NEURODEVELOPMENT

Cocaine Wreaks Subtle Damage on Developing Brains

It had started to look like yesterday's scare story. Beginning about a decade ago, countless reports on television and in newspapers and magazines presented the image of the sickly, inattentive, and inconsolable "crack baby." The fear was that the infants, who had been exposed to cocaine when their mothers abused the drug while pregnant, had suffered severe, irreversible damage, including reduced intelligence and social skills. But in recent years the news has swung to the opposite extreme: In several follow-up studies conducted on preschoolers and school-age children, researchers could link no significant reductions in intelligence to cocaine exposures in the womb.

GIDEON KOREN/THE HOSPITAL FOR SICK CHILDREN, TORONTO

Hope for the helpless. Pinpointing cocaine's effects on the immature brain may lead to treatments for babies exposed to the drug before birth.

Now that conclusion, too, is looking oversimplified. As researchers find ways to sort out the confounding factors that had weakened earlier studies, they are learning that cocaine leaves its mark on developing brains after all. At a meeting* held last month in Washington, D.C., scientists reported that the latest studies of school-aged children reveal that exposure to cocaine during fetal development may lead to subtle, but significant, deficits later on, especially with behaviors crucial to success in the classroom, such as concentrating for long periods of time and blocking out distractions.

"Cocaine is not a sledgehammer in the developing brain," as some originally feared, says Barry Kosofsky, a developmental neuroscientist at Massachusetts General Hospital and Harvard Medical School in Boston. "Exposed infants are, in general, doing well. But looking at more subtle characteristics, there seem to be some real differences in many exposed children."

Studies of animals exposed to cocaine before they were born buttressed that conclusion. Not only did the researchers find behavioral changes similar to those in the children, but they also found specific and permanent changes in the animals' brains. In areas of the brain involved in attention, for example, the animals' brain cells have developed abnormally and respond less efficiently to certain neurotransmitters. Together, say researchers, the epidemiology and the laboratory studies strengthen the case for reducing or preventing prenatal cocaine exposure. They will also enable doctors, parents, and teachers to identify cocaine-exposed children and help them, instead of writing them off as hopelessly damaged.

Snowy picture. Pinning down cocaine's effects on the fetus has been difficult not just because they are often subtle, but because they have to be separated out from those that might be caused by a host of other assaults on the child that often accompany maternal drug abuse. Women who use cocaine during pregnancy are also many times more likely to abuse alcohol, tobacco, and other drugs. They are less likely to get proper prenatal care, and are more likely to give birth to underweight and premature babies. Because the fear of prosecution or separation from their baby makes many women reluctant to admit that they have used cocaine, researchers have a hard time sorting cases from controls. And even in known users, documenting how much cocaine they consume and when is impossible.

Now, however, researchers are using complex statistical methods to sort through the confounding factors, and they are analyzing the hair and urine of infants and mothers as well as newborn feces (meconium) to identify cocaine users and their babies more reliably. These more rigorous studies are beginning to show significant—and consistent—results.

One study comes from pediatrician Ira Chasnoff of the University of Illinois College of Medicine in Chicago, who was among the first to report the effects of cocaine on behavior in newborns. At the meeting, he described his prospective study of nearly 200 children in inner-city Chicago. The team recruited pregnant mothers in drug-treatment programs and conducted random drug tests throughout pregnancy. During follow-up studies, the researchers collected information on the home environment, including the mother's current drug use. They correlated these data with intelligence quotient (IQ) test results and a detailed assessment of the children's behavior from questionnaires filled out by the child's primary caregiver and teacher.

When he and his colleagues did a careful statistical analysis of the correlations, they found support for the idea that prenatal cocaine exposure may have a limited impact on intelligence. The home environment—in particular whether the mother was currently using drugs—turned out to be the strongest predictor of IQ, overwhelming any prenatal effects of cocaine. As Chasnoff puts it, "The greatest impediment to cognitive development in young children is poverty."

The team also found, however, that children exposed to cocaine prenatally have significantly more behavioral problems. Their mothers and their teachers reported that as a group, cocaine-exposed children were more aggressive, had more trouble paying attention and staying focused, and were more likely to be impulsive. At the same time, they were more anxious and depressed.

