COULD BRONCHIAL ASTHMA BE AN ENDOGENOUS, PULMONARY EXPRESSION OF RETINOID INTOXICATION?
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1. ABSTRACT

Asthma has become a major public health problem, affecting about 17 million people in the United States, including 4.8 million children. A striking increase in asthma and other forms of atopy has occurred in children in the U.S. and other western countries during the past 30 years. Several studies have reported an inverse association between childhood infectious illness and the development of atopy, suggesting that certain forms of infection protect against and even inhibit asthma. This may involve a shift in the balance of CD4 T lymphocyte helper cells from a Th2 to a Th1-type cytokine profile. However, the underlying mechanisms remain uncertain. Based on a review of the literature, it is conjectured that in the absence of certain types of childhood infection, retinoids (vitamin A and its congeners) accumulate in the lung. Later, upon exposure to known triggers for asthma, retinoid metabolites may be produced in such high concentration that they produce an acute, localized form of retinoid intoxication, recognized as status asthmaticus.

2. INTRODUCTION

Asthma affects an estimated 17 million (6%–7%) people in the United States and is the most common chronic disease of childhood. Onset usually occurs by age 3; more than 470,000 people are hospitalized and 5,000 people die annually of asthma, death rates being highest in African-Americans ages 15-24(1,2). Once considered solely an abnormality of airway smooth muscle, asthma is now viewed as a chronic inflammatory disorder involving a variety of cell types and mediators(3). A major feature of asthma in older children and young adults is atopy—the state of hypersensitivity or allergy to mainly innocuous environmental antigens contained in house-dust mites and pollens(4). Rising trends in asthma prevalence, morbidity, severity, and mortality rates in recent decades(5), along with concerns about the safety of high-dosage inhaled corticosteroids(6), highlight the urgency of elucidating the etiology and pathogenesis of asthma.

Several studies have reported an inverse association between childhood infectious illness and the
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Development of atopy, including asthma, suggesting that certain forms of infection protect against and even inhibit asthma. The basis of the protective phenomenon is assumed to be immunological in origin, involving alterations in the balance of CD4+ T lymphocytes from a Th2 to a Th1-type cytokine profile(7). but the exact mechanisms are uncertain. Based on a review of the literature, a biochemical model of bronchial asthma is proposed here that incorporates the immunological findings. The model proposes that in the absence of certain types of infection, retinoids (vitamin A and its congeners) accumulate in the lung, creating a state of susceptibility to asthma. Upon exposure to the known triggers for asthma, retinoic acid is metabolized from retinyl esters in the lung in such high quantities that it produces an acute, localized form of retinoid intoxication, recognized as status asthmaticus.

3. INFECTION AND ASTHMA—CLUES TO ETIOLOGY?

The virtual elimination of many infectious diseases in the United States and other western countries, in part through the development and widespread use of vaccines, is one of the greatest public health achievements of the 20th century. In the past two decades, the national incidence rate of diphtheria, mumps, measles, pertussis, polio, rubella, and tetanus has been reduced by over 97%. Until 1964, when measles rates began to drop precipitously, polio, rubella, and tetanus has been reduced by over 97%.

Along with the steep decline in infectious diseases, however, a striking but unexplained increase in atopic diseases has occurred among children in the United States, as well as the United Kingdom and other countries(9-11). This increase, especially noticeable during the past 30 years, appears to be associated with higher socioeconomic status and a western lifestyle, but not with identified environmental agents or pollutants(12), and it has not been satisfactorily explained by changes in genetic factors or improvements in diagnosis.

A relationship between respiratory viral infections and asthma is well known(13). On the other hand, many observations support what is now called the hygiene hypothesis—the notion that exposure to natural infections in early childhood serves to reduce or prevent atopy, while an infection-free or overly hygienic environment promotes it(14-17). Indeed, clinical data indicate that remission of asthma often occurs following the onset of infectious diseases such as hepatitis, jaundice, measles, and chickenpox(18). An attack of measles is often followed by a transient remission of lipoid nephrosis, eczema, or bronchial asthma(19).

