MEDICINE

San Francisco Examiner

On the cutting edge of allergy research

For the first time, several real research advances may lead to better control of allergies — finally

By Margie Patlak
SPECIAL TO THE EXAMINER

BASIC RESEARCH on allergies has taken some impressive strides recently that suggest new and more effective treatment avenues for the one out of every six Americans who, according to the National Institute of Allergy and Infectious Diseases (NIAID), are plagued with sneezing, wheezing and other allergy miseries.

It's an exciting time to be in allergy research, according to scientists, because the pace of discovery has stepped up so dramatically.

The new treatments include drugs to counter the actions of other compounds besides histamines, which foster allergy symptoms. Others target steps further up in the chain of events to prevent an allergic response from ever occurring.

In an allergic reaction, bodily defenses against invaders go overboard and attack normally harmless substances, such as pollen, dust, mold or animal dander. When allergic persons first come into contact with these allergens, they make large quantities of antibodies called immunoglobulin E (IgE). Like sentries, these IgE molecules lodge themselves in the IgE receptors that dot the surface of certain immune system cells called mast and basophil cells. The next time the enemy allergen bumps into IgE housed in the receptors, it triggers these cells to spill out powerful chemicals such as histamine, which cause allergy symptoms like sneezing, congestion and itching.

The Holy Grail of allergy research

If IgE couldn't lock onto the receptors on mast and basophil cells, however, an allergic response would never ensue. Figuring out the structure of the IgE receptor in order to concoct drugs that block it, consequently, has become the Holy Grail of allergy research. Last January Jean-Pierre Kinet and his colleagues at the National Institute of Arthritis and Musculoskeletal and Skin Diseases in Bethesda, Maryland reported that they had pinpointed the structure of the IgE receptor. The next step will be to shape proteins to fit into the receptor and block IgE from binding to mast and basophil cells.

"If this strategy works," says Michael Kaliner of NIAID, "it would be a terrific way to approach the disease. Mast cells release more than 25 different compounds that foster allergy symptoms, and you can't counteract them all. You're much better off stopping the allergic reaction from starting."

Another allergy battle tactic researchers are toying with is to selectively kill or paralyze mast and basophil cells. To do this, investigators are trying to hook on to IgE poisons or compounds that prevent these cells from releasing their contents. Because IgE only binds to mast and basophil cells, the IgE complexes would only damage the cells responsible for allergies. "This tactic is embryonic but very promising," Kaliner says.

At last, *researchers have learned enough about the human response to allergens that they may be able to block it on several levels at once.*

Allergy researchers are also diligently searching for drugs that can prevent mast cells from releasing their misery-causing cargo, even when primed by an allergen hobnobbing with IgE molecules lodged in their receptors. A number of drugs, including several antihistamines, do this in the laboratory, according to Kaliner, and are currently being tried on humans in clinical trials. The preliminary results from some of these trials are quite promising, he says.

Also promising are drugs that counter compounds called leukotrienes, which Lawrence Lichtenstein and his colleagues at Johns Hopkins University in Baltimore discovered are released by mast cells during an allergic response. Drugs aimed at countering leukotrienes are faring well in preliminary clinical trials, Lichtenstein says.

Preventing key enzyme action

Allergy drugs are also being modeled after powerful compounds called antiflammins. These pro-

[See ALLERGIES, D-3]

EXAMINER FILE PHOTO

New frontiers *in allergy research include drugs to counter the actions of other compounds besides histamines. Others target steps further up in the chain of events to prevent an allergic response from ever occurring.*

◆ *ALLERGIES from D-1*

On cutting edge of allergy research

teins prevent the action of a key enzyme called phospholipase A2, which triggers the production of leukotrienes, prostaglandins and other compounds generated during an allergic reaction. The enzyme is also used by histamine to foster many of the annoying symptoms of allergies, according to Anil Mukherjee of the National Institute of Child Health and Human Development, in Bethesda, Maryland.

Mukherjee discovered the antiflammins in the uterus of pregnant rabbits while searching for an understanding of why a pregnant animal's immune system does not attack the foreign tissue of its own fetus. The antiflammins, he discovered, latch onto the surface of a fetus and prevent the mother's white blood cells from reacting to the fetus's proteins.

