sampling and measurement will allow progress in development of methods to minimise personal exposure to aeroallergen.

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Role of house-dust endotoxin exposure in aetiology of allergy and asthma

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Endotoxin and its purified derivative lipopolysaccharide (LPS) are Gram-negative bacterial potent pro-inflammatory constituents continuously shed into the environment.[1] A number of different Gram-negative bacteria inhabits the normal body surfaces including the skin, oral cavity, respiratory tract, gastrointestinal tract, vagina and urinary tract. Humans can be exposed to endotoxin via several ways. In addition to the septic shock frequently

caused by translocation of Gram-negative microorganisms normally present in the gut of the host to the circulation, there is continuous exposure to airborne endotoxin. The release of endotoxin from Gram-negative bacteria that colonise the respiratory tract in the majority of patients with chronic bronchitis can contribute to the lung function decrease by initiating release of inflammatory mediators from bronchial epithelial cells.[2] High levels of airborne (up to 1 $\mu g/m^3$) endotoxin have been reported from a variety of occupational environments (e.g. swine confinement, poultry farm, cotton mill, brewery, waste processing).[1] A number of cross-sectional studies reports an association between exposure to endotoxin measured in the dust from those occupational settings and the risk to develop non-atopic chronic obstructive pulmonary diseases,[3-6] toxic pneumonitis and systemic effects.[7,8] In the domestic environment, there is also endotoxin contaminating house dust[9-12] that, by itself or in association with allergen exposure, could be an important determinant of asthma severity.[9,10] Recently, Hasday *et al.* reported that high levels of endotoxin are produced by cigarette smoke.[13]

Inhalation of pure endotoxin may elicit, in some individuals, dyspnea, chest tightness, myalgia, shivers, fatigue and malaise associated or not with fever.[14,15] A similar clinical response is observed after exposure to dust containing endotoxin such as grain handlers,[16] cotton workers,[5] fibre-glass manufacturing employees,[8] or animal farmers.[17] A large inter-individual variability in the sensitivity to endotoxin has been reported.[18-20] In humans, inhalation of pure endotoxin is associated with bronchoconstriction,[14,15,18-21] change in the level of non-specific airways responsiveness,[14,20,21] and reduction in alveolar-capillary diffusion.[22] Compared with asthmatics, in normal subjects a higher dose of pure endotoxin is required to produce bronchoconstriction.[14,15,18,19,23] Although the endotoxin response is reproducible in a given subject,[19] there is a large between-subjects variability[14,18,19,20] at least partially related to the airways inflammatory status[24] and to the level of non-specific airways responsiveness.[25]

Local and systemic inflammatory responses have been measured after endotoxin inhalation in normal and asthmatic subjects. Significant blood leukocytosis and neutrophilia were observed 4–8 h after inhalation of endotoxin both in normal[14-16,18,22,26] and asthmatic subjects.[21,27] This neutrophilia was not related with the change in lung function.[21,27] *In vitro*, small amounts of endotoxin (< 1 ng/ml) activate human airways macrophages, releasing several pro-inflammatory cytokines (tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6) and metabolites of arachidonic acid. The presence of LPS-binding protein and the soluble fraction of CD14 receptor (sCD14) in the airways[24] may increase the macrophage activation by endotoxin.[24,28] Six hours after an inhalation of endotoxin-contaminated dust, high concentrations of IL-1, IL-1 RA, IL-6, IL-8 and TNF-α and their specific mRNAs were measured in the bronchoalveolar lavage.[29] These cytokines are potential activators of the hepatic acute-phase protein response, consistent with the rise in the blood concentration of the C-reactive protein (CRP) 24 h after endotoxin inhalation.[13,17,21,26] We speculate that cytokines produced into the airways are released in the blood and stimulate the hepatocytes.

Airway inflammation characterized by neutrophil recruitment in broncho alveolar lavage (BAL) was observed after bronchial challenge with endotoxin-contaminated dusts like allergen extracts,[30] grain dust[29] and swine dust,[17] while in normal subjects 100 μg of inhaled pure endotoxin induced a 100-fold increase in neutrophils from BAL.[31] A significant increase in neutrophils measured in the induced sputum occurred after 5[15,32] to 60 μg[33] endotoxin. The sputum concentrations in myeloperoxidase (MPO) (from neutrophils), eosinophil cationic protein (ECP) (from eosinophils) and TNF-α rose significantly 6 h after endotoxin.[15]

There are some published data suggesting that environmental endotoxin could be a synergic factor on the amplitude of immunoglobulin E-mediated response. On one hand, in allergic mild asthmatics, an exposure to air containing low levels of endotoxin (250 ng/m^3) for 4 h before bronchial challenge with allergen increases significantly both bronchial reactivity and antigen-induced airway eosinophilia.[34] The airways cellular inflammation to inhaled allergen is modified by endotoxin contamination of the allergen extract. Indeed, while detoxified pure allergen extract results in bronchial eosinophil recruitment, endotoxin contamination (1 ng/ml) causes neutrophilia.[30] On the other hand, inhalation of allergen in sensitized subjects leads to airways plasma exsudation including extravasation of sCD14 and lipopolysaccharide-binding protein (LBP).[24] These proteins may enhance the capacity of inhaled endotoxin to activate an inflammatory cascade that may amplify the inflammatory response to inhaled antigen in some asthmatics, as was suggested by several field studies.[9,10,35] In the home environment, the amount of endotoxin in house dust has been related to the severity of asthma both in atopic[9,10] and non-atopic subjects.[35] In dust-mite-sensitized subjects, the level of exposure to mite allergen was higher in subjects with asthma than in those with rhinitis, while the severity of the asthmatic disease was significantly associated with a low forced expiratory volume in 1 sec (FEV1) and FEV1/forced vital capacity, and the daily need for oral and topical corticosteroid, as well as with the asthma score.[9] More recently, Douwes *et al.*[36] did not find an association between endotoxin exposure and peak

