

Review Article

Early-Life Environment, Developmental Immunotoxicology, and the Risk of Pediatric Allergic Disease Including Asthma

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Incidence of childhood allergic disease including asthma (AD-A) has risen since the mid-20th century with much of the increase linked to changes in environment affecting the immune system. Childhood allergy is an early life disease where predisposing environmental exposures, sensitization, and onset of symptoms all occur before adulthood. Predisposition toward allergic disease (AD) is among the constellation of adverse outcomes following developmental immunotoxicity (DIT; problematic exposure of the developing immune system to xenobiotics and physical environmental factors). Because novel immune maturation events occur in early life, and the pregnancy state itself imposes certain restrictions on immune functional development, the period from mid-gestation until 2 years after birth is one of particular concern relative to DIT and AD-A. Several prenatal-perinatal risk factors have been identified as contributing to a DIT-mediated immune dysfunction and increased risk of AD. These include maternal smoking, environmental tobacco smoke, diesel exhaust and traffic-related particles, heavy metals, antibiotics, environmental estrogens and other endocrine disruptors, and alcohol. Diet and microbial exposure also significantly influence immune maturation and risk of allergy. This review considers (1) the critical developmental windows of vulnerability for the immune system that appear to be targets for risk of AD, (2) a model in which the immune system of the DIT-affected infant exhibits immune dysfunction skewed toward AD, and (3) the lack of allergy-relevant safety testing of drugs and chemicals that could identify DIT hazards and minimize problematic exposure of pregnant women and children. *Birth Defects Res (Part B)* 83:547–560, 2008. © 2008 Wiley-Liss, Inc.

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INTRODUCTION

The incidence of childhood allergic diseases including asthma (AD-A) has been on the increase since the 1970s as apparent in many developed countries (Manning et al., 2007; Clement et al., 2008; Wong and Chow, 2008). The various forms of allergic disease (AD) involve misplaced or misdirected immune responses that are determined by a combination of environmental and genetic factors (McLeish & Turner, 2007; Wuthrich et al., 2007; Miller & Ho, 1998; Williams et al., 2008). Because the diseases are hallmarked by pediatric immune dysfunction, environmental contributions (e.g., chemicals, drugs, infectious agents, physical factors and stressors) resulting in increased disease incidence appropriately focuses on environmentally-mediated immune alterations in early life. A significant percentage of these diseases is potentially preventable given that environmental conditions may be altered to minimize problematic exposures (Danov & Guillbert, 2007; Holt & Sly, 2007), and this is consistent with the strategy of a managed early-life immune system (Dietert & Piepenbrink, 2008). However, the potential to eliminate

problematic prenatal-neonatal exposures to xenobiotics is only as strong as the safety testing system used to identify developmental immunotoxicants and/or other environmental risk factors. Currently, there is no regulatory agency requirement for direct preclinical testing of new drugs for their capacity to induce AD-A, or for direct testing of the potential of chemicals to increase the incidence of pediatric AD-A (U.S. EPA, 1998; U.S. FDA nonclinical pediatric drug guidance, 2006; U.S. FDA ICH S8, 2006).

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Because AD-A are among the most common chronic diseases of children, they represent a significant family and societal burden (Eggleston, 2007; Clement et al., 2008; To et al., 2008). The burdens of children living with asthma (To et al., 2008), allergic rhinitis (Nathan, 2007) and atopic dermatitis (Lewis-Jones, 2006) were recently reviewed. In a Canadian study, To et al. (2008) reported that childhood asthma contributed to more than one-third of the total Ontario Health Insurance Plan expenditures. Additionally, several studies suggest that lower socioeconomic children living in urban areas have a greater likelihood of asthma, allergic rhinitis and sensitization (Almqvist et al., 2005; Jeffrey et al., 2006; Clement et al., 2008).

A major focus of this paper is on developmental immunotoxicity (DIT), which is concerned with the effects of exposure to biological materials, chemicals, drugs, medical devices, physical factors (e.g., ionizing and ultraviolet radiation) and, in certain instances, physiological factors on the developing immune system (Luster et al., 2008). DIT is considered largely in the context of pediatric AD-A. However, the health outcomes of DIT can affect all stages of later life. Not surprisingly, Mallen et al. (2008) found that early-life environmental exposures impacting the immune system can result in an increased incidence of AD-A in young adults (Mallen et al., 2008).

Exposure criteria are critical in gauging the potential adverse effects from DIT. Milner and Gergen (2005) proposed that even transient environmental exposure of the developing immune system could alter postnatal immune status and predispose children for AD-A. This concept has been extended by other researchers to a consideration not only of systemic outcomes of toxicants and other environmental factors on the developing immune system but also of effects that may focus on specific tissues (e.g., lung, skin, gastrointestinal tract) (Kajekar, 2007; Selgrade et al., 2008).

As a result of a March of Dimes and EPA-cosponsored workshop, critical windows of immune development were identified relative to environmental insult (Dietert et al., 2000). This facilitated a variety of age-based immunotoxicity studies comparing relative vulnerability and later-life outcomes (Bunn et al., 2001; Luebke et al., 2006; Hogaboam et al., 2008). The results of these studies indicated that the developing immune system was hyper-susceptible to xenobiotics compared with that of adults, and that adverse outcomes of DIT extended well beyond immunosuppression to include both autoimmunity and AD (Dietert & Piepenbrink, 2008; Luster et al., 2008). Proceedings of an EPA-sponsored workshop on environmental risk factors and asthma were among the first to consider, in one setting, the concepts of critical immune maturational windows, environmental chemicals and drugs to DIT, and the role of other environmental factors (e.g., diet and microbial stimulation as per the hygiene hypothesis) in the risk of childhood asthma (Yeatts et al., 2006; Selgrade et al., 2006).

This present review uses the prior environment and asthma workshop (Yeatts et al., 2006; Selgrade et al., 2006) as a foundation for examining the role of DIT in the spectrum of pediatric ADs. The review includes consideration of (1) prenatal and perinatal windows of immune maturation and environmental vulnerability that enable DIT-facilitated pediatric AD-A, (2) the

intersection between prenatal-perinatal DIT and postnatal microbial-driven maturation of the immune system relative to AD, (3) specific xenobiotics (e.g., diet, environmental chemicals and drugs) as early life risk factors in AD-A and, (4) the current deficits in safety testing regulations that could help to address the epidemic of AD-A in children.

