When you're allergic to your Rx

Through drug desensitization at BWH, patients safely receive the life-saving medications they need.

Daniel Chong-Ho Kim, MD, monitors Brenda Bouret in the Medical Intensive Care Unit as she undergoes desensitization to carboplatin. Bouret responded well to the drug after her ovarian cancer was diagnosed seven years ago but had an allergic reaction to it following the tumor's recurrence in 2002.

ONE CRISP DAY IN NOVEMBER 2001, 61-year-old Kristen Schiff* eased into a reclining chair as an oncology nurse prepared her for her first intravenous infusion of the drug Taxol, a mainstay of chemotherapy for patients newly diagnosed with ovarian cancer. Reassured by the sound of caregivers' purposeful bustle in the warm, brightly lit outpatient infusion room, Schiff relaxed as her treatment got under way.

But as the clear liquid began trickling from the plastic IV bag overhead into a vein in her arm, something felt strange. Schiff's face grew hot and red. Her heart started pounding like a fist against her sternum, and her chest felt tight and heavy, "as though someone had dropped a book on it."

With a swift twist of the stop-cock, Schiff's attending nurse cut off the flow of Taxol and called for help. Caregivers in white lab coats came running, but within two minutes, Schiff was already feeling better: The heat in her cheeks dissipated, and her blood pressure fell back to normal. Tests confirmed that her heartbeat had resumed its clocklike rhythm.

Schiff learned she had just had an allergic reaction to Taxol. With less than a cubic centimeter of the drug in her bloodstream, her immune system had staged an all-out rebellion, she says, "the fastest reaction my nurse had ever seen."

**not this patient's real name*

AT MOST U.S. MEDICAL CENTERS, the 3 percent of patients who prove allergic to Taxol must forego it. But Schiff's oncologist at Dana-Farber Cancer Institute, Ursula Matulonis, MD, knew just whom to call for help. She contacted Brigham and Women's allergist-immunologist Mariana Castells, MD, PhD, an expert on systemic allergic reactions, the kind often associated with shellfish, peanuts and bee stings.

In the last decade, Castells has earned a reputation for diagnosing, treating and working with patients to head off these total-body immune reactions. Broadly defined by the term anaphylaxis—from the Greek "ana," against, and "phylaxis," prevention—these reactions are highly variable in intensity and can develop suddenly, without warning.

Symptoms of anaphylaxis often start with a restriction of a patient's air supply as the voice box swells, blocking the windpipe, and the lungs' airways constrict. As blood-oxygen levels fall, blood pressure plummets. The heart, struggling to pump blood throughout the body, goes into overdrive. The face flushes, and an itchy red rash called hives may blanket the skin. Acute abdominal pain also may ensue.

A highly effective, first-line treatment is an injection of the hormone epinephrine, or adrenaline, which restores blood-vessel tone and pushes blood pressure up. Wise patients with known anaphylactic allergies always carry an "epi pen," and use it at the first sign of trouble.

Allergic reactions represent 30 percent of all medication-related side effects. According to Brigham and Women's David Bates, MD, chief of the Division of General Medicine and a national authority on medical errors, "The majority of these are rashes. But severe allergic reactions, when the body has a massive reaction to a drug, can be life-threatening," he says.

Mariana Castells, MD, PhD, with desensitization patient Brenda Bouret.

Unfortunately, a person's risk can't reliably be discerned in his or her medical history. There is no test. A patient might take a medication without incident for years, then abruptly manifest an allergy to it. Genes and environment influence who is at risk.

"Given what we know today," Bates says, "we're unable to predict who will have an allergic reaction to a specific drug—unless we know they have already had a reaction to that drug or another in the same class."

Once a patient has experienced a reaction to a medication, she and her doctor must seek alternatives. The immune system does not often forget an allergy-causing substance, called an allergen, and may respond to it with an equal or greater intensity upon a subsequent re-exposure.

For Kristen Schiff, Taxol was a key weapon in the limited arsenal of drugs for ovarian cancer. Diagnosed at a pivotal point, just as her cancer had begun to spread, Schiff wanted to take advantage of every drug available.

FORTUNATELY FOR PATIENTS like Schiff, Castells has found a way around the drug-allergy dilemma. Building on reports since the 1950s on patients' responses to penicillin, Castells knew that minute infusions of the antibiotic appeared to fly under the immune system's radar, even in people known to be severely allergic to it. In the last five years, Castells has desensitized more than 100 patients by giving them tiny amounts of an allergy-provoking drug, then escalating the concentration over 6 to 12 hours until they have received the full dose.

