratory Tract

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Asthma in adults is largely the respiratory manifestation of atopy and is associated with active T cell immunity to common inhalant allergens that is skewed towards the T helper (Th) 2 cytokine phenotype. In contrast, non-atopic adults mount low-level immune responses to inhalant allergens that are skewed towards the Th1 cytokine phenotype. The situation is very different in infants. Recent studies have demonstrated that cord blood mononuclear cells from virtually all subjects respond to food and inhalant allergens with a low-level Th2 cytokine pattern1, demonstrating that the initial priming of Th-cells against environmental allergens occurs in utero, presumably via transplacental transport of allergens to which the mother is exposed during pregnancy. Emerging data strongly suggests that the failure to switch off these early Th2 responses is a key factor in the eventual development of allergic sensitization. This brief review will highlight some of the recent evidence behind this concept.

Asthma and atopy are complex diseases in which multiple susceptibility genes appear to be involved2. However, having the genetic predisposition is not sufficient to develop asthma and atopy as the concordance in monozygotic twins is less than 1, being reported as 0.59 for females and 0.76 for males3. Clearly the ultimate expression of the diseases involves an interaction between these susceptibility genes and additional (presumably environmental) factors.

We have previously proposed a model where during infancy and early childhood the initial low-level Th2 responses to inhalant allergens are either boosted, consolidating the response into an allergic phenotype, or deviated towards a non-allergic (Th1) response4. The T cell "sensitization" phase of this process is proposed to occur in infancy and early childhood, and progression to chronic airway inflammation, tissue remodelling and airway hyper-responsiveness occurs in later childhood and early adult life and is restricted to a subset of atopics. The questions of major interest in this area are: why some children fail to switch-off their Th2 responses and go on to develop atopy; and why some atopic children develop asthma and others do not?

Epidemiological studies have demonstrated an increasing prevalence of atopy and asthma over the past 20 to 30 years in developed countries. Studies comparing the prevalence in developed and developing countries have lead to the so-called “hygiene” hypothesis, in which a decrease in the overall exposure to microbes in developed countries, particularly during early childhood, has been proposed to be linked to the increased prevalence of atopy and asthma. Children in developed countries tend to have fewer respiratory infections, especially lower respiratory infections, and recent studies have suggested that this may be partly responsible for the increase in asthma seen. The relationships between respiratory infections in childhood...
and the development of asthma are very complex. Viral infections are the most common trigger of acute exacerbations in asthmatic children, yet non-wheezing lower respiratory infections and upper respiratory infections in early life may decrease the risk on subsequent asthma. While the mechanisms by which this could occur are not fully understood, the production of Th1 cytokines and associated inflammatory mediators, as part of the host response to infection, may assist in skewing bystander responses to aeroallergens towards the Th1 cytokine phenotype. It has been proposed that variations in microbial stimulation via the gut flora may be additional factors towards these differences in population prevalence and if so, issues such as antibiotic usage in pediatrics needs to be examined in more detail. Recent studies lend initial support for these possibilities and also raise questions concerning the possible effects of vaccines used in infants.

In contrast to the possible protective effects of upper respiratory tract infections, wheezing lower respiratory infections in the first years of life appear to increase the risk of subsequent asthma. Lower respiratory infections with Respiratory syncytial virus (RSV) are a common cause of hospitalization in infants and are associated with subsequent wheezing and a diagnosis of asthma later in childhood. However, most studies do not show an increased incidence of atopy in these children. Martinez et al. have speculated that it is the immunological response to the RSV infection which discriminates those infants who are likely to develop subsequent asthma, showing an increased incidence of asthma and atopy amongst those infants who develop an increased total serum IgE during the acute infection. These data are supported by the finding of Renzi et al. of a lower IFN γ production from peripheral blood mononuclear cells during the acute RSV infection in infants who subsequently developed asthma. Both of these observations support the contention that the host response to the RSV infection, rather than the RSV infection per se is responsible for the relationship between RSV infection and subsequent asthma.

The diet of children in developed countries is also substantially different from that in developing countries. The Western diet typically includes a greater intake of processed foods, high in salt and unsaturated fats and a lower intake of fresh fruits, vegetables and fish. While the effects of this diet are not known with certainty, recent data suggest that a diet high in omega-3-polyunsaturated fats, as found in oily fish, was associated with less asthma and a lower prevalence of airway hyperresponsiveness. Breastfeeding has also been considered to have beneficial effects in preventing atopy for many years, although objective data have been conflicting. In a recent birth cohort study from Perth, WA, the introduction of milk other than breast milk before the age of 4 months was a significant risk factor for asthma and atopy at the age of six years. The mechanism by which this occurs is not known but is an area of active current research.

