

Was It Something I Ate? Understanding Food Allergies



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The Joseph B. Martin Conference Center
The New Research Building
Harvard Medical School
77 Avenue Louis Pasteur
Boston, MA 02115



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Was It Something I Ate? Understanding Food Allergies

Moderator



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Speakers



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Assistant Professor of Medicine
Harvard Medical School
Director of Population Studies in Allergy
Director of the Food Allergy Center
Brigham and Women's Hospital



Ramnik Xavier, MD, PhD

Kurt Isselbacher Professor of Medicine
Harvard Medical School
Principal Investigator at the Center for Computational and
Integrative Biology
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Senior Associate Member, Broad Institute of MIT and Harvard

About the Speakers:

Jessica Savage, MD, MHS

Jessica Savage is assistant professor of medicine at Harvard Medical School and an allergist within the Division of Rheumatology, Immunology, and Allergy at Brigham and Women's Hospital (BWH) in Boston. She is the director of Population Studies in Allergy at BWH, director of the BWH Food Allergy Center, and a member of the National Institute of Environmental Health Sciences Center at the Harvard School of Public Health. She completed her medical training at Johns Hopkins in Baltimore, MD, where she also completed a Master's degree in epidemiology before joining the Harvard faculty in 2012. Her primary research interests focus on the environmental and genetic factors that influence the development of food allergy and underlie the recent rise in allergic disease. She is specifically interested in how environmental antimicrobial chemicals may influence the human microbiome and skew the developing immune system towards an allergic phenotype.

Wayne Shreffler, MD, PhD

Wayne Shreffler received his MD and PhD degrees from New York University and his pediatrics training at the Albert Einstein College of Medicine. He completed his fellowship in allergy and immunology at the Mount Sinai School of Medicine in 2003. He is board certified in pediatrics and allergy/immunology and is a fellow of the American Academy of Allergy, Asthma and Immunology. He sits on the editorial board for the *Journal of Allergy and Clinical Immunology*, the leading specialty journal for his field. Shreffler has developed a highly integrated research and clinical program to better understand the pathogenic mechanisms of food allergy and asthma, and provide the best current and future care.

The Food Allergy Center at Mass General, led by Shreffler, is focused on conducting clinical and translational studies of immunomodulatory interventions for children and adults with food allergy. Shreffler's experience conducting correlative mechanistic immunological studies in the context of such trials, together with the depth of expertise and resources at the Center for Immunological and Inflammatory Diseases at Mass General/Harvard Medical School, put the group in a unique position to make important new discoveries on how and why these therapies work for some individuals and what can be done improve their efficacy.

Ramnik Xavier, MD, PhD

Ramnik Xavier, an institute member of the Broad Institute of MIT and Harvard, is also chief of gastroenterology at Mass General, Kurt Isselbacher Professor of Medicine at Harvard Medical School, and the director of Mass General's Center for the Study of Inflammatory Bowel Disease. As a clinical gastroenterologist and molecular biologist, he studies the specific molecular mechanisms involved in innate and adaptive immunity as well as the genetic variants associated with Crohn's disease, ulcerative colitis, and autoimmunity. His laboratory uses genetic, structural, computational, animal models, and clinical research to define the mechanisms controlling inflammation and immunity in vivo. Recent studies have focused on understanding how the gut microbiome contributes to allergy and autoimmunity.

Is it a food intolerance, allergy, or something else?

Learn how to tell the difference, and what to do if you're reacting to wheat, milk, or other foods.

Walk down the aisles of your local supermarket, and you'll see something you likely wouldn't have encountered a decade ago—shelves devoted entirely to gluten-free cereals, breads, muffins, and other foods. Restaurants have also jumped onto the bandwagon, revising their menus to include dishes without gluten, a protein found in wheat.

The gluten-free diet was designed for people with celiac disease, who can't tolerate any foods containing gluten because their immune system reacts to it and damages the small intestine in response. Celiac disease is a very real, very uncomfortable, and potentially very serious condition. If left untreated, it can lead to anemia, osteoporosis, and intestinal cancers.

About 1% of Americans, or three million people, have true celiac disease. Another 6%, or 18 million people, are sensitive to gluten. Eating gluten-containing foods doesn't damage their intestines, but it can still produce gastrointestinal discomfort, along with symptoms like headaches and fatigue. People in a third group are allergic to wheat. When they're exposed, they get more traditional allergy symptoms, which can range from tingling around the mouth to hives, throat swelling, and difficulty breathing.

"It's confusing that people can have all these different reactions to the same food," says Dr. Ciaran Kelly, professor of medicine at Harvard Medical School and medical director of the Celiac Center at Beth Israel Deaconess Medical Center. "It's important to make the distinction between food allergies and intolerance, because there is a lot of confusion and there are differences in treatments."

A number of foods—including wheat, milk, eggs, and seafood—are notorious for triggering both food allergies and intolerances. If you have symptoms when you eat certain foods, it's important to distinguish what kind of reaction you're having and which foods are triggering it.

Food intolerance

When you're intolerant to a particular food, it's usually because your body lacks an enzyme needed to break down a component in that food (such as lactose, the sugar in milk). Or, your body might be sensitive to a particular chemical or additive in the food. The process leading to food intolerance often starts early in life, but symptoms can be too subtle to notice at first. "People may become more aware of intolerances as they get older," Dr. Kelly says.

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Examples of food intolerance:

Lactose intolerance. Your body can't break down the sugar lactose because your gut contains reduced levels of the intestinal enzyme lactase. Lactose is found in dairy foods such as milk or ice cream. When you eat these foods, you can develop uncomfortable gastrointestinal symptoms like gas and diarrhea.

Gluten sensitivity. You have many of the same symptoms as someone with celiac disease after eating foods containing gluten (stomach pains, bloating, fatigue), but your immune system doesn't produce the blood test abnormalities seen in people with celiac disease, and there is no evidence of damage in the intestines.

Sensitivity to food additives. You get symptoms like flushed skin and wheezing from eating additives such as sulfites (found in wine, dried fruits, and canned goods), or headaches, palpitations, or numbness after eating foods flavored with monosodium glutamate (MSG).

Symptoms of food intolerance

- You may be able to eat small amounts of the food without having any reaction to it. Your symptoms will come on gradually after you've eaten a particular food.
- Often, those symptoms will involve your digestive system—such as nausea, gas, or diarrhea. Your reaction will be uncomfortable, but it's usually not life-threatening.

How to deal with food intolerance

Keeping a food diary can help you identify the source of the problem. Every day, write down the foods you eat and any symptoms that occur. Once you pinpoint one or a few foods that coincide with your symptoms, you can try cutting them all out of your diet. This is called an elimination diet. Then add one food back in every couple of days. When your symptoms return, you've found the offending food. Ask your doctor or a dietitian for help identifying your trigger food and eliminating it from your diet.

Food allergy

A true food allergy involves your immune system. Your body recognizes a normally innocuous food, such as peanuts or milk, as a potentially harmful foreign invader. It goes into defensive mode, producing high levels of an antibody called immunoglobulin E (IgE). Food allergies often start when you're young, but it's not impossible for them to appear for the first time later in life, Dr. Kelly says.

