

# **The causes of the increasing prevalence of allergy: Is atopy a microbial deprivation disorder?**

## **REVIEW ARTICLE**

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THESE AUTHORS NOTE:

“The atopic diseases, i.e., primarily, bronchial asthma, atopic dermatitis, and allergic rhinoconjunctivitis, were rare a few decades ago, but constitute today an increasingly severe public health problem.”

This increase in allergic diseases is mainly seen in children.

“Formerly, allergic diseases such as hay fever were considered an exclusively upper-class disorder.”

In 1828, John Bostock first described the hay fever symptoms, and could only find 27 in all the clinics of London.

In 1873, Charles Blackley noted that hay fever and asthma were more common among the educated than among the illiterate.

Blackley noted that “the people who were most likely to be subjected to the action of pollen belonged to a social class which furnished the fewest cases of the disorder, i.e., agricultural laborers.”

“The increase in the prevalence of the allergic diseases, especially in those born after 1960, is almost explosive, and there are now epidemics of allergic diseases in many countries.”

“The prevalence of asthma in children and young adults has tripled and quadrupled in many industrialized countries during the last two decades.”

Atopic diseases are more common among the wealthy than among the poor, more common in urban than in rural areas, and more common in the West than in the East.

The authors suggest that:

- (1) The occurrence of factors that stimulate allergic sensitization has increased, or
- (2) That allergy-protective factors have been lost.

#### PATHOGENIC MECHANISMS

- (1) Air pollution
- (2) Diesel exhaust particles
- (3) Tobacco smoke
- (4) Net effects of air pollution factors
- (5) New allergens
- (6) Hormones and environmental poisons
- (7) Reduced frequency of bacterial and viral infections
- (8) Altered gut flora
- (9) Changes in consumption of dietary fatty acids
- (10) Changes in dietary antioxidants
- (11) Acetylsalicylic acid and young children
- (12) Comparison between candidate causative factors

Atopic allergy is characteristically associated with an imbalance between various types of T cells and, specifically, an increased synthesis of IgE.

Human T helper type 1 (Th1) cells produce the cytokine IFN-g.

Th2 cells produce cytokines IL-4, IL-5, and IL-13.

The term 'Th1/Th2 cell balance' refers to the balance between type 1 and 2 cytokines.

Atopic diseases are characterized by an imbalance between type 1 and 2 cytokines, where the type 2 cytokines are formed in abnormally high concentrations relative to the type 1 cytokines.

This imbalance between type 1 and 2 cytokines leads to an abnormally high production of IgE which give rise to allergic symptoms.

A displacement of the delicate balance between type 1 and 2 cytokine production tends to be persistent.

Histamine is produced during Th2-mediated allergic reactions.

Importantly, allergic sensitization may occur in utero.

"An imbalance between Th1 and Th2 cytokine production that occurs early in childhood might have an increased tendency to persist."

"Therefore, regarding the development of allergy, it is believed that the very first months of life are of crucial importance."

One's genes are important for the development of the atopic disease.

Regarding possible factors that may influence the Th1/Th2 cytokine balance, it is noteworthy that prostaglandin E2 (PGE2) enhances the atopic Th2 cytokine response.

"As the synthesis and release of PGE2 is highly dependent on both diet and infectious agents, a search for potential environmental factors that might explain the increase of the allergic diseases should include factors that may stimulate PGE2 activity or otherwise influence the Th1/Th2 cytokine balance."

#### AIR POLLUTION

It is a common belief that the increase of the allergic diseases has occurred because of the increased air pollution from traffic and industries, but there are no scientific data to support this belief.

The prevalence of allergic diseases is very high in New Zealand, where the air is very clean and clear.

Allergic diseases are also more common in Western than Eastern Europe, although air pollution is much greater in the East than in the West.

"Chronic environmental exposure of young children to house-dust endotoxins, derived from the cell walls of Gram-negative bacteria, has recently been found to be associated with protection against allergy in young children."

