The “hygiene hypothesis” has been a topic of contention ever since the term was first coined in 1989 by Professor David Strachan (St George’s, University of London, London, United Kingdom). Derived from his study showing that a child’s risk of developing allergic rhinitis (“hay fever”) was inversely related to the number of older siblings in the family, [1] Professor Strachan suggested that allergic diseases were prevented in the younger siblings by “infection in early childhood, transmitted by unhygienic contact with older siblings.” At that time, this was interpreted as an explanation for the increased prevalence of allergic diseases in Western countries, with the assumption that opportunities for infection had been reduced through the higher standards of hygiene achieved in those countries.

Initially, the "hygiene hypothesis," which Professor Strachan later admitted "owed more to an alliterative tendency than to [an] aspiration to claim a new scientific paradigm,"[2] was greeted with skepticism. Additional studies, however, provided further support for the idea that microbial exposure in early life protects against allergic rhinitis, eczema, and asthma.[3-7] As the prevalence of allergic diseases in children continues to rise in the West, especially in the United States,[8,9] the hygiene hypothesis is now frequently cited as evidence that Western households are "too clean" and that progress in public hygiene has been achieved at the expense of protection against allergy in early childhood. The hypothesis has been extended to explain food allergy[10] and a wide range of other conditions such as autoimmune diseases (type 1 diabetes and multiple sclerosis), inflammatory bowel disease, some cancers,[11] and Alzheimer disease.[12]

The term "hygiene hypothesis" has been criticized as being too vague, including by Professor Strachan himself.[2] Other concepts have been proposed as more accurate descriptions of the model, including: the "microbial hypothesis" (avoiding an overemphasis on cleanliness)[13] and the "old friends hypothesis" (implying that microbes that were beneficial for immune system development have been eliminated or replaced).[14] The "biodiversity hypothesis" expands the hygiene hypothesis to the living environment in general,[15] and the "biome depletion" model views the hygiene hypothesis as an evolutionary mismatch that works in tandem with other mismatches, such as inflammatory diets or vitamin D deficiency, which undermine immune function in westernized societies.[16]

Others have contended that reduced microbial exposure early in life cannot be the sole explanation for changes in allergic disease prevalence, given that some regions have a high prevalence of allergic diseases along with high infection rates.[9] It is generally agreed that more epidemiologic and clinical studies are needed as well as basic research into the mechanisms underlying the protective effects of microbial exposure. As Professor Strachan wrote, "Over 25 years of epidemiological and immunological investigation...little progress has been made in identifying the biologically relevant exposures which 'explain' the frequently replicated epidemiological observations linking allergic sensitization and atopic disease (inversely) to family size and to 'unhygienic' environments;"[2]

For further clarification of the current understanding of the hygiene hypothesis and its implications for the advice physicians should give parents and caregivers of young children about "hygiene in the home," Medscape approached Dr Laurence E. Cheng, MD, PhD, Assistant Professor in the Department of Pediatrics at the University of California, San Francisco School of Medicine and the Mary E. and Oscar L. Frick, MD Endowed Chair in Allergy. Dr Cheng is using basic and translational approaches to research patients with allergic diseases, including food allergy, atopic dermatitis, and asthma. He was coauthor of a recent review on the role of allergic inflammatory responses in maintaining tissue homeostasis[17] as well as an editorial accompanying an observational study of children’s allergies. [18]
What Is the Current Understanding of the "Hygiene Hypothesis"?

A landmark 2002 study among farming and nonfarming households in Europe[^5] extended the principle of a protective effect of early-life microbial exposures beyond viruses, according to Dr Cheng. "You could see that despite genetic similarities between all of the populations, the children who grew up on farms had much lower rates of allergic diseases than their nonfarming counterparts," he recalled. The study demonstrated that allergic diseases and asthma were less likely to occur in children with high environmental exposure to endotoxin (bacterial lipopolysaccharide).