Atopy appears to be a necessary but not a sufficient condition for the expression of asthma in many adults. Approximately 80% of adult asthmatics have positive allergen skin prick tests and approximately two thirds of adults with positive skin tests have asthma. The relationship between atopy and asthma is not as close in children. In the Perth birth cohort mentioned above, approximately 40% had one or more positive skin test at the age of 6 years, approximately 30% had asthma diagnosed by a doctor at some stage during childhood but only 18% had current asthma and only half of these had positive skin tests. A major challenge for the research community is to understand the relationships between the development of allergic sensitization and the development of asthma. An understanding of this relationship may then translate into effective strategies for preventing asthma, and possibly atopy itself.

References

In Favor of a Tolerant Respiratory Tract

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That mucosal tolerance to inhaled antigen represents more than a physical separation of antigen from the immune system has long been accepted by clinicians who have recognized a range of hypersensitivity reactions to inhaled antigen and have used antigen therapy to downregulate established allergic disease. These clinical observations established that the normal tolerant, or non-responsive, state of the respiratory tract to inhaled antigen involves an active and specific immune response to environmentally sampled antigen. Epidemiological and experimental studies demonstrated that the mechanisms responsible for the induction of mucosal tolerance are poorly developed in early life and that exposure to environmental allergens at this critical time may influence the subsequent pattern of allergic disease. The clinical observations established that the normal tolerant, or non-responsive, state of the respiratory tract to inhaled antigen involves an active and specific immune response to environmentally sampled antigen. Epidemiological and experimental studies demonstrated that the mechanisms responsible for the induction of mucosal tolerance are poorly developed in early life and that exposure to environmental allergens at this critical time may influence the subsequent pattern of allergic disease. The aim of this discussion is to build on the lessons of allergy to identify what we have learnt about mucosal tolerance with particular reference to the respiratory tract, to enable more focussed studies in man and to better define opportunities for immunotherapy to reconstitute defective mucosal tolerance under circumstances where inhaled antigen has induced hypersensitivity.

For over 30 years a range of hypersensitivity disorders characterized by predominant IgE, IgG or T lymphocyte responses to inhaled antigen has been recognized, with particular syndromes identified by their clinical, spirometric and radiological features. Clinical studies made it clear that tolerance involved a downregulation of a cluster of effector mechanisms, though attention focussed on immunopathogenesis rather than the question of why immune-mediated damage was the exception rather than the rule. Little attention was given to tolerance to inhaled microbes, because damage caused by microbes and antibiotic treatment, drew attention to the microbe and its interplay with effector mechanisms of immunity. Tolerance to microbes was little considered as a therapeutic option, even where hypersensitivity reactions caused tissue damage. Earlier clinicians thought in terms of a continuum between tolerance and hypersensitivity, with protection correlating with the latter. More recent understanding of the subtlety of the T cell response indicates that various factors can switch cytokine secretion profiles, leading to a range of outcomes for the host-parasite relationship. For example, in subjects colonized with Helicobacter pylori reduction of the antigen load with antibiotics induced a switch from a Th1 to a Th0 response. Tolerance to bacteria colonizing the bronchus is poorly understood. Mucosal damage initiates colonization of normally sterile bronchi especially by nontypeable Haemophilus influenzae (H1). Acute bronchitis is uncommon and both the local and systemic antibody response is poor, especially when colonization is established within the first few months of life. Recognition of the importance of immunization through aspiration of bronchus contents into the gut, with presentation of antigen to aggregated gut lymphoid tissue, has led to development of an oral vaccine to protect against acute bronchitis, though it is unclear whether protection against acute bronchitis involves up- and/or down-regulation of the immune response. Reduced numbers of circulating antigen reactive T lymphocytes, following repeated oral immunization, suggests a downregulation of T cell production from the gut-associated lymphoid tissue. Despite this evidence of tolerance continued protection against episodes of acute bronchitis correlates with an ongoing fall in the bacteria and neutrophil count within the sputum.

What cellular mechanisms underpin mucosal tolerance? Most experimental studies have been in oral tolerance in animals, though induction of tolerance following inhalation of antigen suggests a more generic mucosal phenomenon. The relevance of tolerance to man was formally established when keyhole limpet haemocyanin induced oral tolerance. The mechanisms of mucosal tolerance (best studied in oral tolerance) are those common to other forms of peripheral tolerance. Thus a variable mix of altered T lymphocyte regulation (especially immune deviation and bystander suppression), anergy, and deletion is described, with specifics relevant to the particular situation. Limited attention has been paid to quantitative, time course, and interaction aspects of specific mechanisms. Rather, most studies record phenomena at a particular time point, attempting to correlate outcome events with mechanisms in models of oral and respiratory tolerance.
ence with antigen and conditioning factors, different 'states' of antigen presenting cells and reactive T lymphocytes exist, making interpretation difficult.

