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MEDICAL DISPATCH

THE PEANUT PUZZLE

Could the conventional wisdom on children and allergies be wrong?

BY JEROME GROOPMAN



Jill Mindlin prides herself on being a good parent. An attorney who lives on the North Shore of Long Island, she read books about how to raise healthy and happy children and dutifully followed their advice. She bought the car seat with the highest safety rating and covered her son and daughter with sunblock whenever they went outside. With her pediatrician's approval, she breast-fed her children until they were at least a year old and gave them "no formula whatsoever" and no milk products or peanuts. As the American Academy of Pediatrics recommended in 2000, she introduced solid foods slowly and in small amounts.

In 2002, when her daughter, Maya Konoff, was nine months old, Mindlin

took Maya for a checkup, and she got several immunizations. After they came home, Mindlin gave her a little yogurt. Soon, Mindlin told me, "Maya blew up like a tomato, bright red, swelling from head to toe." She called the office, assuming that her daughter was reacting to the immunizations. The pediatrician told her that it was more likely an allergy of some kind. "Fortunately, there was liquid Benadryl in the house, and I was able to get Maya to take some," Mindlin said. The reaction slowly subsided.

Several days later, Mindlin took Maya to see a pediatric allergist at a hospital on Long Island, and he told her it was unlikely that her daughter had a dairy allergy, since she had been breast-fed and

Food allergy is likely a problem that we've created through our diet and environment.

RICHARD MCCURIE

was on a restricted diet. But Mindlin asked that Maya be examined, and the allergist placed a small amount of milk protein under the baby's skin. Within minutes, she broke out in hives. As it turned out, Maya was also allergic to eggs, peanuts, tree nuts, and sesame seeds.

Despite her mother's vigilance, Maya has had other frightening reactions. On a family outing to the Long Island Children's Museum a few months later, after eating something labelled "vegetarian cheese," Maya struggled to breathe and then lost consciousness. On vacation in South Carolina in 2003, Maya wanted a hot dog. "We asked the waiter to be sure that there were no dairy products in the food," Mindlin recalled. "He came back to the table and said that the package said a hundred per cent beef." But a few minutes after eating the hot dog Maya began vomiting and swelling. Mindlin later learned that the hot dog contained a milk protein. This time, the doctor in the E.R. gave Maya an epinephrine injection. Epinephrine, another term for adrenaline, can rapidly shut off a severe allergic reaction, and Mindlin now makes sure there are syringes of it in each of her handbags and in Maya's knapsack.

Dr. Hugh Sampson, the director of the Jaffe Food Allergy Institute at Mount Sinai Medical Center in New York and an international expert on food allergy, is Maya's doctor. He is a tall sixty-year-old with an athletic build and a full head of graying hair. Sampson and Dr. Scott Sicherer, a pediatric allergist who is also at Mount Sinai, have conducted extensive studies throughout the United States that show that the rate of allergy is rising sharply. Sampson estimates that three to five per cent of the population is allergic to milk, eggs, peanuts, tree nuts, or seafood. In the past decade, allergies to peanuts have doubled. Other researchers have found the same phenomenon in Great Britain. "This increase in the incidence of food allergy is real," Sampson said when we spoke recently. He cannot say what is causing the increase, but he now thinks the conventional approach to preventing food allergies is misconceived. For most of his career, he believed, like most allergists, that children are far less likely to become allergic to problematic foods if they are not exposed to them as infants.

But now Sampson and other specialists believe that early exposure may actually help prevent food allergies.

Sampson recalls that, in 1980, when she started researching the subject, as a fellow in immunology at Duke University, "food allergy was not a field that anybody wanted to get into." Many doctors said that patients who claimed that food allergies were causing stomach aches and rashes were often just manifesting psychosomatic symptoms. "I approached the subject with the assumption that I would prove it didn't exist," Sampson said.

In one early test, he gave a girl in the first grade a bit of egg camouflaged in applesauce. To Sampson's astonishment, she started wheezing and projectile vomiting. Five years later, he found that his one-year-old daughter was allergic to eggs. As Sampson got deeper into his work, he was struck by how little was known about the condition. No one knew why some children react to a food protein when it is placed on their skin but not when they eat it, or why others have antibodies in their blood that predict allergic reactions they don't end up having.

