Studies of Cocaine-Exposed Human Infants

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INTRODUCTION

No reminder is necessary that the so-called cocaine problem took society by surprise. It struck the academic, health, political, government, and legal communities and quickly became known as an epidemic. Based on little scientific evidence, early reports of the effects of cocaine were exaggerated (Mayes et al. 1992) and people were soon ready to write off an entire generation of children.

On the positive side of this rush to judgment is the valid concern for the health and development of drug-exposed children. This concern has led to a substantial effort on the part of the scientific community to understand the effects of prenatal drug exposure on the developing child. In a relatively brief amount of time there has been an explosion of research in this area including an infusion of cross-fertilization and interdisciplinary collaboration. No doubt because of the attention that this particular area of scientific inquiry has drawn, the process of scientific inquiry has been accelerated. This process has, however, resulted in some misinformation, compelling society to understand what is known and what is unknown as the second generation begins.

Investigators have begun the second wave of research on in utero cocaine exposure and child outcome. The purpose of this chapter is to review what was learned from the first wave of work and to consider how this knowledge can be applied in the second wave of research. This chapter focuses on neurobehavioral studies and presents a quasi-meta-analysis. The analysis is quasi in the sense that it is more descriptive than statis-tical. One goal of this chapter is to address the question: Is there enough information in the database of neurobehavioral studies to even attempt a formal meta-analysis?

META-ANALYSIS

The Meaning of Neurobehavioral. The starting point for this analysis is to define “neurobehavioral” so that the appropriate corpus of literature can be identified. In actuality, the term "neurobehavior" was developed to refer to older children but is now applied to infants as well. In older children the term refers to an expanded neurological examination that involves sophisticated observation of higher cortical function and motor output, often combined with an assessment of the maturation of the central nervous system (CNS) or a search for minor neurological indica-tors. The authors use the term broadly to reflect the notion that all human experiences have psychosocial as well as biological or organic contexts.

The term "neurobehavioral" recognizes bidirectionality—that biological and behavioral systems dynamically influence each other and that the quality of behavioral and physiological processes is dependent on neural feedback. Neurobehavior becomes the interface of behavior and physiol-ogy and includes neurophysiological mechanisms that mediate specific behaviors or psychological processes. Thus, the authors include the study of specific physiological systems that reflect these neurophysiological mechanisms. For example, some aspects of cardiorespiratory function such as vagal tone (Porges 1991), a measure of respiratory sinus arrhyth-mia, are thought to mediate behavior by facilitating attention. Therefore, this kind of measure would be included as a neurobehavioral measure. On the other hand, studies that are interested in structural defects of the heart would not be included because such studies do not involve a psychological process. Neurobehavioral measures provide an estimate of biobehavioral function and integrate the influences of neurobiology, thought, affect, and experience.

Inclusion Criteria. In order to be included in this chapter, studies had to include a neurobehavioral measure or study a neurobehavioral process in human subjects using cocaine during pregnancy (other drugs could also be present). Based on the criteria used in the Lutiger and colleagues' (1991) meta-analysis on prenatal cocaine exposure and pregnancy outcome, the authors were able to identify a total of 60 neurobehavioral studies. Ten studies that did not include original empirical data (N = 2), acontrol or comparison group (N = 7), inferential statistical analysis (N=2), and publication in a refereed or peer-reviewed journal (N = 1) were excluded (two studies were excluded for more than one methodological limitation). The appendix lists the 50 studies that met the criteria for inclusion in the review.

Subject Characteristics. Inspection of the publication dates of the 50-studies included in the appendix shows the recency of this area of investigation. The first studies of cocaine use during pregnancy and child outcome were published in 1985. However, of the 50 studies, 45(90per-cent) were published since 1989. Not surprisingly, with most of the work being recent, there are very few studies of older children. The majority of subjects were less than 1 month old when tested. Some studies included preterm and term infants. Twenty studies included preterm infants tested before they reached term and 41 studies included term infants. Only seven studies (14 percent) included infants up to 4months of age. In addition, there are only two longitudinal studies (4percent) in which infants have been followed from birth into the second or third year of life. There is considerable variation in the sample size of these studies. The typical sample size for the exposed infants across all 50 studies ranges from 21 to 50; 7 studies were conducted with fewer than 10 exposed infants.

WHAT IS NOT KNOWN

Drug Information. Table 1 shows the drug information from the 50-studies. The table shows the number of studies and the percentage inwhich each drug was reported; the means by which the drug was identi-fied; and the amount, frequency, timing of use, and route of administration. The data clearly show that the cocaine problem is really a polydrug problem; "cocaine only" use was described in only two studies (4 percent). Marijuana (23 percent), alcohol (21 percent), and nicotine (26 percent) are the substances most often used with cocaine. It is surprising that in six studies (12 percent) no information about other drug use was even reported or addressed.

A few studies attempted to address the polydrug problem by controlling for the use of drugs other than cocaine. Four methods were used to control for polydrug effects: stratification, matching, exclusion, and statistical. Depending on the drug, stratification was used in 1 study, matching was used between 1 and 9 times, exclusion of other drugs was used between 3 and 15 times, and statistical control was used between 2and 4 times. In other words, the majority of studies failed to use any method of control for polydrug use. No method of control was reported for phencyclidine (PCP) in 38 studies (76 percent), heroin or barbiturates in 37 studies (74 percent), methadone in 36 studies (72 percent),

TABLE 1. Number and percentage of studies reporting drug information (N = 50).

	Number of Studies	Percentage
Drug type		
Cocaine alone	2	4
Alcohol	21	42
Tobacco	26	52
Marijuana	23	46
Heroin	7	14
Methadone	7	14
Opiates	6	12
PCP	3	6
Amphetamines/methamphetamine	6	12
Methaqualone	1	2
Unspecified narcotics	4	8
Unspecified polydrug use	6	12
Unspecified use of legal drugs (e.g., alcohol and tobacco)	7	14
Not reported	6	12
Method of detection		
Urine only	23	46
Self-report only	2	4
Meconium only	1	2
Urine and self-report	11	22
Meconium and urine	1	2
Hair and urine	1	2
Urine and/or self-report	10	20
Not reported	1	2
Pattern of use		
Frequency of use	3	6
Trimester of use	8	16
Amount used	4	8
Not reported	35	70
Route of administration		
Intranasal	4	8
Intravenous	4	8
Freebase	4	8
Not reported	35	70

marijuana or alcohol in 35 studies (70 percent), tobacco in 33 studies (66percent), and opiates in 32 studies (64 percent).

The term "polydrug use" is also confusing and studies do not explain how they are using the term. For example, polydrug use can mean the simul-taneous use of more than one drug such as when cocaine and alcohol are ingested together. The term can also mean that multiple substances are used but not necessarily together. In the first case, the neurobehavioral outcome may be affected by cross-reactivity or the interaction between two drugs. It has been suggested, for example, that alcohol can potentiate the effects of cocaine. In the second case, different neurobehavioral consequences may result from multiple exposures to different drugs.