Examples of foods that commonly cause allergic reactions include eggs, fish and shellfish, milk, peanuts, soy, tree nuts (hazelnuts, walnuts, almonds), and wheat.

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Symptoms of a food allergy

- You could have a reaction from eating just a tiny amount of the food, or simply from being around the food.
- You can experience allergic symptoms such as hives, swelling, and itchiness, as well as gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea.
- If your allergy is severe, you might have an anaphylactic reaction, which can begin with a rash, swelling of the tongue and throat, trouble breathing, dizziness, or fainting. It can be life-threatening.

How to treat a food allergy

See an allergist who has experience treating food allergies. The doctor can do a skin test, which involves placing a solution containing an extract of the food just beneath the skin of your forearm or back to see if it produces a skin reaction. Or you may get a blood test to look for IgE antibodies to the food. If you have an allergy, you'll need to avoid the food. Your doctor might also recommend that you carry around an epinephrine injector (EpiPen) to treat anaphylaxis if your allergy is severe.

Don't shortchange your diet

Avoid foods that bother you, but don't do a full-scale purge of your diet without good cause (for example, celiac disease or true food allergies). Because of the abundance of gluten-free foods available, many Americans have begun to think that all wheat and other grain products are bad for them. "There's a way of thinking that gluten is an unhealthy food," Dr. Kelly says. "Somehow if a food is gluten-free, it's considered healthier, and there's little basis for that."

Cutting out foods like wheat, barley, and rye (which all contain gluten) can rob your diet of nutrients such as fiber, calcium, and B vitamins. Going gluten-free could have a similar effect on your purse. One Canadian study found that gluten-free foods cost 242% more than comparable regular foods. Work with a doctor or dietitian to create a diet that's safe for your system, while still healthy and well rounded.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the April 2014 issue of the *Harvard Women's Health Watch*, available at hvr.d.me/JEuoj.

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Children who eat peanuts at an early age may prevent peanut allergies

Posted February 23, 2015, 8:14 PM

Gregory Curfman, M.D.

Editor in Chief, Harvard Health Publications



The [No Nuts Moms Group](#) website lists some of the young people who have died from food allergies—many from peanut allergy—going back to 1986. The lengthy list is a sad reminder that a peanut allergy can cause a severe and sometimes deadly allergic reaction. Parents who have a child who is allergic to peanuts do many things to keep him or her out of harm's way.

A study published online today in *The New England Journal of Medicine* offers some hope for parents of infants who may be headed toward a peanut allergy. That hope is peanuts.

For the study, an international team of researchers recruited infants who had an egg allergy or eczema, an allergic disorder that affects the skin. Both are indicators that a child is prone to a peanut allergy. The children were randomly divided into two groups. The parents in one group were asked to make sure their children didn't eat any peanuts, peanut butter, or other peanut-based products until age five. Parents in the other group were asked to give their children [a peanut-based snack called Bamba](#) or peanut butter three times a week until age five.

The results were surprising and dramatic. A peanut allergy developed in 1.9% of children who ate Bamba or peanut butter, compared with 13.7% of those who didn't eat peanuts. One explanation for this difference is that the children who ate peanuts early developed what is called immune tolerance to them. Their young immune systems adapted to the proteins in peanuts so that they did not react to them.

The researchers got the idea for this trial from a previous study of theirs. They knew that Israeli children are typically fed peanuts much earlier in life than British children. So they compared peanut allergies in Jewish children living in Israel with those in Jewish children living in London. The risk of peanut allergy was 10 times higher in the British children than in the Israeli children.

In an unrelated study, a team from the Jaffe Food Allergy Institute at Kravis Children's Hospital at Mount Sinai in New York City [presented similar findings](#) at the annual meeting of the American Academy of

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Allergy, Asthma & Immunology in Houston. They showed that a wearable patch that gradually exposes the body to small amounts of peanut protein may be effective in easing the allergy. After wearing the patch for a year, people with peanut allergies could tolerate the equivalent of four peanuts at a time. The patch, called Viaskin, is made by DBV Technologies, which funded the study.

What does this new work mean for parents? If an infant is allergy-prone, it may be a good idea to ask his or her pediatrician about skin-prick testing for peanut allergy. If adding peanuts to the child's diet early is feasible, the *New England Journal of Medicine* study suggests that such a strategy may prevent a peanut allergy down the line. And while the Viaskin results are still preliminary, if further research bears out these results, this approach could be a lifesaver.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at hvrld.me/JwuR1.

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6 tips for managing food allergies

April 6, 2013

Dealing with food allergies can be daunting. The effects of a reaction range from somewhat bothersome to potentially deadly. There is no cure, so anyone with a food allergy must vigilantly avoid the foods that trigger a reaction.

So how best to protect yourself? These six tips can help you create a system that's manageable, even routine.

1. **Always read labels.** Today, food labels include important allergy information such as whether any additives contain milk protein or byproducts of wheat, or whether a food was produced in a facility that processes nuts. Still, you need to read every label, every time—even if you have purchased the item hundreds of times before. Manufacturers frequently change ingredients and a new formula may contain allergens.
2. **Take care when cooking.** If everyone in the household isn't following an allergen-free diet, you want to be sure to avoid cross-contamination. It's a good idea to have two sets of cooking and eating utensils—one exclusively for the allergic person—so that a knife used to cut a peanut butter sandwich isn't inadvertently pressed into service buttering the toast of someone who's allergic to peanuts. All dishes and utensils should be thoroughly washed in hot, soapy water between uses.
3. **Dine out defensively.** It's wise to let the manager or chef know about your food allergy before you order. People with food allergies often carry a chef card—a printed note specifying all the ingredients you are allergic to as well as a request that all dishes, utensils, and preparation surfaces be free from traces of that food. You can customize a template of such a card on the Food Allergy and Anaphylaxis Network website, www.foodallergy.org. Fast food restaurants and coffee shops are no exception. Read labels and ask questions before deciding what to eat and drink.
4. **Formulate an action plan.** Make a list of steps to take should you accidentally eat the food you are allergic to, and carry a printed copy of the plan with you.
5. **Wear a medical ID bracelet.** Make sure it lists relevant information about your food allergy.
6. **Always carry your medication, ideally two doses.** If your doctor has prescribed emergency medication for you (such as EpiPen or TwinJet), always take it with you and always carry two to be sure you're prepared in case you get into trouble. Some people with food allergies also carry antihistamines. Don't leave home without your medications.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our HEALTHbeat email newsletter, available at hvrld.me/JEv9u.

Adult-onset food allergies

If you escaped a food allergy in childhood, you're not necessarily off the hook; you can develop food allergies at any point in your life. Fish and shellfish allergies are more likely than others to begin in adulthood. Moreover, allergies that develop in adulthood tend to stay with you forever.

Adult-onset food allergies differ slightly from those that develop in infancy. Most cases seem to rely on other factors to trigger them, including cross-reactivity to allergens from plants or animals or even exercise, which arouses the immune system.

Fish and shellfish allergy

Fish and shellfish are the most common sources of adult-onset food allergy, and African Americans and women are more likely to develop allergies to them than are Caucasians and men. Finned fish and shellfish do not come from related families of animal species, so being allergic to one does not necessarily mean that you must avoid both.