Exposure to hepatitis A(20) or tuberculosis in early life15 is also associated with a reduced risk of asthma, and people heavily exposed to orofecal and foodborne microbes have a reduced risk of allergic asthma and rhinitis(21). An epidemiologic study on children of Guinea-Bissau, West Africa, suggested that measles protects against the development of atopy(22). In the latter study, a strong inverse association was found between measles and atopy after adjusting for potential confounding factors, including nutritional status. The rate of atopy (defined by skin-prick test positivity greater than or equal to 3 mm weal to one or more of seven allergens) was also directly associated with family income.

Although respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and other forms of lower respiratory tract (LTR) infection in infancy, RSV-induced LRT infections in early life do not lead to atopic asthma(23), and the progressive reduction in symptom prevalence during the first decade is different from the natural history of the respiratory morbidity associated with atopic asthma(24).

In a Swedish study of atopy rates among children attending Rudolph Steiner schools, in which antibiotics and vaccinations are used restrictively, twice as many children in the control schools were found to have a history of bronchial asthma (25% versus 13%). Among those in the control schools, 93% had MMR vaccinations compared to 18% in the Steiner schools, and 61% of children in the Steiner schools had a history of measles compared to only 1% in the control schools(25). Illi et al (26) investigated the association between early childhood infections and the subsequent development of asthma in a cohort of 1,314 children born in 1990 and followed from birth to age 7. Children with more than two episodes of runny nose before age 1 were half as likely to be diagnosed with asthma at age 7, or to have wheeze at that age, compared to children with only one such episode. Likewise, having one or more viral infections of the herpes type in the first 3 years of life was inversely related to asthma at age 7. Repeated lower respiratory tract infections up to age 3, on the other hand, were positively associated with wheeze and asthma up to age 7, suggesting that children predisposed to asthma may be more prone to develop lower respiratory tract symptoms when infected, rather than the virus causing the development of asthma (“reverse causation”). A dose-response relation between early infection and subsequent decreased risk of asthma was thus seen, with the effects generally strongest for infections occurring in the first year of life.

The inverse association between infection and atopy has been explained on the hypothesis that invasive or repeated infection in early life selectively enhances the development of CD4 T lymphocyte helper cells with a Th1 cytokine profile (leading to cell-mediated immunity), which inhibits the proliferation of Th2-type cytokines and the development of allergic sensitization in genetically predisposed children(7,27,28). T lymphocyte cells are a major source of cytokines and bear antigen specific receptors on their cell surface that allow for the recognition of foreign pathogens. The T lymphocyte subset expressing CD4 surface molecules (also known as helper T cells) is subdivided into two types: Th1 and Th2. The former group, of which interferon gamma is the major representative, produces the proinflammatory responses responsible for
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... killing intracellular parasites, but excessive Th1 expression leads to uncontrolled tissue damage. Balancing the Th1 response are the Th2-type cytokines, which include interleukins 4, 5, 10, and 13, associated with IgE and eosinophilic responses in atopy. It is assumed that these two cell phenotypes are mutually inhibitory, that environmental factors determine the dominant T-cell phenotype in children, and that the absence of systemic infections in childhood fails to allow for the Th1-type cytokine profile to develop from the Th2 phenotype present during pregnancy and at birth(29). However, this hypothesis does not satisfactorily explain the lack of effect of early vaccination on the development of atopy, nor the cause of the shift in cell phenotype(30).

Hansen et al.(31) observed that a single dose of allergen (Ag) plus heat-killed Listeria monocytogenes as an adjuvant in immunotherapy significantly reduced airway hyperreactivity in a murine model of asthma and reversed established airway hyperreactivity when given after allergen sensitization. Heat-killed Listeria monocytogenes also dramatically inhibited airway inflammation, eosinophilia, and mucus production, significantly reduced Ag-specific IgE and IL-4 production and dramatically increased Ag-specific IFN-gamma synthesis. These results showed that heat-killed Listeria monocytogenes mediated the switch from a pathological Th2-dominated response toward a protective immune response in peripheral lymphoid tissues and in the lungs.

