


Is there a link between hygiene and allergic disorders?

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 The human fetus develops in a sterile maternal environment. Soon after birth, it is exposed to a large number of environmental stimuli, including microbes that rapidly colonize the gastrointestinal and respiratory tracts, as well as the epidermal layer of the skin. It has been estimated that within a few years the viable cells of the gut, respiratory and skin microflora outnumber the human host by a factor of ten. In most cases, this microbial flora is beneficial since it helps in the maturation of the intestinal tract. Constant microbial stimulus from the developing gastrointestinal and respiratory microflora is also required for the successful maturation of the gut and respiratory mucosal immune system. Numerous experimental studies have shown that the lack of such a stimulus results in decreased intestinal surface area, altered mucosal enzyme patterns, defects in the non-immunologic barrier of the intestine, reduced capacity for inflammatory responses and a defective mucosal IgA system.

Improved sanitation and a boost in hygiene have led to the end of many parasitic and microbial diseases. News about the germs lurking in mattresses and salmonella-yielding chopping boards has nearly everyone reaching for soaps, lotions, disinfectants and antibacterial hand gels. Between 1992 and 1998 nearly 700 new antibacterial products came on to the market. However, experts suspect that our widespread obsession with cleanliness and all things antibacterial may actually be harming our immune systems. Modern vaccinations, fear of germs and obsession with hygiene are depriving the immune system of the information input on which it depends for maturation and development. This fails to maintain the corrective cytokine balance and fine tune T-cell regulation, and some scientists believe that this may, at least in part, explain the increasing incidence of some immune disorders over recent years.

The prevalence of allergic diseases such as asthma, allergic rhinitis and allergic dermatitis have more than doubled over the past two generations. Interestingly, this increase appears restricted to first-world countries, particularly amongst the high socio-economic groups. Frequency of atopy (hypersensitivity to allergens) and asthma symptoms in children have been shown to vary from 2 to 4 % in China, India and Africa to 20–30 % in Britain, USA and Australia. Although there is a clear inherited predisposition to atopic diseases, the rapid recent increase and the 15-fold disparity in reported allergic disorders among countries probably reflect the influence of environmental factors. Some scientists have suggested that the rise in allergic disorders is linked to our ever greater preoccupation with cleanliness.

● The 'Hygiene Hypothesis'

The 'Hygiene Hypothesis' for allergic disorders was first proposed in 1989 by David Strachan based on his observation that hay fever, skin prick positivity and

specific IgE in children correlated inversely with family size. He stated that higher standards of personal cleanliness over recent years have reduced opportunities for cross-infection in young families, and that this may have resulted in more widespread clinical expression of atopic disease. He also indicated that the development of allergic diseases could be prevented by infections during early childhood, transmitted by unhygienic contact with older siblings or acquired prenatally. Since then, several other epidemiological studies from different parts of the world have reported similar observations.

● Epidemiological link between hygiene and allergic diseases

The earliest association between hygiene standards and allergic disorders was observed by John Brostock, who first described hay fever in 1828 and was puzzled to find that this condition occurred mainly in the urban educated classes rather than those who lived on farms, despite their lower levels of exposure to pollen. More recently, the opening of former socialist countries of Eastern Europe to western investigators during the early 1990s brought important insights into the epidemiology of atopic disease. Before the Berlin wall came down, the incidence of allergies in East Germany was 5 %. Children were born in less-than optimal living conditions, ate less sterile food and lived in apartments that were not clean. In West Germany, at the same time the incidence of allergies was 25 %. Ten years after the unification the incidence of allergies in the old eastern Germany equalled that of western Germany, and some scientists have suggested that this has been mainly due to embracing the Western ideal of cleanliness.

Significant differences in the prevalence of allergic diseases have also been reported between urban and rural areas. An analysis of the prevalence of asthma in 1,375 children from the Xhosa tribe in South Africa showed that more than 3 % of the city-dwelling Xhosa children had asthma, compared with 0.14 % of rural children. A study in Basel, Switzerland showed that children of part-time farmers had a 76 % higher risk of hay fever and allergy than those of full-time farmers, suggesting that the greater exposure to livestock and the farm environment was protective for the development of allergic disorders. More recent studies have also shown a protective effect from living on a farm, particularly if there is contact with poultry, livestock or domestic animals. Of 500 children tested by the Medical College of Georgia, Detroit, those living with two or more pets (dogs or cats) were significantly less likely to have a positive skin test to allergens or allergen-specific IgE antibodies in the serum.