Another study out of Detroit, the Childhood Allergy Study, was able to show a similar effect in a more urban environment in the United States.[^6] "Basically, having dogs and/or cats as pets protected children against allergies, and the effect was additive, so the more dogs or cats they had, the better protection they had," Dr Cheng said. He also pointed out the GABRIELA study (Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community [GABRIEL] Advanced Study), which was "a very nice correlative piece, in which not only could you look at the same exposures but you could actually look at the microbiome itself and see that early-life exposures also led to greater diversity of environmental microbial exposure that was correlated with less allergy, even in these urban environments."[^7] "I think these are incredibly important data...but I do not think it is as simple as feeding bacteria to your kids," Dr Cheng cautioned.

What Do Recent Studies Add to Our Knowledge?

Two recently published studies reported by Medscape[^19,20] appeared to lend further support to the hygiene hypothesis, although, as Dr Cheng pointed out, "They did not really answer the same question." One of the studies, carried out in more than 1000 Swedish children aged 7-8 years found that children living in households where dishes were washed by hand had a 43% lower risk of developing allergic disease, primarily eczema, than children from households with a machine dishwasher.[^21] The investigators concluded that the less-efficient hand-dishwashing method probably induced tolerance by increased microbial exposure. In the accompanying editorial, however, Dr Cheng and his coauthor cautioned that the study had "definite limitations."[^18] "It is interesting; it is an association, but in many ways, as our commentary laid out, there are some holes in their argument," Dr Cheng told Medscape. "The study looked at 8-year-olds as opposed to very young children—less than 6 months old—in whom we believe this sort of protective effect happens," he explained. He also questioned how only hand dishwashing showed an effect despite "much clearer and heavy microbial exposures" seen with ingestion from fermented foods or [unpasteurized dairy] foods from a farm that appeared to have no effect. "These associations, although they can drive the formation of testable hypotheses, remain just associations," he stressed.

Despite adjustment for a number of potential confounding variables such as pet keeping and parental history of allergy, Dr Cheng believes that hand dishwashing in the study was a proxy for the real reason behind the effect. "Hand dishwashing vs machine dishwashing is probably passed down culturally; maybe you do it, along with a number of other learned behaviors, because it's what your parents did," he suggested. "People who want to use this study to support their arguments will use it, whereas others will say this is yet another study that doesn't bring us closer to a genuine understanding," he cautioned. "I am somewhere in the middle; I think it is interesting, but I would not use this paper as a reason to stop using my machine dishwasher."

Does Eating Peanuts Reduce Peanut Allergy?

An investigation of the extended hygiene hypothesis was reported from a trial in infants aged younger than 11 months at high risk for peanut allergy, which is the leading cause of anaphylaxis and death related to food allergy in the United States.[^22] In the Learning Early about Peanut Allergy (LEAP) trial, children aged 4-11 months who were randomly assigned to consume peanuts up to 60 months of age showed significantly reduced frequency of peanut allergy development and modulated immune responses to peanuts.[^23] "This paper emphasizes that although we don't necessarily know what we can do to prevent global allergy, we can do something about specific food allergies, even in high-risk children," Dr Cheng said. "This paper is useful in that it validates cultural norms present for generations in
other parts of the world, which is earlier introduction of food than we have previously recommended in the United States," he continued. "This is the first evidence scientifically that early exposure to food may be of benefit in those who are otherwise destined to develop food allergy, and it is something that we should consider codifying for the future." Dr Cheng added that it was particularly interesting that the children would be presumed to have similar microbiomes to others living in urban Western environments, with a predisposition to allergic responses. By early introduction of food, "you might be able to get them on a different track. You are not predestined to allergy; rather, there is a way to modulate the outcome."