Sampson watched as the incidence of food allergies rose alarmingly in the West while cases remained rare in Africa and Asia. He and other researchers began to investigate whether the problem could be prevented if Western mothers continued breast-feeding as long as possible. This would keep their babies away from potentially allergenic foods until their immune systems had developed sufficiently. Laboratory studies reinforced the theory. Sampson's research group and others found that mice that had never been exposed to a particular food protein couldn't mount an allergic reaction to it. This suggested that isolating young children from even minor exposure to potentially allergic foods would be beneficial.

In 1989, Dr. Robert Zeiger, a pediatric allergist and immunologist at Kaiser Permanente Medical Center in San Diego, published related results from one of the only controlled research studies on the subject. In the Zeiger study, which appeared in *The Journal of Allergy and Clinical Immunology*, mothers prone to allergy were randomly assigned a restricted diet. They avoided cow's milk,

eggs, and peanuts during the last trimester of pregnancy and during breast-feeding; their infants were given the supplement Nutramigen, derived from casein, and kept off all solid foods for six months; cow's milk, corn, soy, citrus, and wheat were prohibited for twelve months, and egg, peanut, and fish for twenty-four months. After one year, the infants on the restricted diet had significantly fewer allergies than those in the control group. "Reduced exposure of infants to allergenic foods appeared to reduce food sensitization and allergy primarily during the first year of life," Zeiger wrote.

A few experts believed that Zeiger's research had not yielded results from which one could draw major conclusions. But Sampson was influenced by the article, and most of the other leading thinkers in the field agreed with the findings. "We know that the human immune system is immature for the first year or so. So I was thinking initially that, as long as we don't expose babies to a food, they can't make an immune response," Sampson said, "and if we can wait until their immune system matures after a few years they could do better when later exposed to the food."

In 1998, the Department of Health in the United Kingdom issued guidelines for doctors and families codifying these recommendations. In 2000, the American Academy of Pediatrics did the same.

The proteins within eggs, milk, peanuts, tree nuts, fish, shellfish, wheat, and soy that trigger allergic reactions don't readily decompose when exposed to heat in certain types of cooking or to the acid in our stomachs. Within the gastrointestinal tract, the immune system battles pathogens while it ignores harmless food proteins and allows nonthreatening bacteria to reproduce. Proteins that are easily broken down by heat or digestion, such as many of those found in fruits, generally pass by. Proteins that resist breakdown are more likely to stimulate an allergic reaction.

People with the worst food allergies usually have very high levels of an antibody called immunoglobulin E (IgE). When someone like Maya drinks milk, the IgE grabs hold of specific proteins that trigger the body's release of potent molecules like histamine and

cytokines. The immune system overreacts to fight the protein that most people's bodies ignore. When Maya "blew up like a tomato" and stopped breathing, it was because these molecules created so much swelling and inflammation that her throat closed up. For reasons that are still not completely understood, some people manifest their allergic reactions with nothing more than an outbreak of eczema. While there is a genetic predisposition to food allergies, no one has identified the specific genes, and there is no biological explanation for their existence.

"From an evolutionary-biology point of view, food allergy makes no sense at all," Dr. Scott Sicherer, Sampson's colleague at Mount Sinai, said. Hunters and gatherers who had potentially fatal reactions to tree nuts, peanuts, seeds, and fish would be at a distinct evolutionary disadvantage and were less likely to pass on their DNA to progeny. "It seems pretty clear that food allergy is a condition that resulted from the environment we created," Sicherer said.

One explanation for the rise in food allergies is called the "hygiene hypothesis." The natural environment exposes us to microbes that help teach our immune system to differentiate between dangerous pathogens and nonthreatening nutrients. When we shield children from dirt in the playground and from sick kids in preschool, we may limit their infections while also reducing their exposure to healthy microbes. This could make them susceptible to food allergies. Studies of mice raised in a germ-free environment show that they have abnormal immune systems and are more prone to allergic reactions. It is possible that we are doing the same thing to ourselves.

Researchers have also proposed several theories based on observations of geography and diet. Vitamin D is believed to reduce the development of allergies, and sunshine promotes vitamin-D production. Doctors in cold parts of the United States write three or four times as many prescriptions for epinephrine to treat food allergies as do doctors in warm locales. Dietary changes might also play a role. Eating more animal fat can increase the presence of a chemical, prostaglandin, that contributes to the body's inflammatory responses. And as people also eat fewer fresh fruits and vegetables

they fail to take in substances, such as beta-carotene, that limit inflammation in tissues.

