Hygiene hypothesis

In medicine, the **hygiene hypothesis** states that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g., gut flora or probiotics), and parasites increases susceptibility to allergic diseases by suppressing natural development of the immune system. It is hypothesized that the T_H1 polarized response is not induced early in life leaving the body more susceptible to developing T_H2 induced disease.[1] The rise of autoimmune diseases and acute lymphoblastic leukemia in young people in the developed world has also been linked to the hygiene hypothesis.[2][3]

There is some evidence that autism is correlated to factors (such as certain cytokines) that are indicative of an immune disease;[4] One publication speculated that the lack of early childhood exposure could be a cause of autism.[5]

History

Although the idea that exposure to certain infections may decrease the risk of an allergy is not new, David P. Strachan was one of the first people to formally suggest the theory in an article published in the *British Medical Journal* (now the *BMJ*), in 1989.[6] In this article, the hygiene hypothesis was proposed to explain the observation that hay fever and eczema, both allergic diseases, were less common in children from larger families, which were presumably exposed to more infectious agents through their siblings, than in children from families with only one child.

The hygiene hypothesis has been extensively investigated by immunologists and epidemiologists and has become an important theoretical framework for the study of allergic disorders. It is used to explain the increase in allergic diseases that has been seen since industrialization, and the higher incidence of allergic diseases in more developed countries. The hygiene hypothesis has now expanded to include exposure to symbiotic bacteria and parasites as important modulators of immune system development, along with infectious agents.[7]

Mechanism of action

Allergic diseases are caused by inappropriate immunological responses to harmless antigens driven by a T_H2-mediated immune response. Many bacteria and viruses elicit a T_H1-mediated immune response, which down-regulates T_H2 responses. The first proposed mechanism of action of the hygiene hypothesis stated that insufficient stimulation of the T_H1 arm, stimulating the cell defence of the immune system, leads to an overactive T_H2 arm, stimulating the antibody-mediated immunity of the immune systems, which in turn led to allergic disease.[8]

The first proposed mechanistic explanation for the hygiene hypothesis cannot explain the rise in incidence (similar to the rise of allergic diseases) of several T_H1-mediated autoimmune diseases, including inflammatory bowel disease (IBD), multiple sclerosis (MS), and type I diabetes. The major proposed alternative mechanistic explanation is that the developing immune system must receive stimuli (from infectious agents, symbiotic bacteria, or parasites) to adequately develop regulatory T cells, or it becomes more susceptible to autoimmune diseases and allergic diseases because of insufficiently repressed T_H1 and T_H2 responses, respectively.[9]

Breadth of the hypothesis

The hygiene hypothesis has expanded from eczema and hay fever to include exposure to several varieties of microorganisms and parasites that humans have coexisted with throughout evolutionary history, as necessary for balanced and regulated immune system development.[10] In recent times, the development of hygienic practices, elimination of childhood diseases, widespread use of antibiotics, and relative availability of effective medical care have diminished or eliminated exposure to these microorganisms and parasites during development. Examples of organisms that may be important for proper development of T regulatory cells include lactobacilli, various mycobacteria, and certain helminths.[11]

Supporting evidence

The hygiene hypothesis is supported by epidemiological data, but there is currently no well documented explanation for the inverse relationship between infections and certain diseases. Studies have shown that various immunological and autoimmune diseases are much less common in the developing world than the industrialized world and that immigrants to the industrialized world from the developing world increasingly develop immunological disorders in relation to the length of time since arrival in the industrialized world.[]

Recently, *Opisthorchis felineus* chronic helminthic infection in the endemic region of Russia, was found to be associated with lower serum total cholesterol levels and a significant attenuation of atherosclerosis in humans.[12]

Studies in mice have shown that exposure of young mice to viruses can result in a decreased incidence of type I diabetes.[13]

In *Cell*: Homeostatic Expansion of T Cells during Immune Insufficiency Generates Autoimmunity [14]Wikipedia:Link rot they showed that when short lived T cells were replaced during a state of too few long lived T-cells (Memory T cell), because of lack of infections, the risk of developing autoimmune diseases increases. They showed that in a state of too few long lived T-cells, because of lack of infections, not enough short lived T-cells could be produced by long lived T-cells during homeostatic expansion. Therefore, more auto reactive T-cells divide in such a state, causing multiplying auto reactive T-cells with a greater risk of causing autoimmune diseases like type I diabetes or multiple sclerosis.[15]

One conclusion is that a clean environment, with lack of infections (like early life infections) increases the risk of an autoimmune disorder.

