

Respiratory Rescue

Taking aim at allergy's drip and asthma's wheeze

By KATHY A. FACKELMANN

Jeanette Bolden's road to the 1984 Olympics — and a gold medal — was a particularly arduous one. Before she could challenge other runners, the U.S. sprinter had to surmount the extra hurdle of a chronic respiratory illness that had severely debilitated her as a child. Though Bolden persevered through the rigorous Olympic training, refusing to let her disorder slow her down, she admits to being one of the disease's luckier victims.

Like 10 million others in the United States, Bolden suffers from asthma — an inflammatory disorder in which smooth muscle fibers surrounding the bronchial tubes sometimes contract, making breathing difficult. For many of these people, exercise, cold air and exposure to dust, pollen or even a pet's dander can trigger the bronchial narrowing, sticky mucus secretions and airway swelling that make breathing a high-stakes struggle.

A new class of drugs may help Bolden and other asthmatics breathe easier as they follow their individual paths to success. Preliminary data suggest that these experimental compounds may not only prevent airway narrowing in asthmatics but also head off nasal congestion in people with allergies — a related inflammatory disorder affecting an estimated 40 million people in the United States. If further studies confirm their efficacy and safety, these drugs might one day revolutionize the treatment of both conditions.

Physicians currently prescribe inhaled bronchodilator drugs to relax the muscles that periodically squeeze asthmatic bronchial tubes. And to fight inflamed and swollen airways, they often turn to synthetic steroids in the form of pills or sprays.

For the sneezing and itching that allergy sufferers experience, most physicians recommend antihistamines. In addition, some prescribe steroid nasal sprays to combat nasal inflammation.

Today's asthma and allergy treatments generally provide incomplete relief, however, and some can provoke serious side effects. Steroids, for instance, have been linked to bone loss, bleeding, seizures and other health problems, especially when taken in pill form. Yet steroids remain the drug of choice for controlling asthma's underlying inflammation, as

emphasized last month by a federal report (SN: 2/9/91, p.86).

Recent reports, including three in the Dec. 20, 1990 NEW ENGLAND JOURNAL OF MEDICINE (NEJM), describe an entirely new class of drugs for controlling inflammatory disorders. "These are encouraging studies," says allergist Daniel J. Stechschulte at the University of Kansas Medical Center in Kansas City. Together with other recent findings (SN: 5/5/90, p.277), the NEJM reports spur hope for more effective treatment of asthma, allergy and perhaps a range of other inflammatory diseases such as ulcerative colitis, rheumatoid arthritis and psoriasis.

These drugs trace their origins back to a discovery made five decades ago, when scientists found that the lungs of guinea pigs secrete mysterious substances that constrict the bronchial tubes. Subsequent research showed that human lungs also released these compounds, which became known collectively as "slow-reacting substance of anaphylaxis." Then, in 1979, Swedish scientists characterized the chemical structure of one of the compounds, paving the way for identifying other substances in this chemical family, now called leukotrienes.

Researchers know that certain immune cells, including a class known as mast cells, produce leukotrienes by using the enzyme 5-lipoxygenase to break down arachidonic acid, a fatty acid. Normally, these immune cells release leukotrienes in order to help fight infection or heal injured tissue.

In some people, however, allergens or other factors may spur a misguided immune response in the mast cells of the respiratory passages, in effect "tricking" these cells into churning out a needless supply of leukotrienes. This triggers bronchial constriction and general airway inflammation. Some researchers believe that inappropriate leukotriene production may underlie some or most symptoms of allergy and asthma.

Those speculations have prompted a number of pharmaceutical firms to design drugs that block the production or the cell-surface activity of leukotrienes. If these firms achieve their goal — and if

leukotrienes are indeed the primary "bad guys" of asthma and allergy — the results could spell relief for millions of people, not to mention hefty financial returns for the drug companies.

Congestion is the bane of many allergy victims, but pharmacologist Howard R. Knapp hopes to change that. In the Dec. 20 NEJM, Knapp describes his study of an experimental drug that blocks the activity of 5-lipoxygenase. The trial, conducted while Knapp was at Vanderbilt University in Nashville, tested the drug's ability to clear stuffy noses in five men and three women with allergies to ragweed, grass or cat dander.

Half the volunteers received an 800-milligram dose of zileuton, a drug being developed by Abbott Laboratories. The others received an outwardly identical but inactive capsule. Neither Knapp nor the study participants knew who got the active drug or the placebo capsule.

Knapp then inserted a catheter into each person's nostril and squirted onto the nasal membrane a drop of saline solution containing an allergen known to trigger reactions in that individual. Two weeks later, he repeated the experiment but switched groups so that people who had received placebo got zileuton and vice versa.

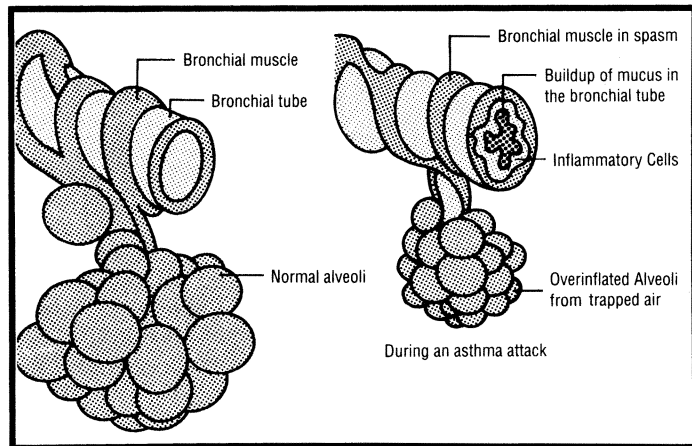
Knapp found zileuton significantly reduced nasal congestion resulting from the allergy challenge. In fact, seven of the eight people correctly identified the session in which they received zileuton because they felt so much less stuffed up.