Non-lymphoid cells participate in tolerance induction. Of importance is antigen handling by enteric epithelial cells, where defects in binding of antigen switches the mucosal response away from tolerance. Most studies have examined inflammatory bowel disease, but subtle variations may have a significant influence on mucosal and systemic events. The role of epithelial cell handling of inhaled antigen and the contribution of defects in such a mechanism on respiratory, mucosal, and systemic inflammation, is unknown. A role of epithelial cell-derived factors on down-regulation of mucosal inflammation is described. Regional variation of mucosal tolerance to local antigen can be affected by non-lymphoid cells. Within the respiratory tract, the level and nature of macrophage activation has a profound effect on tolerance and immunity to inhaled antigen through direct effects on the subepithelial dendritic cell carpet and T lymphocytes sequestered within the lung. The interaction between these three cell types appears to be dynamic, multidirectional, and reversible creating a functional unit that profoundly modulates the outcome of antigen handling within the respiratory tract environment through altered cytokine secretion patterns and cellular responses, including downregulation of signal transduction and phenotype variation. It is likely that environmental factors early in life, especially infections, influence the 'tolerance-immunity set' of this antigen handling 'unit' with respect to effector outcomes. The profound downregulation of cell proliferation by memory T cells in human bronchus mucosa is consistent with this concept.

What can we take away from our current understanding of mucosal tolerance in its application to man, and the pathogenesis and management of respiratory disease? First, it is clear from clinical and experimental studies that tolerance is crucial to the integrity of the respiratory tract mucosa, and that a range of inflammatory mucosal, parenchymal, and intraluminal disorders of the respiratory tract are due to a breakdown in the processes that induce and maintain down-regulation to environmental antigen. Genes, the environment and defects in the physical apparatus that maintain a sterile environment within the bronchi, are major determinants of any breakdown in mucosal tolerance. Second, regional differences exist in both antigen processing and in the control of inflammation in the respiratory tract, probably involving a two-way interaction between lumenal contents and the various mucosal mechanisms that contribute to tolerance. Regulation of these events is likely to be of special importance early in life. The role of antigen handling by local lymphoid tissue in the induction and maintenance of antigen-specific traffic patterns of T lymphocytes in cervical nodes, direct delivery of antigen to cells relevant to respiratory mucosal tolerance, or quantitative deficiencies in gut-to-bronchus T cell traffic. Demonstration of tolerance to lumenal bacteria following oral immunization with particulate and multiple bacterial antigens, may involve different mechanisms and different regional requirements. The importance in both human and animal models of local antigen in determining the extent and duration of protection emphasizes the contribution of local processes, albeit different ones from those influencing IgE mechanisms. Third, interpretation of data obtained from animal models must be made with caution when attempting to understand respiratory mucosal tolerance in man and the diseases that reflect its breakdown. Thus the precedent and genetic issues in outbred man, with time factors of exposure and conditioning factors, determine a complicated situation. It is probable that the contributions of the different mechanisms of down-regulation differ amongst species. While CD8+ T cells are potent mediators of respiratory tract inflammation in the rodent, a definitive role for these cells in man remains to be documented. Bystander suppression, moored as a mechanism of tolerance to organ restricted antigen in animal models, may contribute less to down-regulation...
of organ-specific inflammation in man, explaining the disappointment in results of oral immunization in autoimmune disease. It is crucial that quantitative, timeframe and regional analysis of contributing mechanisms to tolerance be made, if mucosal antigen therapy is to make significant gains. This becomes more challenging as successful products capable of driving immune tolerance are documented in animal models. The most studied factor is the B subunit of cholera toxin (CTB), which enables small amounts of antigen to induce oral tolerance. Immunological benefits of CTB in man have been unimpressive, limited to a mild adjuvant effect with oral cholera vaccine. Additional agents, such as lipids and bacterial exotoxins that facilitate tolerance in animals, may prove valuable in man. Trials need to be carefully assessed using controlled conditions where variables can be minimized. An area of interest is the influence of gut flora on immune tolerance to inhaled antigens. Epidemiological and animal studies show the influence of colonic bacteria on mucosal T cell cytokine patterns, driving the immune response towards different ends of the Th1-Th2 spectrum. Fourth, the balance between tolerance and immunity may be relevant to the resolution of infection within the respiratory tract, as well as influencing the outcome of oral immunization. In a murine model of oral immunization against influenza, IgA antibody responses in the upper airways could only be detected over a 2 log oral antigen dose range. Protection against intranasal challenge with live virus remained following immunization with doses above and below those that induced detectable IgA antibody. In man, a reciprocal relationship between sensitization to bacterial antigen (detected as antibody in saliva), and responsiveness to an oral bacterial vaccine (detected as a rise in saliva antibody following oral immunization), indicated a mucosal bias towards tolerance. The dependence and duration of protection in chronic bronchitis taking an oral vaccine depends on the presence of antigen (ie specific colonization) within the bronchus rather than continued production of specific T cells from gut lymphoid tissue. Much needs to be learnt about infection and the influence of tolerance on its outcome before effective second-generation mucosal vaccines can be developed.