expiratory flow (PEF) variability in a group of children defined by asthma symptoms. However, the daily PEF variability was very low (6.4%), suggesting asthma was intermittent or doubtful. Therefore, endotoxin should be considered as an enhancing rather than inducing factor in asthma.

We recently challenged 15 normal subjects with inhaled endotoxin (0.5, 5, 50 μg).[18] Subjects who developed significant increase in body temperature had a larger increase in the systemic inflammatory response (blood neutrophilia and blood concentrations of CRP and LBP), while subjects who developed a significant increase in airways responsiveness had an increase in the sputum concentration of ECP. The amplitude of the systemic response and decrease in FEV1 were inversely associated with the atopic status, suggesting a link between atopy and LPS responsiveness. This observation reinforces the hypothesis for a mechanism linking the macrophage susceptibility to LPS stimulation with the increase in macrophage production of cytokines that inhibits the T helper cell (Th)-2 response and, consequently, the risk to become atopic. Environmental exposure to LPS and other bacterial wall products, present in house dust[9–12,35,36] and/or from the intestinal tract,[37] could be a necessary step for maturation the immune system and the development of a Th1-like response through the presentation of antigen in conjunction with IL-12.[38–40] In mice, endotoxin sensitivity is genetically determined, involving mutation in the Toll-like receptor-4 (TLR4) gene,[41] a co-receptor essential for the LPS signalling. In human, recent data suggest that polymorphisms in the genes encoding the TLR4[42] or the LPS receptor CD14[43] may be related to symptoms and diseases.

exposure to endotoxin in early life could be protective for the risk of atopy, while in symptomatic asthma it could be a risk factor of a severe disease.

Finally, available data on the protective effect of anti-asthmatic drugs on the endotoxin-induced response are quite limited. An acute pre-treatment with sodium cromoglycate[44] or with short or long acting B_2-agonists completely prevents the bronchoconstriction induced by an acute exposure to LPS[45] while, given in a single dose, an inhaled corticosteroid does not prevent the endotoxin-induced blood inflammation.[45] Studies are in progress to evaluate the possible protective effect of chronic treatment with oral corticosteroids on the response to endotoxin.

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Asthma, atopy, antibiotics and the bowel

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The past three decades have seen an increase in reported asthma and allergic diseases from many studies around the world, recently described as an epidemic.[1] While many hypotheses have been developed to explain these changes, the hygiene hypothesis has for the past decade encompassed an expanding link between the epidemiology and immunology of both atopic sensitisation and atopic diseases. These associations and the utility of the hypothesis have recently been reviewed by David Strachan,[2] who first reported the associations between birth order and hayfever, and articulated the hygiene hypothesis as an explanation.[3] Inverse relationships between atopic and infectious disease was first raised a decade earlier by Gerrard *et al.* in a comparison of atopic disease amongst the Metis (native Indian) and white communities of northern Saskatchewan.[4] The immunological basis for the hypothesis rests on the concept of immune deviation in early life towards T helper cell (Th)1 immune responses induced by microbial exposure, with Th1 responses suppressing Th2 responses and immunoglobulin E (IgE) production. The hypothesis therefore refers to IgE-mediated diseases such as hayfever but is less applicable to asthma, where atopy plays an important but not exclusive role.

The relationships between asthma, bronchial hyperresponsiveness (BHR) and atopy have recently been examined among 20- to 44-year-old adults, in five Spanish centres involved in the European Community Respiratory Health Survey. The adjusted proportion of BHR attributable to atopy was 21% and the proportion of asthma symptoms and BHR attributable to atopy was 42%.[5] Factors associated with the hygiene hypothesis such as birth order or specific infections will vary in their strength of association with asthma depending on the proportion of asthma attributable to atopy. An important feature of any useful hypothesis is that it should unify disparate observations. The hygiene hypothesis does this, suggesting explanations for socio-economic variations in atopic disease both within and between countries, and a plausible explanation of some of the long-term upward trends in prevalence. Studies of the relationship between infection or microbial exposures and atopic disease also tend to support the hygiene hypothesis.

The influence of antibiotics on these associations has recently been studied. Farooqi *et al.* found a twofold risk of doctor-diagnosed atopic diseases with antibiotic treatment in the first 2 years of life, among a general practice birth cohort.[6] The increased risk was apparent for all classes of antibiotics, although greater for cephalosporins and macrolides; it was independent of the underlying condition being treated, and was similar for those with and without a history of maternal atopy. Antibiotic exposure was the strongest predictor of atopic disease in this study.

The other two studies have examined antibiotic use among children in Sweden and New Zealand, whose families have some association with an anthroposophic lifestyle. Families embracing this lifestyle, whose tenets were set out by Rudolph Steiner in the nineteenth century, tend to minimise their involvement with conventional medical