Endotoxin is a marker of the bacterial content of the house dust.

Various types of bacteria, and glucans or spores from molds, which occur as air pollutants, may actually improve the Th1/Th2 cytokine balance and thus protect against the development of allergic sensitization.

Several recent studies have unequivocally shown that children who are raised on farms are less likely to develop atopic allergy and allergic sensitization to allergens such as grass pollen and tree pollen than children raised in other environments.

Studies "suggest that an environment characterized by a high content of bacteria and other particulate matter in the air may indeed protect against development of allergy, at least if an individual is subjected to such an environment during infancy."

It is unlikely that the global increase of the allergic diseases in childhood is dependent upon a worsening indoor household climate.

#### DIESEL EXHAUST PARTICLES

The increase of the allergic diseases has occurred in parallel with the increased use of fossil fuels, especially diesel exhaust particles, which have been found to stimulate the formation of IgE.

Diesel particles stimulate gene expression and the formation of Th2 cytokines.

#### TOBACCO SMOKE

Studies show that tobacco smoke enhances the formation of IgE antibodies.

Children who are exposed to environmental tobacco smoke have been found to have increased serum IgE and to develop frequent respiratory symptoms.

"Passive smoking during or after pregnancy has been shown to be a risk factor for the development of both allergic sensitization and obstructive respiratory disease in the child."

"Even if smoking has a proven effect on allergic diseases, it does not seem probable that it is a major causative factor in the global increase of these diseases."

#### NET EFFECTS OF AIR POLLUTION FACTORS

- (1) Bacterial products possibly prevent the development of allergy.
- (2) Diesel exhaust particles and tobacco smoke enhance the development of allergy.

However, "epidemiologic studies provide convincing evidence that increased air pollution in general is not responsible for the increasing prevalence of allergy."

"Rather, it seems more likely that decreased air pollution, such as that by bacterial products, may be causally related to the increasing prevalence."

## NEW ALLERGENS

"Introduction of new allergenic chemical compounds, or 'new allergens', from the animal or vegetable kingdom is often suspected of causing the increase of allergic diseases."

"The often cherished thought that cleaner air and fewer chemicals in the environment would lead to an allergy-free community has no solid scientific basis."

"A person who is already sensitized to allergens will always be at risk of developing allergic symptoms when living in environments where allergens are prevalent."

"In other words, although secondary allergen prevention is necessary in the battle against allergies, it seems less probable that allergen avoidance could be effective in primary allergy prevention."

## HORMONES AND ENVIRONMENTAL POISONS

"Stress may modulate the immune system and change the balance between Th1 and Th2 cytokines toward Th2 immunity."

This effect could possibly be mediated through stress-related production of glucocorticosteroids and catecholamines, which stimulate the production of Th2 cytokines.

Female sex hormones occur in increasing amounts in nature in the Western world due to the increased use of contraceptive pills. This altered relation of sex hormones contributes to the skewing of the immunity toward the Th2 type of immunity.

"In many countries an increase of environmental toxins such as DDT and PCB in nature has coincided with the increase in the prevalence of atopic diseases."

## REDUCED FREQUENCY OF BACTERIAL AND VIRAL INFECTIONS

"Children with many siblings have a reduced frequency of allergic diseases."

"The more children in the family, the more infections they encounter."

"This has led to the hypothesis that a high load of infections during early childhood may help to prevent allergy."

"As most infections during childhood are caused by viruses, the interest has been focused on viral infections."

"Further evidence that early viral infections might be protective has been obtained for measles and hepatitis A."

The results regarding viral diseases suggest that most viral infections seem to be protective against allergic disease.

Viral infections generally induce a strong immune response that is mainly driven by Th1 cells.

Intracellular bacteria such as mycobacteria have the same ability.

"If the assumption that early viral or bacterial infections protect against the development of allergic diseases is correct, vaccination should lead to an increase of allergic disorders." **[WOW!]**

A Swedish study found that the atopy was positively correlated to MMR vaccination (measles, mumps, rubella) and with the administration of antibiotics.