This discussion of the respiratory tract mucosa in man focussed on tolerance in health and disease, and directions that may be taken in the prevention and management of disease. Results of animal studies are of limited value; controlled clinical trials of antigen therapy for hypersensitivity disease are needed. Care needs to be taken in correlating outcome events with time profiles of the mucosal and systemic immune response to facilitate a logical evolution of antigen therapy.

References

5. Pang GT, et al. (Book Title) Recent Advances in Mucosal Immunology 1987; 2168:1731-1739.
Announcements

Society Business

- Recently, the Governing Council approved the suggestion by Drs. Kagnoff and Kiyono to create an educational fund in support of mucosal immunology in developing countries. The goals of this fund are to facilitate the development of educational efforts in these countries. Currently, the priorities are to increase the cash available to support of these efforts, hence, a request for contributions from members was included in your renewal notices. Interested individuals are asked to seek contributions from industry, government or private foundations to augment the fund as well as provide suggestions for their use. Consideration of requests for projects will begin in 1999. Please contact the Secretary-Treasurer, Peter Ernst, at the Society Business Office with your suggestions and requests.

- The Annual Business Meeting for the Society for Mucosal Immunology will be held during the AAI meeting in Seattle on Monday, May 15 from 6 p.m. until 8 p.m. The site is too be announced, hopefully in the next issue of MIU and in the AAI program.

- Members are also requested to provide Nominations for Councillors in Australasia and North America. Pending the receipt of these nominations, a ballot will be mailed to all members.

Meeting Announcements

- The Society for Mucosal Immunology (SMI) Symposium at AAI is entitled “Lymphoid Cell Trafficking and Cell Interactions at Mucosal Surfaces”. It will be held on Monday, May 15 2:45-4:45 PM, Room 611/612. Chair: C.C. Whitacre, Ph.D., Ohio State University, Columbus OH; Co-Chair: P.B. Ernst, Ph.D., University of Texas Medical Branch, Galveston, TX.

- The 11th International Conference of Mucosal Immunology will be taking place June 16-20, 2002 at the Wyndham Palace Resort and Spa in Orlando, Florida, USA. More information will become available through mailings as well as the website for the Society for Mucosal Immunology (www.scmuimm.org) over the coming months and years. For more information about SMI, including membership, visit the website or contact smi@paimgmt.com.

Employment Opportunities

- An immediate opening exist for a PhD student at the Division of Immunopathology at the Dept. of Pathology, University of Bern, Switzerland. This position is funded by the Swiss National Science Foundation and the salary ranges from approximately US $17,800 p.a. (1st year) to US $21,600 p.a. (3rd and 4th year). The project is focused on the analysis of immunoregulatory pathways in the intestinal mucosa and the contribution of deregulated immune responses to the development of colitis in a mouse model. Candidates with a background in immunology, cellular or molecular biology/biochemistry and with strong interests in pursuing studies on the regulation of mucosal immune responses using in vivo and in vitro systems are kindly invited to submit their application including a curriculum vitae and the address of at least one referee to: Christoph Mueller, PhD, Professor of Immunopathology, Dept. of Pathology, University of Bern, Murtenstrasse 31, CH-3010 BERN/Switzerland. Phone 41 31 632 8904; FAX 41 31 381 8764 e-mail: christoph.mueller@pathology.unibe.ch

Society for Mucosal Immunology — Application for Membership

Membership in the Society for Mucosal Immunology is open to all immunologists, physicians, dentists, veterinarians, biochemists, or other scientists who do research in or who have an active interest in mucosal immunology, and who have published at least one first-authored paper in a peer-reviewed journal. Society membership includes a subscription to Mucosal Immunology Update. (Please Type or Print)

Name: ____________________________________________ Degree: ______________________________ Title/Position: ______________________________

Institution: __________________________________________ Address: ______________________________ City/State/Country/Zip Code: ______________________________

Primary Specialty: ______________________________ First-Authored Publication: ______________________________

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Please mail completed application form with $10 application fee and $60 annual dues (total $70) payable by check in U.S. dollars or by VISA or MasterCard account number (please include expiration date and MasterCard 4-digit interbank number) to Dr. Peter Ernst, Secretary-Treasurer, The Society for Mucosal Immunology, 4340 East West Highway, Suite 401, Bethesda, MD 20814-4411, U.S.A. Or e-mail to smi@paimgmt.com