



G germs can be good for us. This 'hygiene hypothesis' claims the urban 'Western' lifestyle, with its relatively limited exposure to infectious agents during childhood, might be behind the post-war epidemics of asthma, eczema and food allergies. But can the explosion in allergies in the developed world really be explained so simply? A more complicated theory is emerging.

JOE POUILLON/GETTY

For, while it is apparent that there is something about Western living that increases the risk of developing allergies, research has shown that it's not just a culture of antibacterial soaps, antibiotics and excessive cleanliness that's to blame. There is evidence to suggest there is more about the way children are raised — where they are raised, what they are fed and how many siblings they have — that influences their burgeoning immune systems. It's not just that their exposure to microbes or potential allergens seems to be limited. Sanitary living conditions disrupt the delicate balance between our bodies and a complex ecology of microbes and parasites with which we co-evolved, and through which our immune systems are balanced and regulated (see 'Gut reaction', page S5).

In 1989, epidemiologist David Strachan proposed the theory that a reduced exposure to dirt could render a person prone to allergy. The idea originally had a far narrower scope and, as Strachan, then at the London School of Hygiene and Tropical Medicine, but now at St George's University of London, is at pains to point out, he didn't actually use the term 'hygiene hypothesis'. Strachan, like others, was trying to understand a perplexing public health paradox. With clean drinking water, sanitation, vaccinations and advances in medicine, many diseases were on the wane. So why was it that allergic diseases were becoming more prevalent, particularly in industrialized and urban parts of the world?

The prevalence of allergies varies considerably, but many Western countries experienced a twentyfold increase in incidence. Asthma affects as much as 40% of the population in regions of New Zealand, Australia and the United States^{1,2}. Cases of eczema identified as atopic, meaning that they are associated with a propensity for allergies, doubled and even tripled in some industrialized countries. While these increases appeared to plateau, allergies rose rapidly in developing nations where living conditions and hygiene standards were becoming more like those in the West. It was starting to look as though the causes of allergies had something to do with the nature of Western lifestyles.

Strachan's insight was to link increases in allergic disease to the declining size of families. In his landmark study, which involved following more than 17,000 British children born in 1958,

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LIFESTYLE

When allergies go west

Modern living seems somehow to make our immune systems overly sensitive. Is cleanliness at fault — or something else?

BY DUNCAN GRAHAM-ROWE

he found that there was an inverse correlation between allergic rhinitis, or hay fever, and the number of older siblings. This, he suggested, “could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings or acquired prenatally”. Older siblings appeared to increase the range of bugs that either a pregnant mother or a younger sibling would be exposed to, boosting a younger sibling’s protection either indirectly or directly.

A QUESTION OF BALANCE

“The initial response from the immunologist community was highly sceptical,” recalls Strachan. The consensus was infections acted as triggers of allergic sensitization rather than as offering some form of protective influence. Strachan’s theory went against the grain.

A few years later, in 1992, a plausible mechanism came along and people started taking Strachan’s idea seriously.

This new explanation hinged on the upsetting of the delicate balance between populations of white blood cells, specifically two types of helper T cells — Th1 and Th2. Bacteria and viruses tend to elicit an immune response mediated by Th1 cells in which immune cytokines, such as interleukin-2 and interferon-gamma, are released. However, in animal models it was found that this Th1 response also serves to downregulate the Th2-mediated response, which can produce immunoglobulin E (IgE), the class of antibody that reacts to common allergens. This discovery supported Strachan’s theory — in developed countries, where the microbial burden might be low during

The hygiene hypothesis gained ground, and was applied to other autoimmune diseases.

childhood, insufficient stimulation of the Th1 response would fail to dampen Th2 leading to overactive Th2 responses. Evidence for the hygiene hypothesis, as it quickly became known, started to pile up. Anne Wright and colleagues at the University of Arizona in Tucson found that children attending day care during the first six months of life were less likely to develop both eczema and asthma. Researchers started to study why farmers’ children suffer so much less from allergies (see ‘Benign exposure’). The hygiene hypothesis gained ground, and was applied to other autoimmune diseases, such as multiple sclerosis, inflammatory bowel disease, Crohn’s disease and type 1 diabetes.

Meanwhile, the fall of the Berlin Wall in 1989 had opened up a unique opportunity to compare the effects of lifestyles of the East and West. Throughout the 1990s, Erika von Mutius, an allergist at Munich University Children’s Hospital in Germany, carried out a series of studies that found substantially lower incidence

of asthma and atopy among East German children compared to those growing up in the more developed West Germany, despite the fact that those living in East Germany were exposed to far higher levels of pollution. These results were echoed by other studies of children from Poland or Estonia and Sweden — relatively similar cohorts in terms of their genetic make-up, but which for 40 years had lived under very different economic and environmental circumstances.