[Alm JS, Swartz J, Lilja G, Scheynius A & Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999;353:1485-1488]

Some studies report an association of pertussis vaccination with development of allergy.

Antibiotics act nonspecifically and have the ability to kill not only pathogenic but also commensal bacteria.

Studies show a significant relationship between treatment with antibiotics during the first 2 years of life and later development of allergy.

[Farooqi IS & Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998;53:927-932]

"Particularly convincing are the dose-response relationships; i.e., the finding that multiple courses of antibiotic treatment are associated with higher allergy prevalence, and the finding that treatment with broad-spectrum antibiotics appears to be more likely associated with allergy development than is ordinary penicillin."

"Microbial agents do indeed play a protective role in the development of allergic disease."

“It is hard to find any other explanation for these findings than that the exchange of infections among the children was the cause of the lower allergy prevalence.”

“It is tempting to assume that the protective effect may be primarily evoked by bacterial infections.”

“From an evolutionary perspective [INNATE], it is perhaps not unexpected that the immune system, which over millions of years has adapted to a heavy microbial load, may react in an ‘inadequate’ way upon a sudden, radical decrease of this load, caused by vaccinations, antibiotics, and especially improved hygienic conditions.”

“The disappearance of certain viral diseases that earlier were very common among young children (e.g., polio and measles) and a drastic reduction of the number of severe bacterial infections (e.g., tuberculosis) could be of particular importance in this regard.”

“These circumstances add to the probability that a changed spectrum of infections could be an important cause of the increased allergy prevalence.”

There is a clear association between poor hygiene and protection against atopy.

#### ALTERED GUT FLORA

“Allergies can be regarded as manifestations of aggressive immune responses to antigens that are usually well tolerated by the host.”

Substances introduced orally are normally ignored by the immune system, a phenomenon called oral tolerance.

In order for oral tolerance to be induced, normal microflora in the gut would be mandatory.

“Thus, animals raised in a sterile, germ-free environment will not develop normal tolerance.”

“Formerly, healthy neonates were rapidly colonized by *E. coli* or other enterobacteria during their first days of life, but in countries characterized by a Western lifestyle the colonization seems to occur much more slowly.”

“The spread of *E. coli* can be considered a sign of poor hygienic conditions,

and with an improved hygienic level fewer children will show early colonization with these bacteria.”

“If the children do not encounter enterobacteria, they will be colonized by other bacteria.”

“Early colonization by *Staphylococcus aureus* seems to be increasingly common in developed countries.”

“It seems clear that the hygienic standard correlates with allergy, as well as with the type of intestinal microflora.”

Bacterial DNA contains immunostimulatory nucleotide sequences which are able to stimulate Th1 immunity.

An altered bacterial colonization, especially in the very young baby, might lead to a persistently predominant Th2 type of immunity and to the development of allergic diseases.

#### CHANGES IN THE CONSUMPTION OF DIETARY FATTY ACIDS

“Atopic allergy is more common in rich than in poor countries.”

“It has been known for many years that atopic individuals have abnormal proportions of various polyunsaturated fatty acids in their blood.”

There is a greater prevalence of allergic disease in different regions with a high ratio between the plasma concentrations of omega-6 and omega-3 fatty acids.

“In Western countries, there has been an increase in the consumption of linoleic acid-containing food, such as margarine, whereas the consumption of omega-3 fatty acids that are present in high amounts, as in fish oil, has diminished.”

“The practice of giving small children fish oil to provide them with fat-soluble vitamins has largely been abandoned.”

“In many countries, the consumption of fish containing large amounts of omega-3-polyunsaturated fatty acids has decreased.”

Increased consumption of margarine instead of butter increases the prevalence of allergic diseases.

Linoleic acid [omega-6] is a precursor of arachidonic acid, which, in turn, is a precursor of prostaglandin E2 (PGE2).