Some studies have shown that the use of antibiotics in early years leads to some children developing asthma and other allergic diseases later on. It has been argued that early childhood infections have a protective effect on

Allergic diseases are increasing rapidly. Is this linked to our rising standards of hygiene? Sundeep Salvi and Stephen Holgate explore the pros and cons of the 'Hygiene Hypothesis'.

RIGHT:
Owning a pet, like 'Bertie Hogg',
may be a mixed blessing for
children.

PHOTO AIDAN PARTE, SGM

BELOW:
Allowing children to be exposed
to the world around them and each
other may be of benefit to their
immune system.

PHOTO DARIEL BURDASS, SGM

the development of asthma. An ecological analysis conducted in 85 centres from 23 different countries showed that those with higher notification rates for TB had lower prevalences for asthma, allergic rhinoconjunctivitis and atopic eczema and it has been suggested that exposure to *Mycobacterium tuberculosis* may reduce the risk of developing asthma.

In 1,659 Italian military cadets aged 17–24 infections transmitted by contaminated food and the orofecal route, such as hepatitis A, were inversely related in a dose-dependent manner to atopy and respiratory allergies. Cadets who lacked antibodies to hepatitis A virus, *T. gondii* and *H. pylori* were 2.7 times more likely to be highly atopic than those with antibodies to two or three of these microbes (20.1 vs 7.8%). Furthermore the researchers detected asthma in 0.4% and allergic rhinitis in 7% of the cadets exposed to at least two of the three microbes, in contrast to 5 and 16%, respectively, in the group with no exposure to these microbes.

Bacterial endotoxins are found ubiquitously. The levels are particularly high in farms, being 18 times greater than those found in average homes. A recent study from the National Jewish Medical Centre, Denver, has demonstrated that exposure to bacterial endotoxin early in life may protect against the development of allergen sensitization, such as asthma. The researchers found that the homes of children who were most sensitive to allergens had significantly lower concentrations of bacterial endotoxin than those of children who were not sensitized to any allergens. It has been suggested that endotoxin drives the immune system to produce the cytokines that inhibit certain processes in the body which may lead to asthma. More recently, it has been observed that in some populations, polymorphisms that increase the expression of CD14 (receptor for endotoxin) may be associated with lower levels of IgE, and a potential explanation is that increased CD14 signalling

enhances Th1-predominant responses and thereby less likelihood of developing IgE-mediated immunity.

● Evidence for the Hygiene Hypothesis

Although the Hygiene Hypothesis was initially based on epidemiological evidence, a plausible underlying biological mechanism was suggested only when Tim Mosmann discovered the two polarized arms of the T-helper immune system, and the observation that allergic disorders were associated with overactivity of one arm. Th1- and Th2-helper cells are two polarized arms of the CD4⁺ T-helper immune cell system which reciprocally inhibit each other. Th1 cells produce IFN γ , IL-2 and TGF β , which have effects on the production of opsonizing and complement-fixing antibodies by B cells, activation of macrophages, cell cytotoxicity and induction of cell-mediated immunity. On the other hand Th2-helper cells produce cytokines IL-4, -5, -10 and -13, which evoke strong antibody responses, including IgE, and favour eosinophil differentiation and activation. Because cytokines released by Th2 cells mainly regulate IgE production as well as mast cell and eosinophil function, cells that are believed to drive the allergic responses, the Th2 system is believed to drive allergic responses to foreign organisms.

Pregnancy is associated with a strong skewing towards Th2-type immunity and if this does not occur at the correct time in gestation, there is an increased risk of abortion. As a consequence, neonatal immunity is Th2-skewed and allergen-specific T cell responses are already common at birth. The development of a counterbalancing Th1 immune response depends upon encounters with harmless microbes or through fighting microbial infections. According to the Hygiene Hypothesis, lack of microbial infections or contact with microbes causes the Th1 system to develop poorly, and as a consequence the Th2 system flourishes, which then favours the development of allergic diseases.

It has been suggested that the intestinal microflora is the most likely source of microbial pressure to enhance Th1-type responses. Experiments have shown that germ-free pups have a prolonged period of Th2 immune responses and a delayed development of oral tolerance. When the animals are colonized with bacteria of the normal commensal intestinal flora, oral tolerance and immune deviation toward Th1 responses rapidly develop. Also, treatment of mice with bacterial DNA products has been shown to inhibit the development of allergic airway inflammation.