Antiflammins won't be tested on humans for a few years yet but Mukherjee is optimistic that they'll play a role in fighting allergies in the future.

Other studies are furthering understanding of the different stages in an allergic reaction and how to best utilize allergy drugs currently available so that each stage is covered. Lichtenstein discovered, for example, that in addition to the immediate allergic reaction a person may have when encountering an allergen, which lasts about a half hour, many allergic people also launch a second allergic attack about 6 to 12 hours after initial exposure.

The Baltimore investigators found that corticosteroids can abort this late-phase response but standard dosages of antihistamines (both over-the-counter and prescribed) do not. Antihistamines combined with topical corticosteroids, consequently, have become the treatment of choice for hay fever sufferers, Kaliner says.

The late-phase response also explains the mysterious resurgence of allergy symptoms people can have in the absence of re-exposure to an allergen. If they do encounter the same allergen during this phase, which can last as long as two days, studies show they will be 100 times more sensitive to it. Such increased sensitivity accounts for the progressive worsening of symptoms many people experience during allergy season, Lichtenstein says. And because some people can have a late-phase response without an early phase one, many allergies get overlooked because symptoms crop up hours after exposure to an allergen.

Even more mysterious are the anecdotal reports in the medical literature of people allergic to rose pollen, for example, who experience an allergic reaction when encountering artificial roses. Intrigued by these reports, researchers at the Brain-Behavior Research Center at the University of California in Eldridge are exploring the powerful role the mind can have in an allergic response.

Kathleen Dark and Harman Peeke used standard Pavlovian conditioning to teach guinea pigs to have an allergic reaction whenever they were exposed to a specific odor. The scientists initially exposed the animals to the odor while giving them injections of compounds that stimulate an allergic response. After two weeks, however, the guinea pigs had an allergic reaction, as indicated by increased blood levels of histamine, whenever they were exposed to the odor — even without the injections. Similar studies by Dutch researchers done in the 1950s show that people, too, can be conditioned to have an asthma attack when exposed to an innocuous substance.

"It's clear that conditioning and learning plays a role in an allergic attack," says Peeke. "It probably worsens an allergic reaction, but it can't account totally for the majority of allergic responses." If a person can learn how to enhance an allergic reaction, Peeke points out, they also may be able to "unlearn" it so their allergic attacks are less severe.

Truth can be stranger than fiction

By Margie Patlak
SPECIAL TO THE EXAMINER

ALLERGIES NOT only rank second in chronic disorders to afflict Westerners, but they also are responsible for some of the strangest maladies humankind has known:

- Dr. Michael Kaliner of the National Institute of Allergy and Infectious Disease recently discovered, for example, that some women have life-threatening allergic responses to their own hormones. These women have episodes of shock or hives, asthma, vomiting or diarrhea during the latter half of their menstrual cycles when progesterone is secreted.
- Kaliner has also treated women allergic to some of the proteins found in their husband's seminal fluid. After intercourse, these women get swelling and itching of the vagina, or hives, asthma, or they sometimes even go into shock.
- Allergies may also affect people's hearing. It's been known for some time that the nasal symptoms of allergies can make people more prone to ear infections, which can hamper hearing. Jennifer Derebery of the House Ear Institute in Los Angeles, in addition, has some evidence that certain food allergies can prompt temporary hearing loss, ringing in the ear and dizziness.
- A more common allergy is "tennis-shoe dermatitis." This itchy contact dermatitis rash is caused by an allergy to the chemicals used to process the rubber found in the insoles of athletic shoes.
- And while some people are allergic to everything under the sun, others are allergic to the sun itself. Exposure to sun or artificial light in these people makes them break out in hives. They apparently are allergic to a substance that forms when light waves interact with their skin.
- Not to be ignored are the people whose work makes them sick — literally. The more a person is exposed to a substance, the more likely he'll develop allergies to it, so many people find themselves allergic to compounds they encounter daily in their work. Clerical workers can become allergic to the chemicals found in carbonless copy paper, for example, and bakers to flour.