Sensitivity of the Developing Immune System and Adverse Health Outcomes

Because many of the immune maturational processes are either restricted to early-life or have different implications when they occur in the adult, early life events represent critical windows of immune vulnerability. The developing immune system exhibits an increased sensitivity for environmental insult versus that of the adult, which takes several forms: (1) adverse responses at lower doses, (2) greater persistence of adverse outcomes, (3) broader spectra of adverse health risks, and (4) a rewiring of the immune system for the appearance of latent effects following adult exposure to toxicants (Dietert et al., 2000; Holladay, 2005; Dietert & Piepenbrink, 2008; Luebke et al., 2006). Because of the increased sensitivity of the immune system in early life versus adulthood (Dietert & Piepenbrink, 2008), direct assessment of xenobiotic risk for pediatric allergy is required, and the use of adult-exposure models to identify risk of pediatric allergy is problematic (Dietert & Piepenbrink, 2008; Dietert, 2008).

Environmental disruption of these immune maturational events produces a wide range of adverse outcomes in the form of immune dysfunction and increased disease risk in the offspring (reviewed by Luster et al., 2008). These are shown in Table 1 and include an increased risk of infectious disease (Dallaire et al., 2006; Heilmann et al., 2006), cancer (Dietert, 2008), AD-A (Wang & Pinkerton, 2008), autoimmunity (Mustafa et al., 2008), and neuroinflammatory-associated conditions (Herz-Piccolotti et al., 2008; Dietert & Dietert, 2008a,b). Much of the focus of immunotoxicology in the past two decades has been on immunosuppression, and this is certainly important with early-life toxic exposures as well (Dallaire et al., 2006; Heilmann et al., 2006). But while immunosuppression has a significant place in DIT, it could be argued that the most likely adverse outcomes of prenatal exposure to environmental chemicals and drugs involve increased risk of later-life AD-A and autoimmunity. This is due to three specific features of prenatal development: the immunology of the pregnancy state, the immunological identification of self from non-self, and the capacity of some xenobiotics to effectively freeze the developing immune system in an allergy-biased dysfunctional state.

DIT and the Allergy Archetype: Disrupted Immune Maturation – Pediatric Immune Dysfunction

Among the myriad of outcomes and later life health problems associated by DIT, AD-A represent a virtual default condition. DIT-promotion of allergy does not require major toxicant-induced cell death or major reorganization of any lymphoid tissues. Instead, only a delay of, minor interference in, or blunting of, subsequent perinatal-neonatal responses to the environment

Table 1
Matrix of Major Childhood Diseases and Conditions Featuring Immune Dysfunction and Having Prenatal-Neonatal Environmental Risk Factors

Average Age of Onset (years)	Allergic Diseases	Infectious Disease and Host Response	Autoimmune Diseases	Neuro-Inflammatory Diseases	Cancer
0–1.5	Atopic Dermatitis	Late-Onset Neonatal Sepsis			
1.5–4	Food Allergy and Pediatric Celiac*	Otitis Media	Kawasaki Disease	Autism and Autism Spectrum Disorders	
4–8	Childhood Asthma	Childhood Vaccine Problems (failures and adverse reactions)	Type 1 Diabetes		Childhood Leukemia
8–14	Allergic Rhinitis		Juvenile Idiopathic Arthritis	Childhood Myalgic Encephalomyelitis	
14–18			Childhood Multiple Sclerosis		

*While celiac disease is primarily an allergic disease, it also has an autoimmune component in some patients.

(e.g., microbial exposure) can leave the offspring with incomplete immune maturation, pediatric immune dysfunction (Hales et al., 2008; Prescott et al., 2008) and the allergy archetype. The reason that pediatric allergy is tightly linked to DIT stems from the fundamental requirements for a successful pregnancy and birth. A successful pregnancy requires maintenance of a semi-allogeneic fetus, and this imposes certain immunological constraints on both the mother and fetus (Seavey & Mosmann, 2008). Conditions favoring tolerance, relative immaturity of dendritic cells and macrophages, the down regulation of interferon-gamma (IFN- γ) and increased production of certain T helper 2 (Th2) cytokines are all hallmarks of the pregnancy state. Additionally, the status of T regulatory cells (Tregs) is important in fetal tolerance (von Rango, 2008). Bjorksten (2008) recently suggested that Tregs may be an early life environmental target affecting the risk of pediatric AD.

Pregnancy-Driven Immune Considerations

In normal pregnancies, this specialized pregnancy state helps to protect against T helper 1- (Th1) driven rejection of the fetus and elevated Th1/Th2 ratios have been linked with recurrent spontaneous abortions (Hill et al., 1995; Daher et al., 2004; Kwak-Kim et al., 2007). There is some suggestion that the kynurenine pathway may be involved in suppression of a graft rejection response and Th skewing (Gonzales et al., 2008). In fact, adjustment of T helper (Th) balance during pregnancy has been suggested as a strategy for addressing pregnancy complications (Raghupathy and Kalinka, 2008).

As discussed by Holt and Sly (2007), at birth the immune system requires further maturation to achieve effective host resistance to disease and to shift out of an allergy-favoring dysfunctional state. The newborn emerges in an imbalanced state with an immature innate immune phenotype (Levy, 2007) and an acquired immune capacity skewed toward Th2 responses (Wegmann et al., 1993). Adjustments in immune balance (Schaub et al., 2004; Chen et al., 2006) and further maturation of dendritic cells and other immune cells (Danis et al., 2008; Koga et al., 2008) are needed for the child to meet infectious disease challenges and to minimize the risk of AD-A. Therefore, any prenatal-neonatal environment exposure that can perpetuate

the newborn's dysfunctional state could be a risk factor for AD.

