Alcohol-Loving Mice Spur Gene Search

Mice bred to exhibit various degrees of preference for drinking alcohol may, by virtue of their scientifically controlled couplings, help scientists identify genes that contribute to alcoholism. Which genes influence an animal's imbibing seems to depend on the animal's sex.

Two groups of genes show links to excessive alcohol consumption in the offspring of these mice, assert Lee M. Silver, a molecular biologist at Princeton University, and his colleagues. A particular chromosome 2 region, when inherited from either parent, appears to promote alcohol drinking in males, the researchers contend; a specific variation of a portion of chromosome 11 inherited from the father boosts alcohol use in females.

Both chromosome segments contain genes of known function that may correspond to human genes and could plausibly contribute to alcoholism, though not causing it on their own, Silver's group asserts in the June NATURE GENETICS.

Studies conducted by other investigators have uncovered statistical links between extreme alcohol preference in mice and the same portion of chromosome 2 tagged in the new data, as well as segments of chromosomes 3 and 9.

"Silver's study has more statistical rigor than any prior work," asserts John C. Crabbe, a behavioral geneticist at the Veterans Affairs Medical Center in Portland, Ore. "But I'm not sure how to relate its findings to the existing scientific literature."

The Princeton researchers began with 234 mice bred to exhibit one of three conditions if given access to both an alcohol solution and pure water—avoidance of alcohol, moderate intake of alcohol, or consistent preference for alcohol.

The moderate alcohol drinkers, a hybrid strain that had been produced by breeding heavy alcohol consumers with alcohol avoiders, possess naturally occurring genes that inhibit both extremes, the scientists theorize.

They then bred 262 mice by mating hybrid fathers with alcohol-preferring mothers and bred 73 mice by mating hybrid mothers with alcohol-favoring fathers.

Male offspring that drank excessive amounts of alcohol displayed a signature chromosome 2 segment more frequently than other mice, regardless of which parent engaged in heavy drinking, the investigators contend. This segment contains a cluster of seven genes that help regulate sodium activity in the brain and that may contribute to an alcohol preference, they argue.

Female offspring that favored alcohol had a unique chromosome 11 region more often than other mice, a trait they inherited from fathers that drank large amounts of alcohol, Silver's team says. A gene that inhibits the action of the neurotransmitter serotonin lies in this part of chromosome 11. Previous research has linked low serotonin concentrations to increased alcohol consumption.

Researchers have not yet located the exact genes in mice that influence alcohol drinking, asserts David Goldman, a neurogeneticist at the National Institute on Alcohol Abuse and Alcoholism in Rockville, Md., in an accompanying comment. Human genes equivalent to those that operate in alcohol-favoring mice may not exist, he adds. Intensive study of the human genes that regulate serotonin activity will be required for insight into alcoholism and other psychiatric disorders, in Goldman's view.

Rodent research still offers a promising starting point, according to Crabbe. In his earlier studies of female mice, he found a link between elevated alcohol use and a chromosome 9 region bearing a gene that regulates certain serotonin receptors in the brain. This statistical relation is significant but relatively weak, Crabbe says.

"It would be nice to find specific genes with powerful effects on alcohol drinking," Crabbe remarks. "But it's likely that many genes have moderate effects on this behavior."

Other independent research on the same strains of mice studied by Silver's group has linked a chromosome 10 area to morphine preference. Alcohol and morphine preference may be genetically distinct traits in these mice, according to the Princeton group. —*B. Bower*

Freezing water droplets to novel icy peaks

A water droplet rests on a frigid aluminum plate. As it freezes rapidly from the bottom up, the droplet undergoes a subtle change in shape, bulging slightly upward. By the time the droplet turns completely to ice, a distinctive cusp protrudes from its top surface.

When Stephen H. Davis of Northwestern University in Evanston, Ill., first asked his colleagues the question of what would happen as a water droplet freezes, he suspected that its shape would change, perhaps because water expands as it turns to ice.