Table 1 also shows that the single index of a urine screen was used in almost half of the studies. Urine analysis and self-report account for almost all of the studies. The limitations of these methods are that for women who used drugs during pregnancy but did not use within 72 hours prior to delivery (the range of the urine screen), a urine test for cocaine will be negative and these women could be included in the control group. Similarly, with self-report, a mother who used drugs but denies use may also be included as a control. In the two studies in table 1 mentioned earlier that claimed cocaine as the only drug used, a single urine screen at birth with no history was used as the method of drug detection. Thus, there is a reasonable likelihood that other substances may have been involved.

Meconium assay, which is fast becoming the scientific standard, was used in only two studies. Information on the amount, frequency, timing, and route of administration was reported in only a few studies.

Demographic and Medical Information. Table 2 shows the number and percentage of studies reporting demographic information. It is unfortunate that so little demographic information has been reported in these studies because it makes it virtually impossible to understand the populations on which the neurobehavioral data are based. There appears to be an implicit assumption that studies are conducted on lower socioeconomic status (SES) families but there is little supporting documentation. In addition, there is substantial variability within social class stratum, parenting, childrearing, caretaking, the quality of the physical environment, and factors such as stress and violence—all of which can affect the neuro-developmental outcome of the child. Determining that samples are from lower SES families does not provide an environmental control.

TABLE 2. Number and percentage of included studies reporting demographic information (N = 50).

	Number of Studies	Percentage
Race/ethnicity	50	100
Gender	35	70
Maternal: Age	22	44
SES	10	20
Education	14	28
Welfare status	6	12
Work status	5	10
Prenatal care	32	64

KEY: SES = socioeconomic status.

Table 3 shows the number of studies that have attempted to control for demographic and medical (obstetrical and perinatal) variables. Most studies have not controlled for these factors. Of the methods used to control for confounding variables (demographic or medical), matching was used in 25 studies (50 percent), exclusion in 18 (36 percent), stratification in 4 (8 percent), and statistical control in 7(14-percent) studies. Confounding variables were reported as controlled but the methods were not specified in 7 studies (14 percent).

As with demographic factors, medical factors can also have an effect on child neurobehavioral outcome. The argument is sometimes raised that factors such as prematurity should not be controlled because cocaine may cause prematurity, so that controlling for prematurity would blur the effects of cocaine. The problem with this argument from the neuro-behavioral perspective is that prematurity is known to potentially affect neurodevelopmental outcome. If prematurity is not controlled, it becomes impossible to separate the effects of cocaine from the effects of prematurity on neurobehavior. For example, is the cocaine-exposed preterm infant different from the unexposed premature infant given comparable medical insult and illness history?

Two other interesting if not disturbing findings emerged from this survey. First, of the 50 studies reviewed, only 20 (40 percent) reported that the

TABLE 3. Number and percentage of studies attempting to control for demographic and medical variables (N = 50).

	Number of Studies	Percentage
Demographic variables		
SES	7	14
Race	24	48
Gender	10	20
Maternal age	22	44
Maternal education	5	10
Maternal welfare status	4	8
Maternal work status	1	2
Maternal marital status	2	4
Medical variables		
Prenatal care	14	28
Parity	14	28
Gravidity	8	16
Medical complications	23	46
Prematurity	16	32
Gestational age	20	40
Birthweight	10	20

neurodevelopmental examiners were masked or unaware of the exposure status of the child. Information on masking was not even reported in 24(48 percent) of the studies. The second issue has to do with inter-vention. Intervention services for the mother (e.g., drug treatment), the child (e.g., early intervention), or both are common in this population and can affect neurodevelopmental outcome. Yet, information about such services was not reported in 36 (72 percent) of the studies.

Little is known about the actual environments in which these children are raised or about measures of who the caregivers are. The kind of informa-tion that is necessary includes the number and duration of caretakers; the age of the child with each caretaker; whether relatives or other foster parents are involved; how many other children are being cared for at the same time; continuity of care; and intervention by the protective service system, the healthcare system, the legal system, and the caregiving system. Are these children actually afforded the time to develop adequate interpersonal relationships?

To summarize, the knowledge base of neurodevelopmental studies comes mostly from studies of young infants; the problem is one of polydrug use, not cocaine alone; the methods used to identify exposure status are ques-tionable; and there is a serious confounding of demographic and medical factors. In addition, there appear to be problems in how and what informa-tion is reported in peer-reviewed journals. Basic information such as the route of administration, timing and amount of drug used, social class, masking of examiners, and role of social services is underreported.

WHAT IS KNOWN

Neurobehavioral Effects. The authors divided the neurodevelopmental measures reported in these 50 studies into three domains: behavior, medical, and psychophysiology/neurochemistry. Table 4 shows the neurodevelopmental measures that were used in each of the three domains and the number of studies that showed statistically significant effects related to prenatal drug exposure. Of the 16 measures in the behavior domain, most were used in only one or two studies. Two measures of abstinence were each used in four studies; one measure showed three significant effects, the others showed three nonsignificant effects. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) was used in eight studies, and showed significant effects in seven. However, only one finding from the BNBAS was reported in more than one study. Two studies found poorer habituation in exposed infants.

The medical domain includes 1 study that showed no seizures in exposed infants and 22 studies using the Apgar score, 12 of which showed no effects. In the psychophysiology/neurochemistry domain, most measures were used once or twice.

In a traditional meta-analysis, one goal is to estimate effect sizes and determine whether findings replicate across different studies. Table 5 shows what such an analysis could look like if focused on the behavioral measures. In order to calculate effect size, the number of subjects and mean and standard deviation (SD) per group need to be reported. This information was not available in some of the behavioral studies, hence some are not represented in table 5. Effect size is determined in SD units

TABLE 4. Summary of results of neurodevelopmental studies.

	Number of Studies	
	Significant	Not Significant
Behavior		
BNBAS	7	1
Neonatal Abstinence Score	3	1
Stress/abstinence/withdrawal	1	3
Neurobehavioral status and state organization	1	0
Sucking	1	0
Neonatal perception inventory	0	1
Nursing child assessment of feeding	1	1
Cry	2	0
Glabella reflex	2	0
Movement assessment of infants	1	0
Bayley Scales	0	1
Fagan Test of Infant Intelligence	1	0
Developmental quotient	1	0
Attachment	1	0
Play	1	0
Behavior/development problems	1	0
Neurological		
Seizures	0	1
Apgar scores	10	12
Psychophysiology/neurochemistry		
EEG	2	0
Auditory brainstem response	1	1
Blood pressure	1	0
Respiration	3	0
Heart rate	1	1
Vagal tone	1	0
MRI	0	1
Catecholamines	2	0

and effect type is based on Cohen's criteria, with small, medium, and large effect sizes corresponding to < 0.5 SD, 0.5 to 0.75 SD, and >-0.75SD, respectively. For example, five effects were reported using the BNBAS. The differences between exposed infants and controls

TABLE 5. Summary of effect sizes of neurodevelopmental studies.