Developmental pediatrician Linda Mayes of Yale University reported similar results in direct tests of children. She heads a team that has been following a group of 475 children in inner-city New Haven for 6 years. About half of their mothers either admitted to using cocaine or had a drug-positive urine test while pregnant. The researchers decided to focus on attention and arousal, she says, because cocaine affects the brain's dopamine and serotonin systems, which play key roles in regulating those behaviors (see p. 35).

The team began detecting cocaine-related effects in infants as young as 3 to 6 months. The cocaine-exposed babies were more irritable than those in the comparison group (babies exposed to alcohol, tobacco, and other drugs, but not cocaine) on standard assessments of infant development—a conclusion supported by other researchers. At a year or a year and a half, the cocaine-exposed children began showing signs that they were having trouble focusing their attention. When given a box of toys, for example, they spent less time exploring the new toys than did the control children. Instead they would look aimlessly around the room or hold a toy without exploring it, Mayes says.

The latest data, from 125 children who are

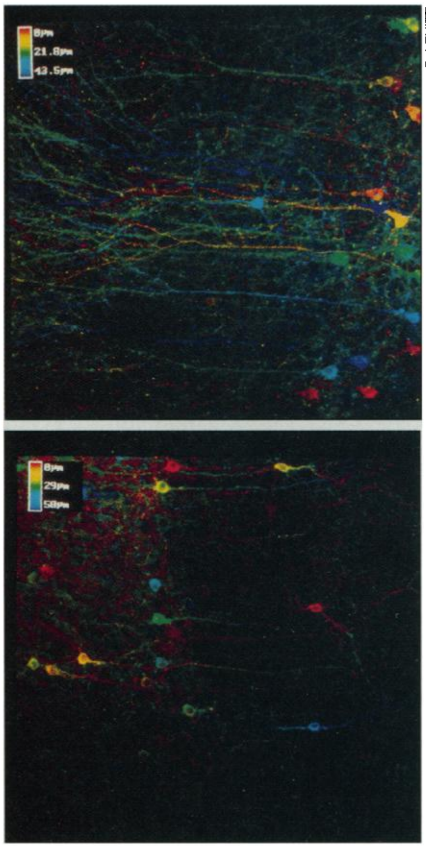
* The meeting, "Cocaine: Effects on the Developing Brain," was held from 16 to 19 September and sponsored by the New York Academy of Sciences and Allegheny University of the Health Sciences.

now 4-and-a-half years old, shows that their problems with focusing and blocking out distractions have persisted. When the researchers asked the children to hit a button whenever a certain picture, say of a car, flashed on a computer screen, the cocaine-exposed children actually responded faster than their peers. But when the researchers complicated the game by adding pictures of houses or people, which the children were instructed to ignore, the cocaine-exposed children had much more trouble. While they still reacted faster than control groups, they responded to the distracting pictures more often. This suggests, says Mayes, that cocaine-exposed kids are more impulsive and more easily distracted than their peers. At the same time, they are less easily startled by a sudden noise.

The overall picture, Mayes says, is of a child who has a higher threshold for arousal, but once aroused, is harder to control. Chicago's Chasnoff agrees. "The kids are more fragile," he says. Although these deficits do not directly impact intelligence, they are a severe handicap in the classroom. "It's much harder for these children to concentrate on what their teacher is saying when there are competing stimuli," such as a sunbeam through a window or a strange noise, says neuroscientist John Harvey of Allegheny University of the Health Sciences in Philadelphia.

Similar cocaine-induced behavioral problems are also cropping up in lab animals, which opens the way to drawing precise links between the behavioral effects and changes in the brain. Some of this work comes from Harvey's team. In one test, for example, the researchers trained cocaine-exposed and control rabbits to blink in response to a warning tone or light, which preceded a puff of air aimed into the rabbits' eyes. As long as the task was kept simple, the cocaine group had no problem learning the response. In fact, just like the children, they reacted faster than controls did.

