Brain Data Fuel Alcoholism Gene Clash

Alcoholics fall into two groups, depending on whether their brains exhibit a dramatically lower or slightly elevated flow of dopamine, a chemical that helps regulate pleasurable emotions during eating, drinking, and sex, a new study finds. Controversial studies suggesting that a substantial minority of alcoholics inherit a gene associated with depressed dopamine transmission appear to be on the right track, the new study's authors hold.

Nonviolent alcoholics have many fewer and less widely distributed dopamine reuptake sites—cellular gateways for recovering and recycling dopamine at key nerve junctions—than do nonalcoholics, asserts a team of Finnish scientists led by Jari Tiihonen, a psychiatrist at the University of Kuopio. These reuptake sites prove slightly more extensive in highly violent alcoholics than in nonalcoholics, the researchers report in the July NATURE MEDICINE.

The findings fit with evidence associating one form of the D2 dopamine receptor gene, known as the A1 allele, with reduced numbers of dopamine receptors in the brain (SN: 11/14/92, p.332). People with fewer receptors have a greater likelihood of developing severe alcoholism or other types of drug abuse, some investigators theorize. The receptor disparity between violent and nonviolent alcoholics is not due to alcohol-induced changes in blood flow or shrinkage of brain tissue, withdrawal effects, or poor nutrition, the Finnish scientists argue.

Earlier studies lumped violent and nonviolent alcoholics together, which "might be one reason for the previous controversial findings concerning the association between alcoholism and [dopamine] abnormalities," Tiihonen's team writes.

But controversy permeates all aspects of these studies, and the genetic significance of the new data has already become a matter of dispute.

The Finnish researchers studied 19 habitually violent alcoholics (who had committed murders or other violent crimes), 10 nonviolent alcoholics, and 19 nonalcoholic adults. Each volunteer received an injection of a minute amount of a radioactive substance that attaches to dopamine reuptake sites. An imaging device then translated radioactive emissions into data on the number and extent of dopamine receptors in brain areas thought to regulate pleasurable sensations.

A separate brain imaging study, reported in 1994 by another research group, also found sparse dopamine reuptake sites in nonviolent alcoholics, compared to nonalcoholics. That project, however, did not include alcoholics with a history of severe violence.

David Goldman, a psychiatrist at the National Institute on Alcohol Abuse and Alcoholism in Rockville, Md., doubts that such findings stem from wayward genes. "If confirmed, [the data] would indicate that alcohol exposure or other experience common to alcoholics is capable of inducing a long-lasting alteration of [dopamine] function," Goldman writes in a comment accompanying the new study.

Reduced dopamine transmission may contribute to cravings for alcohol, making it difficult for alcoholics to abstain from imbibing, Goldman says.

Tiihonen's group did not look at whether nonviolent alcoholics carry the A1 allele more often than violent alcoholics or nonalcoholics. But Goldman, whose research has found no link between alcoholism and the A1 allele, suspects it played no part in the Finnish findings.

The dopamine transporter (DAT1) gene, which helps to organize critical reuptake sites, may contribute more strongly to alcoholism, Goldman holds.

Ernest P. Noble, a psychiatrist at the University of California, Los Angeles, disagrees. Noble coauthored the first study to report a link between the A1 allele and severe alcoholism (SN: 9/21/91, p.190).

"The new data show that some alcoholics have greatly reduced dopamine function, as we argue," Noble holds. "Our findings indicate that there is an inherited form of alcoholism that includes the A1 allele and a reduced number of dopamine receptors in the brain."

Alcoholics bearing the A1 allele show marked drops in anxiety and alcohol craving after 3 to 6 weeks of treatment with a drug that boosts dopamine transmission through D2 receptors, Noble and his coworkers report in the April NATURE MEDICINE. The same drug yielded only mild improvement in alcoholics possessing another form of the D2 dopamine receptor gene.

Alcoholism researchers need to pin down the influence wielded by the A1 allele and other genes that affect dopamine's action, Noble contends.