Since the decline in infectious illnesses has been brought about partly by widespread immunization programs, a direct association would be expected between immunization and asthma. Odent et al.(32) (1994), in a study of 446 British children aged 8 years on average, found that 91 had not been vaccinated. Only one of these non-vaccinated children had asthma compared to 11% among the vaccinated. Kemp et al.(33) investigated the records of 1,265 New Zealand children born in 1977 who were enrolled in the Christchurch Health and Development Study. Only 23 children received neither DPT (diphtheria/pertussis/tetanus) nor polio immunizations. However, none of these children had a recorded asthma episode or consultation for asthma or other allergic illness before age 10, whereas 23.1% of the immunized children had experienced asthma episodes, 22.5% had asthma consultations, and 30% had had consultations for other allergic illness. Similar differences were observed in the same children at ages 5 and 16. No potential confounding effect was identified with respect to the differential use of health services, ethnicity, socio-economic status, parental atopy, or parental smoking.

Hurwitz and Morgenstern(34) used data from the Third National Health and Nutrition Examination Survey on infants aged 2 months to adolescents age 16 to estimate the association between diphtheria-tetanus-pertussis (DTP) or tetanus vaccination on allergies and allergy-related respiratory symptoms in the past 12 months, based on parental or guardian recall. Results showed that the odds of having a history of asthma were twice as great among vaccinated subjects as among the unvaccinated (Adjusted OR, 2.00: 95% confidence interval, 0.59-6.74), while the odds of having any allergy-related respiratory symptom in the past 12 months were 63% greater among the vaccinated than in the unvaccinated subjects (Adjusted OR, 1.63; 95% CI, 1.05-2.54). Thus, DPT or tetanus vaccination appears to increase the risk of allergies and allergy-related respiratory symptoms in children and adolescents.

On the other hand, most forms of immunization do not appear to cause asthma directly. Short-term studies (up to 4 years post-immunization) indicate that children immunized against pertussis are not at increased risk of developing asthma(35,36), and neither killed-subunit nor live influenza vaccine triggers asthma(37). How, then, could immunization be related to an increased risk of asthma and infection to a decreased risk?

4. RETINOID THEORY OF STATUS ASTHMATICUS

Immunization may contribute indirectly to the development of asthma by preventing the occurrence of many childhood infections, but what is the mechanism by which infection prevents asthma? Several lines of indirect evidence suggest the possibility that asthma could be associated with a localized, endogenous form of retinoid overexpression, involving the pulmonary accumulation and catabolism of vitamin A. Upper respiratory illnesses deplete pulmonary stores of retinol (vitamin A alcohol),38 and high levels of retinoic acid, one of the major metabolites of retinol, induce an inflammatory syndrome resembling the atopic state. The signs and symptoms of asthma also resemble certain features associated with retinoid intoxication. Based on these and other observations cited below, it is conjectured that asthma results in part from the presumed existence of unusually high concentrations of retinyl esters in the lung, due to the absence of childhood infection, and possibly other developmental factors. Upon exposure to environmental allergens and other asthma-inducing conditions such as cold, physical exercise, and inhaled airborne proteins (e.g., soybean dust(39)), the suggestion is that retinyl esters are catabolized to retinoic acid in such high concentration in the lung that they induce a localized form of retinoid toxicity recognized as status asthmaticus. Sensitivity (“allergy”) to certain substances and conditions could thus be due to an increased background concentration of retinol, and exposure to these conditions may result in the production of toxic concentrations of retinoic acid, which in turn produce the signs and symptoms of asthma. Persons with asthma may be more sensitive to common allergens because they have higher amounts of stored retinyl esters in the lung than non-asthmatics.