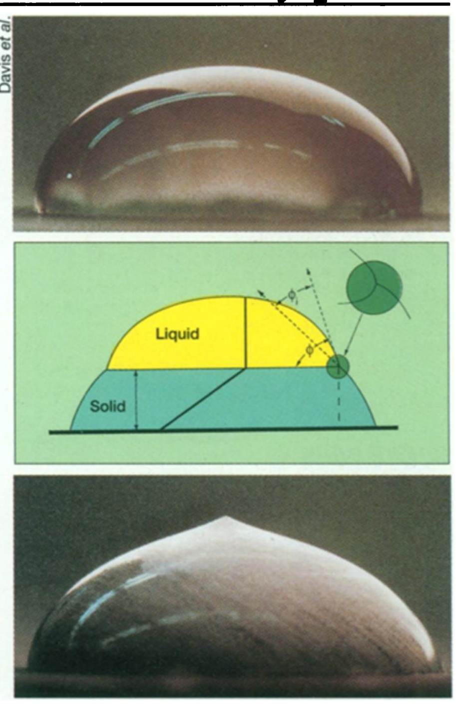
"We did get this very peculiar shape—a sharp point instead of a rounded top," Davis says. The explanation of this unexpected shape, however, turned out to involve the angles between solid, liquid, and air at the interface where all three meet, which moves as the water freezes.

Understanding this effect may prove useful for modeling what happens when materials confined by surface tension rather than the walls of a container solidify on Earth—or in space under microgravity conditions. Containerless solidification is an important technique for producing ultrapure materials.

Davis, M. Grae Worster of the University of Cambridge in England, and Daniel M. Anderson, now at the National Institute of Standards and Technology in Gaithersburg, Md., report their findings in the June JOURNAL OF CRYSTAL GROWTH.

The researchers used 35-microliter droplets of distilled water, freezing them from below at a range of plate temperatures. Freezing times were typically about 40 seconds, providing insufficient time for

Davis et al.



A water droplet at room temperature rests on an aluminum plate (top). The cold plate causes the droplet to freeze from the bottom up, producing a solidification front that advances upward. In the middle illustration, the inset shows a magnified view of the solid-liquid-air interface at the droplet's edge. The difference (ϕ_i) between the contact angles of the liquid (ϕ) and the solid lead to the formation of a cusp on the top surface of the frozen droplet (bottom).

the slower formation of flat crystal faces.

They discovered that cusp formation occurs quite readily. In fact, Anderson had first observed the effect, without using any elaborate equipment, in the kitchen of his parents' home in Minneapolis.

The key factor in producing a frozen droplet with a sharp point is the difference between the angle that the solid makes with the solidification front during freezing and the angle that the liquid makes with the front. These angles also change as solidification proceeds from bottom to top, eventually forcing the formation of a cusp.

Similar effects should occur in other substances, Davis says. During his kitchen stint, for example, Anderson noticed that drops of splattered beef gravy congealed on the walls of a freezer have peaks.

These insights may prove of interest to scientists and engineers who freeze materials in containers in which some portion is exposed to air. They may be helpful, too, in understanding an important industrial process in which metal surfaces are melted rapidly by powerful lasers, then allowed to resolidify to strengthen the material. *— I. Peterson*

Drug extends life of Lou Gehrig patients

After decades of disappointment, researchers are proclaiming a "first step" toward a remedy for Lou Gehrig's disease. In a recent study of nearly 1,000 people, a promising drug has briefly prolonged the lives of sufferers.

The drug, riluzole, marks the only advance in treatment for victims of Lou Gehrig's disease—known to doctors as amyotrophic lateral sclerosis (ALS)—in the half century since the famed Yankee first baseman died of it.

Researchers caution, however, that the drug is only partially effective and is not an answer to anyone's prayers. Although riluzole extends life, it cannot halt the degenerative nerve disease, repair the nervous system, or even make patients feel better.

"No drug will improve any ALS patient as motor neurons are destroyed. It is impossible at the moment to think about a recovery, whatever drug is used," concedes Vincent Meininger of the Salpêtrière Hospital in Paris, a member of an international research team that reported its findings in the May 25 LANCET.

That doesn't mean the drug is valueless, the researchers conclude. "Our experience as clinicians suggests that psychological well-being is enhanced by the availability of a treatment that is safe and well-tolerated and has a proven effect on the disease—in contrast to the many drugs (some of them unsafe) to which thousands of patients have been exposed over the years."

Jeffrey D. Rothstein of Johns Hopkins Medical Institutions in Baltimore says the new study has shown that "the drug can work in ALS, it can work in all patients, and we've figured out which dose is the best dose. This is the first drug we've had that does something reliably in ALS."