Creating the Newborn's Immune Imbalance

The basis for pregnancy-driven immune skewing and innate immaturity has been described by several researchers. In mice, Blois et al. (2008) found that uterine dendritic cells and natural killer (NK) cells collaborate to create a tolerogenic environment that is dominated by Th2 cytokines. In humans, it has been suggested that the action of 17-Beta estradiol (E2) on dendritic cells may help to create the Th2 preferred environment during pregnancy (Uemura et al., 2008), although placental growth factor has also been suggested to act on dendritic cells and produce a down regulation of Th1 cytokines (Lin et al., 2007). Backy et al. (2008) reported that maternal dendritic cells are shifted to a less mature state favoring Th2 responses during the last trimester. Shi et al. (2007) reported a significant down regulation of IFN- γ among both NK and NKT cells during pregnancy. Aris et al. (2008) found that the Th2 bias emerges and is most pronounced during the second half of gestation. Mor (2008) suggested that innate immune cells are maintained in a specialized state of trophoblast-regulated differentiation and activation during pregnancy.

Perinatal Biomarkers Predicting Allergy

Recent findings support the tenet that gestational environmental exposures overlaying the genetic background can drive the risk of pediatric AD. Various hematopoietic-immune cord blood profiles are reported to be useful in predicting risk of childhood AD. Kerkhof et al. (2005) found a relationship between prenatal exposure, total immunoglobulin E (IgE) at birth, and allergic sensitization during childhood. Additionally, Fernandes et al. (2008) identified cord blood hematopoietic progenitors that serve as biomarkers for predicting acute respiratory symptoms in infants. Zizka et al. (2007) tracked perinatal cytokines as indicators of future AD. They found that a cord blood Th2 bias involving higher levels of interleukin (IL)-5 and IL-10 were associated with increased risk of postnatal allergy. IL-5 is one of the central components facilitating Th2 driven eosinophil activity and subsequent allergic airway inflammation (Asquith et al., 2008). Consistent with the utility of

Th2-associated biomarkers at birth, IL-4 receptor was identified as another useful biomarker. Grzela et al. (2007) found that expression of IL-4 receptor on monocytes and T lymphocytes of newborns correlated with the risk of developing allergy. Additionally, Zizka et al., (2007) reported a reduced level of EGF in the cord blood of newborns, who developed childhood allergic disease. Reduced EGF was thought to delay intestinal maturation and potentially influence risk of AD. These findings reinforce the concern that xenobiotic-exposures capable of delaying or reducing the efficiency of perinatal immune maturation could promote pediatric AD.

Critical Developmental Windows of Immune Vulnerability in Risk of AD

For some time, attention has been focused on postnatal events that help to promote immune maturation and balance and, thereby, reduce the likelihood of AD (Adler et al., 2005; Alfvén et al., 2006). However, more recently attention has shifted toward consideration of pre- and postnatal exposure to environmental factors that interfere with immune maturation, promote immune dysfunction and facilitate AD. Holt and Sly (2007) recently discussed the significance of the prenatal and early neonatal period of development for the risk of childhood immune dysfunction and development of AD. A variety of immune cell types and maturational processes are involved and each process can be disrupted by several

different categories of environmental factors and conditions.

Figure 1 depicts a timeline of human development from conception to 2 years after birth. A subset of the critical windows of immune development that are those most closely aligned with pediatric allergy-associated immune dysfunction is shown below the timeline. Four different categories (toxicants, diet, microbial exposure, birth delivery mode) of potential environmental risk factors for AD-A are illustrated above the timeline. No single immune parameter appears to hold all the answers regarding risk of AD. Rather, it is the intersection between innate and acquired immunity that appears to be central for the risk of childhood AD (Holt & Sly, 2007). Likewise, no single environmental risk factor explains the recent rise in childhood AD. Because of this, it is useful to consider the full range of potential prenatal-neonatal factors that may disrupt a key immune maturational process and promote AD (i.e., toxicants, maternal diet, physical factors and stress, birth conditions, infectious agents). It should be recognized that early life exposure to a single toxicant (e.g., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) can disrupt the immune system in such a way as to increase the risk of more than one disease (Vorderstrasse et al., 2006; Mustafa et al., 2008). For this reason, it is not surprising that some forms of allergy are often associated with an increased risk of autoimmune conditions (Kokkonen & Niinimäki, 2004; Hvatum et al., 2006).