Because childhood infections substantially deplete pulmonary vitamin A concentrations, the absence of exposure to such illnesses (e.g., possibly due to immunization) would be expected to result in the accumulation of large tissue stores of the vitamin. In fact, vaccination with both monovalent and combined live attenuated measles vaccines also results in a decline in serum retinol levels, but the effects appear to be temporary(40). The reason that short-term follow-up
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Vitamin A toxicity may occur when retinol is presented to cell membranes in a free form, unbound to its transport protein (retinol-binding protein). Following excessive intakes, the liver becomes saturated with the vitamin so that considerable amounts of retinyl esters spill over into the circulating blood. Plasma vitamin A levels (retinol), while often elevated in hypervitaminosis A, can be normal or even low. In hypervitaminotic humans the retinyl ester values can be as high as 67% of the total plasma vitamin A. Because retinol esters react more randomly with the membranes of cells than the physiologically-sequestered retinol bound in holo-RBP, they are a major form of vitamin A toxicity. Endogenous and/or administered retinoid acid (and other acidic retinoids) is considerably more biologically active and more toxic than retinol itself. Retinol and retinyl palmitate are 10-100 times less toxic than retinoid acid, the latter of which is metabolized fairly rapidly to more polar, oxygenated compounds. Low concentrations of retinoid acid stimulate growth of certain cell types, acting as growth factors under these conditions, whereas in high concentrations retinoids inhibit cell growth and act as cellular toxins. Several lines of indirect evidence are cited in support of the retinoid toxicity model of asthma.

6. RETINOIDS

Retinoic acid is ultimately produced from free retinol, first by hydrolysis of retinyl esters stored in the liver and the release of retinol into the circulation and delivery to the target organ tissues bound to retinol-binding protein; secondly, by oxidation of retinol to retinal (aldehyde) via the action of an alcohol dehydrogenase; thirdly, by synthesis from retinaldehyde via an aldehyde dehydrogenase reaction, primarily within the cell microsomes. Retinoic acid exerts its effects by binding to nuclear receptors belonging to the transcription-factor family that includes the receptors for steroids, thyroid hormone, vitamin D, and a diverse group of “orphan” receptors whose ligands are unknown. These nuclear receptors are of two types: retinoic acid receptors and retinoid X receptors. Both types of receptors are members of the steroid/thyroid superfamily of ligand dependent nuclear transcription factors and share homology with nuclear receptors for other molecules, including colecacidic (vitamin D), thyroxine, and glucocorticosteroids. Retinoic acid receptors and retinoid X receptors exist as three distinct gene products—alpha, beta and gamma—and further heterogeneity is a consequence of alternative splicing and alternate promoter use of these isoforms. Retinoic acid receptors bind tretinoin and 9-cis-retinoic acid, whereas retinoid X receptors only bind 9-cis-retinoic acid. Subsequent gene expression occurs as a result of retinoic acid receptors/retinoid X receptors binding to two directly repeated consensus motifs (AGGTCA) separated by 1, 2, or 5 nonspecific nucleotides—either as a homodimer (RXR/RXR) or a heterodimer (RXR/RZR). Both retinoic acid receptors and retinoid X receptors exist in human skin, whereas retinoid X receptor-alpha predominates in human epidermis. Retinoic acid receptor-beta is expressed solely in the dermis and, unlike retinoic acid receptor-alpha, retinoic acid receptor-gamma and retinoid X receptors, its expression is further induced by tretinoin.

6.1. Vitamin A accumulates in the lung

Retinol and retinoic acid play important roles in differentiation and in maturation of the lungs. Adult as well as fetal lungs accumulate retinyl esters, the storage form of vitamin A; they also contain specific retinol- and retinoic acid-binding proteins and express several isoforms of nuclear retinoic acid receptors. Lipid-laden, fibroblast-like cells in adult rat lungs can store vitamin A. Retinyl esters are hydrolyzed to retinol by retinol acyl hydrolase and mobilized from storage cells under conditions of low dietary intake or increased retinol utilization. Cells that are consuming retinoids acquire retinol and oxidize it to retinaldehyde via alcohol or retinol dehydrogenases for direct utilization (e.g., in the retina), or further oxidize it via aldehyde dehydrogenase to retinoic acid. Endogenous retinoic acid may also contribute to the postnatal increase in elastin production by pulmonary fibroblasts.