Measure	Effect Size	r	r^2	Effect Type
BNBAS				
State organization	1.14	0.48	0.23	Large
Autonomic	0.45	0.19	0.04	Small
Reflexes	0.70	0.33	0.11	Medium
Habituation	0.57	0.26	0.07	Medium
Habituation	0.81	0.37	0.14	Large
MAI				
Muscle tone	1.19	0.51	0.26	Large
Primitive reflexes	0.93	0.41	0.17	Large
Volitional movement	0.64	0.30	0.09	Medium
Fagan Test	0.70	0.33	0.11	Medium
Sucking	0.36	0.15	0.02	Small
Developmental quotient	0.87	0.39	0.15	Large
Play	2.16	0.71	0.50	Large

KEY: BNBAS = Brazelton Neonatal Behavioral Assessment Scale; MAI= Motor Assessment Inventory.

ranged from 0.45 to 1.14 SD, including one small effect, two medium effects, and two large effects. The r value in the table is the correlation between exposure status and the outcome variable. The percentage of variance in the outcome variable explained by exposure status is r^2. On the BNBAS, between 7 and 23 percent of the variance was explained by drug exposure. Habituation appears twice because, as mentioned above, it is the only finding that was reported more than once.

This analysis is meant only to illustrate what could be done, and should not be considered a legitimate meta-analysis for several reasons. First, the analysis assumes that the exposed and control groups have equal sample sizes. Second, the analysis was done on a subset of measures. Third, only one effect (habituation on the BNBAS) was found in more than one study. An adequate meta-analysis requires a consistent set of findings that appear across studies so that effect sizes can be estimated. In short, the authors have concluded that a meta-analysis of behavioral effects is not possible at this time.

As can be seen from the data in tables 1 to 5, knowledge about the effects of in utero cocaine exposure is fairly limited. Most studies have been conducted with young infants using a wide array of instruments, making it difficult to compare findings across studies. Few findings have been replicated and longitudinal data are sorely lacking. There are several issues embedded here. One is the stability and reliability of a finding, which cannot be determined because most studies use an assessment at a single point in time. A repeated-measures design of the same measure within a short period of time would shed light on the stability of a single finding and help determine whether reported effects are transitory or more long lasting. Longitudinal studies are affected by attrition; thus the cohort available for analysis at one point in time is usually different from the cohort available later. If these cohorts represent different populations, the generalizability of the findings is different at one age from another. A related issue is that even if comparable effects are reported across age, the same children may not be affected.

Differences in group mean scores do not reflect individual differences. For example, to show that exposed children differ on the Bayley Scales at 12 and 36 months does not necessarily mean that the children with low scores at 12 months were the same children with low scores at 36 months. Yet this is exactly the information needed from a clinical as well as scientific point of view. Are the same children consistently affected? If they are not, intervention programs would not know which children to target. One would have to conclude that individual differences with regard to effects of drug exposure are not stable.

At this time only one cohort of children has been followed to 3 years of age (Azuma and Chasnoff 1993). At age 3 the drug-exposed children are performing within normal limits on standard intelligence quotient (IQ) tests. There are more drug-exposed children than controls who fall out-side the normal range, and drug-exposed children show lower scores on some subscales of function (e.g., language). However, the average IQ of the drug-exposed and control groups does not differ. This study is complicated by the fact that the mothers were in and out of drug treat-ment and followup. Thus, intervention effects may have mitigated the effects of prenatal drug exposure.

HOW KNOWLEDGE IS MOVING THE SECOND WAVE

The Four A's of Infancy. The subtlety of the effects reported in the Chasnoff study (Chasnoff et al. 1990) is consistent with other reports of short-term and long-term effects. There is a consensus in the literature that when drug effects are observed they tend to be found in more subtle domains of function rather than along gross developmental measures such as general mental or motor developmental scores or IQ.

There has been some attempt to understand the effects of cocaine on development through the study of neurotransmitters and behavior. Monoaminergic neurotransmitters (norepinephrine, dopamine, and serotonin) play an important role in the central control of basic processes, including autonomic function, state regulation, and responses to sensory stimuli. The effects of cocaine on autonomic system activity mediated by monoaminergic transmitters are suggested by findings that elevated circulating norepinephrine levels and heart rates were found in prenatally exposed infants at 2 months of age. A preliminary study provided some evidence that higher levels of norepinephrine were related to poorer responsivity on the BNBAS (Mirochnick et al. 1991).

Cocaine use during pregnancy may very well affect neuroregulatory mechanisms that result in disorders in behavioral regulation. Effects on the monoaminergic system would lead to activity associated with limbic, hypothalamic, and extrapyramidal function (Volpe 1992). Lester and Tronick (1994) (figure 1) suggested that the associated disorders in behavioral regulation are manifest as the "four As of infancy": attention, arousal, affect, and action. These four areas seem to be particularly affected by prenatal drug exposure.

- *Attention* refers to perceptual abilities that relate to the intake and processing of information from the environment.

- *Arousal* includes control and modulation of behavioral states from sleep to waking to crying, ability to display the entire range of states, excitation, and inhibition to incoming stimuli.

- *Affect* relates to the development of sociality and emotion, the mutual regulatory processes of social interaction and social relationships.

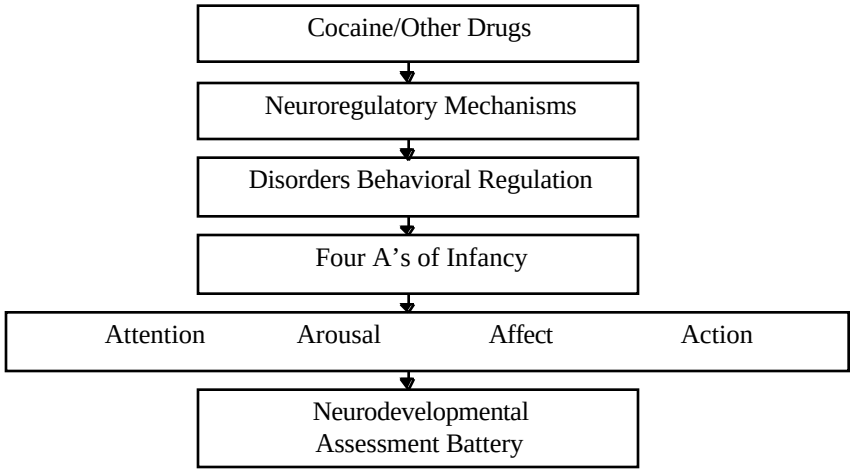

Figure 1. Theoretical model of the effects of prenatal cocaine exposure on child behavior.