One of the few pediatric allergists who questioned the guidelines written in 1998 and 2000 was Dr. Gideon Lack, at St. Mary's Hospital in London. Lack studied philosophy and psychology before medicine, and his background is evident in his approach to science. "If eating eggs or eating peanuts in an allergic sufferer causes a reaction, then clearly the way to prevent a reaction from occurring is by not eating egg or peanut," he said. "That makes sense. But that's different from saying that clearly the way to not become allergic in the first place is not to eat egg or peanut."

Lack published letters in *The Lancet* and the *British Medical Journal* that pointed out the absence of compelling evidence used to support the expert guidelines. His skepticism was not well received. "It was very hard to get any grant support to study my ideas," he said.

In 2003, Lack gave a lecture in Israel about the apparent rise of peanut allergies in the United Kingdom. "It was a large lecture hall in Tel Aviv, filled with pediatricians and allergists. And I asked them, 'How many of you have seen a case of peanut allergy in the past year?' Something like three hands shot up." Lack told me that if he had asked that question in the United Kingdom, ninety to ninety-five per cent would have raised their hands.

Working with researchers in Israel, Lack surveyed more than five thousand children in Jewish schools in North London and more than five thousand schoolchildren in an ethnically and economically similar region of Tel Aviv. The team obtained detailed information about the families' consumption of foods like peanuts, sesame, and tree nuts. They also catalogued other allergic diseases, such as asthma, eczema, and hay fever. The risk for peanut allergy among Jewish children in the London area was nearly eleven times higher than among those in Tel Aviv. Tree-nut allergy was fourteen times higher, and sesame five times higher in the United Kingdom. The relative risk for milk and egg allergy was about two to three times higher.

Lack's study does not offer any proof about the cause of the variance in allergies between Jewish children in London and

in Tel Aviv, but he believes the striking discrepancy may be due to a difference in diet between Israel and England. "The joke in Israel is that the first three words a child says are *abba*, meaning 'father,' *ima*, meaning 'mother,' and Bamba," Lack said. Bamba is a peanut concoction that looks like a Cheez Doodle, and it is a staple of infants' diets in Israel.

Lack did part of his training in pediatric allergy at the National Jewish Medical and Research Center in Denver, where he discovered that mice could develop allergies to a particular egg protein that was first rubbed on their skin or inhaled before they had ever eaten it. He wondered whether children in the United States and the United Kingdom might become allergic to peanuts through a similar mechanism. In a study published in *The New England Journal of Medicine* in 2003, he reported that children with eczema had often been previously exposed to an ointment containing peanut oil and were later found to be allergic to peanuts. He also determined that there was no correlation between women who had eaten peanuts while pregnant and the development of peanut allergies in their children. His study challenged the idea that restricting a mother's diet would prevent peanut allergy, and highlighted how children can inadvertently be exposed to food proteins.

In 2006, Lack received support from the National Institutes of Health as well as from two charitable organizations, the Food Allergy Initiative and the Food Allergy and Anaphylaxis Network. He is now more than halfway through the LEAP study—Learning Early About Peanut Allergy. Six hundred and forty babies have been enrolled in the trial. The children are randomly selected either to eat peanut products or to avoid them entirely. The study will compare the rates of peanut allergy between the two groups. Lack is also conducting a study funded by the Food Standards Agency and the Medical Research Council, in the United Kingdom, about when to wean children from breast-feeding and how a baby's consumption of allergenic foods affects her later development of allergies. As part of that work, he is examining thirteen hundred babies in the United Kingdom.

Lack believes that a child becomes tolerant to a variety of food proteins through exposure in the first six months of life. In developing countries, he notes, children

often consume solids, initially chewed by their parents, at two or three months. "Years ago, nobody had blenders or food mixers, and today in developing countries people still don't. The easiest way to get solid foods into a baby's mouth is to chew it up, so it's moist and coated with saliva, and then spit it into the baby's mouth."

A paper published in *Maternal and Child Nutrition* in January, 2010, reported that some two-thirds of students at a university in China were given pre-masticated food as infants. Only about fourteen per cent of American infants receive solid foods in this way. Saliva is a rich source of enzymes that can help break down solid foods and of antibodies that might coat food proteins in a way that makes them less allergenic to infants.