6.2. Severe respiratory infections reduce vitamin A

Serum vitamin A levels decline in a variety of febrile infections, often by as much as 20-30 μg/dl. In children with rheumatic fever, serum levels can drop by 50% when body temperature exceeds 100 degrees F(25,124). Vitamin A is especially decreased by
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6.3. Retinoic acid can be highly toxic

As noted, retinoid acid is considerably more biologically active and hence more toxic than the parent compound retinol, especially in high concentration(44), and sufficient retinol is stored in the liver to last the average well-nourished person for 1-2 years(56). While vitamin A is a key nutrient and vitamin A deficiency is an important public health issue, the use of supplementary vitamin A for reducing child mortality and morbidity is controversial. In a study on the efficacy of vitamin A for reducing preschool child mortality in Nepal, West et al.(61) found that vitamin A significantly reduced the mortality risks with respect to diarrheal diseases but increased the risk with respect to respiratory diseases. Among infants supplemented with vitamin A (three doses of 25,000 IU) or placebo at the time of DPT/OPV immunizations, 10.5% of the vitamin A group showed evidence of bulging fontanel (indicating increased intracranial pressure, a recognized sign of hypervitaminosis A), compared to 2.5% in the placebo group(62).

6.4. The manifestations of asthma resemble those of hypervitaminosis A

6.4.1. Retinoids enhance T-helper 2 cytokine production

Administration of retinoic acid in a animal model of chronic relapsing experimental allergic encephalomyelitis induced by the transfer of myelin basic protein-specific lymph node cells resulted in an improved clinical course, associated with a considerable increase in IL-4 mRNA (Th2 type cytokine profile), and a decrease in mRNA for IL-2, TNF-alpha and IFN-gamma (Th1-like profile).63 These findings support the proposed model insofar as they suggest that T cell activation in the presence of retinoid acid results in a switch from a Th1-like immune profile to a Th2 phenotype, as seen in asthma. A study of the anti-inflammatory effect of Tretinoin, a synthetic retinoid, on human keratinocytes and superantigen-stimulated peripheral blood mononuclear cells (PBMCs), showed that Tretinoin strongly inhibited phorbol ester-stimulated IL-6 release in human epidermoid carcinoma cells while strongly stimulating IL-5 release and inhibiting IFN-gamma release(64). Another in vitro study of the effect of retinol on cell-mediated immune responses in mice infected with Leishmania major infection showed that, when added to cell cultures, vitamin A inhibited secretion of type 1 (IFN-gamma, GM-CSF, IL-2) cytokines but not type 2 (IL-4 and IL-10) cytokines, possibly through an inhibitory effect on protein kinase C activity(65). Vitamin A supplementation (250,000 IU/kg diet or 75,000 retinol equivalents (RE/kg)) given before and during viral pneumonia in BALB/c mice significantly increased salivary immunoglobulin A responses compared to a control group given a recommended daily amount of vitamin A (4000 IU/kg or 1200 RE/kg); moreover, while production of interferon-gamma, a Th1 cytokine, was lower in the high level vitamin A diet group, production of interleukin–10, a Th2 cytokine, was significantly higher in the high level diet group, and supplementation had no effect on disease severity(66). Thus, retinoic acid or high dose vitamin A supplements appear to enhance the Th2-mediated cytokine profile seen in asthma, as the model predicts.

6.4.2. Retinoic acid causes asthma-like effects

Signs of asthma include increased interleukin-5 expression, eosinophilia(67), basement membrane thickening, bronchospasm, epithelial desquamation(68), and growth retardation in children independent of drug treatments(69). Over time, disruption of the epithelium with a range of growth factors results in a tissue regenerative and remodeling response. Proteolytic destruction of the epithelial basement membrane and proliferation and stimulation of subepithelial myofibroblasts lead to the deposition of interstitial collagens types III and IV. Proliferation of airway smooth muscle and the microvascular tissue leads to a structurally altered airway that contributes to disease chronicity(70). Interleukin-5 is implicated in eosinophil regulation(67), and a striking feature of asthma is peripheral blood eosinophilia. Rising eosinophil counts are associated with increasing bronchial obstruction. In individuals dying of status asthmaticus the entire thickness of the bronchial wall, the adjacent parenchyma, and the bronchial lumen are infiltrated with eosinophils. In late stages of asthma, areas of desquamation, impaired ciliary function, mucosal plugging and basement membrane thickening are seen in association with eosinophils and their granular products(71).