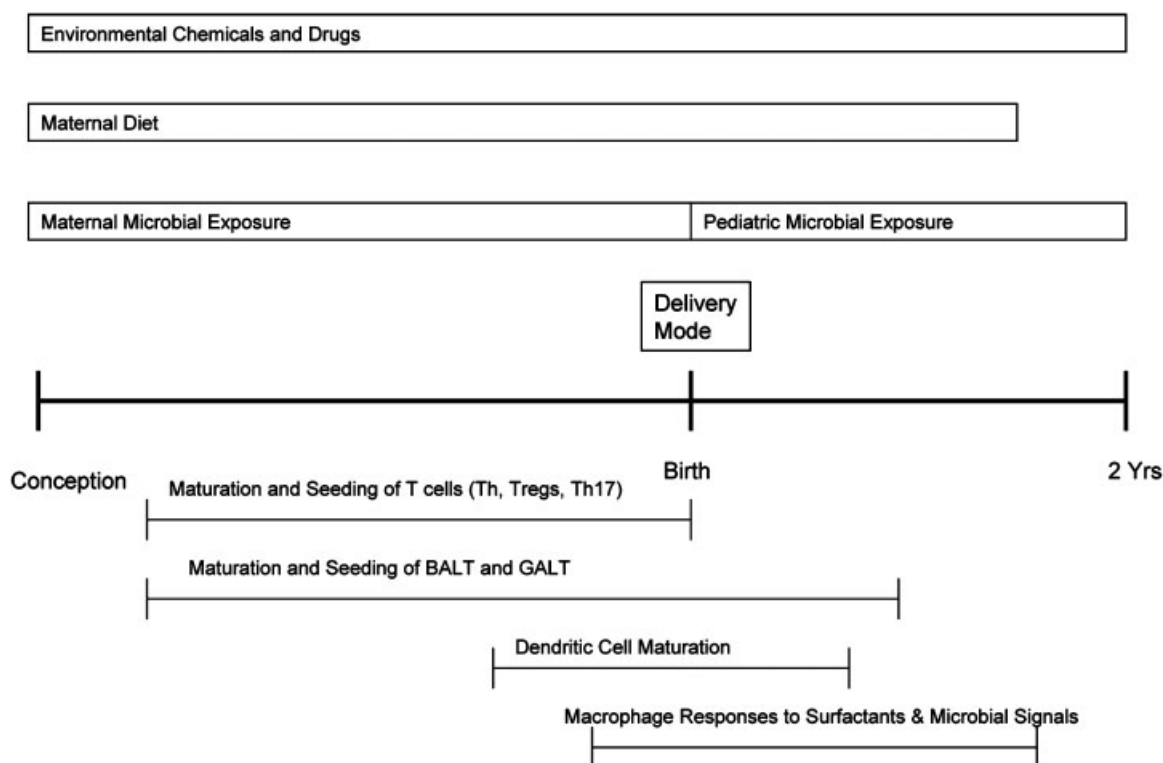


Fig. 1. The figure shows a timeline for human development including conception, prenatal development, birth and neonatal maturation to 2 years of age. Above the timeline, four categories of environmental risk factors are shown that have been reported to contribute to both postnatal immune dysfunction and pediatric allergic disease. Below the timeline, four developmental windows of immune maturation are illustrated that have particular relevance to allergic disease and asthma (AD-A). Disruption of maturation among any of the four windows is likely to impact the risk of childhood AD-A. Among the designations, BALT (bronchus-associated lymphoid tissue) and GALT (gut-associated lymphoid tissue) are specialized immunological tissues that represent part of the mucosal immune tissue. Th = Th1 and Th2 cell populations; Treg = T regulatory cells; Th17 are a specialized population of T cells that produce interleukin-17.

Early-Life Immune Targets Predisposing for Allergy and Asthma

While a wide range of immune cells, cytokines, chemokines, and cell surface receptors are involved in allergic responses, specific forms of immune maturational problems and postnatal immune dysfunction seem to be most closely aligned with childhood allergy. The four developmental processes shown in Figure 1 are of particular interest in the risk of AD. These include the development of T cells including Th1, Th2, Th17, and Tregs, maturation of dendritic cells, maturation of macrophages and other inflammatory cells, and the development and organization of mucosal immune tissues.

Th1, Th2, Th17 cells, and Tregs play various roles in determining the risk of AD. Therefore, their maturation in early development is central to the risk of pediatric AD-A. The molecular mechanisms involved in the differentiation and activation of human Th cells was recently reviewed (Rautajoki et al., 2008). In addition to direct promotion of Th2 responses, increased apoptosis of Th1 cells is one route for Th2 bias and increased risk of atopy (Akkoc et al., 2008). Th2 directed responses can promote allergic lung disease and appear to involve the indoleamine 2,3-dioxygenase enzymatic pathway (Xu et al., 2008). Th2 lymphocyte homing is regulated by specific integrin molecules that play an important role in certain allergic lung responses (Lee et al., 2008). Different antigens themselves can either promote or inhibit Th2 responses. For example, fungal proteases can polarize responses toward Th2 by limiting dendritic cell maturation (Lamhamedi-Cherradi et al., 2008). Among the T cell populations of importance, Th17 is a recently identified Th cell population that produces IL-17 (Schmidt-Weber et al., 2007) and appears to play a role in AD pathogenesis (Oboki et al., 2008). Suppression of Th17 cell differentiation promotes oral tolerance (Ehricht et al., 2007). In contrast with Th17 cells, production of Tregs is associated with peripheral tolerance and can provide protection against (Umetsu & DeKruyff, 2006; Elkford, 2006) and/or resolution of, allergic responses (Leech et al., 2007). Quantitative and functional impairment of Tregs have been reported in the lungs of children with pediatric asthma (Hartl et al., 2007). Similarly, children with egg allergy were reported to have a reduced number of Tregs (Smith et al., 2008). Therefore, maturation, seeding and activation of Tregs is a potential environmental target of concern for risk of pediatric AD.

Dendritic cells play a key role in risk of allergy (Aiba, 2007). Effective dendritic cell maturation is needed to promote postnatal Th1 responses (Koga et al., 2008) and represents a key step in protection against AD (Lundell et al., 2007). If this process is disrupted during development via DIT or other environmental considerations (e.g., diet), then the infant can be left with an improperly skewed immune response capacity (Th2 bias). A persistence of T-cell activating apoptosis-resistant dendritic cells has been reported to selectively promote Th2 responses and IgE production (Arques et al., 2008). Likewise, activation of c-kit and production of IL-6 by dendritic cells helps to depress Th1 responses and promote Th2 and Th17 responses (Krishnamoorthy et al., 2008). Dendritic cells from allergic subjects were reported to have a reduced capacity to produce

interferon-alpha (Tversky et al., 2008). Dendritic cells can influence allergic responses not only via production of Th1 versus Th2 cells, but also through the generation of suppressive Foxp3⁺ Tregs. In fact, some strategies for suppressing allergic responses via dendritic cells involve the generation of Tregs (Larche, 2007; Jin et al., 2008; Wu et al., 2008).

Myelomonocytic cell maturation is a sensitive pre-natal-perinatal target of DIT (Dietert and Piepenbrink, 2008; Dietert and Dietert, 2007). In the first trimester, generation, distribution and seeding of tissue macrophages are critical events that can impact later life tissue function (Pace et al., 2000). In the case of AD, there is always the possibility that this maturational process involving resident macrophages may be an important window particularly in the local setting (lung, skin, gastrointestinal tract). However, to date little information has been available concerning this window and allergies, and most of the focus has been on later perinatal maturation processes of macrophages disrupted by environmental chemicals and drugs. For example, surfactant-D driven maturational events are key to allergic events at the level of the mast cell (Malherbe et al., 2005), and surfactant D can block the chemotaxis of eosinophils (von Bredow et al., 2006). Surfactants A and D have been reported to protect against allergic airway disease (Wang & Reid, 2007). But prenatal exposure to alcohol has been seen to disrupt lung surfactant production (Lazic et al., 2007), impair alveolar macrophage function (Ping et al. 2007) and increase the risk of neonatal infections (Gauthier et al., 2005).