"I was kind of surprised," says Knapp, who describes these results as "striking."

The study also provided some of the first evidence that zileuton inhibits immune-cell secretion of leukotrienes. Knapp collected nasal fluid before and after the squirt of allergen. Analyses of those samples showed that the drug dampened production of two chemical markers for leukotriene production by 70 to 90 percent compared with the placebo.

Zileuton proved less successful at controlling allergy-triggered sneezing, a symptom that plagued some volunteers throughout both the placebo and zileuton trials. The drug apparently does not block mast cell production of histamine,

When a person with asthma encounters a "trigger" such as dust or cold air, muscles around the bronchial tubes respond by contracting. This bronchial constriction combines with mucus production and swelling of airway tissue to cause wheezing and difficulty breathing.



Courtesy: NHLBI

which precipitates the "ah-choo" factor, says Knapp, now at the University of Iowa in Iowa City. He suggests that physicians may someday treat allergy patients with over-the-counter antihistamines in tandem with drugs like zileuton for a double whammy to prevent sneezing and to clear congestion.

For many asthmatics, cold air can precipitate a frightening inability to breathe.

Elliot Israel, a pulmonary specialist at Harvard Medical School in Boston, reasoned that cold air must somehow direct mast cells to release the airway-narrowing leukotrienes. He tested the theory by studying zileuton's power to prevent breathing trouble when asthmatics inhale frigid air.

He and his co-workers selected 13 asthmatic men aged 19 to 43 and gave half of them 800 milligrams of zileuton; the other half got placebo capsules. The researchers then challenged each volunteer with a blast of cold, dry air. Ten to 18 days later, each man received the opposite type of capsule and again sucked in cold air. The amount of icy air needed to spur an asthma attack increased by nearly 50 percent after the men took zileuton, Israel and his colleagues report in their NEJM paper.

Israel says the dramatic results suggest that "this may be a potential new therapeutic tool for the treatment of asthma."

At a minimum, it holds out the prospect that recreational joggers — and even Olympic athletes — may one day run longer in the cold. As things stand today, "we know that if you have asthma, the chances are eight out of 10 that if you go running in the cold, you're going to have to stop," Israel says.

A third investigative team tried another tack, specifically targeting the workout-induced wheeze.

For years, Paul M. O'Byrne has pursued the underlying origin of asthma. Like Israel, he suspects that leukotrienes play

a role in the development of this disease. "So when the opportunity came to study a potent and selective antagonist of these [leukotrienes], we jumped at it," says O'Byrne, a lung specialist at McMaster University in Hamilton, Ontario.

Merck Sharp & Dohme Research Laboratories offered O'Byrne and his co-workers a chance to test the experimental drug MK-571. Unlike zileuton, MK-571 does not interfere with leukotriene production by mast cells, but instead interacts with a specific protein receptor on the surface of smooth muscle cells surrounding the airways. When MK-571 binds with this receptor, it blocks at least one type of leukotriene from docking, and thus may prevent airway constriction.

O'Byrne's team studied a total of 12 asthmatic men and women, aged 19 to 42, who developed wheezing after vigorously pedaling a stationary bike. The researchers injected half the study group with 160 milligrams of MK-571 and the other half with a placebo solution, then sent each participant for a ride on the stationary bike. One week later, they repeated the trial, switching the experimental and placebo groups. Neither the researchers nor the volunteers knew when the participants received drug or placebo injections.

Compared with the placebo, MK-571 reduced exercise-induced airway constriction by about 70 percent, the team reports. Three people bicycled without a single wheeze after their MK-571 injections, O'Byrne adds.

In addition, the drug seemed to help volunteers recover from wheezing attacks. After exercise sessions, the average time needed to breathe easily again dropped from 33 minutes with placebo to 8 minutes with MK-571 treatment, the researchers report.

Scientists caution against overly optimistic assumptions regarding the effectiveness of the experimental drugs.

"These studies nicely show that such

drugs inhibit the bronchoconstrictor response," Stechschulte says. "That's a very exciting lead, but it doesn't necessarily mean they will be effective treatments for asthma."

Experiments that demonstrate brief reprieves from lab-induced episodes of bronchial constriction may not translate into a long-term solution for asthma's chronic effects, such as swelling and scarring of airway tubes, notes immunologist K. Frank Austen of Harvard Medical School. Likewise, says Knapp, there's more to treating allergy than simply blocking experimentally induced congestion.

The investigators add that they still don't know how great a role leukotrienes play in the development of asthma or allergies. As the research drama unfolds, these substances may emerge as major players or merely as bit actors, Stechschulte says.

The promise of the anti-leukotriene compounds rests with the hint that the body's mistaken immune reaction to some irritant produces an inappropriate outpouring of leukotrienes. If that interpretation proves correct, blocking the production of leukotrienes or their action at the receptor could ease allergic and asthmatic symptoms, perhaps providing physicians with a steroid substitute that doesn't pose dangerous side effects.

The trio of new studies turned up no significant side effects from zileuton or MK-571. Before either drug can win FDA approval, however, larger clinical trials must demonstrate their safety and their ability to hold off the symptoms of asthma or allergy.

The preliminary studies conducted to date have not addressed whether the experimental drugs provide greater relief than current treatments for asthma or allergy. Researchers may ultimately find, as Knapp suggests, that these compounds work best in combination with other drugs. Even so, the prospect of novel treatments that could help people surmount long-standing limitations might encourage more potential winners to take their shot at the gold. □