• *Action* indicates motor function, the development of fine and gross motor skills, and the acquisition of knowledge and social exchange through motor patterns.

Direct and Indirect Effects. It is possible that different neurobehavioral effects may result from direct and indirect effects of cocaine on the fetus and infant (Jones and Lopez 1988). Preclinical studies have shown that the teratogenic effects of a drug can be produced by an action on the maternal animal, directly on the fetus, or by alteration of normal maternal-fetal metabolic pathways (Inglass et al. 1952). Direct effects include the action of cocaine on the fetus consequent to transfer of the drug through the placenta. These systemic effects of cocaine on the nervous system are

probably mediated by the changes in synaptic transmission resulting in an excess of neurotransmitter at the receptor sites (Richie and Greene 1985). This mechanism affects the sympathetic nervous system and produces vasoconstriction, an acute rise in arterial blood pressure, tachycardia, and a predisposition to ventricular arrhythmia and seizures (Cregler and Mark 1986; Tarr and Macklin 1987).

Indirect effects can be attributable to changes in the fetal environment and effects on the mother's CNS that place the infant at risk. During preg-nancy, uterine blood vessels supplying oxygen and nutrients to the developing fetus are maximally dilated, but they vasoconstrict in the presence of catecholamines. Cocaine blocks the reuptake of catechol-amines (Richie and Greene 1985), thereby increasing their concentration, resulting in vasoconstriction of the uterine arteries and impaired oxygen delivery to the fetus.

In pregnant cocaine-using women, vasoconstriction, sudden hypertension, or cardiac arrhythmias may interrupt blood supply to the placenta and reduce perfusion to various fetal tissues in early gestation, causing deform-ation or disruption of morphogenesis in late gestation (Bingol et al. 1987). Vasoconstriction, tachycardia, and increased blood pressure caused by cocaine all increase the chance for intermittent intrauterine hypoxia, pre-term labor, precipitous labor, and abruptio placentae followed by hemor-rhage, shock, and anemia (Tarr and Macklin 1987). Vasoconstriction at the uterocomplex coupled with anorexic effects of cocaine might explain the growth retardation that occurs in some of the offspring of cocaine-using mothers (Fulroth et al. 1989; Hadeed and Siegel 1989; Yoon et al. 1989). Hypoxia resulting from vasoconstriction has been shown to reduce fetal weight in animal studies (Mahalik et al. 1984).

In summary, cocaine has a specific direct effect on brain function and an indirect effect through the influence of fetal nutritional status. It is possible that these direct and indirect effects have different influences on neurobehavioral functioning. Support for this hypothesis comes from a study of the direct and indirect effects of cocaine using acoustic cry analysis as the neurobehavioral outcome (Lester et al. 1994). Two neurobehavioral syndromes were identified as related to direct versus indirect effects of cocaine. Excitable cry characteristics (e.g., higher pitch, more variability, and longer cries) could result from the direct effects of cocaine. The action of cocaine on mesolimbic systems (Wise 1984) triggers the cry, which is activated by the hypothalamic-limbic system and controlled by the midbrain and brainstem regions (Lester and Boukydis 1992). The effects of

cocaine on the tegmentum and raphe nuclei (Wise 1984) could directly affect midbrain and brainstem control.

Depressed cry characteristics (longer latency to cry onset, fewer cries, and lower amplitude cries) could result from the indirect effects; cocaine resulted in lower birthweight or intrauterine growth retardation (IUGR) in infants, which in turn affected cry. The cocaine effect on placental vasoconstriction can result in decreased nutrient supply to the fetus, hypoxia, and IUGR. Depressed catecholamine responses have been found in IUGR rat pups (Shaul et al. 1989), and depressed behavior in IUGR human infants has been reported in other studies of cry (Lester and Zeskind 1978), feeding behavior (Mullen et al. 1988), and infants assessed using the BNBAS (Lester et al. 1986).

The notion of excitable and depressed neurobehavioral syndromes in cocaine-exposed infants is supported by studies using other assessments of similar behaviors. For example, in studies using a narcotic withdrawal index, some findings suggest heightened responsivity, increased motor tone, and irritability consistent with excitability, whereas other studies describe the infants as underaroused and lethargic. In the authors' clinical experience with the BNBAS, these patterns have been observed. In addition, there appears to be a third or mixed pattern in which cocaine-exposed infants initially appear underaroused, hard to wake up, and difficult to bring to a quiet alert state. They then become highly excitable, irritable, and hypertonic, and remain in an insulated cry state. These infants appear to be unable to modulate their level of arousal once awake. They are mostly in lower (sleep) states or higher (cry) states and are unable to maintain a state of quiet alertness. In some infants, massive consolability maneuvers by the examiner can achieve brief periods of quiet alertness.

Table 6 shows a system for scoring the BNBAS on the excitable and depressed dimensions. This system is currently being used in several studies. In a study by Tronick and colleagues (1994), a dose-response relationship was reported between prenatal cocaine use and the excita-bility score.

Neurodevelopmental Assessment. Traditional tests of developmental outcome such as the Bayley Scales provide global estimates of neuro-behavioral function and have the advantages of being standardized, widely known and accepted, and relatively easy to administer and score.

TABLE 6. Proposed drug scoring system for the Brazelton Neonatal Behavioral Assessment Scale.

Recent research has used the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) to study the effects of prenatal substance abuse, primarily cocaine, on newborn behavior. The effects of cocaine are sometimes difficult to detect due, in part, to methodological problems including determining patterns of cocaine use and confounding with other drug and nondrug effects, but also because some of the effects of cocaine may be relatively subtle.

The traditional seven-cluster scoring system for the BNBAS may not be adequate to capture effects due to prenatal cocaine exposure. Specifically, reading of the cocaine literature suggests that at least two patterns or neurobehavioral syndromes can be described in these infants, an excitable pattern and a depressed pattern. The seven-cluster scoring system does not readily lend itself to describing these patterns of behavior. Therefore, the data reduction system described below was developed.

To use this system, the infant is assigned 1 point for each item that he or she meets the criteria for excitable or depressed behavior. There are 13 items on both the excitable and depressed scales. Therefore, each infant may have a range of 0-13 for the excitable and depressed scores. Please note that each infant will have two scores. If missing data is a problem (some infants do not have all scores) it might be useful to compute the mean (i.e., divide the total excitable or depressed score by the number of excitable or depressed items that are available for the infant).