Much research has focused on asthma and eczema, although it remains unclear how the hygiene hypothesis explains food allergies. It is clear, however, that they too are on the rise. This has directed attention to the link between food allergies and other allergic diseases. While genetics definitely play a role, so too do environmental factors such as diet and antibiotics, says Clare Mills at the Institute for Food Research in Norwich, UK. “Environment affects the kinds of microflora in your gut. So if you live in a clean environment you may end up with a different group of bugs that promote allergy.”

Little is known about the prevalence of food-specific allergies, particularly in developing countries, but efforts are underway to understand more. Mills led a project called EuroPrevall, which set out to study the allergy problem in Europe. This project also involves other studies in India and China, trying to understand how socioeconomic factors, diet, lifestyle and geographic variation can influence food allergies. The results of this work in Asia, which have yet to be published, were very revealing, says Mills. “What we found, particularly in India, was that they had virtually no food allergies.” The exception was highly developed Hong Kong, she says, where allergy incidences differed from the rest of China and were more like the West.

Other longitudinal studies in developing countries are now recording increases in immunological disorders as countries become more affluent. One such study led by Emmanuel Addo-Yobo at the Komfo Anokye Teaching Hospital in Kumasi, Ghana, consisted of a 10-year study, comparing atopy, an inherited propensity to allergic hypersensitivity, and exercise-induced asthma in urban-rich, urban-poor and rural children. In partnership with Strachan and Adnan Custovic, at University of Manchester, UK, Addo-Yobo’s work shows that it was the urban and richer middle class Ghanaian children who were most likely to have developed both allergies.

Other evidence does not always fit so well with the hygiene hypothesis. In highly urbanised Japan, where hygiene standards are high, asthma levels are much lower than in the United States or Australia. In the United States, asthma is increasing among children who live in very poor housing. And people in Barbados who live close to main roads and have high levels of endotoxins in their homes appear to

BENIGN EXPOSURE

Help on the farm

In 1999 Charlotte Braun-Fahrlander, an epidemiologist at the University of Basel, Switzerland, confirmed what rural doctors had observed for years, but which surprised most others: children who grow up on farms tend to have a reduced risk of developing hay fever and other allergies. This was backed up by work by Erika von Mutius, head of the Asthma and Allergy Group at the Munich University Children’s Hospital in Germany, who says that such children could be as much as three times less likely to develop allergies, compared with both city children and those from rural, but non-farming households.

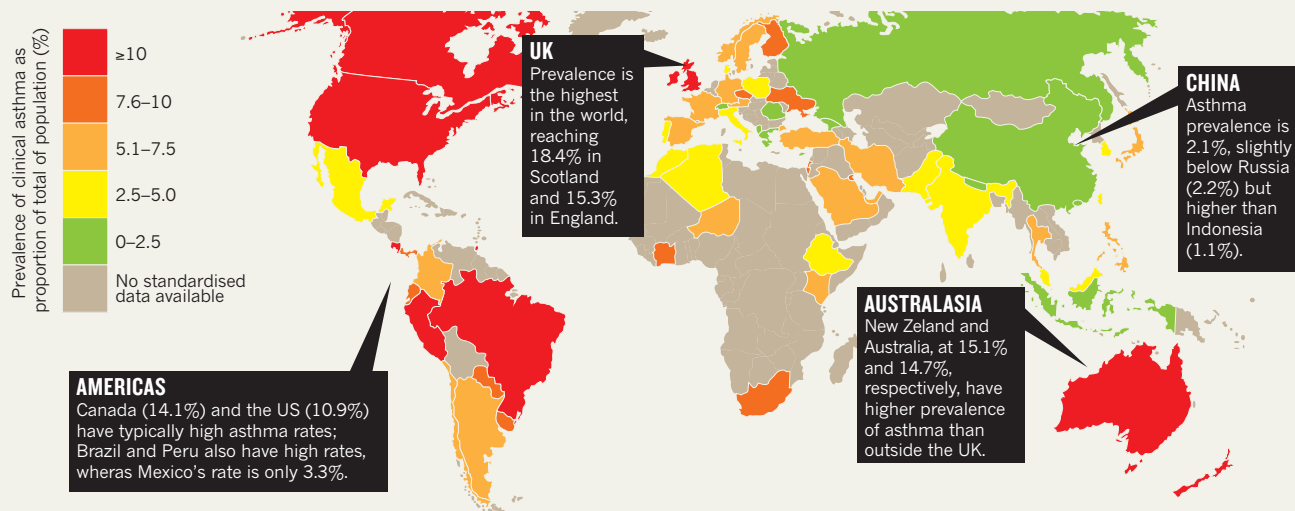
In 2002 the farm studies produced a fresh insight. Roger Lauener, head of allergy research at Zurich University Children’s Hospital in Switzerland, published research with von Mutius that showed that children growing up on farms had blood cells with significantly higher levels of toll-like receptor 2 (TLR2), which binds to microbes known to trigger innate immune responses. Yet none of them had any signs of infection and their white blood cell counts were normal. “How could it be that the environment was having an effect on the immune system without triggering an inflammatory response?” asks Lauener. The answer appears to be genetics: microbial exposure modulates the immune system at a genetic level by triggering the expression of these toll-like receptors, all without infecting the child.

