NEUROSCIENCE

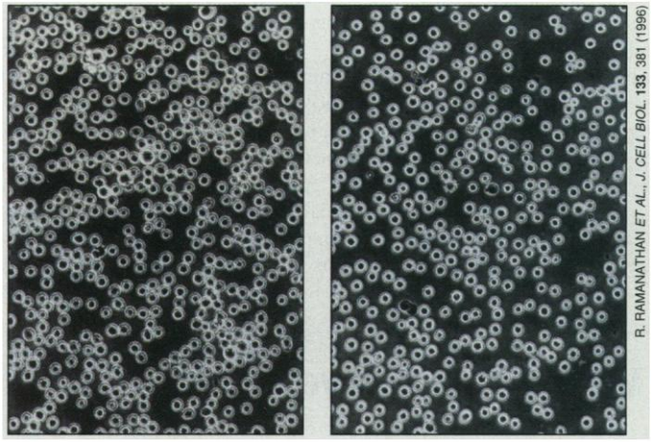
New Experiments Underscore Warnings on Maternal Drinking

Physicians have known for years that when pregnant women drink heavily, their fetuses may suffer harmful long-term consequences. Indeed, fetal alcohol syndrome (FAS), a constellation of physical and central nervous system abnormalities, is the leading preventable cause of mental retardation in the developed world. But exactly how much drinking is too much has been a debatable question, in part because for years scientists haven't been able to suggest a way that moderate doses of alcohol might adversely affect a developing brain.

Now findings announced at a recent meeting of alcohol researchers* are revealing subtle, alcohol-induced changes in fetal neurons that could lead to later mental defects. The work, mostly done in rat neurons, shows that even moderate maternal drinking (defined as one to three drinks per day by the U.S. National Institutes of Health) can cause molecular changes in the fetal brain that affect its ability to learn and remember as an adult. "We continue to be amazed at the changes we're finding at these low levels of alcohol exposure," says pharmacologist Daniel Savage of the University of New Mexico, one of those doing this research.

To be on the safe side, the Surgeon General has warned pregnant women not to drink at all. But data compiled by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) show that 20% ignore that warning. As a result, many more fetuses are exposed to moderate levels of alcohol—similar to those used in the studies—than are exposed to the heavy or binge drinking that can lead to FAS. The new knowledge is helping to set the U.S. Surgeon General's advice on firmer scientific ground, says Enoch Gordis, NIAAA director: "The research picture is bringing the threshold for [alcohol-induced] abnormalities downward. This reinforces the public policy message that abstention is the best policy for pregnant women."

One way to trace alcohol's impact on the fetus is to begin with a known disorder that mimics alcohol-induced effects. That's what Michael Charness and colleagues at Harvard Medical School and the Brockton/West Roxbury Veterans Administration Medical Center in Massachusetts did. The group noted that the same kind of mental retardation and brain malformations seen in FAS are also found in people with a rare genetic mutation in the *L1* gene, which codes for a cell membrane protein essential for normal brain development. The L1 protein is an adhesion molecule, so-called because it helps neuronal cell membranes stick to other neural cells as well as to components of the extracellular matrix. When L1 molecules bind together, they set up a cascade of chemical reactions that affect neuronal migration and other processes crucial to developing the brain's functional circuits, which support everything from breathing to abstract thought.



R. RAMANATHAN *ET AL., J. CELL BIOL.* 133, 381 (1996)

Coming unglued. Mouse cells carrying the human *L1* gene stick to one another (*left*), but treatment of the cells with an alcohol solution (*right*) causes them to lose their stickiness.

Charness and colleagues reasoned that one way alcohol might harm the brain is by interfering with L1 proteins in fetuses. So they applied weak ethanol solutions to cerebellar cells from rat brains and found that L1 is indeed exquisitely sensitive to alcohol. At doses equivalent to those found in humans after a single drink, the adhesiveness of L1 molecules dropped significantly; the molecules lost their stickiness completely when the cells were dosed at levels corresponding to the 0.08% blood level that defines legal intoxication in many states. "We know that L1 binding ... can lead to morphological changes and altered cell migration," says Charness. "If L1 doesn't work, those things may not work either."