Within the inpatient Medical Intensive Care Unit, where they can be very closely monitored, patients can safely receive a host of medications. Chemotherapeutic agents for cancer. Antibiotics, which combat infection. Aspirin, one of the most widely used drugs in the world, effective in preventing heart attack and stroke. Insulin, a hormone that converts blood glucose into energy. Even fertility drugs.

No one knows why desensitization works. But Castells and her colleagues have some theories. Their eyes are trained on the mast cell, for more than 50 years the favorite subject of K. Frank Austen, MD, leader of Brigham and Women's Research Section on Allergy and Immunology. A giant in these overlapping fields, Austen has trained Castells and scores of other outstanding physician-researchers.

Mast cells help guard the body against invasion. Like ubiquitous sentries, they are stationed wherever foreign organisms and proteins might enter the body, such as the skin, nose, mouth, lungs and gastrointestinal tract. They also populate the bone marrow and surround blood vessels.

When susceptible individuals first confront an allergen—be it pollen, cat dander or an antibiotic—their immune systems make antibodies called immunoglobulin E, or IgE, which are said to "sensitize" mast cells (see illustration below). When the mast cells re-encounter that same allergen at some later date, they "fire," spewing forth copious chemicals that under other circumstances are designed to be beneficial by subduing invading micro-organisms.

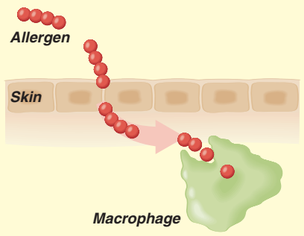
One of these chemicals, histamine, prompts blood vessels to leak, which leads to the swelling and itching so familiar to allergy sufferers. Also disgorged are molecules called leukotrienes and prostaglandins, which cause blood pressure to drop and airways to clamp down.

Researchers are looking for ways to tame the mast cell. To stop it from firing, Castells and others are hunting for molecules on the cell that act like brakes on a speeding car. "We know such brakes must exist, because when we mix mast cells with an allergen in a test tube, the mast cells start firing, then stop," Castells says. "What signal is telling them to stop?"

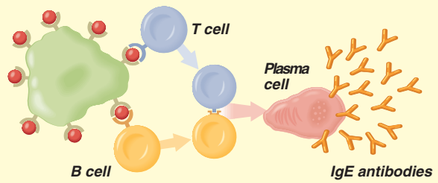
Castells suspects one or more brakes are engaged when patients are exposed to micro-doses of a drug during desensitization. To shine light on this mechanism, she plans to study cells in blood drawn from patients before, during and after their desensitizations.

Ready, set, fire: Extreme allergy

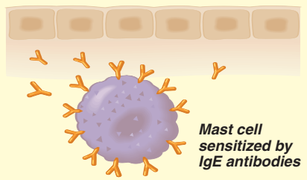
SENSITIZATION



An allergen invades the body through the skin, lungs, gut or other portal. Once inside, it is engulfed by immune scavenger cells called macrophages.

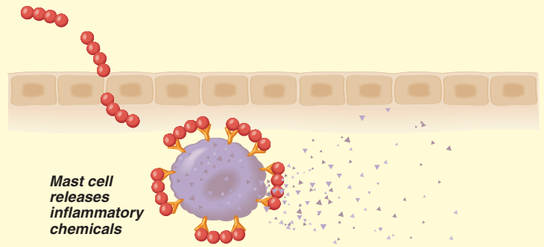


The macrophages chop the allergen into pieces and display the fragments on their surfaces. When a fragment docks with immune B and T cells in lymph nodes, the B cell is transformed into a plasma cell. In some individuals, the plasma cell makes antibodies called immunoglobulin E (IgE), which play a pivotal role in allergy.



IgE antibodies persist long after the allergen is gone, latching onto mast cells stationed in skin and other tissues. The mast cells are now "sensitized," ready to respond to any future encounters with the allergen.