About 40% of those allergic to fish and 60% of those allergic to shellfish experienced their first allergic reaction as adults. Researchers have yet to find a definitive explanation for this phenomenon. Some speculate that because fish accounts for a bigger slice of the dietary pie than it once did, people now have more opportunities to become sensitized to it. Others, looking at connections between fish and other environmental allergens, have found some surprising associations. Several studies have found that people who are allergic to lobster, shrimp, and other shellfish are also likely to be allergic to dust mites and cockroaches. The suspected antigen (allergy-triggering agent) is a protein called tropomyosin, which is shared by mollusks, roaches, and mites.

Oral allergy syndrome

If you suffer from hay fever and you've ever experienced an itchy mouth, scratchy throat, or swelling of the lips, mouth, tongue, or throat after eating certain raw fruits or vegetables or some tree nuts, you may have oral allergy syndrome (OAS).

An allergic person's hyperactive immune system will sometimes mistake another protein for the one causing the allergy, a phenomenon called cross-reactivity. OAS is caused by cross-reactivity between airborne pollen proteins from trees, grasses, or other plants and proteins in fruits or vegetables that bear a molecular similarity to the pollen proteins. (Latex, which is made from a sap, can also cause a cross-reaction with some foods.) In people who are already allergic to pollen, the body's immune system mistakes the protein in the produce for that of the plant and unleashes the reaction normally produced by pollen. However, in this case, the site of the reaction is different, centering around the mouth rather

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than the nose and sinuses. The problem is common among people with seasonal allergies, and while it may be more severe during hay fever season, it isn't confined to that part of the year. It can strike whenever the fruit or vegetable is eaten.

If you have OAS, the food that will trigger an oral reaction depends on the pollen you're allergic to (see the table). If you find that a food you love is compounding your hay fever distress, try cooking it. The protein is usually altered during cooking so that it is no longer recognizable to the immune system. Also, because the antigenic proteins in fruits and vegetables congregate near the surface, peeling an apple, peach, or pear before eating may prevent the reaction. Antihistamines taken to reduce the symptoms of pollen allergy can also blunt an allergic reaction to food.

The pollen–food connection: Oral allergy syndrome

If you're allergic to latex or certain types of pollen, you may also develop a mild allergic reaction to foods that share certain proteins.

| Plant | Foods |
|-------------------------------------|--|
| Birch tree (early spring allergies) | Peach, apple, pear, kiwi, plum, coriander, fennel, parsley, celery, cherry, carrot, hazelnut, and almond |
| Grasses (late spring) | Peach, celery, tomato, orange, cantaloupe, watermelon, and honeydew |
| Ragweed (late summer, early fall) | Banana, cucumber, cantaloupe, watermelon, honeydew, zucchini, sunflower seeds, dandelion, chamomile, and echinacea |
| Latex (year-round) | Banana, avocado, kiwi, chestnut, and papaya |

Source: American Academy of Allergy, Asthma & Immunology.

Food-dependent exercise-induced anaphylaxis

Food-dependent exercise-induced anaphylaxis is a clinically distinct form of anaphylaxis in which symptoms occur only when a person exercises within a few hours of eating an allergenic food. The foods implicated include the most common food allergens—wheat, peanuts, shellfish—as well as soy, tomatoes, corn, peas, beans, rice, and some meat. Neither eating the food nor exercise alone triggers symptoms. In the nonspecific form of food-dependent exercise-induced anaphylaxis, eating any food prior to exercise induces anaphylaxis.

Moderate to vigorous exercise, such as jogging, tennis, dancing, and bicycling, usually provokes the attacks. People who have had an attack report first feeling suddenly exhausted, hot, and itchy, and then

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developing widespread hives. If the attack proceeds, many people have difficulty breathing, become nauseated, vomit, or lose consciousness.

Because the same type of exercise doesn't necessarily lead to anaphylactic episodes in everyone, people who have had an allergic attack while exercising should avoid the triggering food and wait several hours after eating before any kind of physical activity. At the first sign of symptoms, they should stop what they are doing and sit or lie completely still. Sometimes this is enough to cause the symptoms to subside. They are also advised to carry two epinephrine autoinjectors (EpiPen, TwinJet) and to work out with a partner who is aware of their condition and recognizes the warning signs of anaphylaxis.

Red meat allergy

Meat allergy is unusual, and it occurs mostly in adults. However, researchers at the University of Virginia have noted a connection between tick bites and the development of allergic reactions several hours after eating red meat, specifically beef, pork, or lamb—but not chicken, turkey, or fish.

The culprit appears to be galactose-alpha-1,3-galactose (or alpha-gal, for short), a complex carbohydrate molecule. Alpha-gal appears to be abundant in the intestinal tract of ticks, so people might get exposed to it when a tick bites them. The tick bite may then trigger some people to produce allergic IgE antibodies to alpha-gal, which is also present in the meat of mammals. When people with the allergic alpha-gal antibody eat red meat, they can break out in hives, angioedema (swelling), itching, and, in the worst case, experience anaphylaxis. The allergy has been traced to the aggressive lone star tick, widespread in the Southeast, Mid-Atlantic, and Northeast regions of the United States; however, other types of ticks may be responsible too.

This allergy is a game-changer, because until now, food allergies have always been associated with proteins—but alpha-gal is a sugar. Another difference is that allergic reactions to food are usually immediate, whereas a person with the alpha-gal allergy doesn't react for four to six hours. As a result, the allergic reaction can occur in the middle of the night, long after dinner is forgotten, making it more difficult for sufferers and allergists to identify the cause. Because alpha-gal is a sugar that attaches to fat molecules, the way fats are absorbed in the body may explain the delay in developing a reaction.

Standard allergy skin tests are not accurate for meat allergy. However, this allergy can be diagnosed through a blood test for IgE antibodies to alpha-gal.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Understanding and Controlling Your Allergies*, available at hvrld.me/JKiPT.

Why you have allergies

Allergic reactions are inappropriate, overblown responses mounted by the body's immune system against a harmless substance. Take milk, for example. Milk is not poisonous, infectious, or in any way harmful to humans. But in some people, it triggers an attack by the immune system—an allergic reaction. When this happens, the milk (or any other offending substance capable of triggering an allergic response) is called an allergen.

You can develop allergies at any point in your life. Allergies typically develop for two reasons. First, you may be genetically predisposed to be allergic. Second, factors in your environment, especially when you are young, may make you more susceptible. Most allergies are caused by some combination of these genetic and environmental influences.

Your genes

While many people suffer from allergies, most don't. In the United States, one person in five is an allergy sufferer. To some extent, being allergic runs in families. For instance, a child with one parent who has allergies has a 50% risk of developing allergies. This risk increases to 70% if both the child's parents are allergy sufferers.

Someone with a genetic predisposition to allergies is said to be "atopic," and therefore more likely to suffer from childhood allergies, which are also known as atopic diseases. People who are atopic are typically afflicted with one or more types of allergy throughout their lives.