Lack's research has gradually gained influence with leading allergists, including Hugh Sampson. By 2006, Sampson realized that his recommendations about food avoidance did not conform to what he termed "the real world." Doing nothing more than inhaling or touching an allergen could prompt a reaction in some children. "You can't avoid food proteins," Sampson said. "So when we put out these recommendations we allowed the infants to get intermittent and low-dose exposure, especially on the skin, which actually may have made them even more sensitive."

Sampson believes that some eighty per cent of infants who are allergic to eggs or milk will outgrow the allergy by their teen-age years, and that preventing them from being fed products with these foods may prolong the time that takes. "I spent most of my career telling mothers to avoid these types of foods for their babies," he told me. "Now we're testing to see if we should advise mothers to give the foods to them."

In January, 2008, the American Academy of Pediatrics released a clinical report by Mount Sinai's Dr. Sicherer and other researchers that overturned the expert advice of the past decade: "Current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation. . . . There is also little evidence that delaying the timing of the introduction of complementary foods beyond four to six months of age prevents the occurrence of [allergies]." Dr. Frank Greer, a specialist in newborn nutrition at the University of Wisconsin School of Medicine and Public Health and an author of the

clinical report, told me, "There is so much out there about how to feed infants, when to begin rice cereal, how to phase in yellow vegetables and then green vegetables, that has no basis in scientific evidence. It's not surprising that recommendations were made which were based on so little data."

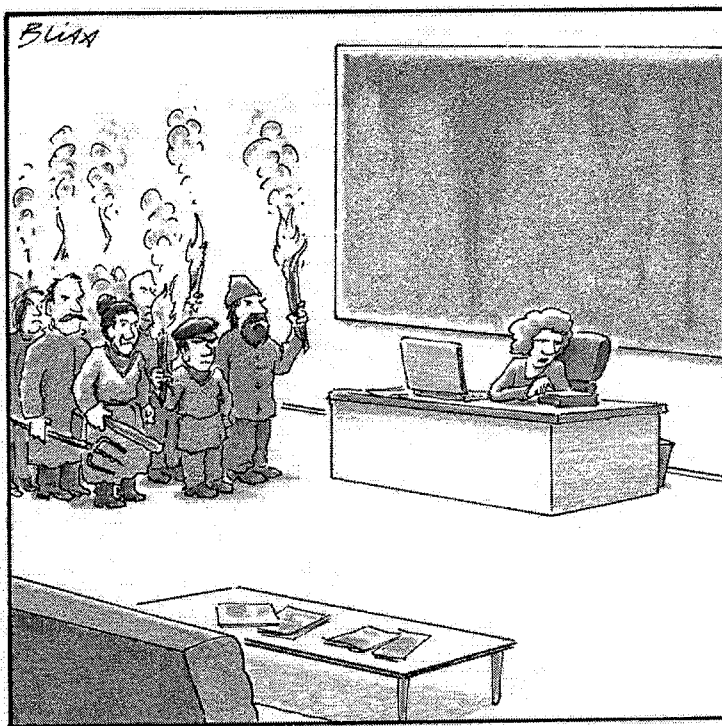
Dr. Susan Baker, a professor of pediatrics at the State University of New York at Buffalo and an expert on nutrition for children, chaired the committee overseen by the A.A.P. that released the recommendations in 2000. She told me that safety concerns drove the experts to recommend restricting exposure of infants to potentially allergenic foods, particularly cow's milk. "At the time, there was a proliferation of infant formulas on the market. Babies not only have cow's milk allergy with eczema, but some who are intolerant of milk also develop bloody diarrhea. The real concern was that the formulas might do harm. That sort of propelled us." The committee, she said, moved from milk products to restricting other allergenic foods, like peanuts and fish. "We in medicine are making a lot of decisions and recommendations based on

not a lot of solid evidence. So you toe a fine line. You want to try to get pediatricians something that is as good as it can be to help guide their practice and their thinking. Did we overreach with peanuts and other foods? Probably. Could it have been better? Absolutely."

The 2000 recommendations have now been overturned, but Gideon Lack is disturbed by what families now face. "Basically, we are all in limbo," he said. Sicherer told me, "This is a tricky area. The A.A.P. has backed away from making recommendations, since the evidence is weak. I try to emphasize with my patients not to feel guilty that they did or did not do something that would have resulted in their child having a food allergy. Even the experts are not certain what to advise."

People with food allergies live under a constant threat, in a society that is still poorly informed about the condition. For people with peanut and tree-nut allergies, incidents in restaurants account for nearly a quarter of unintentional exposures and about half of all fatal reactions.