PGE2 tends to polarize the Th1/Th2 cytokine balance toward Th2 dominance.

“Long-chain fatty acids from the omega-3 series compete with omega-6 fatty acids regarding several different enzymes that lead to the formation of PGE2, an effect which therefore will occur in reduced amounts in the presence of omega-3 fatty acids.”

“A change in diet to a higher intake of omega-6 and a reduced intake of omega-3 fatty acids should therefore lead to an increased activity of PGE2 and a polarization toward Th-2 type immunity.”

The neonate has an immature immune system influenced by the intrauterine immunity.

The breast milk of atopic mothers appears to have a higher linoleic acid/a-linolenic acid (i.e., omega-6/omega-3) ratio than milk of nonatopic mothers.

A high dietary intake fish oils gives a lower risk of developing asthma.

Fish oil decreases the production of PGE2.

#### CHANGES IN DIETARY ANTIOXIDANTS

Free radicals have the capacity to polarize the immune system toward Th2 immunity.

Treatment with antioxidants polarize the immune system toward Th1 immunity.

“Antioxidants in the diet may have an anti-allergic effect.”

“The continually decreasing intake of dietary oxidants that has been observed in developed countries over the past 30 years may therefore have contributed to the rising allergy prevalence.”

#### COMPARISON BETWEEN CANDIDATE AND CAUSATIVE FACTORS

These environmental factors are suspected of contributing to the increase in the prevalence of the atopic diseases:

(1) “A diminished microbial load, mainly caused by improvement of hygienic conditions, may be assumed to be the most important factor.”

Improved hygiene is associated with a decreased frequency of Th1 immunity-stimulating infections, and with changes in the commensal bacterial flora.

(2) "Alteration of the proportions between omega-6 and omega-3 fatty acids and decreased intake of antioxidants, both of which may lead to Th2 polarization of the immune system."

## CONCLUSION

The most plausible causative environmental factors for increasing prevalence of allergic disease are factors that polarize the immune system toward a Th-2 dominated cytokine profile.

"A change in the 'microbial load' seems to be the most probable cause of the increase in the allergic diseases."

"This conclusion is based on the known propensity of many microbes to stimulate the Th1 immune system, which suppresses Th2-type immunity; the apparently allergy-protective effect of poor hygiene; the probable allergy-stimulating effect of early antibiotic treatment in infants; the inverse relationship between certain infections and allergy as well as between indoor air content of endotoxin and allergy; and, finally, the association between certain bacteria of the gut microflora and development of allergy."

"It thus seems likely that atopy is a 'microbial deprivation disorder'."

Other factors include:

- (1) Diesel exhaust particles
- (2) Environmental toxins and pollutants
- (3) Altered fatty acids ratios
- (4) Reduced dietary antioxidants

## KEY POINTS FROM DAN MURPHY

- (1) Atopic diseases were rare a few decades ago and are rapidly exploding to epidemic levels, especially in children.
- (2) Atopic sensitization begins in utero, and the first few months of life are also crucial.
- (3) Once atopic sensitization occurs, it tends to be persistent.
- (4) Prostaglandin E2 (PGE2) enhances atopic sensitization. The synthesis and release of PGE2 is dependent on both diet and infectious agents:  
Infections **decrease** PGE2.  
Omega-3 fats **decrease** PGE2.  
Omega-6 fatty acids **increase** PGE2.  
Saturated fats **increase** PGE2.
- (5) Infections seem to be protective against allergic disease.
- (6) Antibiotics act nonspecifically, killing both pathogenic and beneficial gut bacteria. Antibiotic killing of bacteria significantly enhances atopic sensitization by side stepping the normal immune system response. Antibiotics also significantly enhance atopic sensitization by the killing of beneficial gut bacteria.
- (7) If early viral or bacterial infections protect against the development of allergic diseases, then vaccination would lead to an increase of allergic disorders.

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DIET, INFECTIONS, HYGIENE, ANTIBIOTICS, VACCINATIONS, ETC.