EXCITABLE	DEPRESSED
Tone > 6	Ball < 4
Motor maturity < 4	Rattle < 4
Cuddliness < 3	Face < 4
Consolability < 4	Voice < 4
Peak excitement > 7	Face and voice < 4
Rapidity buildup > 6	Alertness < 4
Irritability > 5	Tone < 4
Activity > 6	Pull to Sit < 4
Tremulousness > 5	Defensive < 4
Startles > 4	Peak excitement < 4
Lability skin > 7	Rapidity buildup < 4
Lability state > 3	Irritability < 3
Self-quieting < 3	Activity < 4

However, this measure may not be suitable for detecting the specific areas affected by cocaine. Thus, it is possible that findings reported to date that show no significant differences or that show findings that are difficult to interpret or contradictory may be due to the type of tests being used. Lester and Tronick (1994) developed a neurodevelopmental battery for drug-exposed infants based on the four A's of infancy as part of a large, multisite longitudinal study of prenatal drug exposure and child outcome for the National Institutes of Health (NIH), National Institute of Child Health and Human Development (NICHD), and the National Institute on Drug Abuse (NIDA). It includes state-of-the-art assessments that should be sensitive to even subtle effects of cocaine. The battery should also help identify neurobehavioral patterns such as the excitable and depressed syndromes described earlier. The ability to describe these patterns of individual differences will enable researchers to study specific mechanisms by which cocaine affects behavior as well as to develop clinical programs that deal with the specific behavioral domains affected.

LESSONS FROM THE PAST

There is a certain deja vu associated with the study of prenatal cocaine exposure. Prenatal influences and insults on child development are much studied areas and it might be useful to consider cocaine exposure as a special case of this larger problem. In doing so, researchers need to understand what can be learned from the past as well as what is unique about this particular problem. Arguably, the study of preterm infants provides a good model.

Starting in the 1950s with the Collaborative Perinatal Study of some 20,000 pregnancy and delivery outcomes, substantial effort was devoted to the effects of prematurity (Niswander and Gordon 1972). The prevailing zeitgeist was that being born prematurely was a form of biological insult likely to affect CNS development and the long-term outcome of the child. As supporting evidence, studies showed that premature infants were overrepresented in many populations of abnormal outcomes, including cerebral palsy and mental retardation (Lilienfeld and Parkhurst 1951; Pasamanick and Knoblock 1966). A related movement called for the development of early stimulation programs to help these infants make up for their biological deficits and perhaps prevent poor developmental outcome.

The second wave of studies of the effects of preterm birth told a different story. Research showed that the evidence that preterm infants were overrepresented among the handicapped population, even if true, was based largely on retrospective data. Prospective longitudinal studies showed that when preterm infants were followed from birth, most developed normally. Studies such as the Kauai study showed that in fact it was the environments of these children that were predictive of their developmental outcome rather than their medical status at birth (Werner et al. 1971). The seminal paper by Sameroff and Chandler (1975) brought these issues to the forefront in the form of the transactional model, in which the dynamic response of the caretaking environment to the characteristics of the child is seen as the primary determinant of child outcome. Parallel work in the biological domain showed substantial plasticity and mechanisms for recovery of function from insult and injury to the developing nervous system (Waddington 1966). Doom was replaced by optimism for the developing preterm infant.

It was learned that preterm infants are not a homogeneous group. As babies began to survive at lower and lower birthweights, the medical community distinguished between low birthweight (1500 to 2500 grams) and very low birthweight (< 1500 grams). Today reference is made to the "micropreemie," an infant weighing less than 900 grams. Smaller babies are at higher biological risk not only because they are smaller, but also because they are more prone to insult, injury, and illness. Brain injury such as intraventricular hemorrhage and respiratory illness such as bronchopulmonary dysplasia mostly occur in smaller babies and often occur together.

There has been a longstanding bias in the research community, influenced in part by funding and public policy issues, that cognitive and intellectual outcomes are of primary importance. Most studies of preterm infants looked only at cognitive and intellectual outcomes so that differences were viewed only in terms of intelligence. However, more recent work with preterm infants has reflected an appreciation of the importance of noncog-nitive outcomes, including social and emotional development, parent-child relationships, temperament, and peer interaction. These noncognitive outcomes are important in their own right. Researchers have learned that it is somewhat simplistic to separate cognitive from noncognitive outcomes, because factors such as social and emotional behavior, temperament, and motivation influence intellectual achievement and school performance. A child with emotional or behavioral problems may not do well in school even if he or she is intellectually competent.

Preterm infants also are not homogeneous with respect to their behavior and development. They show a wide range of behavioral and develop-mental trajectories that are multidetermined. The dynamic response of the caregiving environment to the changing behavioral organization of the infant is the best window into the long-term developmental outcome of the preterm infant.

Application to Drug-Exposed Infants. Like prematurity, drug exposure can be viewed as another potential insult or injury to the developing fetus. Researchers do not know whether and how drugs affect the fetus; the effects of polydrug use; or the effects of timing, dosage, and frequency ofuse. In some infants there may be true injury, in others there may be anydegree of insult, and many infants may escape unscathed. It is also possible that there are effects that simply cannot be measured or effects that are not manifest until the child is older. Drug effects also interact with other prenatal factors such as poor nutrition or illness, which also potentially compromise the infant.

There is a relationship between drug exposure and early delivery, probably because of the effects of cocaine on labor, although possibly related to lack of prenatal care. Thus, drug-exposed infants constitute an increasingly large percentage of the infants in the special care nursery. It is not known if the drug-exposed preterm infant is any different from the unexposed preterm infant with a comparable medical history. That is, does drug exposure have an additional or synergistic effect when factors such as birthweight, other sickness, and insults are taken into account?

The vast majority of drug-exposed infants are not born prematurely. Many are born at term and are otherwise normal and healthy, while others are born at term but are growth retarded (IUGR or small for gestational age (SGA)). As with preterm infants, drug-exposed infants are not a homogeneous group with respect to how they present medically or behaviorally. Researchers have just begun to describe some of the different behavioral patterns that drug-exposed infants manifest, and it islikely that these different beginnings may result in different develop-mental trajectories as the demands of the caregiving environment come into play.

Study of preterm and other high-risk infants revealed that many standard developmental tools are not sensitive to the behavioral variations of these infants. Not surprisingly, this is also turning out to be true for the drug-

exposed infant. In preterm infants, measures that are more sensitive to behavioral processes such as the four A's of infancy are better able to describe the behavioral organization of these infants than tests of gross developmental outcome or milestones.

Although the database is very small, studies have shown differences in symbolic play and attachment relationships in drug-exposed infants who score within normal limits on developmental tests (Beckwith et al. 1994). In a 3-year followup (Azuma and Chasnoff 1993), although drug-exposed infants fell within normal IQ range, they showed differences on some subtests such as language.

From the study of preterms and other at-risk populations, multiple risk models have been developed that should be useful in the study of drug-exposed infants. Cumulative risk models suggest that it is the number (rather than the nature) of specific risk factors that determines develop-mental outcome (Sameroff et al. 1987). Other models study the resilient or invulnerable children, those who do well despite the presence of multiple risk factors (Garmezy et al. 1984; Lester et al. 1994). Despite exposure to similar adverse factors, some substance-exposed infants are able to survive and develop well, whereas others are not. There is a need to understand the individual differences in reactions to similar adverse factors and identify characteristics of resilience (Johnson et al. 1990). This had lead to the study of protective factors that may serve as regulators or re-regulators of development and help buffer the effects of high-risk factors. These models need to be applied to the study of drug-exposed infants.