In most cases, ALS strikes after age 40. Nerve cells in the brain stem or spine begin to die. Some people first experience a mild weakness in their arms and legs, others difficulty swallowing or speaking. Ultimately, ALS ravages the nerves and muscles, turning the body into a coffin enclosing an intact mind. After diagnosis, patients survive an average of just 2 to 5 years.

Researchers believe the disease results from overstimulation of nerve cells by a chemical messenger called glutamate, which ferries nerve signals across the tiny gulf separating nerve cells. In ALS patients, excess glutamate lingers in the gap, exciting nerve cells to death. Riluzole slows the damage temporarily by blocking the release of glutamate from nerve cells.

In the 18-month study of 956 patients in Europe, Canada, and the United States, riluzole reduced the risk of death by 35 percent. It also diminished the need for a tracheostomy—a procedure in which doctors surgically create an airway into the throat to bypass unresponsive respiratory muscles.

The researchers randomly divided study participants into four groups. One group was given a daily dose of a placebo. The others were given riluzole in daily doses of 50, 100, or 200 milligrams.

Those who received 100-mg doses fared better than the others. For instance, 57 percent of volunteers in the 100-mg group survived 18 months, compared to 50 percent of those in the placebo group. There were no severe side effects.

The LANCET study represents an improvement over an earlier trial involving 155 patients (SN: 3/26/94, p. 202). That study suggested that riluzole worked primarily in people whose ALS began in the brain stem. The recent report says those mixed results were a statistical blip caused by the small number of volunteers.

On the basis of this and other studies, the Food and Drug Administration approved riluzole last year. *— S. Sternberg*

Deep desires in Antarctica and Greenland

Laboring in the coldest spot on Earth, an international team of scientists has reached a new milestone in drilling through ice, providing a chronicle of climate going back nearly 400,000 years. This record, set in January at Russia's Vostok Station in Antarctica, won't stand for long, however. Several research groups plan to perforate Antarctica and Greenland further in the next few years, hoping to unlock fresh secrets about how Earth's climate works.

The drilling at Vostok Station, about 1,200 kilometers from the South Pole, goes back to the early 1970s, when Soviet crews extracted their first deep core at this site. Working with French and U.S. collaborators, the Vostok team began a fifth core in 1990 and reached a depth of 3,348 meters early this year.

"This is the deepest site in the world," says Jean Jouzel of the Laboratoire de Modélisation du Climat et de l'Environnement in Gif sur Yvette, France. He spoke last week in Baltimore at a meeting of the American Geophysical Union.

The latest Vostok core reaches back through four ice ages, each roughly 90,000 years long, and the intervening warm periods known as interglacials, which last about 10,000 years each. Scientists are eager to study the oldest glacial cycles because previous cores drilled at Vostok and in Greenland record only the two most recent ice ages.

Ice sheets and glaciers grow annually, layer by layer, trapping information about climate in more than a dozen ways. By measuring the ratios of oxygen and hydrogen isotopes in the ice, for example, researchers can tell how atmospheric temperature rose and fell through the millennia. Dust and ash layers reveal wind patterns and volcanic eruptions. Gas bubbles tell how concentrations of greenhouse gases have shifted.

The Vostok squad expects to renew drilling later this year, hoping to deepen the hole by another 300 m, which will bring it to within 50 m of the base of the ice sheet. The team plans to stop there to prevent polluting what appears to be a lake of water below the ice, says Jouzel. Scientists want to develop ways of sampling the water, which may contain ancient microbes that have been locked away for 500,000 years or more.

Later this year, nine European nations and Japan plan to begin a 3,300-m-long core at Dome C, 600 km from Vostok. After 3 years of drilling there, the team plans to establish a hole in Dronning Maud Land, Antarctica. Because of its proximity to the Atlantic Ocean, this site should help scientists match Antarctica's climate history with information gleaned from Greenland.

U.S. researchers are focusing on the other side of the continent, West Antarctica. Early next year, they plan to begin a 1,000-m-long ice core at Siple Dome, upstream from the Ross Ice Shelf. Meanwhile, a Danish crew is scheduled to start a deep core in central Greenland this summer to resolve debate about the next-to-last interglacial, 115,000 years ago. *— R. Monastersky*