
**AREAS IN WHICH MORE RESEARCH ON THE EFFECTS
OF COCAINE IS NEEDED**

This chapter summarizes three areas in which research can increase understanding of effects of prenatal cocaine exposure: (1) the specific action of cocaine on the developing brain and its manifestation in infants and children, (2) the role of environmental factors that either act alone or interact with cocaine, and (3) community and educational interventions required for cocaine-exposed infants and children.

THE NEUROBIOLOGIC SPECIFICITY OF COCAINE ACTION

Mechanisms of Action of Cocaine

As noted earlier, the precise mechanism of action of cocaine is not well understood. In addition to its influence on neurotransmitters, cocaine can affect the developing brain by inducing hypoxia (oxygen deprivation) through direct toxicity; it can also induce cortical dysgenesis (impaired development of the cortex) by altering aminergic signals required for normal brain growth (Chiriboga, 1998).

Understanding the precise effects of cocaine requires elucidation of the mechanisms of the drug's absorption, distribution, metabolism, and excretion; molecular and cellular alterations following exposure; effects on specific neurochemical systems in the brain; and the interaction or combination of cocaine with other drugs and insults such as malnutrition.

Both animal and human studies support the hypothesis that gestational exposure to cocaine affects the way the fetal brain grows and develops (Chiriboga, 1998; Ferriero, 1998 [Table 1]; Kosofsky and Wilkins, 1998; Mayes et al., 1998; Nassogne, Evrard, and Courtoy, 1998; Romano and Harvey, 1998). There is also a dose-response relationship between cocaine exposure and head size (Kosofsky and Wilkins, 1998), although the timing and specificity of the gestational exposure on development and behavior remain to be defined (Ferriero, 1998; Mayes et al., 1998).

It is not clear how the structural changes apparent in the brains of cocaine-exposed animals and humans cause cognitive and/or behavioral deficits. For example, cocaine-exposed infants have lower mean head circumferences than do unexposed infants, and microcephaly (small head size) predicts poor cognitive performance; however, the way in which microcephaly leads to poor performance is not understood (Chiriboga, 1998; Nassogne et al., 1998).

Mayes et al. (1998) present three plausible links between prenatal cocaine exposure and the mechanisms affecting cognition and behavior, specifically, arousal and attention regulation in infants and preschool-age children. These links may be attributable to the association of prenatal cocaine exposure with (1) alterations in the development and function of the monoaminergic systems, (2) alterations in brain structures underlying the response to stress (the brain systems that secrete hormones during stressful events such as disease and injury are important for recovery), and (3) alterations in other brain systems that mediate regulation of arousal (Mayes et al., 1998).

Animal models have helped to elucidate some of the relationships between brain structure and neurobehavioral function. For example, cocaine-exposed rabbits display abnormal structural and neurochemical development of the anterior cingulate cortex, a region of the brain known to be involved in associative learning, attentional processes, and motor function (Romano and Harvey, 1998). Cocaine-exposed rabbits demonstrate impairments in motor function, associative learning, and discrimination learning, which Romano and Harvey (1998) interpret as a consequence of deficits in attentional processes caused by the abnormalities within the damaged anterior cingulate cortex.

Thus, although animal and human studies indicate that gestational exposure to cocaine affects the growth and development of the brain, it is not yet clear how the structural changes in the brain cause cognitive or behavioral deficits. Preclinical and clinical research is needed gain a better understanding of the neurobiologic specificity of cocaine's action in the developing human brain.

Compensatory Mechanisms in the Developing Brain

One of the conundrums in studies of children prenatally exposed to cocaine is that although some of them suffer neurobehavioral injuries (Chasnoff et al., 1998; Lester, 1998), others with similar exposure do not. One conference attendee noted, "Not every child exposed to cocaine demonstrates brain growth retardation, inattention, cognitive impairments, or language delay. Even those children with a significant cocaine exposure and evidence of developmental compromise may not demonstrate all of these deficits" (see Kosofsky and Wilkins, 1998). Understanding how some children compensate for the effects of cocaine exposure is therefore very important.