In 2007, Sicherer published the re-



"Mr. Butler, your ten-o'clock is here."

sults of a survey of a hundred managers, servers, and chefs in establishments ranging from continental restaurants to bakeries and delis. Focussing on New York City and Long Island, Sicherer found that about a quarter of managers and workers believed that consuming a small amount of the allergen would be safe; thirty-five per cent believed that frying would destroy it; and a quarter thought it was safe to remove an allergen from a finished meal, like taking walnuts out of a salad. Nearly three-quarters of food workers believed that they knew how to "guarantee" a safe meal. Most states do not require that food providers attend educational programs, and there are no national requirements.

Sampson, acutely aware of the risks facing food-allergy sufferers, is now trying to work out a way to help desensitize people. To do this, he is relying on the idea behind the hygiene hypothesis and some of Lack's investigations: that exposure in small doses, in controlled circumstances, can build tolerance. He is trying to identify how the IgE antibody attaches to different proteins, and he uses this knowledge to have foods cooked in a way that would make the proteins less allergenic. Researchers at Mount Sinai observed, for example, that baking caused milk proteins to change shape in a way that could be less provocative to the immune system. An allergic person might be able to eat the altered proteins and become tolerant of them in all their forms. Sampson and other researchers have also configured an experimental vaccine that contains fragments of peanut protein that might "reeducate" the immune system of allergic people. Safety studies of the experimental vaccine are under way at the Jaffe Institute.

In 2008, when Maya Konoff was seven, her mother enrolled her in a research study being conducted by Dr. Sampson at the Jaffe Food Allergy Institute, funded by the N.I.H. She was given allergens in an altered form, and if she achieved tolerance she would be given foods that contained the allergen in its more natural state.

The treatment rooms at the institute are painted in soft tones and the hallways are decorated with large photographs of fruits. The institute has a spotless stainless-steel kitchen; all the refrigerators and cabinets are kept locked. Diego Baraona, the chef, prepares the foods. When I vis-

ited, he showed me a batch of small muffins he had baked, with applesauce and milk, and cups of rice pudding tightly sealed in plastic. With a nurse and Jill Mindlin at Maya's side, the child was given a muffin. Maya tentatively took a bite, waited, and seemed to have no reaction. In short order, she ate the rest of the muffin. "It was very exciting for our family," Mindlin recalled, "because it meant that she was one of those kids whose bodies didn't recognize the milk protein when it was broken down in baking, so now she had potential to eat baked foods."

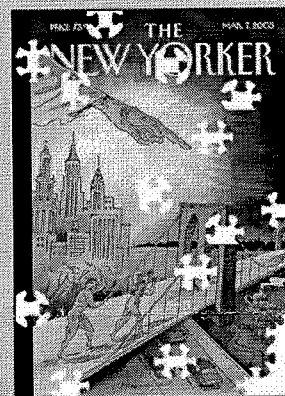
The next step was to try a taste of pizza. Maya took her first bite, waited, smiled, and then took another two bites. "I knew right then that things were not going well, even though Maya had not exhibited any physical symptoms," Mindlin said. "She had been so giddy, riding off the high of eating the muffin, happy and chattering, and then all of a sudden there was this pall that came over her." Maya soon broke out in hives and began vomiting. Sampson gave her an epinephrine injection. As the drug took effect, the anaphylactic reaction was arrested.

According to the protocol, Maya was supposed to come back in six months. Dr. Sampson counselled that in the meantime she should eat baked foods that included milk. When she returned, an intravenous line was inserted and an epinephrine inject pen was placed at the bedside before Maya was offered a slice of the same pizza. "It was nothing less than miraculous," her mother told me. "She ate the entire slice of pizza." Maya was observed for several hours and then given a bowl of rice pudding. The doctors told Mindlin to expect a reaction. "But instead she ate the whole bowl of rice pudding and was fine. She jumped two levels, just by eating muffins every day," Mindlin said.

Maya returned to Mount Sinai the next day for a glass of milk. "That didn't go quite as well," Mindlin said. As Maya finished drinking, her nose began to run and she vomited. The allergic reaction was mild enough to be treated with Benadryl. When I spoke to Mindlin in December, she told me that Maya can now eat macaroni and cheese but that she is still unable to drink milk. "Even if she never progresses past this, I have no regrets about being in the study, because now she can go to a birthday party and have a slice of pizza. It's huge." ♦

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