In farmers’ children, says von Mutius, the trigger has to do with contact with animals, and also the consumption of unpasteurized milk. Several studies have now shown a protective effect from unpasteurized cows’ milk against asthma, eczema, hay fever and allergic sensitization. It has even been found that both animal exposure and unpasteurized milk consumption during pregnancy can pass on protection to the unborn child for the first two years of a child’s life.

It is not exposure to any single microbe that seems to count, but their diversity. In early 2011, von Mutius reported that children growing up on farms are exposed to a significantly wider range of microbes than other children, and she described an inverse correlation between the diversity of microbial exposure and the risk of asthma. Later in 2011 she published findings on the influence of unpasteurized milk consumption, which indicate that whey protein is implicated, although the mechanism has yet to be explained.

ASTHMA AROUND THE WORLD

Global studies confirm an association with westernized lifestyles



MASOLI, M. ET AL. THE GLOBAL BURDEN OF ASTHMA (2004).

receive no allergenic benefit, and instead have high levels of asthma.

TV, CARPETS AND CULTURE

Thomas Platts-Mills, at the University of Virginia in Charlottesville and a former president of the American Academy of Allergy, Asthma and Immunology, says that the problem may lie with the word 'hygiene'. He believes in the hypothesis, he says, but not that hygiene alone is responsible; other aspects of lifestyle must play a part too. Platts-Mills sees a clue in the timeframe of these allergy epidemics. It's no coincidence, he says, that asthma rates in the United States started to rise after the advent of

popular children's TV shows such as the Mickey Mouse Club. "Prior to 1955 children came home from school and went outdoors to play. We now have a population that sits around the house and sits still in ways that children have never sat still before," he says.

This is important because research by his group has shown that people tend to sigh fewer times when watching TV, compared with when reading. Without these periodic expansions of the lung, the bronchial smooth muscle suffers, leading to non-specific bronchial reactivity, he says. Combine this with less exercise (which also reduces the amount of deep breathing and thereby stretching of

the lungs), and dust mites lurking in wall-to-wall carpeting, and the conditions are ripe for asthma.

Carsten Flohr, a paediatric dermatologist at St Thomas's Hospital, London, makes another point about the influence of lifestyle factors. Despite evidence that suggests introducing foods early may reduce the risk of developing food specific allergies, concerns about food allergies have made parents in developed countries more cautious. As a result, we are introducing foods to children later in life, a behaviour which may inadvertently be making the problem worse, Flohr says (see 'Picky eaters', page S8).

Strachan agrees that the term 'hygiene hypothesis' has become a little tired. Microbial deprivation still seems the most promising candidate to explain the rise in allergies, he says, and the evidence remains solid that sibling numbers are an influence, but attributing it to Westernization rather than hygiene is a better way of capturing the multifaceted nature of the phenomenon.

Regardless of what the theory is termed, no one is advocating that the developed world abandon modern urban lifestyles and move en masse to the countryside to work on farms. Nor is it reasonable to have more children or deliberately catch a bad case of worms (see 'Lost protection') just to develop better protection against allergies. Yet the evidence continues to mount that there is something amiss about modern urban life in the developed world, and something about the West cleaning up its act that is exacerbating the burden of allergies. ■

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LOST PROTECTION

The helminth connection

Another, perhaps unlikely, source of protection against allergies might come from parasites. Many parasitic diseases that persist in developing countries, such as filariasis and schistosomiasis, have been almost eradicated in developed countries.

While commendable from a public health standpoint, a perverse effect of this eradication might be a loss of protection from allergy. Parasitic worms, or helminths, were implicated in providing protection against allergies even before the hygiene hypothesis was proposed, says Maria Yazdanbakhsh at the Leiden University Medical Center in the Netherlands. Her research in Ghana has shown that catching schistosomiasis disease can modulate the expression of toll like receptor 2 (TLR2), a similar effect to that found by Roger

Lauener and Erika von Mutius among children growing up on farms in Europe. This supports the idea that the organisms with which we co-evolved are important in helping to prop up our immune systems.

Other studies in Gabon and Venezuela, and work in Vietnam by Carsten Flohr, have also shown that helminth eradication increases atopic skin sensitization. What's more, research in 2011 by Harriet Mpairwe of the Uganda Research Unit on AIDS, established by the UK's Medical Research Council and the Uganda Virus Research Institute in Entebbe, found that treatment against helminths during pregnancy is associated with an increased risk of infantile eczema — suggesting that, conversely, any protection against allergens afforded by helminths could be passed down to the as yet unborn child.

1. Peat, J. K. et al. *The Med. J. Austria* **163**, 22–26 (1995).
2. ISAAC Steering Committee. *Lancet* **351**, 1225–1232 (1998).