Development and organization of mucosal-associated lymphoid tissue (MALT) (Blumer et al., 2007), which includes both the bronchus-associated lymphoid tissue (BALT) (Heier et al., 2008) as well as the gut-associated lymphoid tissue (GALT) (Cheroutre & Lambolez, 2008; Coombes & Powrie, 2008; Fulkerson & Rothenberg, 2008; Talley, 2008), has been touted as an important factor in risk of AD. This pertains both to protection against environmental insult as well as promotion of tolerogenic or protective strategies. For example, Hamelmann et al. (2008) recently discussed the importance of understanding and utilizing tolerance induction in the gut as a means of protecting against allergy. Processes in the GALT and BALT are not mutually exclusive. In fact, in a recent experiment using mice, gut allergen-primed CD4⁺ T cells from the mesenteric lymphoid nodes were able to induce experimental allergic asthma after adoptive transfer (Ozdemir et al., 2007). Alvarez et al., (2007) reported that the location of the allergic reaction (gut, lung, skin) may be determined in part by the site of initial Th2 differentiation and differential homing molecule expression, which can restrict Th2 immune-inflammatory responses.

Integrating DIT and the Hygiene Hypothesis

Because pregnancy constraints cause the newborn's immune system to be Th2 biased with incomplete innate immune maturation, additional postnatal maturational steps are needed to minimize pediatric AD risk. These include the stimulation of toll-like receptors (TLRs) on antigen-presenting cells via exposure to various bacterial products capable of triggering additional maturation and selective activation. If unimpeded by

prior prenatal-perinatal exposure to xenobiotics, interaction of the newborn with environmental factors can help the immune system to complete maturation of innate immune components as well as a shift in balance among Th-driven responses. The "hygiene hypothesis" in its various incarnations (Vercelli 2006; Renz et al., 2007; Garn & Renz, 2007) helps to explain the efficiency of this immune balance (or, alternatively, the lack thereof in some individuals).

However, postnatal microbial-driven immune maturation does not occur in a vacuum. In fact, pre- and postnatal toxicant exposure such as that caused by tobacco smoke, alcohol, and other chemicals and drugs can effectively freeze Th bias as well as dendritic cell and macrophage maturation. For example, Mainali and Tew (2004) and Mainali et al. (2005) showed that dexamethasone exposure effectively locks human cord blood derived DCs into an immature and allergy promoting phenotype. A similar result was reported for the effect of lead on DCs in mice (Gao et al., 2007). As previously indicated, alcohol in late gestation can interfere with macrophage function (Ping et al., 2007). Taken together, these findings suggest that developmental exposure to xenobiotics, diet, physical, and microbial factors should all be considered for the most effective protection of the pediatric population against AD-A.

Allergic Diseases Impacted by DIT

Not surprisingly, risk of most pediatric ADs appears to be influenced, at least in part, by prenatal and neonatal exposure to xenobiotics. The individual ADs are often considered separately in the literature (e.g. asthma or food hypersensitivity). But because many of these pediatric diseases appear to be interconnected by environmentally mediated immune dysfunction, it is useful to briefly consider that range of AD that appears linked with early-life xenobiotically-induced immune insult.

Asthma

Asthma is a disease with marked early life origins (Saglani & Bush, 2007) where early life conditions influence not only the pediatric incidence of the disease, but also the risk for adult lung disease (Landau, 2006). Both environment and genetics are known to play an important role in the risk of the disease (Ober & Thompson, 2005; Gao et al., 2007; McLeish & Turner, 2007; Miller & Ho, 1998). However, established risk factors cannot account for the global occurrence of asthma among children (Pearce & Douwes, 2006). Therefore, new approaches to identify environmental risk factors need to be considered. Early life risk factors reported to date include selected environmental chemicals and drugs (e.g., maternal smoking, paracetamol), specific dietary intake (e.g., micronutrient and fatty acid status, daily consumption of nuts), stress, and respiratory infections caused by specific agents (e.g., respiratory syncytial virus).

Much of the focus on environmental chemicals has concerned air pollutants. In a California study, Morimer et al. (2008) found that prenatal exposure to air pollutants (i.e., ozone, carbon monoxide and nitrogen dioxide) had a significant negative impact on postnatal lung function among subgroups of children. This is consistent with the observation of higher childhood asthma incidence with

other problems in lower Manhattan following the 9/11 World Trade Center disaster (Landrigan et al., 2008). Wigle et al. (2008) also reviewed the epidemiologic evidence for an elevated risk of childhood asthma associated with environmental tobacco smoke (ETS) and other air pollutants. In contrast, where there was a significant presence of street trees, there was a lower risk of childhood asthma (Lovasi et al., 2008). Several recent studies have reported that Caesarian delivery increased the risk of childhood asthma (Metasala et al., 2008; Thavagnanam et al., 2008; Tollanes et al., 2008), although it may depend upon the subgroups compared (e.g., offspring with maternal atopy or not) (Pistiner et al., 2008).

For drugs, one recent study suggested that prenatal exposure to paracetamol was associated with an increased risk of childhood asthma (Rebordosa et al., 2008). Additionally, numerous studies involving children from different ethnic and geographical backgrounds all found that early childhood use of paracetamol was a risk factor for asthma or wheezing (Kanabar et al., 2007; Wong et al., 2007; Del-Rio-Navarro et al., 2008; Foliaki et al., 2008; Rodriguez Martinez et al., 2008). Among immune effects considered, paracetamol is known to alter pulmonary macrophage function by depleting glutathione (Dimova et al., 2005).

Allergic Rhinitis

Allergic rhinitis (hay fever) tends to overlap significantly with asthma in terms of early life risk factors and increased susceptibility to environmental factors during prenatal and early postnatal life. Johansson et al. (2008) showed that pre- and postnatal exposure to ETS increased the risk of rhinitis in children. Rasanen et al. (2001) found that gestational maturity and neonatal hospitalization were both risk factors for adolescent allergic rhinitis. Similarly, with risk of asthma among some populations, a recent study found that Caesarian section versus vaginal delivery significantly elevated the likelihood of allergic rhinitis among those children with a parental history of atopy (Pistiner et al., 2008).

