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Fetal Brains Suffer Badly From Effects of Alcohol

By LINDA CARROLL

Thirty years ago, scientists linked prenatal alcohol exposure with a perplexing pattern of birth defects including neurological problems, low birth weight, mental retardation and a set of facial malformations.

Up to that time, many doctors had assumed that alcohol was so harmless that it was sometimes administered intravenously to women who were thought to be at risk of losing their pregnancies.

But in recent decades, scientists have discovered that alcohol can be remarkably toxic — more than any other abused drug — to developing fetuses. New research with imaging techniques is helping experts uncover which parts of the developing brain are damaged by alcohol exposure.

By pinpointing the damaged areas, they are beginning to understand the origins of the problem behaviors and learning disabilities linked to alcohol.

Scientists are also homing in on a protein important to the developing brain that is affected by alcohol. It is possible, they say, that a medication can be created to protect the brains of developing fetuses, even if pregnant women cannot quit drinking.

It is not surprising that it has taken researchers so long to tease

out the link between alcohol exposure and birth defects. For one thing, the effects of alcohol exposure seem to vary widely.

Some fetuses seem to escape unscathed, even when their mothers drink heavily, while others are severely damaged. No one knows why.

"It's not like thalidomide, where anyone who took it had an affected child," said Dr. Sandra W. Jacobson, a professor at Wayne State School of Medicine in Detroit, referring to the morning-sickness drug linked to birth defects in the late 1950's and early 1960's. "There's a range with alcohol. You might get the full-blown syndrome in 4 out of 100 heavy drinkers."

There are also many babies who are affected, but not severely enough for the syndrome to be diagnosed. Some with fetal alcohol effects may appear relatively normal but have behavioral problems and learning deficits like those with the syndrome.

Further complicating matters is the question of how much alcohol it takes to cause harm. In the past few years, successive studies have shown an effect at increasingly lower levels. One study, published last year, found a small but significant effect on average in children born to women who consumed just a drink and a half a week.

"We were surprised by this," said the lead author, Dr. Nancy Day, a professor of psychiatry at the Western Psychiatric Institute and Clinic in Pittsburgh. The women in the study were recruited from a prenatal clinic between May 1983 and July 1985.

"The children were in the normal range of growth," Dr. Day said, "but if you compare them to children whose mothers didn't drink at all, they weighed less, were shorter and had smaller head circumferences."

The effect of low levels of alcohol appears to be subtle, said Dr. James R. West, head of the department of anatomy and neurobiology at the Texas A&M medical school.

"Perhaps instead of having an I.Q. of 120, you might end up with 115," he said. "You might seem perfectly normal, but not have the motor skills to make the high school football team."

Another factor making it difficult to tease out the impact of alcohol is its widespread effects on the developing brain and body.

"Alcohol is a dirty drug," Dr. West added. "It affects a number of different neurotransmitters, and all cells can take it up." Compare this with cocaine, Dr. West said, which is taken up by only one neurotransmitter.

It is also difficult to identify the effects of alcohol because a woman's drinking habits seem to make a big difference. Experts say it matters when a pregnant woman drinks, how often she drinks and what her pattern of drinking is: whether she drinks small amounts daily or periodically binges.

Drinking in the first trimester can lead to facial malformations, while in the second it can interrupt nerve formation in the brain, Dr. West said. During the third, it can kill existing neurons and interfere with nervous system development, he added.

Researchers have also determined that babies are more likely to be affected if mothers drink in a binge pattern, like five drinks one day rather than a single drink daily, Dr. Jacobson of Wayne State said.

Because alcohol affects so many sites in the brain, researchers have come to believe that alcohol is far worse for the developing fetus than any other abused drug.

Dr. Jacobson's study included cocaine users who also used varying quantities of alcohol. "We found more serious cognitive impairment in relation to alcohol than cocaine or other drugs, including marijuana and smoking," Dr. Jacobson said.

