



SHUTTERSTOCK

Two decades ago, guidelines recommended that babies at risk of allergy should avoid peanuts — but now that advice has been reversed.

How a peanut snack triggered a fresh approach to allergy prevention

Early oral exposure to some allergenic foods is now seen as a key prevention strategy, but tackling inhalant allergies remains a challenge. **By Sarah DeWeerd**

It's not often that a snack food helps to shape the course of scientific history. But that's what happened when Gideon Lack, a paediatric allergist at King's College London, visited the Sea of Galilee in Israel with some friends in 2003.

As the group relaxed on the front porch, Lack remembers, his friends fed their six-month-old baby with peanut-butter-flavoured puffs of corn called Bamba, a popular snack in Israel. Many allergists at the time might have recoiled in horror. The prevailing wisdom was that parents should avoid feeding their babies foods containing peanut for the first year of life to prevent them from developing an allergy.

But Lack had already come to suspect that the prevailing wisdom was incorrect — and the lake-shore moment crystallized his suspicions. Just before his visit, Lack had given a lecture in Tel Aviv. He asked the audience of Israeli doctors how many of them had seen a case of peanut allergy in the past year. “Only two or three of the entire audience put up their hand,” Lack says. “In the UK, every paediatrician or GP would have put up their hand.”

Israel didn't have peanut-allergy-prevention guidelines because peanut allergy wasn't a big problem there. At the lake, Lack recalls his friends explaining that everybody they knew gave these peanut snacks to babies. His hunch

was that the solution to the rapid rise in peanut allergy in the United Kingdom and many other countries might be for babies to eat peanut-containing foods, rather than avoid them. “That's really when I decided there was mileage in this hypothesis and we ought to pursue it.”

In the following years, Lack and his collaborators helped to overturn the conventional wisdom about food-allergy prevention. Today's guidelines no longer recommend dietary avoidance. And there is growing evidence that introducing certain allergenic foods such as peanut and egg to a baby's diet early, at around four to six months of age, can help to prevent allergies to those foods.

Throughout much of the twentieth century, allergies to foods such as eggs and milk were rare, and nut allergies were almost unheard of. But rates began rising sharply in many high-income countries in the 1990s. In the United States, for example, the prevalence of peanut allergy among under-18s more than tripled¹ from 0.4% in 1997 to 1.4% in 2008. The reasons for this change aren't entirely clear. Allergies have a genetic component, but such a rapid rise is more likely to be due to changing diets, lifestyles and other environmental factors.

As a consequence, UK and US guidelines began recommending that pregnant women, breastfeeding mothers and infants with a family history of allergy should avoid allergenic foods such as peanuts. "There wasn't a lot of data to support that. It was kind of a reflex," says Kari Nadeau, a paediatric food-allergy specialist at Stanford University in California.

Lack's doubt was the result of an accumulation of disparate evidence. "The penny dropped very gradually," he says. As a research fellow at National Jewish Health in Denver, Colorado, in the early 1990s, he worked on experiments inducing allergy in mice. Some of his colleagues showed that mouse pups became allergic to egg-white protein when they inhaled it or when it was scraped onto their skin, but not when they ate it². Later, after setting up an allergy clinic in Bristol, UK, Lack was struck by the increasing number of young children with peanut allergies – and the lengths to which their parents had gone to protect them. Mothers reported diligently avoiding peanuts during pregnancy and breastfeeding, as well as holding off on feeding their babies peanuts for the first year of life. "And they would say to me, 'I don't understand,'" Lack recalls. "I did everything I could to protect them and it didn't work."

Meanwhile, it was found that babies with peanut allergies often had eczema, a skin condition linked to allergies that results in itchy and raw skin. In the United Kingdom, this was often treated with creams containing peanut oil³. Other studies showed that peanut and other food allergens are ubiquitous on surfaces in people's homes⁴. And, oddly, children who had dental braces containing nickel were protected from developing skin irritation associated with wearing jewellery later in life⁵.

Cracking the peanut

"It occurred to me that the way children become protected is by eating the foods early," Lack says. "And the way they become allergic is by exposure through the alternative route, through the skin, in the absence of the protective oral exposure." He called this the dual-allergen exposure hypothesis⁶.