The study of drug-exposed infants is probably best viewed as a special case of the infant at risk. This suggests that study of drug-exposed infants would benefit from the knowledge gained in the study of high-risk infants. This includes the abandonment of preconceived biases that these infants are damaged and doomed to fail and that they are all alike. The long-term developmental outcome of these children is likely to be a function of how the caregiving environment responds to the behavioral constellation of the infant, with the understanding that both the behavior of the infant and the caregiving environment make dynamic adjustments to each other and are influenced by other forces. The study of the exposed infant should be approached from a holistic perspective in which the full range of child behavior (i.e., cognitive as well as noncognitive) is examined.

Unique Aspects of Drug-Exposed Infants. It is important to address issues that may be unique to the study of the drug-exposed child. One issue is whether there is a unique pharmacological effect of drugs and how this effect interacts with other pre-, peri-, and postnatal biological and

environmental factors. A second issue is SES. Although many high-risk infants grow up in impoverished environments, drug-exposed infants (at least those the authors study) are almost exclusively from the poorest segment of society. The developmental consequences of poverty have only recently been acknowledged and require far more investigation. Beyond the obvious problems of nutrition and health, children raised in poverty are likely to face homelessness, violence, and crime. Families ranked as low SES are not, however, a homogeneous group. The varia-tion in parenting and other environmental caretaking factors within social strata that can affect child outcome requires study.

Poverty is also associated with minority status, race, and ethnicity. The complexities of these issues affect the ability to communicate and establish rapport, to understand cultural factors that affect use of drugs, and childrearing practices. There are psychometric concerns regarding the appropriateness of tests that have been developed and standardized based on middle-class American values. How does one determine what behavioral processes to study and how to interpret the findings without knowing the meaning of these processes in the local culture? For example, there is a belief in much of the United States that eye contact between mother and infant is important in the development of the mother-child relationship. Some cultures, however, discourage this practice and the relationship is based on other behaviors. Clearly, one would not want to penalize a mother from a different culture if she did not look at her baby the way many American mothers do. This illustrates the need to incor-porate cultural issues in instrument development when studying families from different cultures.

There are also other subpopulations that need to be studied separately, such as teenage mothers. There is already a parenting risk associated with teenage mothers. There is the belief that the teenage mother using drugs puts her child in double jeopardy, but this is probably too simplistic. Like their infants, teenage mothers are not a homogeneous group. For example, depending on their level of emotional development, some are better parents than others. The effects of drug exposure need to be understood in the context of the teenage parenting phenomenon.

In the case of the exposed infant there is the potential involvement of the social service and legal community because drug use is illegal and has implications for child abuse and neglect. There is also the issue of multiple caretakers and multiple placements. Some children experience as many as eight foster care placements in the first year of life (Beckwith et al. 1994). When studying the attachment relationship, it is not always obvious who the primary caretaker is.

In fact, researchers may even be asking the wrong question about attachment in these situations. Rather than identifying the attachment classification in children who undergo multiple placements, perhaps the question should be, “How do children form attachments in the face of multiple placements? What is the role of the biological mother in these cases?"

The unique problem of maternal drug use and possible addiction needs to be treated somewhat independently of the child. On the other hand, maternal preoccupation with drugs, associated personality disturbances, possible psychopathology, and a chaotic lifestyle clearly impact on the mother-child interaction (mutual regulatory system) and on the ability of the child to thrive in this environment.

Finally, there is the issue of identification of exposure status. The 1992 NIDA Household Survey showed that although the prevalence of crack cocaine use has declined overall, in certain groups the drug continues to be used at high or increasing rates (NIDA 1992). Not surprisingly, it is inner-city minority groups that are most affected. Also, women of childbearing age seem to be particularly susceptible. Prevalence rates range from 3 percent to almost 50 percent, with the highest rates reported by centers that serve poor inner-city mothers. However, there are two problems with this survey data. First, it is based on self-report, and self-report is known to be especially unreliable when illegal activities are involved. Second, the report is based on individuals living in households. That is, respondents had to live in a household to be in the survey. These criteria do not identify a group representative of the drug-using population.

Epidemiological statistics will improve as better toxicology assays become available. Moreover, currently available techniques (discussed below) only provide reliable qualitative information on the presence or absence of drugs. They do not provide quantitative information about the frequency, timing, or amount of drug use necessary to establish dose-response relationships.

Epidemiological information is also affected by the populations that are screened. Depending on hospital policy, pregnant women can be screened if they have a prior history of drug use or when there are clinical reasons to suspect drug use. There are no official criteria for clinical suspicion but, in general, criteria include obstetrical events such as no prenatal care, premature labor, and placental abruption. Since these conditions are more often associated with poverty, poor people and minorities are more often screened. Therefore, most of

the data about drug use comes from pregnant women living in poverty. It is possible to do anonymous screens in which the patient is not identified. One such study was done of pregnant women in Florida and the surprising finding was that the incidence of illegal drug use was comparable between lower-class and middle-class patients (Chasnoff et al. 1990). This study, if replicated, would change the way society thinks about illegal drug use during pregnancy. Further, a middle-class study sample would provide the methodological opportunity to study drug-exposed children growing up in more enriched environmental conditions.

Toxicology Assays. There are many issues unresolved in the use and development of toxicological assays. Urine screens have been the stan-dard but reflect only use over the preceding 72 hours. The meconium assay is a more recent development and has the advantage of recording drug use through the second half of pregnancy. Hair analysis is a third technique that has the potential to provide an even longer record of drug use. However, there are methodological problems with hair assay and the need for informed consent that have so far limited the use of this technique.

Toxicological assays involve a two-step process. There is an initial screen that can yield a presumptive positive. The screen is presumptive until it is confirmed by a second assay. Many presumptive positive screens are not confirmed, resulting in a high false-positive rate. Therefore, it is important to verify presumptive positive results with a confirmation analysis. Some methods for screening and confirmation are more reliable than others. For example, in forensic work, gas chromatography/mass spectrometry (GC/MS) is used for confirmation. However, this method is usually considered too expensive for clinical use. Also, some metabolites are more difficult to confirm than others. For example, tetrahydrocannabinol (THC), the metab-olite of marijuana, is much more difficult to confirm than drugs such as cocaine and opiates.

As previously mentioned, all of the toxicology assays in current use provide limited qualitative data. Quantitative methods have not been established. One cannot determine how much of the drug was ingested, how many times it was ingested, or at what stage during gestation it was ingested. There is no biochemical marker for alcohol, so toxicology cannot be used to determine alcohol use during pregnancy. This information has to be determined from maternal report.