Food Hypersensitivity

While the risk of food hypersensitivity has both prenatal and postnatal risk factors (Schuller, 2005), at least part of the early life risk appears to be predictable based on immune functional profiles at birth. Prescott et al. (2008) found that cord blood monocytes stimulated with TLR-2, 4, and 5 activators produced more IL-6 among children who would develop food allergy at 12 months of age compared with those who were non-allergic in later life. Additionally, newborns producing lower Th1 responses (IFN- γ) were more at risk. This suggests that the prenatal environment may play a significant role in the risk of pediatric food allergy. Yang et al. (2007) found that a novel molecule on the cell surface of mucosal dendritic cells (TIM-4) plays a pivotal role in causing a shift toward Th2 activity and facilitating food-antigen-specific intestinal allergy.

In a longitudinal study, Ostblom et al. (2008) reported that even a transient food hypersensitivity reaction in early childhood increased the risk for later asthma, eczema, and allergic rhinitis by the age of 8. Kjaer et al. (2008) found that food hypersensitivity was frequently associated with other ADs among sensitized children,

and Rance (2008) emphasized the interconnections between food allergy and eczema. This is consistent with the finding by Lannero et al. (2008) that exposure to ETS increased the risk of sensitization of infants to food allergens as well as inhaled allergens.

Food hypersensitivity includes the more specialized category of pediatric celiac disease. Pediatric celiac appears to have not only allergic but also autoimmune implications. The disease is in lower incidence among children with lower economic status and higher microbial exposure in early life (Kondrashova et al., 2008). The disease overlaps with type 1 diabetes (Franzese et al., 2007; Deja et al., 2008) and is seen in higher incidence with other childhood autoimmune conditions (Stagi et al., 2005). Because of this, immune dysfunction appears to be a hallmark of the disease. This may also be reflected in the suggestion that certain dental infections are more likely in children with celiac disease (Avsar & Kalayci, 2008).

Atopic Dermatitis

Atopic dermatitis (also called eczema) is the most common chronic skin disease of children (Horii et al., 2007). Horii et al. (2007) also reported a recent increase in physician and outpatient visits of children with atopic dermatitis by comparing doctor visits during 1997–2001 versus 2001–2004. Additionally, atopic dermatitis has been increasing in incidence among Taiwanese children during the past two decades (Lee et al., 2007). The disease has both genetic and environmental components resulting in dysfunctional immune and inflammatory responses (Bones & Bieber, 2007). It has been suggested that environmental factors in the home during early life may play a role in risk of the disease (Karadag et al., 2007; Miyake et al., 2007). Given that the pediatric population is the primary susceptibility group for the disease, most environmental components contributing to the disease would fall within the scope of DIT.

Atopic dermatitis has been characterized as a biphasic inflammatory skin disease that involves sequential T-cell responses promoted by two different dendritic cell subpopulations. The initial phase is Th2 preferred, which later shifts to a chronic Th1-associated inflammation (Novak et al., 2007). Several investigators have suggested that maturation and functional status of infant myelomonocytic cells is important in atopic dermatitis and that shifts in these cell populations are important biomarkers of the disease. For example, Mandron et al. (2008) tracked differences in peripheral blood monocyte responses to bacterial toxins among patients of different ages. They reported that atopic dermatitis patients had inherently activated monocytes, which were refractory to further certain bacteria-driven toll-like receptor stimulation. However, these investigators were able to track the development of the disease in children by the acquisition of this bacterial tolerance. Additionally, several researchers have noted that patients with atopic dermatitis exhibit a deficiency of type I interferon-producing plasmacytoid dendritic cell populations in their skin suggesting that immune dysfunction drives the disease (Novak et al., 2007; Wollenberg & Klein, 2007). This dendritic cell population deficiency contributes to an additional susceptibility of patients to viral skin diseases (Wollenberg & Klein, 2007). Additionally, infants with

atopic dermatitis were found to exhibit a reduced diversity of microbial flora (Wang et al., 2008). It is not known whether this might be a result of the overall environmentally associated immune dysfunction or more specifically functional shifts among macrophage and dendritic cell populations.

Environmental Risk Factors for Allergy Including Xenobiotics Affecting the Developing Immune System

Early life environmental risk factors for asthma have been the subject of prior reviews (Gilmour et al., 2006; Selgrade et al., 2006; Yeatts et al., 2006; Ng et al., 2007), although fewer reviews have examined prenatal and postnatal contributions across a more complete spectrum of childhood allergic diseases.

Maternal Smoking and Environmental Tobacco Smoke

Airway and lung diseases of later life can be greatly influenced by environmental exposures occurring during critical windows of development for the immune and respiratory systems (Dietert et al., 2000). This is further emphasized by Landau et al. (2006) who discusses the pediatric basis of adult lung disease. Among the environmental risk factors that influence the immune system, tobacco smoke is a major concern.

Two recent reviews emphasize the importance of prenatal and early postnatal ETS exposure and risk of later-life asthma. Tager (2008) discussed the importance of prenatal and early postnatal exposure to tobacco smoke as a risk factor for asthma, and this was also recently reviewed by Wang and Pinkerton (2008). Whu et al. (2007) also identified exposure to tobacco smoke as a major risk factor for childhood asthma in one of the areas of the United States with the highest incidence of the disease.

Alati et al. (2006) found that girls whose mothers smoked during pregnancy and postnatally up to the 6-month follow-up examination had a greater risk of developing asthma as evaluated to 14 years of age. In this study, the risk from in utero exposure was greater than that following neonatal exposure. However, in a study of Finnish children, Jaakkola and Gissler (2007) found no gender-specific effects on the increased risk for asthma induced by prenatal exposure to maternal smoking.

In a study among school children in France, Raheerison et al., (2008) reported that parental smoking increased the risk of allergic sensitization by the fifth grade of school. Zuraimi et al. (2008) also reported an increased risk of allergies among children in Singapore raised in the homes of smokers. In studies in mice, Penn et al. (2007) and Rouse et al. (2007) found that maternal smoking during gestation altered gene expression in the lung of the offspring and potentiated the allergenic response in later life. The impact on the developing immune system extends well beyond AD to include reduced cell-mediated immune responses and increased tumor susceptibility as shown in mice (Ng et al., 2006; Ng & Zelikoff, 2007; 2008).