T_H2 immune disorders such as asthma and other allergic diseases are probably related to the hygiene hypothesis [*citation needed*]. A baby has many T_H2 cells, which stimulate the production of antibodies. When not sufficiently stimulated with early life diseases, the immune system as too many T_H2 cells, leading to a greater risk of T_H2 immune disorder. If a child is exposed to infectious diseases, the cell defense is stimulated via T_H1 cells causing a reduction of T_H2 cells and subsequently a reduction of antibody stimulation by T_H2 and therefore a lower risk of developing an allergic disease such as asthma. Unfortunately, vaccination only uses the T_H2 mechanism. [*citation needed*]

In developed countries where childhood diseases were eliminated, the asthma rate for youth is approximately 10%. In the 19th century, asthma was a very rare disease. [*citation needed*]

Longitudinal studies in Ghana demonstrate an increase in immunological disorders as a country grows more affluent and, presumably, cleaner.[] The use of antibiotics in the first year of life has been linked to asthma and other allergic diseases.[16] The use of antibacterial cleaning products has also been associated with higher incidence of asthma, as has birth by Caesarean section rather than vaginal birth.[17][18] However, the studies investigating these links showed only tenuous correlations between the factors described and the conditions they are hypothesized to cause.[*citation needed*]

Several pieces of experimental evidence also support the hygiene hypothesis. Work performed in the laboratory of Professor Anne Cooke [19] at the University of Cambridge showed that mice of the NOD strain (which spontaneously

develop type 1 diabetes mellitus) had a significantly reduced incidence of this disease when infected with the helminth parasite *Schistosoma mansoni*.

In November 2009 a group of researchers at the School of Medicine at University of California, San Diego, found that Staphylococci helped reduce inflammation.[20][21]

A double blind study performed on 2500 pregnant women in Uganda showed that infants of the women treated with anthelminthic medication for worm infections had double the rate of doctor-diagnosed infantile eczema.[22]

Early life exposure to specific microbe-enriched environments decreases susceptibility to diseases such as IBD and asthma, whereas its absence, as in antibiotic treatment during childhood, may have the opposite effect. In a series of experiments,[23] compared germ free mice (GF) and pathogen specific free mice (SPF), challenged with aerosol ovoalbumin to promote allergen-induced airway inflammation. Mice were sensitized using ovalbumin at a concentration of 10 μg/mouse in a volume of 200 μl Imject alum on day 0 and 12. Between days 18 and 23 all mice were challenged daily with 5% aerosolized OVA or PBS via airways for 20 minutes. Monitoring airway resistance, concentration of serum immunoglobulin E, and other parameters they reached several conclusions.

• Asthma development was CD1d dependent.

• Early exposure to conventional microbiota protected animals from developing asthma.

• CXCL 16 is an age and organ-dependent microbially regulated factor that modulates the quantities and function of iNTK cells in the colon and lungs and, consequently, susceptibility to tissue inflammation.

The exact mechanism by which the microbiota regulates CXCL 16 expression and thus iNTK cell accumulation in these organs is unknown.

Helminthic therapy

The use of parasitic worms (also known as helminths) to treat the types of disease described by the hygiene hypothesis is being studied in the UK, USA and Australia.

Because of the promise shown by this research, two versions of Helminthic therapy, using *Trichuris suis* ova or *Necator americanus* larvae, have become available.

Helminthic therapy is the treatment of autoimmune diseases and immune disorders by means of deliberate infestation with a helminth or with the ova of a helminth. Helminthic therapy is currently being studied as a promising treatment for several (non-viral) autoimmune diseases including Crohn's disease,[24][][][] multiple sclerosis,[] asthma,[][] and ulcerative colitis.[] Autoimmune liver disease has also been demonstrated to be modulated by active helminth infections.[25]

In addition to the treatment of immune disorders the anti-inflammatory effects of helminth infection are prompting interest and research into diseases that involve inflammation but that are not currently considered to include autoimmunity or immune dysregulation as a causative factor. Heart disease and arteriosclerosis both have similar epidemiological profiles as autoimmune diseases and both involve inflammation. Nor can their increase be solely attributed to environmental factors. Recent research has focused on the eradication of helminths to explain this discrepancy.[26]

As a result of the hygiene hypothesis helminthic therapy emerged from the extensive research into why the incidence of immunological disorders and autoimmune diseases is relatively low in less developed countries, while there has been a significant and sustained increase in immunological disorders and autoimmune diseases in the industrialized countries.[][][][27][] If helminthic therapy and other therapies using other types of infectious organisms, such as protozoa,[] to treat disease are proven successful and safe the hygiene hypothesis has potentially large implications for the practice of medicine in the future.