One approach being explored is to expose children to dead bacteria or snippets of bacterial DNA to prompt a predominant Th1 immune response and thereby prevent the onset of allergies. A recent study showed that infants exposed to bacteria found in common yoghurt were half as likely to develop eczema as those who had not been given the bacteria. It has also been demonstrated that





Mycobacterium bovis BCG infection can suppress the development of allergen-induced airway eosinophilia and airway hyper-responsiveness in mice.

● Evidence against the Hygiene Hypothesis

Ever since the Hygiene Hypothesis was described in 1989, it has been faced with scepticism and remains an area for hot debate. Although more than 6,000 research reports have been published over the past 3 years examining the links between civilized living and allergies and asthma, not all of them support this link as causal. Some critics say that the disproportionate rise in asthma in most urban environments simply doesn't fit comfortably with the Hygiene Hypothesis. It has been argued that the evidence for a relationship between respiratory tract infections and protection against allergy is circumstantial, inconsistent and inconclusive, and is not supported by comparisons of risk factors and allergy prevalence in different regions.

Studies on the relationship between atopic sensitization and severe respiratory illness in early life have yielded contradictory and inconsistent results. Of particular interest are the findings that the social class bias towards asthma prevalence characteristic of the developed world appears to be reversed among low-income groups in the inner cities of the US, thereby challenging the hypothesis. Some respiratory infections account for around 80% of acute asthma episodes during infancy and childhood. This association persists for 8–13 years, while histamine hyper-responsiveness is evident for at least 10 years after bronchiolitis. Viral infections are also present in up to 80% of adults with asthma, whereas experimental rhinovirus inoculation in adults with allergic rhinitis have been shown to alter the response to allergen bronchoprovocation, favouring development of the late-phase allergic response. Virally infected patients with asthma have been shown to have enhanced cytokine responses, apparently leading to prolonged lymphocyte and eosinophil accumulation in the lungs. Similarly, contrary to earlier observations, a recent Finnish study involving 500,000 children has found that those who get measles are 67% more likely to develop asthma and other allergy-based ailments. This association between measles and atopy was evident at all ages, in both urban and rural dwellers, and among subjects with many or few contacts at home or in day care.

A protective effect of siblings on atopy appears to be evident only in the group with no parental allergy, suggesting that environmental influences on allergic sensitization may be overwhelmed by genetic predisposition to atopy. Although earlier studies showed that

pet ownership was protective against the development of allergic disorders, a recent US study found that there was a 45% increase in asthma rates among children aged 6–17 years who had pets at home. The earlier observation that pets protected against the development of allergies was curiously demonstrated only in boys and not in girls. While some studies looking at measles or hepatitis A virus infections have supported the conclusion that infections protect against atopy, others have shown an association between asthma and allergic diseases and *Mycobacterium tuberculosis* infections only in women and not men, and yet others have failed to show similar associations between atopy and measles or BCG vaccination. Some scientists have even suggested an alternative explanation for the earlier observation that mycobacteria do not lower the risk of atopy, but that atopics have an impaired ability to make a Th1 response to mycobacteria.

● Conclusion

Constant microbial stimuli appear to be necessary for the maturation and development of the immune system, at least during the early years. Some scientists have argued that improved sanitation and increased use of antimicrobial agents have driven the immune system to mount an abnormal response to innocuous external environmental agents and have thereby contributed to the increase in prevalence of allergic disorders. In broad terms the Hygiene Hypothesis envisages that the increasing efficiency of public health and hygiene measures in the developed world, when combined with lower family sizes, has reduced contact with respiratory infections in early life – such contact is believed to exert protective 'bystander' effects on developing Th1 responses to environmental allergens, promoting immune deviation towards the Th2-polarized responses that are characteristic of atopics. Although the Hygiene Hypothesis seems to be an attractive explanation for the recent increase in allergic disorders in the West, it is not clear which infections protect and whether there is a crucial period during which they are most effective. Further work is needed relating early infection to later atopic outcomes, but this is a demanding research agenda requiring longitudinal studies with follow up over several years. More rapid progress might be made by examining the epidemiology of a wide range of infections by age at onset, in relation to sibship size and socio-economic status. In spite of its popularity, the Hygiene Hypothesis remains a highly controversial topic, and there is evolving epidemiological and laboratory evidence to argue against it. Other possibilities for the increase in allergic disorders remain. Some have argued that this increase is due to changes in diet, while others have suggested changes in lifestyles or exposure to air pollutants. As it stands today, the Hygiene Hypothesis for the development of allergic disorders remains just that, a hypothesis, still to be proven or disproven.

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