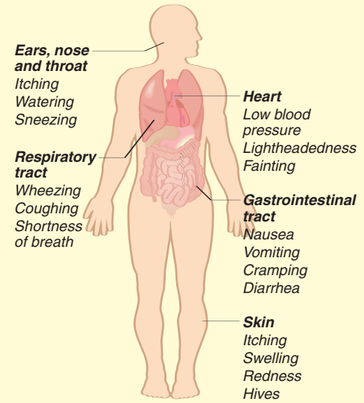
ALLERGIC REACTION



When the sensitized patient re-encounters the allergen weeks, months or years later, the allergen docks with IgE antibodies on mast cells. This prompts the mast cells to fire, spewing forth histamine, leukotrienes, prostaglandins and other inflammatory chemicals that cause allergic symptoms such as wheezing, shortness of breath, itching, redness and swelling, and hives.

ANAPHYLAXIS

Anaphylaxis results when mast cell chemicals flood the body, causing an array of acute symptoms. BWH researchers are studying the chain of molecular interactions involved in allergy as well as the genes that orchestrate them. Their goal: to design drugs that block these interactions.



Graphic ©Ed Wiederer

Meanwhile, Castells hopes to share news of her patient successes with other health care providers. Her efforts are timely, given the federal government's anti-bioterrorist plan to stockpile the antibiotic ciproflaxin, better known as Cipro, for possible use against anthrax. "Between 1 and 10 percent of the population will be allergic to Cipro," she says. "We need to be prepared to respond."

WHAT MATTERS MOST TO PATIENTS isn't how desensitization works, but that it does. Take Edouard Rocher, 70, who came to BWH in 2001 to have a stent inserted into a blocked coronary artery.

Severely intolerant of aspirin since his teens, Rocher now takes 325 mg daily, a strategy proven to ward off heart attack. A mainstay of cardiac care, aspirin thins the blood and retards clotting and inflammation. If Rocher forgets to take his aspirin for longer than 48 hours, he will need to be desensitized to it again, lest his system's radar set off a renewed attack on the drug.

Gail Demaine, 56, came to see Castells almost one year ago at the suggestion of her BWH neurologist, Howard Weiner, MD, who had put her on a regimen of cyclophosphamide to combat the debilitating symptoms of her multiple sclerosis. Before taking the drug, Demaine was using a wheelchair and could no longer write legibly or button her blouse. Cyclophosphamide reversed those symptoms, putting her back on her feet.

Two years later, Demaine developed a severe allergy to cyclophosphamide. Through desensitization, Castells was able to get her back on it.

"I'm elated," says Demaine, who found she could shuffle a deck of cards again even as she lay in her ICU bed. "Few doctors know how to do what Dr. Castells does." Today, she's back working as the associate dean of Student Life at a private school.

Kristen Schiff, too, feels lucky. Completing eight rounds of chemotherapy put her ovarian cancer into remission. "Dr. Castells and her team were a gift," she says.

Today, this busy woman—wife, mom to three grown sons and grandmother of three—is "loving every minute" of her life. She admits to a slight downturn in energy, however.

"I can do any one thing I did before; I just can't do them all," Schiff says with a laugh. "Instead of doing 12 things today, I'll do nine." u

Putting drug allergies into perspective

Patients often have black-or-white opinions about medications. Some view drugs as unnatural and take them sparingly, if at all. Others seek a pill for every ailment.

"To the medical profession, drugs are useful—a good thing," says Brigham and Women's allergist-immunologist David Sloane, MD, who with Mariana Castells, MD, PhD, cares for patients undergoing drug desensitization. "But in the general population, no single drug is all 'good' or all 'bad.' In some percentage of people, many drugs have side effects, including allergy."

When talking with patients, Sloane strives to dispel these common misconceptions:

MYTH 1 **"Drugs are beneficial for every patient."** ***Not so.*** Every medication approved by the federal Food and Drug Administration exerts a scientifically proven therapeutic effect. But given the tremendous variation among people—in their genetic makeup, body chemistry and lifestyles, including diet and exercise habits—a drug that works well for some patients may in others be marginally effective or unhelpful, or have negative effects. For example, aspirin causes an adverse reaction in about 2 percent of the population.

MYTH 2 **"Drugs aren't natural."** ***False.*** Many substances used as medications originate in the body, including hormones such as epinephrine, insulin and testosterone. Most drugs are derived from plants. For example, aspirin comes from the bark of the willow tree. Many antibiotics are made by fungi.

MYTH 3 **"Drugs are toxic."** ***Yes and no.*** Plants, fungi and other organisms produce chemicals to protect themselves from attack. Certain plant chemicals made to ward off insects have been harnessed and used therapeutically as drugs.