Maternal smoking was more important than paternal smoking and prenatal exposure was more significant than postnatal exposure for childhood allergic

sensitization (Raheison et al., 2007). Exposure to maternal smoking prenatally and later also increased the risk of wheezing and asthma (Raheison et al., 2007). Noonan and Ward (2007) had a similar finding of increased risk for wheezing and asthma-like symptoms with early childhood ETS exposure. Increased risk of allergic sensitization (IgE-mediated) from ETS was reported by Lannero et al. (2008). These authors found that exposure shortly after birth was the most significant developmental window. Children carrying certain immune cytokine gene polymorphisms may be at even greater risk from asthma associated with ETS (Salam et al., 2007; 2008).

Among those children at greatest risk of atopy, paternal smoking also produced reduced responses to childhood vaccines (Baynam et al., 2007). Likewise in a mouse study, Ng et al. (2006) found that maternal smoking reduced cell-mediated immunity and increased transplantable tumor growth. This reflects the immune dysfunctional nature of DIT-induced alterations. In addition to maternal smoking and ETS, direct smoking among adolescents is also a risk factor for the development of asthma (Gilliland et al., 2006).

Other Indoor Air Pollutants

Indoor air environments play a significant role in childhood AD-A (Mendell, 2007; Sharma et al., 2007). For example, combustion from stoves burning a variety of fuels has been associated with an increased risk of childhood asthma (Schei et al., 2004; Belanger & Triche, 2008). In a study in Guatemala, Schei et al. (2004) reported that exposure to wood stoves involved in cooking was a risk factor for asthma, and this topic was recently reviewed by Naeher et al. (2007). In a longitudinal study set in California, Duramad et al. (2006) found that exposure to gas stoves in early life was a risk factor for both infant Th2 cytokine bias as well as risk of asthma by 2 years of age.

Outdoor Air Pollutants

Outdoor air pollutants, including diesel exhaust and traffic-associated pollutants, represent a major component of the risk for childhood immune dysfunction and AD-A (Wang & Pinkerton, 2007; Fedulov et al., 2008; Jerrett et al., 2008). Two primary effects have been described. First, among allergic children there is the capacity of diesel exhaust to act as an adjuvant enhancing the potency of allergens during exposure. This results in a lowering of clinically significant allergen threshold dose and/or produces more severe symptoms among those exposed to allergens.

However, a second effect is to alter the early-life immune system such that allergic responses are more likely. Morgenstern et al. (2008) followed 2,860 children from 0–6 years of age tracking proximity to main roads and various allergic disease parameters. Distance-dependent relationships to main roads were identified for asthmatic bronchitis, eczema, allergic rhinitis and sensitization. The group with the highest odds ratio lived within 50 meters of a main road.

Ozone primes innate immune responses in the lung as shown in mice (Hollingsworth et al., 2007), and particular human genotypes may be hyper-susceptible to its effects (London, 2007). Based on murine studies,

disruption of surfactant-macrophage interaction is one way that ozone may contribute to misregulated inflammation in the lung as a component of asthma (Kierstein et al., 2006). Ozone and diesel exhaust also have an additive effect on airway hyperreactivity and inflammation in a mouse model (Jang et al., 2005). It is among the outdoor air pollutants that have been suggested as contributing factors to asthma (Gilmour et al., 2006).

Heavy Metals

Prenatal and early postnatal exposure to heavy metals such as lead have been reported to skew immune responses toward a Th2 bias and elevate production of IgE. Therefore, some metals may have the potential to affect risk of AD-A. Lead exposure and blood concentration have been shown to directly relate to IgE production in both humans (Lutz et al., 1999; Sun et al., 2003; Karmaus et al., 2005) and rodent models (Miller et al., 1998; Snyder et al., 2000). In mouse studies, lead appears to alter the functional capacity of dendritic cells causing them to bias toward promoting Th2-driven responses (Gao et al., 2007). Similar results of Th2-biased cytokine production have been obtained following exposure of human leukocytes to mercury (de Vos et al., 2007). In addition, propensity toward misregulated tissue inflammation is a concern with exposure to heavy metals. Min et al. (2008) recently reported that blood lead levels were directly related to bronchial responsiveness.

Pesticides

In utero exposure to pesticides has been raised as a concern for risk of childhood asthma by some investigators (Weselak et al., 2007; Herz-Picciotto et al., 2008). The potential effect of early life pesticide exposure may be complicated by the generally protective effect of *in utero* exposure to the farm animals setting. For example, Smit et al. (2007) reported that livestock farmers who grew up on a farm have had a significantly lower incidence of allergic rhinitis than crop farmers. Weselak et al. (2008) studied in utero exposure to pesticides via farming families in Canada. They reported no statistically significant associations for wheeze or asthma although some potential male-specific effects were noted for allergic rhinitis.

Oral Exposures: Food, Diet and Drugs, Endocrine Disruptors

Examples of early-life exposure to drugs increasing the risk of AD-A are evident in the literature. Alcohol consumption can influence dendritic cells facilitating promotion of IgE responses and allergic disease in mice (Heinz & Waltenbaugh, 2007). Paracetamol was previously discussed as a risk factor for childhood asthma (Del-Rio-Navarro et al., 2006; Rebordosa et al., 2008). Brooks et al. (2004) questioned whether prior oral contraceptive use may be a risk factor for childhood asthma. Additionally, neonatal treatment with antibiotics has been reported as a risk factor for childhood wheezing (Alm et al., 2008). Among other endocrine-disrupting chemicals of potential interest for AD-A, phalate exposure has been reported to be associated with wheeze in Bulgarian children (Kolarik et al., 2008).