Although the LEAP trial was "an extremely provocative and landmark study, there were some hiccups along the way, as many of the children who ingested peanuts had eczema flares and what in the paper were called viral skin infections. Peanut-ingesting children also had more upper respiratory tract infections," Dr Cheng cautioned. "Whether this will bear out in even larger populations remains to be seen, but regular ingestion of peanuts by at-risk children with eczema wasn't achieved without some perseverance. It might be difficult for some families to knowingly worsen their child's eczema in the hopes of preventing a problem that is not apparent on a daily basis. That can be a tough decision to make, but most of the families in the trial pushed through and successfully completed the trial." Nonetheless, Medscape readers should be aware that some of the children stopped taking the peanuts, and many of these children ended up having food allergies. "So you don't know whether it was perseverance that made it work or whether the development of allergy in some children was so pervasive that it forced you to stop, no matter what the potential benefit," Dr Cheng stressed.

What Is the Best Advice for Preventing Allergies in Young Children?

"In terms of lifestyle changes, unless prospective parents go live on a farm and you regularly come into contact with animals, at this point there are no other data to suggest that any change in lifestyle will be of benefit [in preventing allergies]," Dr Cheng admitted. "The science has been very well done, but in the lay sense, the hygiene hypothesis has been interpreted as, 'We should therefore be putting our kids into dirt, exposing children to manure,' etc. We have come a long way in lowering infant mortality, and we don't want to throw the baby out with the bath water, so I would not agree that somehow people should be less clean." He stressed the need for more research: "Before we go there, we need to understand what is wrong and how it is wrong, and that is the power of basic science."

In cases of food allergies, Dr Cheng suggests that referral to an allergist might be appropriate for high-risk children, such as those enrolled in the LEAP study, who had severe eczema, food (egg) allergy, or both. "I want to be clear that the study had a narrow definition of children who were included in the study. The patients had to meet study-defined eczema activity and/or food allergy," he emphasized.

Severe eczema in this study was defined as:

- A rash that required the application of topical creams and ointments containing corticosteroids or calcineurin inhibitors and, if the participant is:
  - Younger than 6 months of age, lasted for at least 12 out of 30 days on two occasions; or
  - Older than 6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or
- "A very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash," as described by the participant's parent or guardian in a pre-enrollment questionnaire; or
- A rash that is currently or was previously graded 40 or higher using the modified SCORAD evaluation.

He also cautioned about misdiagnosis of food allergy, which in a recent study could be as high as 89% of children who had undergone a food blood test panel.[24] "Sensitization does not equal a clinical allergy diagnosis," he said. "That is why there is confusion, and that is why it has been somewhat overdiagnosed—because people test positive for these
allergens, but in fact some of them are eating those foods and yet not having any issues.” He cited a study of National
Health and Nutrition Examination Survey (NHANES) data that concluded that a large percentage of people with high
food-specific immunoglobulin E levels in the blood are eating the foods without a problem and so do not have true
clinical allergy.[25] “People can have very high levels and yet if they are eating the food and tolerating it, by definition
they are not allergic, no matter what the tests say,” he said. Instead, these tests only corroborate the key clinical
findings in patients with allergy. “Usually the immune response resulting in allergy is very stereotyped. Children get
hives, diarrhea, vomiting, or difficulty breathing,” he explained. New US guidelines for the prevention of environmental
allergies and asthma and food allergies in children are under development. Dr Cheng hopes to see these new
guidelines within the next 2 years, if not sooner. An additional consideration moving forward will be to find safe and
developmentally appropriate vehicles for foods introduced in younger infants.

Is Lifelong Exposure Necessary for Protection Against Allergy?

Some critics of the hygiene hypothesis believe that microbial exposure may need to be continued throughout life to
prevent allergies. [9] Dr Cheng is not so sure. “Those children [who grew up on farms] may be protected long term. It is
quite possible that the early-life exposures set the stage for everything and that at some point the immune system is
set,” he said. “People who don’t have allergies generally don’t develop them later in life; on the other hand, children
with allergies tend to have them lifelong. Let’s face it, those microbial communities in your gut or on your skin or in
your nose are pretty hardy, and they are there for a reason; they have outcompeted other bacterial types, and they
have established connections among themselves. They are truly little communities and are often very stable. They can
be changed, but in general they don’t shift too much. A lot of this is genetics too; the microbes that you pick up are
probably evidence of your genetic makeup,” Dr Cheng added.

