

## Biomedicine

### Fever-causing gene located

Mediterranean fever is a genetic disorder that causes unpredictable bouts of fever, skin rash, and inflammation of the lungs and joints.

Now, two groups have identified the gene that causes this puzzling disorder. Daniel L. Kastner and Elizabeth Mansfield of the National Institutes of Health in Bethesda, Md., and their colleagues report finding the guilty gene on chromosome 16. Their study appears in the Aug. 22 *CELL*. In the September *NATURE GENETICS*, Jean Weissenbach of Genethon in Evry, France, and her colleagues describe identifying the same gene.

Kastner's team studied people from 62 families with Mediterranean fever who had been treated at clinics in Tel Aviv or Los Angeles. The researchers drew blood and zeroed in on a gene that, when mutated in any of several ways, produces the symptoms of this disease.

Their work suggests that this gene normally makes a protein called pyrin. The defective form, they speculate, directs the cell to produce a flawed copy of the protein. The researchers theorize that normal pyrin shuts off inflammation, the body's response to infection that results in fever, swelling, and pain.

The French researchers found that most of the mutations occur within a small area of DNA. Moreover, the DNA around the mutations was similar in most of the affected people. These findings suggest that the disease was spread by a single individual or small group of people who lived in the Mediterranean region many centuries ago.

Today, Mansfield notes, most people with the disease trace their origins to the Mediterranean basin. —K.F.

### Gas therapy for sickle-cell anemia

Inhalation of nitric oxide gas may reverse the defect behind sickle-cell anemia, according to a preliminary report. If nitric oxide's promise is confirmed, it would represent the first treatment to address the underlying flaw in this disorder, says C. Alvin Head of Harvard Medical School in Boston.

Sickle-cell anemia is caused by an abnormal form of hemoglobin, an oxygen-carrying molecule in the blood. The defective hemoglobin molecules stick together after releasing oxygen and form sickle shapes that clog the body's tiny blood vessels. Such jams cause a painful, potentially life-threatening sickle-cell crisis.

A 1977 report had suggested that nitric oxide alters the shape of hemoglobin. Head, Ricardo Martinez-Ruiz, and their colleagues wondered if this gas might help people afflicted with sickle-cell anemia.

The researchers recruited nine people with the disease who were not having a sickle-cell crisis. They had the volunteers inhale a low dose of nitric oxide for 45 minutes. In eight of the volunteers, the experimental treatment increased hemoglobin's affinity for oxygen and thus prevented the molecule from assuming the abnormal shape. Other studies have suggested that such an effect would decrease the likelihood of a sickle-cell crisis. The inhalation of nitric oxide had no effect on hemoglobin in the blood of volunteers without sickle-cell disease. The researchers report their findings in the September *JOURNAL OF CLINICAL INVESTIGATION*.

Head and his colleagues are now beginning to examine whether the gas may help reverse a sickle-cell crisis. They are recruiting 60 volunteers for a study expected to yield results in a year.

"Right now, there is no therapy for [sickle-cell] crisis," Head says, noting that patients generally receive only pain killers and other palliative treatments when they suffer an attack.

Head suspects that nitric oxide, used on a regular basis, would ward off such episodes. He imagines patients someday using a gas inhaler much like an asthma inhaler to prevent their hemoglobin from getting into a traffic jam. —K.F.

## Chemistry

*From a meeting in Las Vegas of the American Chemical Society*

### Nonsmokers inhale carcinogen

The familiar torch song tells only part of the story: Smoke not only gets in your eyes, it gets into the rest of your body, too.

A new study shows that nonsmokers who spend time in smoke-filled rooms absorb and process a potent carcinogen called NNK. This is the first evidence that nonsmokers take up a carcinogen from smoke under real-life conditions, says Stephen S. Hecht of the University of Minnesota Cancer Center in Minneapolis.

Hecht and his colleagues analyzed urine samples obtained from nine people who work in a long-term-care facility in Canada. None of the subjects themselves smoked, but they all spent time in lounges where patients smoked. The concentrations of tobacco smoke in the air were "similar to those in the smoking section of a restaurant," says Hecht.

The urine of all nine subjects contained NNL-Gluc, a substance produced when the body metabolizes and detoxifies NNK. In 1993, the researchers detected NNL-Gluc in the urine of nonsmokers who had breathed in smoke expelled by machines in a laboratory chamber. NNK, which has been found only in tobacco, causes lung cancer in rodents by binding to DNA and red blood cells, ultimately activating cancer-causing genes, Hecht says.

The measured NNL-Gluc concentrations were low—about one-seventieth of those found in smokers. How those concentrations translate into lung cancer risk is unclear. Nevertheless, Hecht says, the results support epidemiological studies that ascribe a small, but significant, increase in risk to nonsmokers who spend prolonged periods of time breathing in a cigarette haze. —C.W.

### Shedding tears for scientific study

To poets and romantics, a teardrop can express a world of emotion. A team of researchers is hoping it can also carry a rich message regarding a person's physical condition. By analyzing the chemical composition of tears and aqueous humor—the fluid that fills the eyeball—the scientists hope to improve their understanding of the biochemistry of diseases such as glaucoma, cataracts, and diabetes.

Over the past 4 years, the group has been developing an analytical method for separating and identifying the molecules present in eye fluids. Tears and aqueous humor contain a complex mixture of proteins, salts, peptides, and organic molecules, says chemist Andy J. Tomlinson of the Mayo Clinic in Rochester, Minn. These substances could be the components of normal eye fluids, the biochemical traces of immune cells, or the remnants of foreign invaders such as viruses.

The aqueous humor used in the studies is extracted with a needle from patients undergoing cataract surgery. For the chemical analysis, the samples of tears and of humor are injected into an apparatus containing a series of thin membranes impregnated with solid materials that separate and concentrate the various fluid components. Additional steps continue the separation and identify the compounds.

The technique is easy to use, Tomlinson says, and extends to the study of other fluids. "For small molecules and peptides, it's well developed. For proteins, we're still learning because of the problems everyone has handling them." Proteins can denature or clump if conditions aren't just right.

Analyzing tears can give hints as to why contact lenses irritate some wearers. Researchers would like to understand what happens as a lens goes into the eye, Tomlinson says.

Looking at eye fluids is relatively novel, so one of the researchers' short-term goals is to determine the composition of normal eye fluids. Even in normal tears, Tomlinson says, the researchers found viral proteins, suggesting that they may be looking in the right place for disease markers. —C.W.