— B. Bower

DNA repair enzyme: A structure revealed

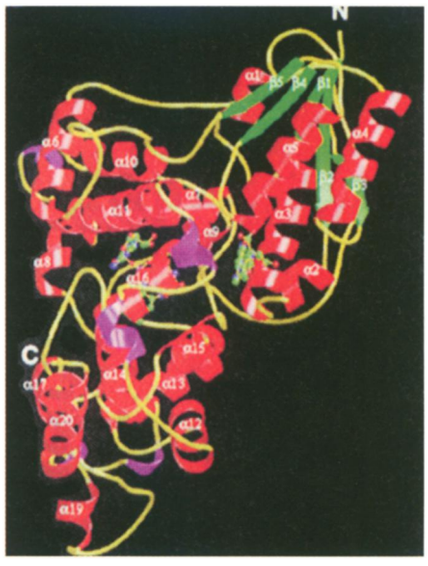
Like any complex machine, DNA has a tendency to break down—particularly under the onslaught of ultraviolet light.

Energetic UV rays from the sun create subtle glitches in the fragile genetic material present in every living cell. Left uncorrected, these glitches can eventually lead to biological disaster. Researchers have long known that intense or prolonged exposure of unprotected healthy cells to UV light and other forms of high-energy radiation can lead to cellular mutations and cancer.

Interestingly, nature has evolved at least one countermeasure to address this problem: the enzyme photolyase, which finds and corrects some of the damage to DNA caused by UV exposure. Present in many organisms—including bacteria, goldfish, rattlesnakes, and marsupials—photolyase meticulously snoops around fragile genes, detecting and fixing a specific type of UV-induced error. Unfortunately, people don't produce photolyase.

Hee-Won Park, a biochemist at the University of Texas Southwestern Medical Center in Dallas, and his colleagues have determined the structure of this intriguing enzyme, they report in the June 30 SCIENCE. By means of X-ray crystallography, the researchers have achieved a complete three-dimensional analysis of the enzyme's structure and binding site, using a form of photolyase culled from the bacterium *Escherichia coli*.

"This is a landmark in the field of DNA repair," says John E. Hearst, a chemist at the University of California, Berkeley. "Photolyase is a fundamentally important enzyme.



Deisenhofer/SCIENCE

The enzyme photolyase.

"Given growing concerns about exposure to UV light, particularly with the thinning ozone layer in the upper atmosphere," Hearst adds, "this enzyme shows us one mechanism by which organisms can protect themselves from UV damage to their DNA."

Ultraviolet radiation disrupts the structure of DNA by causing a chemical reaction that hooks together two distinct bases, forming a so-called pyrimidine dimer. "Pyrimidine dimers kill cells by blocking DNA replication and transcription," says Hearst, and by causing mutations. Photolyase comes to the rescue in a process called photoreactivation. The enzyme binds to damaged DNA, draws energy from light to break apart the offending dimer, then disengages from the double helix.

"The observation of photoreactivation many years ago was one of the first indications to biologists that DNA repair mechanisms exist," says coauthor Johann Deisenhofer, a biochemist at the Howard Hughes Medical Institute at Southwestern Medical Center. "Because this enzyme does not occur in humans, some people may consider it unimportant. Yet it has rather wide distribution in the biosphere, up to marsupials. It appears that placental mammals lost this gene during evolution, though we don't know why that happened."

The enzyme's use of energy from light to drive its repair activities "is quite unusual," Deisenhofer adds. "To my knowledge, there are only two known enzymes that operate this way. The other one is involved in photosynthesis."

While the scientists have no immediate applications in mind for their discovery, Hearst speculates that some biologists may attempt to transfer the gene governing this DNA repair mechanism into organisms lacking the enzyme "to see to what extent the gene protects them from UV damage.

"There's particular interest in protecting plants from ultraviolet exposure," Hearst continues. "DNA repair is such a fundamental aspect of biology that knowing the mechanism by which this repair takes place may give us insights into protection [in humans] against DNA errors and mutations." — *R. Lipkin*

Slowing down the evolution of tough insects

Corn lovers usually have distinct preferences: Some like sweet, white ears, others plump, yellow ones. The corn borer *(Ostrinia nubilalis)* has a preference, too—for taller, more mature plants.

Scientists want to take advantage of the corn borer's choosiness to slow the pace at which the bug is likely to become resistant to a new, genetically engineered variety of corn, Donald N. Alstad and David A. Andow of the University of Minnesota in St. Paul report in the June 30 SCIENCE.