Eczema (atopic dermatitis), one of the most common atopic diseases, typically first appears in very young children with a signature itchy, red rash. As children with eczema grow older, they are more likely to develop the symptoms of nasal allergies or allergic rhinitis—sneezing, runny nose, and congestion. And many then go on to develop the lung symptoms associated with allergic asthma by age 5 or 6. About one-third of children with moderate to severe eczema develop food allergies.

Your environment

Genes alone are not enough to cause allergies. The circumstances of your early childhood influence how likely you are to develop allergies. For instance, if you have siblings, your place in the birth order matters. Firstborn children are more likely to suffer from food allergies than their younger siblings. Scientists think this is because younger siblings are exposed to more germs passed around by older brothers and sisters. Exposure to a wider array of germs early in life may dampen the body's tendency to turn on the allergic response (see "The hygiene hypothesis"). Similarly, children in day care, who are exposed to germs as they come in contact with many other children, seem less likely to develop asthma.

Two types of immune defense

The hygiene hypothesis posits that insufficient exposure to microbes early in life fails to “train” the immune system to distinguish between disease-causing germs and harmless allergens. The immune system actually has two lines of defense.

The innate immune system. Also known as the nonspecific immune system, the innate immune system provides the type of immunity everyone is born with. It is the body’s first line of response to germs or allergens. Though the innate immune system doesn’t have antibodies to specific germs, it triggers a swift inflammatory response to anything it identifies as a “non-self” invader. Response time is typically within minutes to hours.

The adaptive immune system. The second line of defense, the adaptive immune system, targets specific germs and allergens and “remembers” which ones it has encountered before. The adaptive immune system requires “schooling,” however, so it can recognize these pathogens when it meets them again. During an invasion, it takes longer than the innate system to become activated—but once active, it is immensely powerful.

It was once thought that breastfeeding gave a child some protection against developing allergies, but this theory is now controversial. Studying the effects of breastfeeding is difficult, because families who choose to breastfeed are often different from families who don’t in many other ways besides this one choice. To date, there is some evidence that exclusive breastfeeding in the first few months of life may reduce the likelihood that an infant develops eczema, but it has not been clearly shown that breastfeeding has a long-term impact on the risk of environmental allergies, food allergies, or asthma.

The hygiene hypothesis

Since the early 1990s, evidence from around the world has supported the notion that the fewer microbes you encounter early in life, the greater your chance of developing allergies. This theory, commonly referred to as “the hygiene hypothesis,” is a proposed explanation for the development of all types of allergies. Proponents of the hygiene hypothesis point to evidence that exposure to microbes helps “train” the developing immune system by stimulating T cells that dampen an allergic reaction. Without sufficient exposure to the bad guys in early childhood, certain components of the developing immune system don’t develop properly and overreact to harmless things.

Researchers suggest that modern plumbing, cleaner homes, cleaner food and water, and the introduction of antibiotics and vaccines are in part culpable. Such innovations, which have helped lower the rate of infectious diseases and childhood death, also have reduced the number of microbes children

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encounter. American children's contemporaries in less developed countries have a higher rate of infectious diseases, but a lower rate of allergies.

For instance, researchers observed that after the reunification of East and West Germany, seasonal hay fever and asthma were less common in children who had spent their early years in less affluent East Germany. After the rise in East Germany's standard of living following reunification, hay fever increased among East German children. Even today, rates of allergic diseases are high in Western industrialized countries but not in other regions, such as rural areas of Africa and Asia.

Being around animals, especially farm animals, is also protective. Environments with these animals have higher levels of bacteria. Researchers who studied young children living on farms proposed that they are less likely to develop allergies than those raised in urban settings because their immune systems received strong stimulation in infancy from bacteria. Other studies have suggested that having a dog, cat, or other furry creature in the house during early childhood also lowers the risk of allergy, perhaps because of the microbes those pets carry.

So what should we do? Experts absolutely do not recommend that parents purposefully expose their children to germs, or avoid getting a child vaccinated to prevent allergies; vaccines are still vitally important. But a sterile environment may not always be necessary. When infants and toddlers put their "dirty" fingers and other objects into their mouths, not only are they learning about the shape and nature of those objects, but also their immune system may be learning about the outside world. Likewise, although all children should have their hands cleaned before eating, it is not necessary to pull out the hand sanitizer each time a child has been crawling on the floor.

To learn more...

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What happens during an allergic reaction?

Although the various mechanisms that lead to an allergic reaction may vary, the symptoms of all allergic reactions can be remarkably similar, and likewise so are the treatment approaches in many instances.

The role of antibodies

Antibodies account for the astounding versatility of the immune system to recognize a myriad of foreign “non-self” substances, or antigens. Each antibody is programmed to recognize one particular foreign molecule (or even just a small piece of that molecule). Since the immune system produces millions of antibodies, it is prepared to recognize any antigen that enters the body. Without the surveillance capability of antibodies, the human body would be devastated by pathogens (germs).

Antibodies, which are proteins, are also called immunoglobulins. Human blood contains five types of immunoglobulins: IgA, IgD, IgE, IgG, and IgM. Three of these—IgA, IgG, and IgM—play key roles in fighting harmful bacteria and viruses.

In the normal disease-fighting process, antibodies are produced when B cells recognize an antigen on the surface of specific harmful invading pathogens, such as the bacteria that cause pneumonia. This recognition causes B cells to mature into antibody-producing plasma cells. Like a battalion of medieval archers, these plasma cells let fly antibodies that travel to their targets on the outer surface of the harmful invaders. After finding their mark, IgG antibodies neutralize the bacterial toxins or make the bacteria ingestible by other cells of the immune system—neutrophils and macrophages, which eat and destroy the bacteria.

The majority of allergic reactions, however, are caused by IgE antibodies. In a sort of docking procedure, IgE antibodies link up with receptors on other immune cells called mast cells and basophils. Mast cells are specialized cells found in great numbers at points of entry into the body, such as the linings of the airways, the eyes, and the gut. When an innocuous allergen meets up with the IgE that recognizes that allergen and is docked on a mast cell, the mast cell prompts an allergic reaction by releasing histamine, tryptase, and other chemicals such as leukotrienes and prostaglandins. Within minutes, these chemicals trigger sneezing, runny nose, itchy eyes and skin, or wheezing (see the figure).

These fast reactions are not the only danger. Mast cells also produce other chemicals, such as proteases, that cause tissue damage. And activated mast cells produce their own cytokines, or chemical messengers (see “Key players”), that stimulate B cells to produce more IgE, which leads to more IgE docked on the mast cells and more opportunity to release the inflammatory chemicals. At the same time, other cytokines recruit white blood cells called eosinophils to the site of the allergic response, setting up local inflammation. Left unchecked and with repeated encounters with the allergen, this cycle can lead to continual inflammation and, in some people, lasting tissue damage.