People depend on the toxic action of some drugs for their beneficial effects against disease. For example, they use chemotherapeutic agents to kill cancer cells and antibiotics to kill bacteria.

Often, the difference between a positive effect and a negative one lies in the dose. Almost every drug becomes toxic if the concentration is great enough. But every individual is unique: A concentration that is too great for one patient may be just right for a second, and too low for a third.

MYTH 4 **"My drug allergy will go away."** ***Maybe.*** The immune system has an uncanny ability to remember foreign substances and invaders, including drugs, thanks to specialized memory cells that launch an attack upon subsequent encounters. But because these cells generally die off after 10 to 40 years or more, immunologic memory can in some patients be lost. That's why vaccinations eventually lose their power.

Even a trained allergist-immunologist cannot necessarily predict whether a person's immune system has truly lost the ability to muster an allergic response to a particular substance. For safety's sake, patients should avoid drugs to which they have known allergies. Those at known risk for anaphylaxis are advised to carry information about their medication allergies in their wallet or purse and wear a MedicAlert bracelet.u

A strange tale of pecans and a jog around the park

IN THE WAKE OF AN ACUTE ALLERGY ATTACK, patients are often left scratching their heads, guessing at the cause. While drug allergies often crop up right under their physician's nose, it can be extremely difficult to trace an allergy to a particular food or other substance. Only with careful sleuthing will patient and physician pinpoint the source of trouble.

Take 43-year-old Gena Brown. Her nemesis turned out to be an ill-timed combination of nuts and exercise.

On a glorious fall day in 2001, Brown ate a salad sprinkled with pecans, put on her running shoes, and buckled her three children into the car for a trip to the playground. As the kids sprang for the jungle gym, she set off for a run around the nearby track.

Rounding a turn, Brown felt her eyes begin to swell. Hives suddenly covered her hands.

"I thought, 'Maybe it's the powder on the grass' "—an allergic reaction to a weed-killing chemical. Or was that a bee sting she felt on her thigh a minute ago? "I said to the kids, 'We have to go. Now.' "

Brown drove to the home of a friend, who took one look at her and called 911.

"I blow up like a balloon. I can't talk. Alien skin is covering my body," says Brown, reliving the episode. "The EMTs are hitting me with an epi pen. Meanwhile, I can't breathe."

Allergy patient Gena Brown with children (upper left to right) Jake, Jordan and Kendall

Watched for three days in the ICU at a suburban hospital, Brown was soon back to normal, but shaken. What had caused her anaphylaxis? She'd had hay fever before, for which she had taken an over-the-counter medication, nothing stronger.

Doctors referred her to Brigham and Women's allergy specialist Mariana Castells, MD, PhD, who led Brown through a review of her family and medical history. Together they reconstructed events that led up to the allergy attack. Where had Brown been that day? What had she eaten?

In a series of office visits, Castells injected tiny amounts of various substances—bee venom, pecans like those from her lunchtime salad—under Brown's skin. The pecans raised a reddened lump, the hallmark of allergy. But they weren't the whole story.

It was in 1984 that Brigham and Women's Albert Sheffer, MD, first described the phenomenon of exercise-induced allergy. In a paper in *The Journal of Clinical Allergy and Immunology*, he and K. Frank Austen, MD, head of the Research Section on Allergy and Immunology at BWH, described a group of athletes who had experienced anaphylaxis in association with exercise, typically after consuming food, usually wheat. Sheffer tested the theory, putting these patients on a treadmill—first on an empty stomach, then after snacking on the suspected allergen. In each case, a link emerged between food, physical exertion and an allergic response.

Sheffer and others saw that patients with food-and-exercise allergies could still eat as they pleased and exercise afterward—as long as they waited four to six hours before exerting themselves.

Today, researchers have a theory to explain the food-exercise-allergy link. "We suspect that when people exercise, the metabolics of digestion change," says Sheffer, a nationally recognized researcher and the former clinical director of Allergy at BWH.

"A different set of enzymes are released into the gut. They break down food—let's say wheat—into a novel form. A small percentage of people make IgE antibodies to it and develop a severe allergy.

"It's difficult to test this theory in patients because of the risk of anaphylaxis," he notes. "But one could begin with test-tube experiments."

The solution, meanwhile, for patients like Gena Brown? Avoid exercising for several hours after eating. And always exercise with a friend, who can give epinephrine if needed.

Today, Brown can have her pecans and exercise, too.