Cocaethyline is a metabolite of cocaine that is present when cocaine and alcohol are used together. The presence of this metabolite indicates only that cocaine and alcohol were used together some time during pregnancy. Cotanine can be used to determine cigarette smoking, although this variable has not yet been used in a study of prenatal substance abuse.

Another problem that has not been solved is how to separate drugs used licitly from drugs of abuse. Licit drugs may include prescription medica-tion taken during pregnancy or medication used during labor and delivery. Opiates used for pain relief can result in a positive toxicology screen but may not indicate illegal drug use. On the other hand, some mothers abuse prescription medication such as codeine. Even if the validity of a positive toxicology screen is questioned because of prescription medication, the mother may have abused the prescription medication or used illegal drugs as well as prescription medication. These questions cannot be answered by a toxicology analysis alone and in some cases the drug use history may never be known.

There has been some recent investigation of passive exposure, including the absorption of cocaine by a child through environmental exposure such as inhaling smoke or powder. In a study of 460 children between 1 and 60 months of age seen in an emergency department for pediatric problems unrelated to drugs or child abuse (e.g., crying, fever, diarrhea), cocaine was found in 5.4 percent of the urine specimens (Rosenberg et al. 1991). The environment may have pharmacological as well as social effects. There are no studies of other environmental hazards of toxins such as lead or polychlorinated biphenyls (PCBs) and how exposure to these substances may interact with drugs. Inner-city children in some areas of the country are likely to be exposed to lead as well as drugs. There are poor fishing communities where drugs and PCBs likely co-occur.

RESTATEMENT OF THE PROBLEM

Arguably the most important contribution of the first generation of cocaine research is a better understanding of the problem itself (figure 2). Researchers learned that the problem was far more complicated than had been originally described for two reasons. First, the drug issue is one of polydrug use, not of cocaine alone. Most women who use cocaine also use other drugs; alcohol, marijuana, and cigarettes are most common, but other drugs such as heroin are also used. There may be women who use

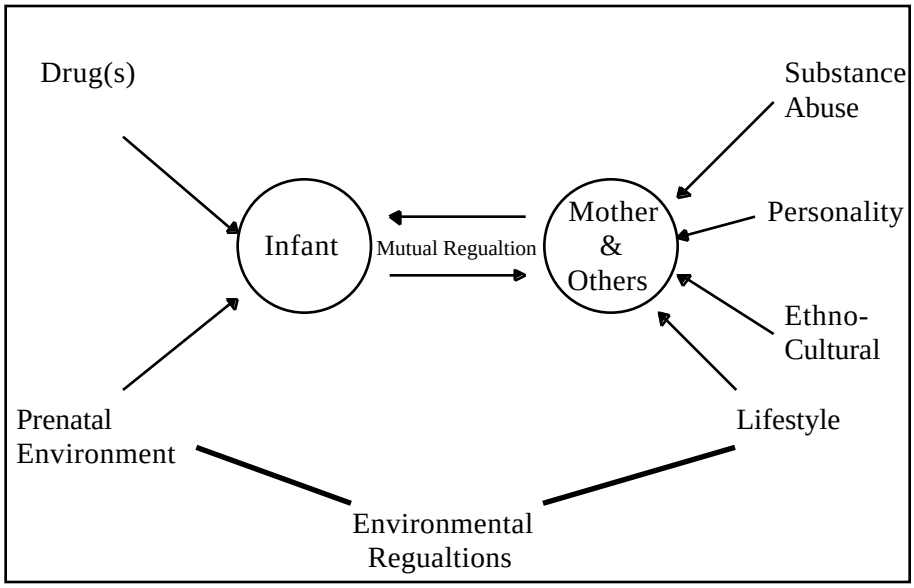

Figure 2. *Systems approach to study of cocaine.*

only cocaine but they seem to be more the exception than the rule. Thus one must assume polydrug use from the outset.

The second complicating factor is what has been termed "environmental" or "lifestyle" issues. Environment is used to describe a complex set of interrelated factors including psychological and social factors that lead a mother to use drugs, as well as the neighborhood and general conditions in which drug-exposed children are often raised. These conditions may involve inadequate and even more disruptive forms of parenting; poverty; high stress; exposure to violence; and a chaotic, disorganized lifestyle, factors that could lead to poor developmental outcome independent of prenatal drug exposure. Therefore, drug effects (pharmacological effects) are confounded by environmental effects. If developmental outcome is compromised, is this due to drug exposure or the environment?

Cocaine seems to be a variable marker for polydrug use and a lifestyle associated with poverty that may jeopardize normal developmental outcome. Figure 2 shows a systems approach to the problem as currently understood. It is reasonable to expect that the combination of prenatal drug exposure and other factors such as poor prenatal care and a poor reproductive history combine to produce, in some cases, an acute neurobehavioral vulnerability or fragility. Many of these

infants are probably not damaged. In fact, many appear quite normal. However, there is a significant proportion of these infants who display many stress behaviors and show disorders of behavioral regulation.

In a reasonably supportive environment, these infants would probably recover and have every chance for a normal developmental outcome. However, environmental factors can be regulators or disregulators, buffers and stabilizers or destabilizers of child behavior. Unfortunately, all too often these infants do not grow up in environments that have a positive effect on even average child behavior. An infant who is already stressed has that much more to overcome and may recover poorly in an unsupportive caregiving environment.

As shown in figure 2, the immediate caretaking of the infant may be compromised by a mother who has a drug problem, by personality disorders undoubtedly related to her use of drugs, and historically based psychopathology. These factors impinge on the mutual regulatory process of the mother-infant interaction that could re-regulate infant regulatory disorders. More distal factors may be added to these proximal factors, including a lack of social support and the larger environmental stressors associated with poverty.

In this model, drugs have a direct acute effect and an indirect long-term effect. Drugs have the potential to predispose the infant to a short-term neurobehavioral vulnerability as a direct pharmacological effect on the four A's of infancy. The interaction between the neurodevelopmental vulnerability and the response of the caregiving environment determines the long-term developmental outcome of the child. The longer-term drug effect is indirect and is mediated by environmental factors.

This model enables study of the effects of cocaine in the context of multiple risk factors that may affect the regulatory capacities of the child. With this framework one can generate a discussion of the issues that need to be addressed based upon this current understanding of the problem of prenatal cocaine/polydrug exposure and child outcome.

THE SECOND WAVE

Researchers learned from the first wave of research in cocaine abuse that drug effects had been exaggerated and had caused a widespread misperception that a generation of children was doomed. It would be equally dangerous to assume that the maternal lifestyle or larger environment is to blame. At this time very little is known about the range of developmental outcomes to expect in drug-exposed children or the etiology of such outcomes. It is probably fair to say that these children are at increased biological and social risk, that their outcome is undeter-mined, that the full range of intellectual and social-emotional outcomes are possible, and that neither biological nor environmental factors have been proven or disproven to determine the developmental outcome in these infants.