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Key players

The allergic response involves a cascade of reactions from different cells in the body, including these key players:

- B cell (B lymphocyte): A type of white blood cell (B is for bone marrow) capable of producing IgE antibodies.
- Basophil: A white blood cell with protein receptors on the cell surface that bind IgE and release histamines and other allergy mediators.
- Cytokine: A type of chemical that signals B cells to produce IgE antibodies.
- Dendritic cell: An immune cell that recognizes an allergen as an invader, initiating the innate immune response.
- Eosinophils: White blood cells that contribute to inflammation associated with allergies and asthma.
- Immunoglobulin E (IgE): The type of antibody most instrumental in allergic reactions.
- Mast cells: Specialized cells found in the linings of the airways, the eyes, the gut, and certain layers of the skin. These cells can release histamine and other allergy mediators instrumental in the allergic response.
- Monocytes and macrophages: White blood cells that eat up debris in tissue and the bloodstream and alert T cells to the presence of antigens, playing a role in delayed hypersensitivity reactions.
- Neutrophils: The most abundant type of white blood cells in the body, designed to fight off infection and disease.
- Th1: A type of white blood cell that handles certain kinds of viral and bacterial infection.
- Th2: A type of white blood cell that helps eliminate certain parasites. In an allergic reaction, Th2 responds to substances that are not actually harmful.

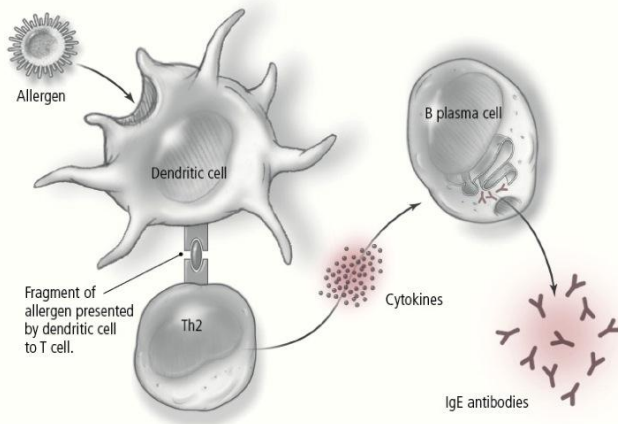
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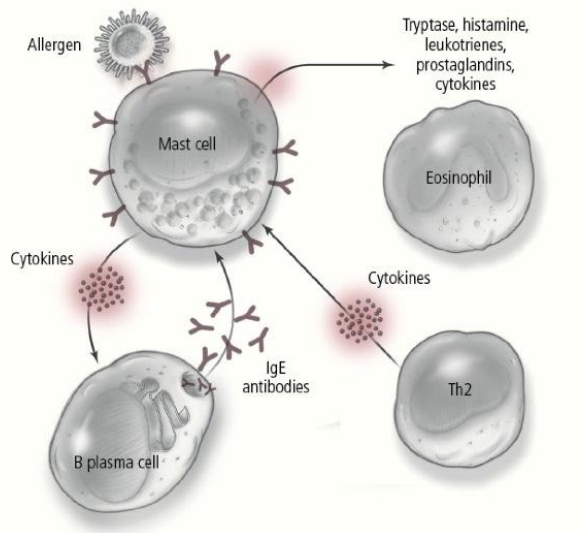
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Figure 1: Developing an allergy: A two-step process



1. First exposure: You produce antibodies that will recognize the allergen in the future.

Dendritic cells, a type of immune cell that monitors the body tissues for allergens and other foreign materials, begin the innate immune response. These cells recognize an allergen as an invader, gobbling it up from wherever it landed (the lining of your nose, for example). They process the invader and display a recognizable portion as an antigen, which activates Th2 cells. This sets off a complex chain reaction involving the release of cytokines, chemicals that signal B cells to produce IgE antibodies; these antibodies will be ready for the allergen the next time.



2. Subsequent exposures: Your IgE antibodies recognize the allergen and trigger an allergic response.

The IgE antibodies that were created on first exposure to the allergen lie in wait on the surface of mast

Was It Something I Ate? Understanding food allergies

Longwood Seminars, March 31, 2015

cells, immune system cells found in the mucous membrane layers at the entry points of the body (such as the nose, eyes, lungs, and gut). When an allergen meets up with the IgE antibodies, the mast cell releases immune system chemicals such as tryptase, histamine, leukotrienes, and prostaglandins.

Mast cells also produce their own cytokines that stimulate B cells to produce more IgE, arming more mast cells so that next time the allergen comes along, the reaction is even stronger. At the same time, other cytokines recruit other immune cells, known as eosinophils, to the site of the allergic response, setting up local inflammation.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Understanding and Controlling Your Allergies*, available at hvrd.me/JKiPT.

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Have GMOs contributed to the rise in allergies?

There is some discussion about the role that genetically modified (GM or GMO) food might play in the escalating incidence of food allergy, food intolerance, and digestive illnesses. Genetically modified food is the result of scientists inserting DNA from another species into the plant—typically corn, soybeans, canola, cotton (the source of cottonseed oil), and sugar beets—to make the plant resistant to insect damage, viral infections, and certain herbicides.

The FDA says that the GMO foods it has evaluated through its voluntary consultation process are not more likely to cause an allergic or toxic reaction than foods from traditionally bred plants. When new genetic traits are introduced into plants, the developer evaluates whether any new material could be allergenic or toxic.

Yet some consumer groups are questioning whether there's a link between the dramatic rise in allergies in the past two decades and the introduction of GMO soybeans into the U.S. food supply in 1996. GMO soy is now ubiquitous in many processed foods. While the timing does not prove any causal link between GMO food and allergies, these groups say it merits research. However, there is currently a lack of long-term independent scientific studies published in peer-reviewed journals that examine how ingesting GMO foods affects humans.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Understanding and Controlling Your Allergies*, available at hvr.d.me/JKiPT.

Cottage Industry

Humans and the life forms they host are in it together

by Susan Karcz



You are a walking ecosystem. And you are not alone. Ever.

Microbial life teems on, and in, your body. If you're healthy, these life forms live in harmony with you in a stable and balanced system, where host and guest alike contribute to the rhythm and hum of a cooperative community.

Humans and microbes have coevolved to a point of mutual benefit—we need each other. The number of microbial cells in our bodies outstrips the number of human cells by about ten to one. And while the human genome contains approximately 30,000 genes, the microbial genome, the microbiome, is made up of more than four million genes. We are more “them” than “us.”

There's a growing interest in studying the ecosystem that is the human microbiome, and it's more than a research trend. It may herald a shift in how we think about human health and medicine and our place in the natural world.

Compartment Living

The human microbiome comprises organisms and their genomes—bacteria, viruses, fungi, and other single-celled eukaryotes—that occupy several body habitats: the gut, mouth, nasal passages, vagina, and skin. Each of these habitats features organisms, collectively the microbiota, that have adapted to, and even shaped, their particular niche. Not only is the mix of microbes living in the gut different from that on the skin, but there are microhabitats within habitats. The microbiota just inside your nostril, for example, differ from those living deeper in the passageway inside the sinus cavity. And that's not all. The continual interplay between a person's genetic makeup and the surrounding environment also influences how a microbiome is populated.

A healthy microbiome is highly diverse, stable, and resilient: diverse, in order to avoid species domination and to provide a wide set of functions; stable, in order to

keep body functions running smoothly; and resilient, in order to recover from the inevitable assaults. Disturb it and it will likely recover, but it will never be the same.

The microbes that live with us are active community members. And as you might find in any community, some members contribute to the greater good, some remain neutral, and some may become harmful given certain conditions. Among other functions, microbes help digest and extract nutrients from food, regulate metabolic processes, guide immune system responses, and protect against invasions by pathogens. In a healthy person, the beneficial bacteria help create a stable environment that promotes and protects the health of the human host.

In fact, these microbes adapt to, and perhaps even determine, the biological properties of the human host. David Relman '81, the Thomas M. and Joan C. Merigan Professor in the Departments of Medicine and of Microbiology and Immunology at Stanford University and chief of infectious diseases at the VA Palo Alto Health Care System in California, describes the microbiome as a “complex set of communities of microorganisms that have chosen the human body as their home and that operate as a unit, as most communities do. By doing so, they are furthering their own beneficial purposes, both for themselves and for their host.”

Home Grown

The microbial species that call us “home” operate in a symbiotic relationship with their hosts in an ancient contract revised over eons of coevolution. In this mutually beneficial system, humans provide food and shelter while the microbes provide protection from harmful invaders and help with essential body functions.

Infants are born with almost no microbiota: They acquire some during birth, although the mix and type of microbes differ depending on method of delivery. Babies born vaginally acquire microbiota from their mothers during the trip through the birth canal, whereas babies born by cesarean delivery receive their introductory dose of microbiota from contact with their mother’s skin. This first exposure is the initial step in developing an immune system and helps determine the composition of an infant’s microbial community. These early differences diminish in importance as other influences, such as diet, health, and geographic location, begin to hold sway and shape a child’s microbiome.

A microbiome can also assemble, or reassemble, after a disturbance, such as treatment involving an extended or repeated courses of antibiotics. Such therapy may well eradicate a targeted pathogen but, as collateral damage, also knocks out some of the beneficial or benign microbiota. If the community is resilient, the microbiome may return to its pre-disturbance state, but this recovery takes time and is far from guaranteed.

And, under the right conditions, an invasive pathogen can take advantage of a vulnerable community to gain a foothold in, or attempt to colonize, the host. Part of the microbiome’s responsibility is to help defend its host from pathogens by making

surface environments inhospitable to invading species, a process referred to as “colonization resistance.”

“The particular difficulty for organisms that don’t normally live with us, ones that are actually pathogens from the outside world,” says Katherine Lemon ’01, an HMS assistant professor of pediatrics at Boston Children’s Hospital and the Forsyth Institute, “is that they not only have to deal with our defenses, like our immune system, they also have to come into an established microbial community.”

While the immune system can generally withstand such assaults, if the pathogen is especially aggressive or plentiful, the invasion may succeed and alter the mix of microbiota.

“Understanding the means of microbiome assembly,” says Relman, “is key to managing pathogen invasions and to thinking of human health as a collective property of the human body and its associated microbiome.”

Balancing Act

The immune response presents a formidable defense, and if the response subsides after a threat has passed, all is well. Sometimes, however, the response continues without reason, a characteristic of autoimmune disorders such as Crohn’s disease, ulcerative colitis, multiple sclerosis, psoriasis, type 1 diabetes, and asthma.

In the United States and other developed countries, the incidence of autoimmune diseases has been on the rise over the past 30 to 40 years, a situation some experts attribute to changes in the microbial balance in humans. A number of factors, such as overuse of antibiotics and of hormones, both in the animals we eat and in therapeutics, have, according to Dennis Kasper, William Ellery Channing Professor of Medicine and an HMS professor of microbiology and immunobiology, “affected the microbiome and caused a shift so that now we don’t have the organisms that were properly balancing our immune system and preventing us from getting some of these diseases.”

Ebbs and flows in the balance of an individual’s microbiota may help explain the cyclic nature of some autoimmune diseases in humans. But it’s not just that gut bacteria become imbalanced. “You also have to have a genetic susceptibility,” says Kasper. “The fact that the bacteria become imbalanced, and you’re genetically susceptible, can partly explain why conditions like multiple sclerosis occur in individuals and why the diseases are relapsing and remitting in nature.”

People living in developed countries may be becoming less dependent on coevolved gut microbiota. Some researchers, including Kasper, think that the increase in autoimmune disorders, sometimes called microbiome-based disorders, could be a consequence of the greater vulnerability of the host–microbiota relationship partly caused by trends such as eating highly processed foods and living in overly hygienic environments.

Seed Catalog

Ecological models have long used the metaphor of a symbiotic, mutually beneficial, and dynamic community to frame discussions of the degree of ecosystem health. The idea of the human body as an ecosystem is gaining traction in microbiome research, with human health being viewed as a “service” delivered in part by resident microbiota.

“All you have to do,” says Relman, one of the principal proponents of this concept, “is borrow the language of ecologists and read their literature, and suddenly you’re looking at the world in a very different way. And the implication of that new perspective for medicine is that we are going to have to develop a whole different set of tools dedicated to restoring and maintaining the beneficial properties of the microbiota.”

Some of these future tools may include using environmental perturbation as a therapy. You could, says Lemon, “introduce an organism and use it to create a colonization blockade, where you have a harmless organism occupy the same niche as a harmful one, for instance, *Staphylococcus aureus*. And allow the harmless one to take hold.” This replanting and reseeded approach is microbiota management—stewardship to promote human health.

Fecal transplantation, another example of replanting and reseeded, is being used in humans now, although only in people who are sickened by recurrent *Clostridium difficile* infections. Although it has enjoyed some success, Kasper says that “the problem with probiotics or fecal transplants is that the introduced organisms will potentially still be there after the disease has ended. And we don’t know what their long-term effects are.”

Microbiome research is in a honeymoon period, when the excitement of discovery peaks. There is a luster to the symbiosis between humans and our resident microbiota that many hope will be burnished rather than tarnished as researchers gain a better understanding of how human health is affected by our own actions and those of our nearest neighbors.

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My microbes

Insights on host-specific bacteria may aid study of autoimmune disorders

June 22, 2012 |

By David Cameron, Harvard Medical School Communications

Gut bacteria's key role in immunity is tuned to the host species, researchers have found, suggesting that the superabundant microbes lining our digestive tract evolved with us — a tantalizing clue in the mysterious rise in human autoimmune disorders.

A new study reports that the superabundance of microbial life lining our GI tracts has co-evolved with us. These bacteria, which are essential for a healthy immune system, are ultimately our evolutionary partners.

This study, the first to demonstrate that microbes are specific to their host species, also sheds light on the "hygiene hypothesis." According to this idea, increasingly hyper-hygienic environments might be contributing to a rise in childhood allergies, as these beneficial host-specific microbes are hindered by a plethora of antibacterial home products and cleaning chemicals.

"For every cell in your body that is you, that contains your specific genetic information, there are approximately nine foreign bacterial cells, primarily in your digestive tract and even on your skin," said Dennis Kasper, Harvard Medical School professor of microbiology and immunobiology and senior author on the paper. "From the viewpoint of cell count, every human being is 90 percent microbial. Now we've found that these bacteria, which we need for optimal health, are species-specific."

The paper appears in the June 22 issue of *Cell*.

That 500 to 1,000 microbial species inhabit mammals has long been documented. Researchers have suggested that when it comes to digestion and other metabolic activities, the particular species of bacteria may not be significant provided the bacteria contain specific, helpful genes. A bacterium that breaks down food in a mouse gut can probably do the same in a human.

But the microbes that fortify our immune system have not been studied in this regard. Are they functionally unique, or would any species suffice?

Hachung Chung, a postdoctoral researcher in Kasper's lab, studied two groups of mice, both bred to lack microbial flora. For one group, she introduced microbial species that are natural to mice, and for the second, she introduced human microbes.

For both groups of mice, an equal quantity of microbes, and an equal diversity of species, soon flourished in their digestive tracts.

But despite this apparent similarity, when Chung examined the intestinal tissue, including intestinal lymph nodes, she discovered that the mice with humanized microbes had surprisingly low levels of immune cells, levels equivalent to mice lacking intestinal bacteria altogether.

“Despite the abundant and complex community of bacteria that were in the human flora-mice, it seemed like the mouse host did not recognize the bacteria, as if the mice were germ-free,” said Chung.

Chung repeated the experiment, only this time populating a third group of mice with microbes common to rats. This new group showed the same immune system deficiency as the humanized mice. “I was very surprised to see that,” Chung said. “Naturally, I would have expected more of a halfway response.”

In a third experiment, Chung infected all the mice with salmonella. Almost from day one, the mice with human flora showed significantly higher levels of salmonella in their system than the mice with normal flora. The immune systems of the mice with human flora were effectively incapable of fending off the pathogenic bacteria.

“This raises serious questions regarding our current overuse of antibiotics, as well as ultra-hygienic environments that many of us live in,” said Kasper. “If the bacteria within us is specific to us and necessary for normal immune system function, then it’s important to know if we are in fact losing these vital bacteria. Are we losing the bacteria we have co-evolved with? If that is the case, then this is yet further evidence supporting the idea that the loss of good bacteria is partly to blame for the increased rates of autoimmunity that we are now seeing.”

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When Good Immune Systems Go Bad

Posted on March 16, 2014 by SITNFlash

Food allergies are a growing problem around the world. These days, if you do not personally suffer from an allergy, you almost certainly know someone who does. Currently, around 3-7% of children have a food allergy—about a 50% increase since 1997 [1, 2]. For many people, allergies are little more than a nuisance, but for others, an allergic reaction can be life threatening.

What is a Food Allergy?

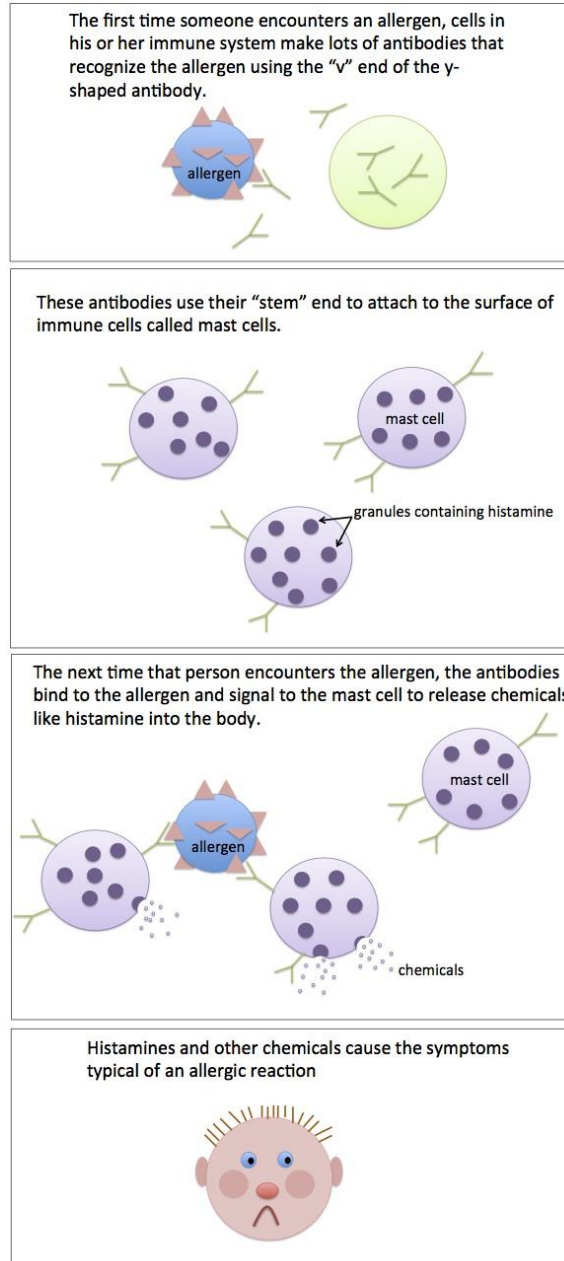
The term “allergy” is often used fairly loosely to describe any adverse reaction to a food. A true allergy, however, is unique in that it is caused by the immune system reacting to a specific protein – an allergen – as if that protein were a threat to the body. Food intolerances are often confused with food allergies, since many of the symptoms of a food intolerance are similar to those caused by an allergic reaction. However, a food intolerance usually results from the inability to digest certain substances due to enzyme defects, not an immune reaction. For instance, lactose intolerance results when an individual does not have sufficient levels of lactase. Lactase is an enzyme required for the digestion of lactose, a sugar found in milk products. In the case of lactose intolerance, the symptoms may be similar to those of a milk allergy, but the immune system is not involved.

What Causes an Allergic Reaction?

If you suffer from an allergy, you can blame it on two main culprits: mast cells, which are cells located throughout the body that are involved in normal immune responses, and a special type of antibody, called IgE. Antibodies are Y-shaped proteins produced by cells in the immune system that recognize proteins on pathogens or other harmful foreign substances invading the body in order to disarm them or target them for destruction by other components of the immune system. The antibody recognizes a certain protein or part of a protein on the foreign object and attaches to the object. IgE antibodies are one of five types of antibodies, all of which have different roles in immune response. The main function of IgE antibodies appears to be to defend the body against parasites, such as the parasite that causes malaria.

No one has a reaction the first time they encounter an allergen. Instead, when a person first meets an allergen, the body makes lots of IgE antibodies that recognize a protein on the allergen. Then the “stem” side of the newly made Y-shaped antibodies attaches to a mast cell. The next time the person comes in contact with the same allergen, these IgE proteins immediately recognize it and signal to the mast cells to release several chemicals, histamine in particular, that are involved in the inflammatory response. These chemicals increase blood flow, allow the spaces

between cells to fill with fluid, and cause local nerve endings to signal pain. When the immune system is responding to a pathogen, increased blood flow is critical for allowing white blood cells in and out of the site of infection, and fluid secretion is important for ridding the body of the intruder. This is great when your body is really under attack by a parasite, bacteria or a virus. However, the release of these chemicals in response to a harmless substance results in the host of symptoms we see during an allergic reaction, such as swelling, itching, coughing/sneezing, rash, runny nose, diarrhea and vomiting (see figure).



What Makes an Allergen an Allergen?

All proteins have the potential to be allergens, but in reality, only a small percentage of proteins cause allergic reactions. In fact, up to 90% of allergic reactions to food are caused by proteins in only eight foods: milk, peanuts, tree nuts, shellfish, soy, wheat, fish, and eggs. Unfortunately, scientists don't know why some proteins are more likely to cause an allergic reaction. Even when researchers looked at the structures of common allergenic proteins, they weren't able to find any similarities. One possibility is that allergenic proteins may be more likely to form clusters of two or more of the same protein, and it is this aggregation that tells the body to attack. On the other hand, researchers do know that many allergenic foods contain more than one allergenic protein. For instance, soy actually contains 15 allergenic proteins, which may help explain why soy is a very commonly identified allergen.

The question of what makes a protein allergenic is just one of many that researchers are investigating. Researchers are also trying to determine why some people differ in their susceptibility to allergies and why allergic reactions vary in their severity. Scientists do know that allergies are often passed down from your parents. Additionally, if a person is exposed more frequently to an allergen, the reaction tends to be less severe. Scientists also have a few ideas as to why allergy cases are rising, but much research remains to be done to answer this question. The ability to predict what proteins will be allergenic and who might be most susceptible would be especially useful in drug development and the creation of genetically modified foods. More critically, understanding why allergy rates are increasing might allow us to make adjustments in our lifestyles in order to prevent the development of allergies in future generations.

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Bacterial Reporters Get the Scoop

Engineered bacteria pave the way to living diagnostics and therapeutics

By KRISTEN KUSEK

March 17, 2014

It's a jungle in there. In the tightly woven ecosystem of the human gut, trillions of bacteria compete with one another on a daily basis while they sense and react to signals from the immune system, ingested food and other bacteria.

Problems arise when bad gut bugs overtake friendly ones, or when the immune system is thrown off balance, as in Crohn's disease, celiac disease and colorectal cancer. Doctors have struggled to diagnose these conditions early and accurately. Now a new, engineered strain of *E. coli* bacteria could deliver status updates from this complex landscape to help keep gastrointestinal diseases at bay.

As reported in Proceedings of the National Academy of Sciences, the new strain non-destructively detected and recorded an environmental signal in the mouse gut and remembered what it "saw." The advance could lead to a radically new screening tool for human gut health.

The key to turning *E. coli* into gut reporters was to insert a well-known genetic switch that flips when it senses a specific environmental cue. This switch confers on the cells the ability to "remember" what they sense for up to a week—long enough for scientists to recover fecal samples and test whether the switch has flipped.

"This achievement paves the way toward living monitors programmed using synthetic gene circuits," said Pamela Silver, senior author on the study, who is the Elliott T. and Onie H. Adams Professor of Biochemistry and Systems Biology at Harvard Medical School and a core faculty member at Harvard's Wyss Institute. "It could lead to new diagnostics for all sorts of complex environments."

Silver's team included James Collins, who is also a Wyss core faculty member and a professor of bioengineering at Boston University, as well as other collaborators from the Wyss Institute, Harvard Medical School and Boston University.

The approach Silver's team took runs counter to the prevailing dogma in synthetic biology, which is to design genetic systems that drive cell behavior from scratch, said study coauthor and Wyss Institute senior staff scientist Jeff Way. On the other hand, Way said, "Nature has a tried-and-true blueprint for memory systems if you know where to look. Why not just accept Nature as it is, and develop the system from there?"

The genetic switch the team inserted in *E. coli* came from lambda phage, a virus that commonly attacks this bacterium.

After invading *E. coli*, lambda typically lies low, living in a stealth mode called lysogeny in which its DNA simply hangs out in the *E. coli*'s genome. But when the bacterium's DNA is damaged—and only then—the switch flips, instructing the virus to enter a mode called lysis in which it multiplies inside the cell and breaks through its membrane in a kind of microbial explosion.

“This is a very stable system in Nature,” said lead author Jonathan Kotula, a postdoctoral fellow at HMS who is also affiliated with the Wyss Institute. “We knew the lambda switch would be a great candidate for the memory element, and we simply tweaked it to meet our needs.”

The cells with the engineered lambda switch would not become lytic under any conditions. Kotula and the rest of Silver's team used standard molecular genetic tools to rig the switch so it turned on only in the presence of an inactive form of the antibiotic tetracycline.

In laboratory experiments, the switch turned on within a few hours of exposure to the antibiotic—and stayed in this “on” state inside *E. coli* for a week or more, even as the bacteria grew and divided. In short, the cells “remembered” that they had seen that molecule in the gut.

“It was truly shocking how cleanly the experiments worked,” said Jordan Kerns, a Wyss Institute postdoctoral fellow.

But to function as a living diagnostic, the engineered *E. coli* also had to survive their trip through the gut intact, which meant they had to compete effectively against rival gut microbes.

The engineered strain worked fine in laboratory experiments, but gradually disappeared when the team introduced it into the gut of the mouse itself. It turned out that it had been outcompeted by the animal's native gut bacteria. The team did not fret in the face of this result because they knew that the classical strain of *E. coli* they used had lived only in the laboratory since the 1940s—losing its ability to compete in the real world, particularly in an environment as challenging as the mammalian gut.

They tackled the problem by isolating a native strain of *E. coli* from the mouse gut, then engineering its genome to incorporate the switch. The switch in the cells flipped within hours, as it had before, and the cells “remembered” for about a week that they had seen the antibiotic in the gut, Kotula said. Moreover, the population stabilized within the gut, holding its own in the presence of other bacteria.

The team envisions a day when a doctor would give a patient a strain of engineered bacteria as a diagnostic, much as they give a probiotic today. The strain would be rigged to monitor the gut for any number of conditions from inflammation to disease markers. At a follow-up visit, the patient would submit a stool sample, and

medical technicians would collect E. coli from the sample and analyze it. Only if the switch (or switches) were on would the doctor perform more invasive tests such as an endoscopy or a colonoscopy.

For now, the team is focusing on genetically tweaking the memory element of their system so the cells remember for even longer periods of time, and engineering it so the switch flips when it senses other chemical signatures as well, such as those of cancer or parasites. In the longer term, their engineered bacteria could sense a disease state and work with other engineered genetic circuits that can produce a specific drug on command, thus producing a dynamic therapy.

“Our increasing appreciation of the role of the microbiome in health and disease is transforming the entire medical field. The concept of using the power of synthetic biology to harness microbes that live in our gut to develop living diagnostic and therapeutic devices is a harbinger of things to come, and Pam’s work provides the first proof-of-principle that this is a viable and exciting path to pursue,” said Wyss Institute Founding Director Don Ingber.

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“Gluten, Dairy, Nuts, Oh My! Why are Food Allergies on the Rise?”

A panel discussion created by the Cambridge Science Festival in 2013.

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Ekaterina Pesheva

June 18, 2012

<http://www.hopkinschildrens.org/Antibacterials-in-Personal-Care-Products-Linked-to-Allergy-Risk-in-Children.aspx>

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Breastfeeding and the Development of Allergic Disease

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<http://www.massgeneral.org/children/news/newsarticle.aspx?id=2991>

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October 3, 2014

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