The differing reaction is probably linked to the body's response to parasites and venoms when they enter through the skin. This provokes the release of immunoglobulin E (IgE) – the same molecule that mediates allergy. Lack compares it to the way a person might take more kindly to a stranger who enters the house through the front door (in this case, the gut) than to one who enters through the bedroom window (broken skin).

But at the time of Lack's trip to Israel, this was all theoretical. After returning to London, he set up a study to compare peanut consumption and rates of allergy among Israeli children and Jewish children living in the United Kingdom. This would help to minimize the possibility of genetics driving differences in allergy rates.

Israeli babies consumed 7.1 grams of peanut protein per week, on average, and began eating peanut-containing foods as early as four months of age, Lack's team reported⁷. Jewish babies in the United Kingdom weren't eating any peanuts at all. And the rate of peanut allergy was about ten times higher among school-age Jewish children in the United Kingdom than among Israeli children.

Because other studies largely failed to show that allergen avoidance reduced the risk of food allergy, more researchers began to question the conventional wisdom. In the late 2000s, most professional-society guidelines dropped the recommendation for allergen avoidance. But it still wasn't known whether early introduction of allergenic foods was a good idea.

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To tackle that question, Lack and his team recruited 640 infants who were already allergic to eggs, had severe eczema, or both, and were therefore deemed to be at high risk of developing peanut allergy. The parents of half of the infants were told to avoid feeding their children peanut-containing foods for the first five years of life, in line with UK guidelines at the time; the rest were told to feed their children peanuts every week.

At the end of the study in 2015, "there was a staggering difference between the two groups", says George Du Toit, a paediatric allergist at King's College London who frequently collaborates with Lack. Early introduction of peanuts reduced the risk of peanut allergy by 70–86%, depending on whether infants already showed skin sensitivity to peanuts when they were enrolled in the trial⁸. "It was

just an overwhelming finding."

Some guidelines now recommend early introduction of peanuts to reduce the risk of allergy. "That's an entire about-shift on the approach towards allergy prevention," Du Toit says. "It's moved from strict avoidance to the encouragement of early, higher dose and frequent consumption."

Begin with the skin

Lack and other scientists think that early introduction of specific foods is likely to prove helpful in preventing most food allergies. For example, a 2016 study indicated that early introduction helps to prevent egg allergy⁹.

But for some allergies, prevention data remain scarce or non-existent. "Shellfish allergy is one of these neglected allergies," says Carla Davis, a paediatric allergist at Baylor College of Medicine in Houston, Texas. Shellfish is the most common food to spark an allergic reaction among adults in the United States, and it can be serious: more than 40% of people with shrimp allergy experience potentially life-threatening anaphylaxis. Davis thinks that early introduction of shellfish is not likely to be harmful and might help to prevent the allergy. "But nobody has tested it," she says.

Davis suspects that shellfish have been neglected because they are not an important part of the diet in populations in which early food-allergy studies were conducted. Her studies have shown that shellfish allergy is more prevalent among Black and Latinx populations¹⁰. "Here in Houston or along the [US Gulf Coast] there are these crawfish festivals," Davis adds. "Some family reunions – they're just fish fries, they're crawfish boils." In these communities, having a shellfish allergy makes people "feel really isolated and kind of shunned by the family", she explains – underscoring the importance of better prevention strategies.

Meanwhile, the insight that damaged skin plays a crucial role in triggering food allergies has spurred a focus on preventing eczema. "Now the big question is, if you protect the skin, will you have a lower rate of food allergies when [children] get to be three or four years old?" Nadeau says. But preventing eczema is easier said than done. A UK trial examined whether daily use of an emollient could reduce the risk of eczema, but found no evidence for this¹¹. In fact, the treatment seemed to put babies at higher risk of developing skin infections.

However, a more detailed understanding of eczema might lead to more-promising treatments. Researchers have identified three key lipids missing from the skin of children with eczema. A team including Nadeau is launching a study to test whether a cream



Preventing eczema could be a way to stop allergies developing in children.

containing these lipids soothes eczema and prevents food allergy in infants who have already developed the skin condition. The researchers also hope that protecting the skin could reduce sensitization to inhaled allergens, including pollen, mould and animal allergens from animals. “It’s not just food allergies that are beginning through the skin,” Nadeau says.

Hygiene hypothesis

Any intervention that reduces the occurrence of inhalant allergies would be welcome news. These allergies can trigger life-threatening asthma, but, so far, researchers have struggled to make progress in preventing them.

Minimizing exposure to inhaled allergens has proved ineffective. As part of the long-term Manchester Asthma and Allergy Study in the United Kingdom, researchers recruited parents who were at high risk of having a child with allergies and asked them to remove carpets from their home, encase mattresses and pillows in protective barriers against dust mites, and get rid of pets. “It didn’t really have any significant impact,” says study leader Adnan Custovic, a paediatric allergist at Imperial College London. In fact, he says, “We removed house-dust-mite allergens and more kids got sensitized to house dust mites.”

One reason for the underwhelming results might be that even if allergens are removed from the home, people will probably encounter them elsewhere. “The reality is, it is very, very difficult if not impossible to completely abolish exposure to inhalant allergens and have a normal, meaningful life,” says Custovic. And eradicating allergens can make things worse. “If you clean the house and remove all house-dust-mite antigen, you actually remove

a lot of bacterial exposure as well,” he says.

Custovic sees the failed experiment as a perfect illustration of the hygiene hypothesis – the widely accepted idea that exposure to a little dirt and certain microorganisms is necessary to set a baby’s immune system on a non-allergic path. He envisions a vaccine that would deliver a cocktail of beneficial bacteria or bacterial compounds to prime a baby’s immune system. This might need to be personalized to each individual, but it could be effective against various inflammatory diseases, he says.

For many other researchers, the quest to translate the hygiene hypothesis into useful interventions has led straight back to the gut. Children who grow up on farms tend to have fewer allergies, and Remo Frei at the University of Zurich in Switzerland has found that children living on the country’s farms consume more dairy products earlier in life than do non-farm-dwelling children nearby. The farm children also have a much more diverse diet, eating lots of different fruits and vegetables, he adds.

Frei and his colleagues realized that one thing dairy products and vegetables have in common is short-chain fatty acids (SCFAs): molecules with a backbone of two to four carbon atoms that are known to have anti-inflammatory effects. Dairy products contain relatively high levels of SCFAs, and fruits and vegetables encourage the growth of gut microbes that produce them.

In an epidemiological study published by Frei’s group last year¹², children with high levels of an SCFA called butyrate in their faecal samples at one year old had a dramatically lower risk of developing allergies later in life. Mice that eat SCFAs are also less likely to develop allergies¹³. But researchers are still unsure of the best way

to introduce fatty acids into infants’ diets.

Breast milk encourages the growth of microbes that produce butyrate, and it contains a host of other molecules that are known to prevent allergy. However, the benefits of breastfeeding for eczema and asthma prevention seem to be modest, and studies have been unable to show that it lessens the chance of food allergies in infants. A few studies have even shown that breastfed infants are at higher risk of food allergy, although the explanation for this is likely to be reverse causality – that is, women at high risk of having a child with an allergy are more likely to breastfeed because of the perception that it might have some allergy-prevention benefit.

In addition, the composition of breast milk varies greatly from one woman to the next. In a study published in June¹⁴, immunologist Valérie Verhasselt at the University of Western Australia in Perth found that infants who consume egg allergen in their mother’s milk have a lower risk of egg allergy. But other studies have shown that not all women who consume eggs have egg allergen in their breast milk – and some women who eschew eggs still have milk containing the allergen. Such differences, which also extend to immune-modulating molecules, might mean that any beneficial effects of breast milk on allergy prevention become obscured in large population studies.

Verhasselt sees the explanation for this in human evolution. “Breast milk is not designed to prevent allergy,” she says. “It’s designed to prevent infectious disease.” She is now investigating whether dietary shifts or other interventions, tailored to the individual mother, baby and environment, could make breast milk more protective against allergy. In this case, the solution might not be as simple as a snack food beloved by an entire country.

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