Such cellular changes may underlie the common structural malformations and mental retardation seen both in people with FAS and those with the *L1* mutation, says Charness, who notes that this is one of the first studies to show neuronal changes linked to such low doses of alcohol. "This is a very provocative finding," says Gordis. "It's opening up a very important and large area, because there are many other adhesion molecules as well, although not all may be sensitive to alcohol."

Indeed, Charness found that alcohol had surprisingly specific effects. Ethanol is a potent solvent and was long thought to act in a general, indirect manner by partially dissolving or "fluidizing" cell membranes. But Charness found that even at high doses, alcohol did not block the function of a structurally related adhesion molecule, called N-CAM. This and other data from Charness's lab suggest that the ethanol binds to a particular site on the L1 protein rather than simply attacking the whole cell membrane, says Charness.

Other researchers are probing the effects of moderate doses of alcohol by studying functional changes in neuronal connections crucial to learning. Many neuroscientists think memory and learning depend on long-lasting increases in the strength of synaptic connections between neurons, a phenomenon called long-term potentiation (LTP). At the meeting, Savage presented the results of a study in which he gave pregnant rats moderate doses of alcohol, roughly comparable to maternal drinking of two to three drinks per day in a human. After their offspring had grown, he and colleague Robert Sutherland studied the learning abilities of the adults as well as the physiology of their brains. Behaviorally, the rats performed as well as controls in the standard water maze learning test, but they were strikingly worse in more difficult variations, requiring seven or eight trials to learn a new test that controls picked up after just one trial.

When Savage looked at the neurons in the brains of these rats, he found a marked reduction in LTP in cells from the hippocampus, a brain region critical for memory formation. He also found that in the face of changing stimuli, synapses of alcohol-exposed animals failed to release a key neurotransmitter—a sign that their neurons had lost the responsiveness or plasticity needed for memory formation and learning.

Taken together, the new findings add to a growing list of molecular mechanisms thought to play a role in the kind of major damage seen in children with full-blown FAS. More importantly, they provide the first evidence that

* Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism Joint Scientific Meeting, Washington, D.C., 22–27 June.

moderate drinking can significantly inhibit neuronal function, even in the absence of the facial malformations and mental retardation accompanying classic FAS. "At the level we're exposing our animals to, we're not finding changes in [body] morphology—they look normal," says Savage. "All the changes are at the level of neurochemistry."

The idea suggested by the work of Charness, Savage, and others—that children with full-blown FAS are only the extreme end of a spectrum of effects that tapers in magnitude as the alcohol dose decreases—corroborates a handful of epidemiological studies. These indicate that children whose mothers drank moderately while pregnant are prone to a variety of learning deficits such as slower reaction times, poorer sustained attention, and lower intelligence quotient scores. Indeed, the Institute of Medicine (IOM) has recently suggested a new category of Alcohol-Related Neurodevelopmental Disorders for these more subtle symptoms. "People talk about FAS as though it was a single, clearly defined category, but in reality it's a continuum," says Claire Coles, an associate professor of pediatric psychiatry at Emory University School of Medicine and a member of the IOM committee that suggested the new category. "Probably, moderate consumption is causing effects appearing in the lower end of the continuum."

But Coles cautions that much work remains to be done, particularly in studying humans exposed to lower levels of alcohol. Forging a direct link in humans between low or moderate fetal alcohol exposures and learning problems years later is difficult, she says, because many other factors such as variations in individual sensitivity to alcohol may influence cognitive abilities. "The human studies are much less refined than the molecular studies," she says.