The damage done to fetuses often has been wrongly connected to cocaine, many experts say.

"The consensus, I think, at this point is that most of the adverse effects that had been reported due to cocaine and crack use were from alcohol use," said Dr. Kenneth R. Warren, the director of the office of scientific affairs at the National Institute on Alcohol Abuse and Alcoholism. "It is the leading cause of birth defects due to an ingested environmental substance in this country."

In 1973, researchers coined the phrase fetal alcohol syndrome to describe babies born with a certain pattern of neurologic and physiologic defects related to alcohol exposure in utero.

Early on, it was clear that exposed children were wired differently from normal ones and that they exhibited an array of disabilities.

Dr. Ann P. Streissguth, the director of the fetal alcohol and drug unit at the University of Washington and a professor at the medical school there, ticked off a list: "These included attention problems, hyperactivity, learning problems — particularly in arithmetic — language problems, memory problems, fine and gross motor problems, poor impulse control, poor judgment, intellectual deficits and difficulty integrating past experience to plan and organize future behavior."

Researchers wondered whether specific areas of the brain were being consistently harmed by alcohol exposure in utero. Poor judgment, for example, might point to damage to the frontal lobes. The lobes, as the control center of the brain, are involved in planning, organizing and inhibiting inappropriate responses, the researchers say.

Thirty years ago, the only way researchers could learn about the effects of alcohol on the brain was to study children who died shortly after birth.

"We knew from brain autopsies that in severe cases the brains were terribly disorganized," said Dr. Edward P. Riley, the director of the Center for Behavioral Teratology at San Diego State University. Now, researchers use imaging techniques like M.R.I.'s to look at the damage caused by alcohol. Several recent

studies using magnetic resonance imaging have shown damage to the corpus callosum, a band of nerve fibers that connects the left and right sides of the brain.

A report published in 2002 compared the brain scans of adults and children who had severe or mild alcohol-related disabilities with the scans of healthy counterparts. The researchers found that the corpus callosa were abnormally shaped in 80 percent of those who had been exposed to alcohol in utero.

Another study found that the corpus callosum was smaller and shifted forward in children and young adults with the syndrome. Using a technique known as diffusion tensor imaging to look closer at the corpus callosum, researchers at Emory University have seen abnormalities in the myelin, the substance that insulates nerve cells.

When the myelin is damaged, signals do not carry as crisply through the cells, said Dr. Claire D. Coles, director of the Fetal Alcohol Center at the Marcus Institute and a professor of psychiatry and behavioral sciences at Emory.

Another study published in 2002 found that frontal lobe structures were smaller in teenagers and young adults who had been exposed to alcohol prenatally.

By pinpointing which sections of the brain are most likely to be damaged by alcohol, scientists may find a way to block its effects.

Researchers recently recognized that some of alcohol's effects were similar to those experienced by children born with defects in genes that control L1 adhesion cells. Fetal cells that are destined to grow into the brain and nervous system bind to one another with the help of adhesion molecules like L1, said Dr. Michael E. Charness, an associate professor of neurology at Harvard.

In laboratory experiments, Dr. Charness and his colleagues showed that alcohol could interfere with L1's stickiness, thus

hampering crucial cell-to-cell attachments. In an article published in The Proceedings of the National Academy of Sciences in July, they showed that a protein, NAP, could block alcohol's effect on L1. When NAP was given to mice exposed to alcohol, the protein appeared to stave off neurological effects.

"The idea of giving drugs to pregnant women is controversial," Dr. Charness said. "Drugs may have their own risks."

But, he said, there are areas of the world where fetal alcohol syndrome is a huge problem. In parts of South Africa, the incidence of the syndrome in first graders is around 4.5 percent, he said. "The rate of drinking is high," Dr. Charness added. "And the women won't stop drinking despite interventions. It might be reasonable to give them a drug that can prevent the more serious effects of alcohol."