Alternative hypotheses

Many other hypotheses try to explain the increase in allergies in developed nations. Major areas of focus in the literature include infant feeding, over-exposure to certain allergens, and exposure to certain pollutants.[*citation needed*] Infant feeding covers a range of topics that includes whether babies are breast fed or not and for how long, when they are introduced to solid foods and the type of these foods, whether they are given cow's milk, and even the types of processing that the milk undergoes. Numerous articles[*citation needed*] have reported that over-exposure to certain allergens in occupational situations can cause allergic diseases, such as Laboratory animal allergy, bird lung, farmer's lung, and bakers lung (See Wheat allergy). The third of these theories suggests that pollution (such as diesel exhaust) might be responsible for the increase of these diseases; however, some also claim that developed nations have also been becoming cleaner, and much more so than in the bleak Dickensian years of the early industrial revolution.[*citation needed*]

For immunological conditions related to Strachan's original version of the hygiene hypothesis, such as atopy and asthma, the pool chlorine hypothesis was proposed by Albert Bernard and his colleagues as an alternative hypothesis based on epidemiological evidence in 2003.[28]

Extended Hygiene hypothesis

Studies examining the interface between infections and metabolic diseases provide an intriguing new dimension to the commonly held “hygiene hypothesis”. Can the raising incidence of metabolic diseases, like the prevalence of obesity, diabetes and hypertension be exuberated by the absence of certain infections? (39) Inflammation has long been recognized as a major etiological factor for metabolic diseases (MD). Chronic inflammation leading to insulin resistance has now been identified to be a major etiological factor for a variety of metabolic conditions apart from obesity and type-2 diabetes. Insulin resistance typically starts as an organ specific inflammation affecting the major organs of insulin action namely adipose tissue, skeletal muscles and liver. With disease progression the inflammation, becomes more systemic and starts affecting the blood vessels leading to endothelial dysfunction a pre-stage for vasculopathies. Infact the inflammation associated with macrovasculopathies like cardio-vascular diseases, cerebro-vascular diseases and perivascular diseases seems to be very different from microvascular complications like diabetic retinopathy, nephropathy and neuropathy. The exact cause of inflammation in IR is not clearly known even though dietary, genetic and a variety of environmental factors have been implicated. Childhood helminth infections can reduce the risk and severity of allergies and autoimmune diseases, by means of immunomodulation, and a decrease in helminth infections could potentially account for the increased prevalence of these diseases in the western world (hygiene hypothesis.The same immunomodulatory effect can have an impact on metabolic diseases like obesity, diabetes, hypertension and atherosclerosis, wherein inflammation plays a crucial role (extended hygiene hypothesis). In this regard reduced prevalence of LF among diabetic subjects compared to non-diabetic and pre-diabetic subjects was noted (39). Interestingly, within the diabetic subjects, those who were filarial positive had reduced levels of pro-inflammatory markers compared to those who were filarial negative (39).

In mice, animals infected with helminths had lesser disease severity compared to uninfected in a diet-induced obesity mice model that is a well recognized model for MD (40,41,42). In light of these findings, the decreasing incidence of filarial infection due to mass drug administration could potentially have an unexpected adverse impact on the prevalence of diabetes in developing countries (39). Infections serve as an important source of inflammation and inflammation itself can serve as a link between infections and metabolic diseases. In general, infections that promote inflammation are thought to augment metabolic diseases while those that dampen inflammation by immunomodulation can confer protection against metabolic diseases. A much higher level of complexity is brought about by the recently identified helminth induced immunomodulation in conferring protection against inflammation/IR.

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External links

- Separating Friend From Foe Among the Body's Invaders (http://www.nytimes.com/2007/11/27/health/27book.html?ref=science)
- Hygiene Hypothesis: Are We Too "Clean" for Our Own Good? (http://web.archive.org/web/20090121140609/http://healthlink.mcw.edu/article/1031002421.html)
- His Parasite Theory Stirs a Revolution (http://www.boston.com/news/science/articles/2007/12/31/his_parasite_theory_stirs_a_revolution/)
- (http://www.dailytitan.com/2013/03/parasites-2/)
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