That many questions remain unanswered is illustrated by the fact that no one yet knows why only about 6% of the children born to women who drank heavily during pregnancy display the classic signs of FAS. "Not every fetus exposed to alcohol will show effects," Savage says. "There are probably genetic predispositions and environmental factors that we have very little understanding of." Although the current research doesn't imply that a single drink by a pregnant woman would necessarily harm her fetus, it strongly suggests that even light to moderate regular drinking could have lasting effects. Says Charness: "If one of my daughters were pregnant, I'd tell her not to drink at all."

–Stephen Braun

Stephen Braun's book, Buzz: The Science and Lore of Alcohol and Caffeine, *will be published by Oxford University Press this fall.*

EVOLUTIONARY BIOLOGY

Genes vs. Teams: Weighing Group Tactics in Evolution

In the Olympics of life, most evolutionary biologists say, it is the individual's score that counts. Individual organisms compete with each other, and the winner is the one that passes the most genes to the next generation. But some evolutionary biologists have argued that this view overlooks the struggles and strategies of "teams"—whether they be species, groups of cells, or groups of organisms—in the evolutionary race. And although the idea of group selection was discredited more than 30 years ago, a growing number of researchers say that it deserves a fresh hearing. Group selection, they say, may explain patterns ranging from how cells are kept in check in a developing organism, to the evolution of honeybee dancing, to the way plants grow in a crowded field.

"There are many levels of selection," says David Sloan Wilson, an evolutionary biologist at New York's Binghamton University, "and the group level is probably far more common in nature than is currently recognized." The idea has gained ground in recent years as an increasing number of biologists chafe against the idea that individual competition explains every aspect of evolution. For example, Wilson argues, it does not explain why parasites seem to strike some balance with their hosts, rather than maximizing their virulence as mainstream evolutionary theory would predict.

So he and other partisans are re-entering the arena armed with new models and data that they say answer some of the key criticisms aimed at group selection: that it is weak theoretically, is hard to measure, and lacks hard evidence from the field. Wilson and others will have their say at a symposium next week when the American Society of Naturalists meets jointly with the Ecological Society of America in Providence, Rhode Island, and they are expecting plenty of attention. Notes Yale University invertebrate zoologist and evolutionary theorist Leo W. Buss, "Multilevel selection theory calls into question the sufficiency of the existing genetic theory of evolution. Contrary to current thinking, the history of life cannot be told solely by the frequency of alleles."

Group selection's critics, however, aren't expecting the theory to perform any better in this round than it has in the past. It just isn't necessary to explain the patterns seen in the natural world, they say. "Is there anything in evolution that can't be answered by individual selection, that needs to be explained by selection acting on groups?" asks Jerry Coyne, an evolutionary geneticist at the University of Chicago. "I can't think of any."

Although the concept of group selection dates back to Darwin, it wasn't seriously debated until 1962. In that year, V. C. Wynne-Edwards, an evolutionary biologist at the University of Aberdeen in the United Kingdom, published his book, *Animal Dispersion in Relation to Social Behaviour*, arguing that many social behaviors evolved for the greater good of the group. For example, dominance hierarchies may have evolved in some primate species to reduce intragroup conflict and so promote an efficient community. But only 4 years later, George C. Williams, an evolutionary biologist at the State University of New York, Stony Brook, showed the fallacy of such thinking in his book, *Adaptation and Natural Selection*. Most tellingly, he pointed out that selection is much faster at the level of the individual than at that of the group—a recognition that ultimately led biologists to focus on the individual organism as the vehicle of selection. In this view, the primates' dominance hierarchy actually evolved not as a group benefit, but as a contest between individuals competing to get their genes into the next generation.

TOM SEELEY/CORNELL UNIV.

Do bees do it? Some biologists say honeybee social behavior like this "waggle" dance is a product of group selection.

After that, group selection seemed dead. But Wilson and others began reviving—and reinventing—the idea about 20 years ago. Even if selection acts primarily on the genes of individuals, Wilson argues, it is also felt at other levels, which in his view may be the cells in a multicellular organism, a parasite