The dose of cocaine that the fetus is exposed to will influence the outcome in the infant and child. As in the case of fetuses exposed to alcohol, there appears to be a relationship between higher levels of maternal cocaine use and greater incidence and severity of deficits in the exposed infants and children (Delaney-Black et al., 1998; Richardson, 1998). However, genetic and environmental factors are also likely to influence the incidence and severity of intrauterine cocaine exposure, and there has as yet been no demonstration of a lower limit (threshold) of drug exposure known to be safe, nor is sufficient information available to establish the dose-response relationship for the amount of maternal cocaine use and outcome.

Animal models of brain development suggest that the developing nervous system is remarkably plastic (Spear et al., 1998). However, while the developing brain may use compensatory processes to overcome the effects of early drug exposure, such neural compensation may have a cost: It may cause a decrease in the adaptability of the animal when stressed. A number of studies substantiate this argument. Dr. Theodore Slotkin, a conference participant, noted, "There

may be sufficient adaptations to normalize the essential behaviors that you need to survive as a human being, but it may be adaptability that's compromised" (Harvey and Kosofsky, 1998, p. 153).

Thus, more research is needed to understand the specific mechanisms of compensation and their location and timing. Particularly valuable will be research to identify specific "recoverable deficits" so that treatments and interventions can be devised that promote compensation and recovery for cocaine-exposed children.

Adaptability in Stressful Situations

The relief provided by compensatory mechanisms has limits, and the mechanisms can break down under stress. Several animal studies demonstrate that cocaine-exposed offspring differ from control animals in their behavioral response to stressful and environmentally challenging situations (Spear et al., 1998). When confronted with stressful situations, for example, normal adult rats typically exhibit increased immobility, whereas adult rats that were exposed to cocaine *in utero* show much less of the immobility response. Cocaine-exposed rats are hyperresponsive in stressful situations, exhibiting excessive fearfulness and frantic behavior (Church et al., 1998).

In clinical populations, infants and preschool-age children exposed to cocaine *in utero* exhibit a low threshold for activating their "stress circuits" when confronted with novel challenges (Mayes et al., 1998); thus, they may be particularly vulnerable to the detrimental effects of stressful environmental conditions. Further, cocaine-exposed children appear to have a pattern of altered stress response that manifests itself by blunting the usual patterns of increased arousal in stressful situations. As a result, cocaine-exposed children need more stimulation to reach optimal states of arousal for responsiveness; at the same time, they can quickly become overaroused, inattentive, and poorly responsive. In other words, while they require more stimulation to increase arousal and attention, they modulate higher states of arousal less well (Mayes et al., 1998). Additional research is needed to discern the relationship between cocaine exposure and limits of adaptability in response to stress.

Clinical Markers of Brain Injury

Clinical markers of neural injury caused by prenatal cocaine exposure would help to identify populations of at-risk children and would facilitate the development of appropriate interventions. The available clinical markers, such as impaired brain growth, hypertonia (muscle stiffness), and impairment of cognitive function, are neither sensitive nor specific because they may also occur in alcohol- or opiate-exposed or malnourished children (see above). However, in the presence of evidence of prenatal cocaine exposure, such markers can help identify a child at potential risk and can suggest specific interventions for treating the deficits. But care must be exercised not to stigmatize such infants or their mothers.

Another important question relates to whether psychopharmacologic interventions may be effective for exposed children who demonstrate the deficits associated with exposure. For example, it is tempting to think that children who have problems with attention would benefit from the stimulants used to treat attention deficit disorders. However, it is not known whether the same neurochemical pathways are affected in the same way in both groups of children, and thus it is not known whether stimulant therapy would be appropriate. At this time, there are no systematic studies that demonstrate the benefits of any specific psychopharmacological intervention in exposed children.

Identification of specific clinical markers of neural injury from prenatal cocaine exposure would help to identify populations of exposed children at risk and would facilitate the development of appropriate interventions. Research should therefore be conducted to identify clinical markers for the exposed brain during early infancy.