Retinoic acid can likewise induce eosinophilia(72). Earlier reports suggested a link between isotretinoin use and the subsequent development of confirmed eosinophilic pleural effusion with shortness of breath on exertion(73). An acute hepatotoxic reaction to the synthetic retinoid etretinate has been reported in association with fever and eosinophilia, possibly indicating a hypersensitivity reaction(74). The “retinoic acid syndrome” observed in people treated with all-trans-retinoic acid for acute promyelocytic leukemia also produces a hyperleucocytic response associated with an acute, asthma-like respiratory distress syndrome, eosinophilia, marked basophilia and hyperhistaminemia, granulomatous proliferation, weight changes, pleural or pericardial effusions, peripheral edema, thromboembolic events, and intermittent hypotension (75–81). The Churg-Strauss syndrome, a rare disorder characterized by the
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histopathological triad of systemic necrotizing vasculitis, extravascular granuloma, and eosinophilic infiltrate, occurs in individuals with a history of severe asthma or allergy. A case of Churg-Strauss syndrome was recently reported with the presentation of pulmonary hemorrhage associated with necrotizing vasculitis, pulmonary capillaritis, and prominent eosinophilic infiltrate. At autopsy, necrotizing granuloma and diffuse alveolar hemorrhage were found in the lungs. Laboratory data showed hyperesinophilia, disseminated intravascular coagulopathy, and positive antiproteinase-3-antineutrophil cytoplasmic antibody(82). The relevance of this observation is that all-trans-retinoic acid Likewise induces a syndrome of diffuse alveolar hemorrhage associated with pulmonary capillaritis(83). Thickening of the epithelial basement membrane and of smooth muscle, predominantly due to hyperplasia, are characteristic features of fatal asthma. Retinoic acid is also associated with increased interleukin-5 (IL-5) expression, as mentioned above(65,84), as well as with eosinophilia, basement membrane thickening(85-87), epithelial desquamation(88), and growth retardation in children(89).

A single case was also described recently of a 41-year-old woman whose asthma was exacerbated by isotretinoin(90). She had taken isotretinoin previously for 5 years to good effect and without side effects. However, upon starting the drug (60 mg daily, or about 1 mg/kg daily) she developed worsening of her asthma, indicated by a wheeze and cough, and a marked reduction in peak flow. Dramatic improvement was noted 24 hr after stopping isotretinoin. It was also noted that 20 reports had been made to the Committee on Safety of Medicines of isotretinoin causing asthma-related side-effects.

6.4.3. Retinoic acid causes mucus hypersecretion

Mucus hypersecretion is a feature common to several upper airway diseases such as asthma, chronic bronchitis, and cystic fibrosis. Consistent with the retinoid toxicity hypothesis, vitamin A contributes to mucus secretion, and the accumulation of mucin (the major component of mucus) is stimulated by retinoic acid(91). Rabbit tracheal epithelial cells show time-dependent mucin gene expression when cultured with retinoic acid. In the absence of retinoic acid, mucin mRNA was barely detectable in the cells; moreover, a mucin antisense oligomer inhibited retinoic acid-induced mucin mRNA expression and secretion(92).

6.4.4. Retinoic Acid, TGF-beta-1, and Airway Wall Remodeling

Airway wall remodeling in both large and small airways due to increased thickness of the basement membrane associated with the activation of fibroblasts and myofibroblasts is an established pathological feature in asthma, and may contribute to the characteristic airway hyperresponsivity of asthma(93). Transforming growth factor-beta-1 (TGF-beta-1), an important pro-fibrotic growth factor, has been hypothesized to play a role in airway wall remodeling in asthma. Indeed, basal concentrations of TGF-beta-1 in broncho-alveolar lavage fluids are significantly higher in asthmatics than in control subjects and these levels increase further in response to allergen challenge(94). TGF-beta-1 expression is also associated with subepithelial fibrosis in asthma and correlates significantly with the thickness of the basement membrane and the number of fibroblasts in patients with asthma(95). The suggestion that retinoic acid could contribute to airway wall remodeling and fibrosis in asthma via TGF-beta production is supported by parallel observations on hepatic fibrogenesis. During hepatic fibrosis, stellate (vitamin A-containing) cells transform into myofibroblastic cells and lose their intracellular droplets of retinyl esters. It was reported that 9,13-di-cis-retinoic acid, a stable and major metabolite of vitamin A in the circulation, stimulates plasminogen activator synthesis and induces activation in hepatic stellate cells, probably via induction of retinoic acid receptor-alpha(96). It was speculated by the authors that the loss of retinyl esters was associated with increased retinoic acid formation, and that this facilitated TGF-beta-mediated liver fibrogenesis. The effect of 9,13-di-cis-retinoic acid was studied on transactivating activity of retinoic acid receptor-alpha in HeLa cells as well as on plasminogen activator and TGF-beta-dependent collagen synthesis in rat and human hepatic stellate cell cultures. 9,13-di-cis-retinoic acid transactivated retinoic acid receptor-alpha and provoked TGF-beta-dependent procollagen synthesis in hepatic stellate cells; moreover, 9,13-di-cis-retinoic acid levels were increased in both activated hepatic stellate cells in vitro and in fibrotic liver accompanying the enhanced expression of retinoic acid receptor-alpha/beta, TGF-beta and procollagen in vivo. These findings have suggested a potential link between 9,13-di-cis-retinoic acid formation and hepatic fibrosis via the formation of TGF-beta in vivo(96), and suggest the possibility of an analogous process occurring in patients with asthma.

6.4.5. RA, Asthma, and Bone Marrow

Increased numbers of proinflammatory cells, including activated eosinophils, basophils, and mast cells are seen at sites of allergen challenge in allergic diseases of the airways. The eosinophil (Eo) and basophil (B) share a common progenitor (Eo-B progenitor). Estimates of Eo-B progenitor frequencies in the peripheral blood in various atopic disorders are 4-5 times higher than those of non-atopic individuals, and a rise in Eo-B progenitors is seen during asthma exacerbations. These facts suggest that bone marrow release of Eo-B progenitors into the peripheral blood compartment plays a role in the development of airway inflammation(97). The potential significance of these observations in light of the proposed model is that retinoic acid is found in relatively high concentration in bone marrow of vitamin A-deficient rats(98). Studies on bone marrow transplantation in which atopy or asthma was examined have also suggested that an atopic donor can transfer skin test responses as well as asthma to a non-atopic recipient(99). The classic interpretation of these findings has been that T cells and, by inference, IL-4 producing T helper 2 (Th2) cells, are transferred to the recipient(97). Alternatively, bone marrow transplantation from an atopic donor could involve the transfer of large quantities of retinoic acid or other retinoid metabolites, and an increased likelihood of retinoid toxicity in the recipient.
6.5. Risk factors for asthma are associated with increased retinoid concentrations

6.5.1. Exercise
Exercise is a frequent cause of exacerbations of asthma, although the cause is unknown. According to the model, exercise-induced asthma results from the immediate production of retinoic acid from the presumably large quantities of retinoids in the lungs of persons with asthma. Consistent with the retinoid toxicity model, exercise-induced bronchoconstriction and wheezing were reported in an atopic but previously non-asthmatic young adult male after starting therapy with synthetic retinoids for acne. Treatment was stopped, and this alleviated the asthma. After resuming retinoid therapy because of acne, exercise-associated wheezing returned(100). In rats, exercise is associated with reduced plasma retinol(101) and with reduced vitamin A content in the liver(102), suggesting that exercise is associated with increased vitamin A mobilization and/or utilization.

6.5.2. Diet
Dietary-induced hypervitaminosis A is associated with increased allergic hyperresponsivity. For instance, induction of hypervitaminosis A in mice by food supplementation was shown to increase responsiveness (manifested by ear swelling) to contact allergens(103,104), including paraphenylenediamine, a major component of permanent hair dyes(105).