Corn engineered to produce a *Bacillus thuringiensis* protein, which kills most corn borers, may soon become commercially available. However, genetic variation in some of these pests may enable them to survive the protein. These tough bugs will reproduce. So if enough farmers use the transgenic corn, and there's no disadvantage to inheriting the survival gene, eventually most corn borers will tolerate the toxin.

Planting so-called refuge fields—fields of normal varieties—near the transgenic crop helps slow the development of a toxin-tolerant pest population, but refuges suffer a lot of insect damage, studies have demonstrated.

Now, Alstad and Andow have developed a computer model which shows that planting the transgenic crop earlier in the season protects the refuge field and helps to slow resistance. The reason? Corn borers will preferentially lay their eggs in the more mature, transgenic crop. Their offspring's first meal may be their last. If the plants prove powerful enough, they will kill both the borers that have some resistance to the toxin and those that don't.

"You can dramatically delay the evolution of resistance if you kill the heterozygotes"—the insects that carry one gene variation that confers resistance and one that makes them susceptible, says Alstad.

The plan could work for other wandering pests as well, Alstad and Andow note. It might extend the useful life of an engineered plant variety from 4 or 5 years to 15, Alstad speculates.

However, the model "doesn't adequately address" the preference of insects born later in the summer for younger plants, says Eric S. Sachs of Monsanto Co. in St. Louis, which is developing a transgenic variety of corn. Indeed, the model assumes that later bugs show no preference. Also, Sachs notes, cool temperatures may cause spring insects to emerge after the normal plants have matured enough to match the transgenic crop's appeal. — *T. Adler*

Andow

If given a choice, some corn borers choose the tall corn.

Spinning nuclei to extreme deformity

The atomic nucleus is typically pictured as a roughly spherical conglomeration of protons and neutrons. But in recent years, researchers have discovered that certain nuclei adopt an elongated, superdeformed shape when they spin rapidly (SN: 7/28/90, p.53).

Now, Demetrios G. Sarantites of Washington University in St. Louis and his collaborators have uncovered evidence that some atomic nuclei can suffer even more extreme changes in shape. In the June 26 PHYSICAL REVIEW LETTERS, the researchers report the first clear indications of hyperdeformation in gadolinium-147 nuclei.

Superdeformed nuclei are usually the products of off-center collisions between two smaller nuclei. The colliding bodies fuse to create a single whirling entity. For nuclei whose mass falls within certain well-defined ranges, rapid spin leads not to fragmentation, but to deformation into a football shape whose length is roughly twice its width.

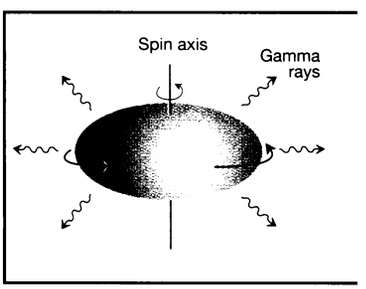
Researchers have observed superdeformation among nuclei of such elements as mercury, thallium, lead, dysprosium, gadolinium, and strontium. At the same time, calculations based on theory have suggested the existence of hyperdeformed nuclear states.

To search for extremely deformed nuclei, Sarantites and his coworkers used a cyclotron at the Lawrence Berkeley (Calif.) National Laboratory to bombard a molybdenum foil with vanadium nuclei. In these high-energy collisions, vanadium-51 and molybdenum-100 nuclei fuse to create heavy, highly excited nuclei, which generally get rid of their excess energy by breaking apart or throwing off protons and neutrons.

However, a small fraction of the rapidly spinning collision products remains intact. Instead of emitting protons, these heavy nuclei radiate gamma rays to get rid their excess spin energy.

By observing the spectrum of gamma rays emitted during the process, the researchers deduced that a spinning gadolinium-147 nucleus has a sausage shape with a length about three times its width. "This is in good agreement with theoretical predictions," the researchers note.

Nonetheless, the existence of these highly deformed nuclei raises questions about the applicability of standard fission theory to nuclei with high spins. — *I. Peterson*



Spinning superdeformed nucleus.