Increased Sensitivity of Tests to Detect Changes in the Brain

At present, a number of tests are used to measure the effect of prenatal cocaine exposure on behavior, including standardized tests such as the Connors Parent and Teacher Rating Scales; the Achenbach Child Behavior Checklist and Teacher Report Form; the Child Behavior Checklist (Parent and Teacher Forms); and the Problem Behavior

Scale (Delaney-Black et al., 1998). Although such tests are generally easy to administer and score, none of them is specific for cocaine (Chiriboga, 1998). Research-based clinical tools have also been developed to investigate the effects of cocaine exposure; for example, Mayes et al. (1998) measure the startle response, which they believe reflects arousal. Although useful, such clinical tests need to be standardized, replicated in other laboratories, and tested in larger populations of cocaine-exposed children.

A fundamental issue for all of these tests is that of whether to use a deviant or discriminant approach in assessing the effect of prenatal cocaine exposure. As discussed by Karmel (Harvey and Kosofsky, 1998, p. 341), commonly used tests such as the global IQ test follow a deviant approach, where the test population is compared to an average, "normed" population and is tested for deviation. This approach may lead to an incorrect attribution of the factors contributing to the deviance from the norm. For example, infants and children raised in impoverished environments demonstrate impaired performance on IQ tests (Lester, 1998). Because many cocaine-exposed infants are raised in impoverished environments, a comparison of performance of such children may incorrectly attribute their impairments to the cocaine exposure rather than to poverty.

A discriminant approach takes into account some of the uniqueness of the particular population being studied and can therefore be more informative. For example, comparison of the outcomes of cocaine-exposed children raised in impoverished environments with non-cocaine-exposed infants from similarly impoverished environments is much more likely to reveal meaningful differences that are specifically attributable to cocaine exposure.

THE ROLE OF THE ENVIRONMENT AND OTHER FACTORS

Because the environment and other factors influence the manifestation of cocaine-induced intrauterine insults, it is important to understand their relative contributions to the problems seen in infants and children. The wide range of outcomes reported in cocaine-exposed children may result partly from factors other than, or interactive with, cocaine. For example, the arousal response is affected by environmental factors as well as by cocaine exposure (Mayes et al., 1998). Cocaine-exposed infants are often born to families with mul-

tiple social problems, including poverty and ongoing drug/alcohol use, that lead to a less stimulating and organized home environment, which affects arousal (Koren et al., 1998, Table 1; Richardson, 1998). Cocaine-using mothers are also more likely to report a history of school-related problems, presumably prior to drug use; such problems manifest as attention deficits and learning disabilities similar to those exhibited by prenatally exposed children (Slotkin, 1998). Malnutrition during pregnancy, common among cocaine-using women, also leads to some of the same physical symptoms in their children as those observed in children prenatally exposed to cocaine (Santolaria-Fernandez et al., 1995).

Teasing out the relative contributions of prenatal cocaine exposure and environmental, genetic, and other factors has proven extremely complicated. However, some progress has been made with animal models. For example, studies in rats suggest that cocaine exposure and malnutrition may have both independent and interactive effects (Galler and Tonkiss, 1998). In these studies, prenatal cocaine exposure and malnutrition both resulted in lower birth weight and delayed physical and neurological (reflexive) development; these impairments were additive when the rats were exposed to both insults. On tests of spatial orientation, however, prenatal cocaine exposure and malnutrition resulted in different deficits, and the impairments were not additive (Galler and Tonkiss, 1998). Other studies of postnatal behavior in mice have identified the relative contributions of cocaine-induced malnutrition, which has an indirect effect on development, and the direct effect of prenatal cocaine exposure. Both malnutrition and cocaine exposure contribute to deficits in blocking (i.e., inability to ignore redundant or extraneous information), suggesting impairments in selective attention (Kosofsky and Wilkins, 1998).

Relevant animal models to assess some other behaviors and deficits, such as selective language delay, are not currently available (Kosofsky and Wilkins, 1998). Kosofsky and Wilkins have argued that “the laboratory setting is an artificial one and may not simulate the real-world challenges that tax the particular behaviors that may be compromised in cocaine-exposed offspring” (p. 257). Several ongoing research projects are now focusing on resolving such complexities.