Gender-specific issues are another factor in defining risk of pediatric AD-A (Carey et al., 2007; Almqvist et al., 2008; Jensen-Jorolim & Utersmayr, 2008; Tantisira et al., 2008). In keeping with this idea, estrogenic or endocrine disrupting factors are also of potential concern in pediatric AD-A (Narita et al., 2007), and the relative risk and/or adverse outcomes may be quite different between exposed genders. For example, in utero exposure of mice to genistein was reported to increase the likelihood of IgE production against sensitizers in the offspring (Guo et al., 2005a). Gender-specific effects were also reported (Guo et al., 2005b) as they were for other endocrine-active chemicals (Guo et al., 2005c). Likewise, early life exposure of rats to lead produced gender-specific DIT effects (Bunn et al., 2001). In fact, gender-specific DIT effects have been observed with a wide variety of xenobiotics (reviewed in Dietert, 2008).

Diet

Just as certain environmental contaminants and drugs can impact the developing immune system altering childhood disease risk, maternal and neonatal diet is a significant factor influencing immune maturation and risk of allergic disease. Several recent reviews have addressed this topic both from the standpoint of perinatal immune maturation as well as risk of pediatric allergic disease (Devereux, 2007; Prescott & Dunstan, 2007; Bjorksten, 2008). Maternal diet can influence specific immune maturation events (Langley-Evans & Carrington, 2006; Prescott and Dunstan, 2007), allergic sensitization (Sausenthaler et al., (2007), and the incidence of childhood allergic disease (Moore et al., 2006; Warner, 2007). Fitzsimon et al. (2007) found that maternal diets higher in fruits, vegetables and fish oils were associated with a reduced risk of early childhood asthma (evaluated to 3 years of age). Similarly, Romieu et al. (2007) reported that elevated intake of n-3 polyunsaturated fatty acids reduced the risk of atopy and asthma during infancy in the offspring, and similar findings were made by Sausenthaler et al. (2007) relative to atopic dermatitis.

Environmental Conditions Surrounding Birth

As previously indicated in the diseases section, Caesarian versus vaginal delivery has been linked to both an increased risk of childhood asthma (Thavagnanam et al., 2008) as well as allergic rhinitis (Pistiner et al., 2008). Most studies report that Cesarean delivery is associated with lower Th1 cytokine levels at least in the perinatal period (Malamitsi-Puchner et al., 2005). It is not clear whether differences are related primarily to levels of stress associated with mode of delivery or might also include differential exposure to environmental stimulants via the birth canal (i.e., bacteria, other factors). Among the different biomarkers identified comparing the two delivery processes are cytokines in cord blood and early neonatal blood. Protonotariou et al. (2003) found that IFN- γ levels were significantly higher in the cord blood taken from Cesarean versus vaginal deliveries, and that Cesarean deliveries was associated with an elevated Th2/Th1 cytokine ratio in the cord blood (Protonotariou et al., 2004). Similarly, in a study in Sweden, Yetaei-Karin et al. (2007) reported that IL-8, E-selectin levels and INF- γ , as well as neutrophil and

monocyte numbers and chemotactic activity were elevated in cord blood samples following vaginal delivery (assisted and unassisted) versus Cesarean delivery. The magnitude of the differences was directly related to fetal stress level (arterial pH and lactate were used as markers of stress)

Future Safety Testing and the Prevention of Pediatric Allergy and Asthma

Despite the significant prevalence of allergic disease and asthma in the pediatric population, advances toward identification and avoidance of environmental risk factors have been relatively inefficient and incomplete. Hazard identification and characterization relevant to pediatric allergy have occurred primarily via experimental research and epidemiological studies conducted only after significant populations of pregnant women and children received problematic exposures. This has remained the status quo despite calls by international organizations for more effective evaluation of health risks in children resulting from exposure to chemicals (WHO EPC, 2006).

This inefficiency in the potential prevention of childhood allergy stems, in part, from the lack of relevant safety testing for potential chemicals and preclinical safety screening of candidate drugs. Currently, there has been surprisingly little emphasis among U.S. or European regulatory agencies for early identification of chemicals and candidate drugs that might contribute to pediatric hypersensitivity risk. In fact, strategies for identification of chemicals and drugs that produce unintended shifts in the developing immune system toward an atopic phenotype are not incorporated into existing regulatory documents. Beyond the U.S. Environmental Protection Agency Office of Pesticides, no U.S. or European regulatory agency expects screening of chemicals or drugs for DIT. Additionally, even when functional immunotoxicity testing might be secondarily requested based on gross toxicologic findings (usually for adult exposures), subsequent testing is geared toward detection of immunosuppression and not hypersensitivity.

With AD-A representing the most significant chronic diseases of children, a better alignment of safety testing with actual pediatric health concerns is needed and should contribute to strategies for more effective prevention of pediatric allergy. Discussion of specific DIT testing protocols is beyond the scope of the present review and has been considered elsewhere (Dietert & Holsapple, 2007; Dietert, 2008a,b). However, based on the nature of early-life immune alterations leading to AD-A, it seems clear that measures of Th functional balance and inflammatory cell regulation should be included in any testing regime capable of determining the potential risk of early life-induced AD-A. This is consistent with the inclusion of multiple immune functional tests in DIT testing approaches (Dietert & Holsapple, 2008; Dietert, 2008a,b).

CONCLUSIONS

Allergic disease including asthma affects a significant percentage of the pediatric population representing the largest category of pediatric chronic disease in most countries. Various forms of childhood allergic disease are

associated with a wide range of environmental risk factors. Because most of the risk factors are controllable, disease prevention by avoidance of prenatal and neonatal environmental risk factors and management of the developing immune system offers significant promise to reduce the prevalence of pediatric allergy (Holt & Sly, 2007; Dietert & Piepenbrink, 2008).

However, established risk factors cannot account for the recent increase in immune-dependent pediatric diseases such as childhood asthma (Pearce & Douwes, 2006). Additionally, early-life immune dysfunction/imbalance has been recognized as a biomarker for risk of pediatric allergy and asthma (Grzela et al., 2007; Hales et al., 2008; Smith et al., 2008). This suggests that current approaches aimed at identification of maternal-neonatal environmental exposures causing allergy-predisposing immunotoxicity are inadequate. Therefore, new chemical and drug safety testing strategies are needed to ensure adequate protection of the most vulnerable at-risk populations, pregnant women and children, for allergy-related developmental immunotoxicity.

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