6.5.3. Nitric oxide
Nitric oxide is a physiological mediator in the lung for bronchodilation(106), and reduced nitric oxide release may be the mechanism underlying hypoxic pulmonary vasoconstriction (HPV)(107). Retinoic acid is inversely related to nitric oxide and it appears to inhibit nitric oxide by inhibiting nitric oxide synthase expression(108-110). On the present hypothesis, nitric oxide should be reduced in asthma. In fact, bronchoconstriction induced by bradykinin is reduced by the release of nitric oxide in the airways of guineapigs; and inhaled nitric oxide causes bronchodilation in asthmatic patients. Moreover, bronchoconstriction after bradykinin inhalation is greatly inhibited by the formation of nitric oxide in airways of asthmatic patients. These findings have suggested that nitric oxide has a bronchoprotective role in asthma(111). However, the presence of nitric oxide in exhaled breath is reportedly increased in asthmatics(112-114), and nitric oxide excretion from the lung could represent increased pulmonary losses of nitric oxide, perhaps due to increased retinoid production and hence inhibition and/or depletion of nitric oxide in the lungs. Airway concentrations of S-nitrosothiols (endogenous bronchodilators) are believed to reflect nitric oxide synthesis expression. Concentrations of S-nitrosothiols, however, are paradoxically lower in asthmatic children than in normal controls but raised in pneumonia(115). Since S-nitrosothiols are catabolized to nitric oxide, facilitated by neutrophils, platelets, and lung tissue cells, low concentrations in the airways of asthmatic children may reflect accelerated S-nitrosothiol breakdown, contributing both to high expired nitric oxide concentrations and to bronchospasm. High concentrations of retinoic acid in lung tissue in patients with asthma would be expected to increase S-nitrosothiol breakdown and in turn lead to an increased catabolism and high concentration of nitric oxide in expired air.

6.6. Glucocorticoid treatment reduces retinoic acid
Inhaled glucocorticoids are effective in all patients with asthma irrespective of age or severity, although the mechanism of action remains uncertain. In the doses needed to control asthma in most patients there are no side effects, and they markedly reduce the number of asthma exacerbations and hospital admissions(116,117). These observations on the anti-asthmatic effects of glucocorticoids are consistent with model proposed here. Georgieff et al.(118) reported that dexamethasone-treated postweanling rats have significantly lower concentrations of total vitamin A, retinol, and total retinyl esters in both liver and lung when compared to placebo-injected controls. Lung ester concentrations were an order of magnitude lower than those in the liver in the vitamin A-sufficient state. Total tissue vitamin A and retinyl ester concentrations were most severely reduced in lung by dexamethasone treatment, whereas tissue retinol concentrations were most affected in liver. Corticosteroids thus lead to increased serum retinol concentrations in postweanling rats by reducing lung and liver stores of vitamin A. The decrease in lung total vitamin A may represent increased local mobilization of lung vitamin A(118). These observations suggest that the efficacy of steroids in asthma may be due in part to steroid-induced decreases in presumably high background concentrations of vitamin A in the lungs of patients with asthma. In view of the known growth-inhibiting effects of excess retinoic acid(89), reports of reduced growth velocity in children with asthma following prolonged use of inhaled corticosteroids(119) may be related to increasing circulating concentrations of retinoids.

6.7. Remission in asthma in adolescence
Asthma symptoms and bronchial hyperresponsivity decline in adolescence for reasons that are not well understood(120,121). To speculate, this change could be due to a gonadal hormone-induced increase in the mobilization and utilization of pulmonary retinoids connected to the adolescent growth spurt.

6.8. Chemical-induced asthma
Isocyanate chemicals are considered the main causes of occupational asthma, inducing bronchial hyperreactivity in a dose-dependent manner. Isocyanate-induced asthma is associated with local accumulation and activation of lymphocytes and eosinophilia(122). The model proposed here suggests the hypothesis that isocyanates could cause asthma by catabolizing retinyl esters in the lung to retinoic acid.

7. CONCLUSION
Based on a review of several lines of indirect evidence, the tentative hypothesis has been proposed that excess storage and catabolism of retinoids in the lung
Bronchial asthma—endogenous expression of retinoid intoxication?

The model provides a possible explanation of rising asthma prevalence, morbidity, severity, and mortality rates in recent decades; and it suggests an explanation for the inhibitory effect of common childhood infections on the development of asthma. Subject to obtaining data in support of the model (e.g., studies of plasma retinoid concentrations in cases and controls), the potential role of retinoid antagonists and inhibitors could be explored for the treatment and prevention of asthma.

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