The Toronto Adoption Study is designed to sort out the role of cocaine exposure while controlling for the postnatal environment. This study found that with prematurity and the postnatal environment controlled for, *in utero* cocaine exposure resulted in decreased postnatal brain growth, significant language delays, and a trend toward decreased IQ in 23 preschool children up to 2 years of age who had been adopted by middle- to upper-class families (Koren et al., 1998). Unfortunately, the investigators were not able to control for concurrent maternal alcohol and tobacco use.

Chasnoff et al. (1998) have examined the interaction of biological and environmental factors on the cognitive and behavioral development of children prenatally exposed to cocaine. Prenatal cocaine exposure was not found to directly affect IQ, but the home environment in families where cocaine was being used did indirectly affect IQ. However, Chasnoff et al. (1998) found that cocaine exposure had a direct adverse impact on the child's behavioral characteristics, in particular, on the child's ability to self-regulate emotional states and transitions.

Bendersky and Lewis (1998) investigated the effect of cocaine exposure on impulse control, taking into account medical factors, exposures to other substances, and caregiver behavior. They found that exposed children exhibited less impulse control than did unexposed children; however impulse control was also influenced by the caregiver's behavior, suggesting that both intrinsic and environmental factors contribute to a child's behavior.

The studies cited above demonstrate the complex influence of cocaine on a child's behavior and the influence on such behavior of myriad environmental factors. Further research is needed to identify the independent and interactive biological and environmental determinants of behavior in children exposed to cocaine *in utero*.

COMMUNITY AND EDUCATIONAL INTERVENTIONS

Treatment and Education Interventions

There is scant information available about treatment or educational interventions for children prenatally exposed to cocaine. Such children frequently experience a host of other difficulties, such as un-

stable families, poverty, and multiple substance abuse. As discussed above, no systematic studies have demonstrated the benefits of any specific psychopharmacological intervention for children with deficits associated with prenatal exposure to cocaine. Therefore, addressing the psychosocial problems of exposed children with support services and school- or community-based interventions is of more immediate concern. Such interventions must be closely tailored to the individual strengths, weaknesses, and specific needs of the affected child. Although no programs have been developed to meet the specific needs of cocaine-exposed children, several studies have provided evidence that well-designed intervention programs are effective.

A team of RAND investigators recently reviewed nine early-childhood intervention programs and found that each one had a favorable impact on one or more developmental, educational, economic, or health indicators measured in children at risk for a host of problems (Karoly et al., 1998). Although the analyses did not represent a complete accounting of program benefits, and most of the evaluations did not include long-term follow-up, the results showed that children in these intervention programs experienced gains in emotional or cognitive development, improvements in educational process and outcomes, and reduced levels of criminal activity. The interventions also resulted in improved parent-child relationships; increased economic self-sufficiency (initially for the parent and later for the child, through greater labor-force participation, higher income, and lower welfare usage); and improvements in health-related indicators, such as child abuse, maternal reproductive health, and maternal substance abuse. In addition, an analysis of long-term costs and benefits for three early intervention programs indicated substantial financial savings to the government (taxpayers) that far exceeded program costs.

Education of Providers About Community Resources

Because the effects of prenatal cocaine exposure go beyond the cognitive and medical realm, it is critical for health-care providers to work in tandem with other care providers (child-care providers, educators, and social workers). However, few pediatricians and obstetricians are aware of the shortage of treatment programs in most

communities, and therefore few are able to advise pregnant women appropriately. Third-party payers and constrained budgets in many communities have also led to declining support for prevention and wellness. It is therefore very important that health-care providers and their support staffs be educated about resources that are available to help women and children in their community and to which those in need can be referred.

Given that dealing with children prenatally exposed to cocaine and their mothers requires a community response, the Center for Substance Abuse Treatment has recommended that training involve not only health-care professionals, but also state child-protective services, child welfare, and alcohol and drug program staff—a broad array of interconnected providers that can provide the necessary diversity of expertise (Center for Substance Abuse Treatment, 1993a). The Center for Substance Abuse Treatment has further recommended that the federal government provide training to state agency staffs, and that state agencies should in turn provide training to local programs and to all those involved in the court process. Federal funds for training would probably be required to ensure compliance with such training regulations.