"It's a wonderful thing," says this busy mom, who runs 15 miles a week. "If I couldn't work out, I'd go crazy." u

Doctors in the lab, scientists in the clinic

Translating today's test-tube discoveries into tomorrow's therapies

©Frank Siteman

Left to right: K. Frank Austen, MD, leader of the Research Section on Allergy and Immunology, with colleagues Joshua Boyce, MD, Mariana Castells, MD, PhD (seated), Jonathan Arm, MD, and Albert Sheffer, MD, emeritus clinical director of Allergy.

OUR PICTURE OF THE PHENOMENON we call an allergic reaction grows sharper every year. Mast cells are in the thick of it. So are dozens of other immune-cell players, from basophils and eosinophils to T cells.

Normally, these immune players have vital roles in the body's defense. How is it, then, that they sometimes overreact and make us miserable?

Why do we break out in a rash when we sample shrimp? By what means can something as wholesome as peanut butter send us, wheezing, to the emergency room? How does asthma take our breath away?

A good deal of what is known about the immune system's machinations in allergic diseases comes from a laboratory headed by K. Frank Austen, MD, director of the BWH Research Section on Allergy and Immunology. Austen has spent over half a century unmasking the mysteries of the mast cell and the proteins it disgorges. His focus is a family of lipid molecules called the leukotrienes. One of these, LTC4, is the principal cause of the airway-muscle constriction, swelling and mucous secretions that endanger asthma sufferers.

Members of Austen's lab are practitioners of "translational research"—that which translates discoveries made at the laboratory bench into new therapies. Moving from the lab to the clinic and back, these physician-scientists blur the line between those two worlds, expanding medicine's understanding of allergy, anaphylaxis, asthma and other immunologic diseases.

In the lab, they dig for the root causes of disease, immersed in studies of immune cells and their governing genes and proteins. While caring for patients, they observe how diseases progress, which treatments work and which fall short.

The partnership between Austen and BWH Emeritus Clinical Director of Allergy Albert Sheffer, MD, underscores the importance of bridging clinic and lab. For more than 30 years, the two have collaborated in developing asthma medications. In the late 1990s, for example, Austen's discoveries provided the blueprint for a new class of drugs called leukotriene inhibitors. Sheffer and other clinicians moved the new treatment through clinical trials into patients' hands.

Their colleague, Joshua Boyce, MD, a pediatrician by training, is also intrigued by asthma, the most common cause of emergency-room visits and hospitalizations in children. To better understand the disease, he came to Austen's lab in 1992. "As time went on, I realized how much I really wanted to do lab work, which was changing the way I looked at disease and my whole level of excitement and interest in medicine," he says.

Boyce is fascinated by the way mast cells are goaded into both over-firing and multiplying by immune-cell-signaling chemicals called cytokines. He is searching for mast-cell genes that are switched on by cytokines. Ultimately, he hopes to find ways to block this process, which is key to diseases such as asthma, hay fever and eczema. Boyce draws inspiration from his young patients, whom he sees two evenings a week.

Last year, Boyce's work got a boost from a grateful patient's family. Their gift of $500,000 has provided funding for a data manager and other expenses, freeing Boyce to design new experiments.

Fellow lab member Jonathan Arm, MD, sees patients one day a week. The bulk of his time is spent tracking in reverse the pathway of leukotriene formation, identifying protein links in that chemical chain reaction.

Arm succinctly argues the need to keep one foot in the lab, the other in the clinic. "As we tease out the process," he says, "we identify new targets for therapeutic intervention." u

HELP COMBAT ALLERGIC DISEASES

Your contributions advance important work in Allergy and Immunology at Brigham and Women's Hospital.

The Albert Sheffer, MD, Professorship in Medicine. Your gift to this professorship, named in honor of a distinguished physician-researcher, will provide salary support in perpetuity for tomorrow's leaders in clinical allergy. An additional $700,000 is needed to meet the $2.75-million goal.

Clinical and translational research. Your donation will further research in drug discovery, drug desensitization, quality-of-life studies and other initiatives that impact patients' health.

Basic research. Help fund investigations of the pathways by which allergens cause acute symptoms seen in anaphylaxis, asthma, and chronic immunologic diseases such as eczema.

Residency and fellowship training. Broaden opportunities for young physicians to answer pressing questions in the lab or clinic.

For more information, contact Joan Freeman, director of Principal and Major Gifts, at (617) 732-5008 or jfreeman1@partners.org.