The authors believe that a wide range of individual differences in patterns of development will be found in these children. These patterns will be lawfully but differentially related to the interplay between biological (including drug exposure) and social forces. Thus, biological vulnera-bility makes a child more vulnerable to the effects of a poor caretaking environment. By understanding these patterns of individual differences and their biosocial etiologies, researchers will be able to understand the developmental outcome of drug-exposed children. This understanding will enable development of effective preventive and ongoing treatment programs to facilitate child development.

SUMMARY AND RECOMMENDATIONS

The authors consider the results of this attempt at a meta-analysis of neurobehavioral studies and cocaine exposure informative and to some extent shocking. Important data are not routinely reported in peer-reviewed publications. When basic information such as the masking of examiners to exposure status in neurodevelopmental studies is not reported in almost 50 percent of the articles, it becomes virtually impossible to draw conclusions about neurobehavioral effects. Even when adequate information is reported, studies have such severe methodological limitations that any attempt to draw conclusions about neurobehavioral effects of prenatal drug exposure is impeded. The authors strongly recommend that journal editors be more stringent and require that minimum information be reported in all studies of drug-exposed infants. Perhaps NIDA could develop a list of recommended or required reporting information and circulate such a list to journal editors.

The good news is that identification of these methodological problems will allow definition of more sophisticated future studies and the methodological issues that need to be addressed. Clearly there is a need for longitudinal followup studies that pay adequate attention to repeatedmeasures analysis of the same factors and individual differences in the stability and reliability of findings.

Some issues, such as polydrug use and the confounding of medical and demographic factors, are issues for which there are methodological strategies. Due to their complexity, these issues require additional conceptual thought. For example, although there are methodological techniques to deal with the problem of polydrug use, it has also been argued that if polydrug use is the norm it should be regarded as the variable under investigation rather than trying to isolate a pure cocaine effect that may actually be a rare event. There are arguments to be made on either side of this issue and scientists need to be clear about the strengths and limitations of each approach.

Other issues such as toxicology analysis await further methodological advances. These include improved ability to detect prenatal drug use, the development of quantitative assays to determine dose-response relation-ships, and how drug interactions may affect behavior.

Finally, this attempt at an analysis was probably premature. Not all studies report the information necessary and sufficient studies using the same outcome measures have not been reported. The neurobehavioral database is small, fragmented, and lacks consistency in measures used as well as in study design. However, by relating the study of prenatal drug exposure to the study of other high-risk populations such as premature infants, researchers can build on the existing knowledge base and also appreciate the uniqueness of the present situation.

This new wave promises to be exciting. With the present knowledge base researchers have a much better understanding of the problem than when the studies reviewed here began. Perhaps the most important contribution of the first wave of research was a solid handle on the problem itself. Answers seem within reach, but there is still a great deal to learn while a sizable and very precious part of part of society, children and mothers, remains in jeopardy.

REFERENCES

Azuma, S.D., and Chasnoff, I.J. Outcome of children prenatally exposed to cocaine and other drugs: A path analysis of three-year data. *Pediatrics* 92 (3):396-402, 1993.

Beckwith, L.; Rodning, C.; Norris, D.; Phillipsen, L.; Khandabi, P.; and Howard, J. Spontaneous play in two-year-olds born to substance abusing mothers. *Infant Ment Health J* 15(2):128-135, 1994.

Bingol, N.; Fuchs, M.; Diaz, V.; Stone, R.X.; and Gromisch, D.S. Teratogenicity of cocaine in humans. *J Pediatr* 110:93-96, 1987.

Chasnoff, I.J.; Landress, H.; and Barrett, M. The prevalence of illicit drug or alcohol use during pregnancy and discrepancies in reporting in Pinellas County, Florida. *N Engl J Med* 322:1202-1206, 1990.

Cregler, L.L., and Mark, H. Special report: Medical complications of cocaine abuse. *N Engl J Med* 315 (23):1495-1500, 1986.

Fulroth, R.F.; Phillips, B.; and Durand, D.J. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am J Dis Child* 143:905-910, 1989.

Garmezy, N.; Masten, A.; and Tellegen, A. The study of stress and competence in children: A building block for developmental psychopathology. *Child Dev* 55:97-111, 1984.

Hadeed, A.J., and Siegel, S.R. Maternal cocaine use during pregnancy: Effect on the newborn infant. Pediatrics 84:205-210, 1989.

Inglass, T.H.; Curley, F.J.; and Prindle, R.A. Experimental production of congenital anomalies. *N Engl J Med* 247:758-768, 1952.

Johnson, H.H.; Glassman, M.B.; Fiks, K.B.; and Rosen, T.S. Resilient children, individual differences in developmental outcome of children born to drug abusers. J Genet Psychol 15:523-539, 1990.

Jones, C.L., and Lopez, R. *Direct and Indirect Effects on Infants of Maternal Drug Abuse.* Washington, DC: National Institute of Health, 1988.

Lester, B.M., and Boukydis, C.F.Z. No language but a cry. In: Papousek,H.; Jurgens, J.; and Papousek, M., eds. *Nonverbal Vocal-Communication: Comparative and Developmental Approaches.*- New York: Cambridge University Press, 1992.

Lester, B.M., and Tronick, E. The effect of prenatal cocaine exposure and child outcome: Lessons from the past. *Infant Ment Health J* 15(2):107-120, 1994.

Lester, B.M.; McGrath, M.M.; Garcia-Coll, C.T.; Brem, F.S.; Sullivan,-M.C.; and Mattis, S.B. Relationship between risk and protective factors, developmental outcome and the home environment at 4-years-of-age interm and preterm infants. In: Fitzgerald, H.; Lester, B.M.; and Zuckerman, B., eds. *Children of Poverty*. New York: Garland Press, 1994.

Lester, B.M.; Garcia-Coll, C.T.; Valcarcel, M.; Hoffman, J.; and Brazelton, B.T. Effects of atypical patterns of fetal growth on newborn (BNBAS) behavior. *Child Dev* 57:1-19, 1986.

Lester, B.M., and Zeskind, P.S. Brazelton scale and physical size correlates of neonatal cry features. *Infant Behav Dev* 1:393-402, 1978.

Lilienfeld, A.M., and Parkhurst, E. A study of the association of factors of pregnancy and parturition with the development of cerebral palsy: A preliminary report. *Am J Hygiene* 53:262-282, 1951.

Lutiger, B.; Graham, K.; Einarson, T.R.; and Koren, G. Relationship between gestational cocaine use and pregnancy outcome: A meta-analysis. *Teratology* 44:405-414, 1991.

Mahalik, M.P.; Gautieri, R.F.; and Mann, D.E. