

The Maternal Cocaine Connection

A tiny, unwitting victim may bear the brunt of drug abuse

By KATHY A. FACKELMANN

The year is 1886. A new bride suffering from melancholia seeks treatment from the local pharmacist, who advises sniffing powdered cocaine. A wonderful new drug, he tells her.

And it is. The veil of depression lifts. She feels giddy, euphoric and energetic. Months later, still taking the miraculous powder, she discovers that she is with child. Her visits to the druggist become even more frequent: What cheers the mother, she reasons, must be good for the baby.

Cocaine's heyday as a legally sanctioned pick-me-up has long since past. Nonetheless, the drug is today distributed illicitly in nearly every U.S. city and most rural areas. Half a million women of childbearing age have tried cocaine at least once, according to the Department of Health and Human Services. And several studies have indicated that as many as one of every four mothers who give birth at inner-city hospitals have used cocaine during pregnancy.

Although cardiologists have linked cocaine abuse to a risky type of heartbeat in adults, teratologists — who study chemically induced birth defects — say they know very little about what happens to an embryo or fetus when the mother snorts, shoots or smokes cocaine.

Recent teratological studies do offer some tantalizing clues, however. Preliminary research with mice, rats and monkeys suggests that cocaine's *in utero* effects may include vascular abnormalities and neurological damage, according to reports presented in June at the joint meeting of the Teratology Society and the Neurobehavioral Teratology Society, held in Boca Raton, Fla.

The investigators acknowledge that laboratory animals seem far removed from the world inhabited by human cocaine addicts. Yet they note that these studies remain crucial to understanding how drugs ingested by a mother can interact with her fetus.

"We would like to be able to give accurate information to pregnant women," says William Slikker Jr. of the FDA's National Center for Toxicological Research in Jefferson, Ark. Hard facts

about drug-induced fetal damage might deter some women from taking cocaine during pregnancy. And for mothers who can't kick the addiction, Slikker says, animal research might suggest ways to help protect the vulnerable embryo or fetus.

Many factors, including genetics and the timing of drug exposure, play a role in the development of birth defects. For example, from the moment the sperm fertilizes the egg until the second week of life, the tiny, dividing egg remains relatively impervious to damaging chemicals, or teratogens. From the second through the eighth week, however, teratogens can damage the embryonic organs and body parts. Indeed, virtually all of the so-called "frank" malformations — overt birth defects such as cleft palates and missing limbs — arise during the embryonic stage.

Although studies have yet to demonstrate that cocaine causes such birth defects in humans, anecdotal reports suggest that mothers who use cocaine during pregnancy are more likely to deliver malformed babies. The illegal stimulant's continued popularity among a large fraction of fertile women has some researchers worried about its potential to trigger structural defects during the critical embryonic period.

Ernest F. Zimmerman, a teratologist with the University of Cincinnati and Children's Hospital Medical Center, set out to determine whether cocaine might cause such abnormalities in mice. He and his co-workers began by injecting some pregnant mice with varying doses of cocaine and others with a harmless saline solution. Fifteen to 60 minutes later, they gingerly removed the 8-day-old embryos and placed them in glass bottles filled with serum, the clear, plasma portion of blood.

The 75 cocaine-exposed embryos and the 17 controls continued their development in these artificial "wombs." After 48 hours, the researchers compared the embryos and discovered that those ex-

posed to cocaine *in utero* showed a "dramatic" pooling of blood in various parts of the developing body, Zimmerman says.

Although the significance of the pooling remains unclear, he and his colleagues hope to learn whether such vascular changes might somehow cause malformations in the embryo. If so, then studies of the biological processes underlying those effects might eventually help scientists find a way to prevent or reverse the cocaine-induced damage, he suggests.

By the end of the second month of gestation, the unborn child — now called a fetus — has developed fingers, toes, arms and legs. Chemicals in the mother's bloodstream generally don't cause frank malformations once the fetal stage has begun. However, the fetus does remain vulnerable to chemically induced brain damage or growth impairment.

How much cocaine exposure does the fetus experience in the womb of an addicted mother? That basic question proves tricky to answer, because there's no direct connection between the maternal and fetal bloodstreams. The two systems are separated by the complex structure known as the placenta, which functions as a highly selective gatekeeper. Although scientists know that cocaine can penetrate the placental barrier, they have had difficulty measuring the precise amounts that get through.

An animal study has now yielded such measurements. Merle G. Paule and his colleagues at the National Center for Toxicological Research in Jefferson anesthetized four monkeys in the third trimester of pregnancy. They then gave each monkey an injection of 1 milligram cocaine per kilogram of body weight — roughly comparable to the dose received when an average-sized human snorts less than one-tenth of a gram of cocaine, Paule says.

Over the next eight hours, with the monkeys still under anesthesia, the team collected blood through tubes inserted into maternal and fetal veins. Analyses of

these samples revealed that blood cocaine concentrations peaked within 10 to 20 minutes in the mothers and within 30 to 60 minutes in the fetuses. More important, the researchers discovered that, on average, 30 percent of the cocaine circulating in the maternal blood entered the fetal circulation.

That's a "significant" amount, they say. Moreover, the experimental injections represented only a single dose of snorted cocaine. Paule speculates that blood cocaine levels are likely to be much higher in the fetuses of women who repeatedly smoke crack cocaine or inject the drug intravenously.

This preliminary study suggests that a pregnant woman who uses cocaine risks exposing her fetus to potentially dangerous levels of the drug, Paule concludes. Yet he says he needs more data to prove that risk.

"Some pregnant women will binge and expose themselves to relatively high quantities of cocaine," he says. "We just don't have any feel for what consequences that kind of exposure has on a developing organism."

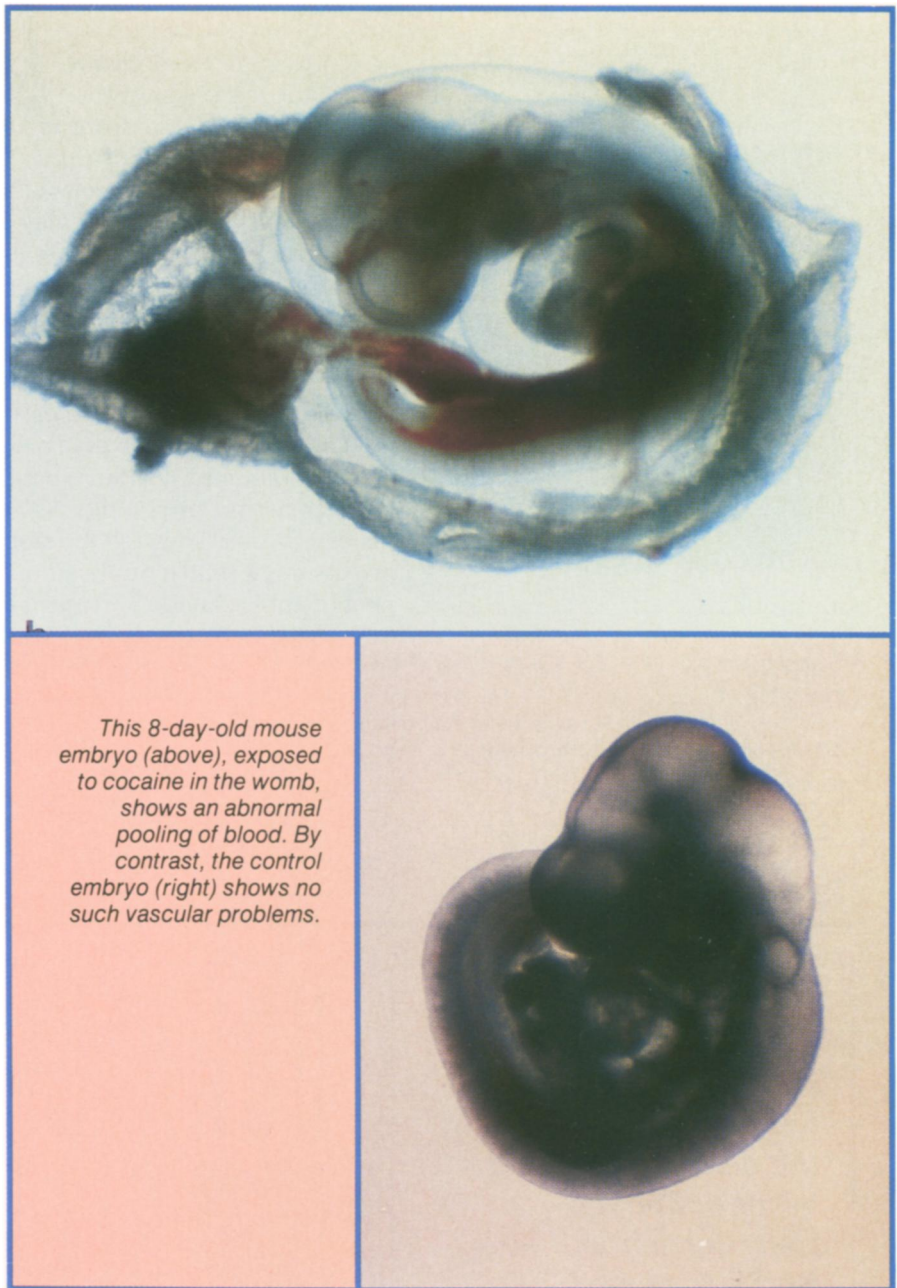
Rat pups provide evidence that cocaine can cause subtle brain damage. Rats exposed to cocaine as fetuses have trouble with simple learning tasks soon after birth, reports Linda P. Spear of the State University of New York at Binghamton.

Spear and her colleagues have observed, for example, that when normal newborn rats receive milk every time they smell a specific odor, they quickly develop a preference for that odor because they associate it with the milk treat. But newborn rats exposed to cocaine *in utero* have great difficulty equating the two, she says.

"It's pretty clear they are having trouble learning," says Spear, who reviewed published data from several of her group's studies at the June meeting.

This finding seems to fit with a human study reported in 1989. Researchers led by Ira J. Chasnoff, a pediatrician at Northwestern University Medical School in Chicago, discovered evidence that human fetuses exposed to cocaine during the first trimester of pregnancy may suffer neurological damage that leads to learning difficulties and behavioral troubles later in life (SN: 4/1/89, p.198).

Indeed, clinicians have noted that so-called crack babies are irritable, cry incessantly, and seem to dislike human contact. Spear and graduate student Lavanya Rajachandran have found evidence that rat pups exposed to cocaine *in utero* show a similar aversion to touch. In humans, such responses interfere with mother-child bonding and may eventually lead to learning deficits, Rajachandran says.



This 8-day-old mouse embryo (above), exposed to cocaine in the womb, shows an abnormal pooling of blood. By contrast, the control embryo (right) shows no such vascular problems.

Photos courtesy of Zimmerman

Teratologists find the new data intriguing, but they emphasize that extensive efforts are needed to establish the details of cocaine's *in utero* impact. Many key questions remain. For example, does cocaine itself cause the neurological problems seen in newborn rats, or does it do its damage through an indirect process?

Maternal cocaine probably follows a complicated path, with multiple mechanisms underlying a variety of effects on the unborn child, says teratologist John M. DeSesso of the Mitre Corp. in McLean, Va. "Unless you've got some really exotic chemical, it's unlikely to have just one effect," he notes.

Furthermore, the drug's prenatal impact is muddled by a tangled interplay of additional influences. Such confounding factors include poor nutrition, smoking and the use of alcohol or other drugs by

the mother, says Nancy Day, an epidemiologist with the Western Psychiatric Institute & Clinic in Pittsburgh.

Day notes that many cocaine addicts also abuse alcohol, which can cause birth defects and learning deficits in their offspring. "I'm not downplaying the problems of drug use during pregnancy," she says, "but I think the [data] suggest we should stop focusing [solely] on cocaine."

It may take years to develop a clear and definitive picture of how — or even whether — cocaine itself harms the human embryo or fetus. But Slikker and others believe animal studies can bring researchers closer to that goal.

"I think we're just beginning to uncover the true effects of cocaine in isolation by using the animal model," Slikker says. And in the long run, he says, revelations such as these may help shield the drug's most fragile and unwitting victims. □