For food allergy, he believes that the issue of lifelong exposure to specific foods to maintain the ability to eat a specific
food remains an open question. For instance, with peanut allergy, “we cannot say whether the children at risk could
stop eating peanuts and retain their ability to eat them, or whether they are just what we would call desensitized and
that if they were to stop regular ingestion, they would go right back to having allergies,” he said. Indeed, the authors of
the LEAP study are in the midst of a follow-up study (LEAP-On) to address this very question.

What Comes First—The Parasite or the Allergy?

When the hygiene hypothesis was first proposed, there was no clear-cut explanation for the observations, which were
based on epidemiologic studies. A number of mechanisms underlying the hygiene hypothesis have since been
proposed; one of the likely contributors involves suppression of proinflammatory signaling via T-regulatory cells,
inducing “anti-inflammatory” effects and control of diseases caused by dysregulated immunity, including allergy. “For
the immune response that we see in allergy, the part of the immune system that drives allergic diseases is also seen in
parasitic infections. So that begs the question: Did that allergic inflammatory response evolve to deal with parasites?
The classic answer would be yes; however, the latest data from animal studies and basic science—though not
necessarily proven in humans—suggest that the response to parasites may not be to the parasite itself but to other
factors, such as the tissue damage caused by those parasites in our bodies.” In a recent review,[17] Dr Cheng and
coauthor Richard M. Locksley, MD (Howard Hughes Medical Institute, University of California, San Francisco School of
Medicine) proposed that allergic inflammatory responses regulate pathways involved in tissue homeostasis and that
parasites feed into these pathways, engaging allergic inflammation to sustain aspects of the parasitic life cycle. In
response to parasite infection, an adaptive and regulated immune response is layered on the host effector response.
However, in the setting of allergy, the effector response remains unregulated due to a lack of induction of T-regulatory
cells, leading to the cardinal features of disease. In their review, Drs Cheng and Locksley suggested that exposure to
pathogens during critical developmental periods may train the immune system to focus on exogenous organisms
rather than allergens.

"We should think of this immune response as not necessarily being so important for fighting infection but for keeping
our barrier surfaces (skin, gut, lungs) intact," Dr Cheng explained. “These barrier surfaces are always being
challenged, whether from sun damage, trauma, or an insect bite, and this response is probably always working in the background. What is unique about parasites is that they probably have evolved (and we evolved with them) to have a response that promotes re-establishment of barrier integrity while not damaging or causing problems with the host at uninvolved sites. Without parasites, for whatever reason, this barrier maintenance machinery that is always in the background runs in overdrive, and there is no brake on the system. It is reacting to barrier damage and leading to an overexuberant response to that damage signal."

"What is also interesting about the parasite angle is that people who have parasites don't tend to have allergic diseases," Dr Cheng continued. "They have all of the evidence of allergic diseases—very elevated levels of biomarkers that we would associate with allergy—but no clinical allergy. So the parasites themselves probably invoke an immune response that for lack of a better term you could call 'balanced.' That is to say that the body is capable of localizing the repair machinery to only the anatomic locations that require it and turning it off once the tissue has returned to normal."

"It comes down to this: For whatever reason, the body is responding to a cue in such a way that it thinks that there might be a parasite there," Dr Cheng concluded. "Without that initial parasite infection, there is no balance to ensure that that response is localized. So the question is: What regulates this balance and what initiates that overexuberant response? Does the microbiome help to set this brake to balance the immune response, or perhaps the microbiome directly regulates the allergic immune response? Further research into these questions will go a long way toward helping us understand how this system works. And once we have a better handle on how it works, how it breaks down, we might be able to develop new and more effective treatments."

References

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