But when the researchers made the task more complicated by adding a different neutral tone that was not followed by the puff of air, the cocaine-exposed animals "just fell apart," Harvey says. They had trouble paying attention to the correct tone, especially if the neutral tone was louder or longer—more "salient"—than the real warning. Although rabbit and human brains are quite different, all of this sounded very familiar, says Chasnoff, who heard Harvey's talk at the meeting. "I wanted to jump up and say, 'You're talking about our children!' " he says. "I didn't expect it to be so similar."



P. LEVITT

Roots of attention? Neurons from normal rabbits *(top)* grow in a single plane. But in cocaine-exposed rabbits *(bottom)*, longer extensions weave through several planes. (Color key indicates depth in micrometers.)

Cellular clues. Other researchers at the meeting presented clues to how cocaine might cause such specific behavior changes. Although the drug has many global effects—constricting blood vessels, for example—its specific action is to prevent neurons from taking up certain neurotransmitters, such as serotonin and dopamine, after these chemicals have been dumped into the spaces between the cells. This causes brain levels of the neurotransmitters to surge. Studies in rabbits and mice now suggest that by exposing the brain to such high levels of the transmitters early on, cocaine causes it to undergo permanent changes in an attempt to compensate.

For example, Harvey's Allegheny colleague, Eitan Friedman, reported that the number of cell surface receptors for dopamine in cocaine-exposed rabbit brains is normal, but these receptors do not transmit their signal into the cells as efficiently as do those in normal brains. In studies of one particular type of dopamine receptor, designated D1, the Allegheny team found a clue as to why the receptor efficiency is reduced. The D1 receptor in neurons relays the dopamine signal into a cell by associating with a protein called G_s. In cocaine-exposed brains, however, that association is weakened.

No one has yet made a direct connection between the weakened signaling that results and the changes in the animals' behavior. But the finding is consistent with other changes seen in the brains of rabbits exposed to cocaine. When the dopamine binds to the D1 receptor in normal brains during development, it inhibits the growth of the neuronal extensions called dendrites. In cocaine-exposed brains, however, this growth limiter may not be working properly, as Pat Levitt of the University of Pittsburgh School of Medicine found.

Levitt studied the same rabbit model as the Allegheny team used, looking carefully at the development of brain cells in the anterior cingulate cortex, a part of the brain known to be involved in attention and learning. In cocaine-exposed brains, he found, the dendrites grow 30% to 50% longer, and—perhaps to accommodate their length—seem to weave in and around one another. Neurobiologist Hazel Murphy, also of Allegheny, has shown that the longer neurons have more connections to one another. What effect these changes have on cognition is difficult to say, Levitt says, "but clearly the circuitry is not normal" in areas involved in attention and learning.

The change in the D1 receptor may also help explain the anecdotal reports that some children with impaired attention due to drug exposure do not respond as well to stimulants, like Ritalin, that help other children, says Harvard's Kosofsky. Ritalin acts much like the drug amphetamine, increasing the release of dopamine into the gap between brain cells. But if the problems are related to ineffective signaling through that receptor, such a drug would do little to help. Kosofsky is currently testing drugs that stimulate the cellular response to the dopamine receptor to see if he can lessen the behavioral deficits caused by cocaine in mice.

In the meantime, he and others are looking for ways to exploit their findings. Now that scientists know what behaviors to watch for as a result of cocaine exposure in the womb, they can begin to figure out which kids born to cocaine-addicted mothers will need help and what kinds of intervention will work best. For example, he says, "if mom does a little less drugs, is her child less vulnerable? If you intervene postnatally, is the outcome going to be better?" Such studies, he says, may show how to soften the "double whammy from nature and nurture" that these children have received.

–Gretchen Vogel

Additional Reading

P. Levitt *et al.*, "New evidence for neurotransmitter influences on brain development," *Trends in Neuroscience* **20**, 269 (1997).

V. Delaney-Black *et al.*, "Prenatal cocaine and neonatal outcome: Evaluation of dose-response relationship," *Pediatrics* **98**, 735 (1996).

L. Mayes *et al.*, "Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine," *Pediatrics* **95**, 539 (1995).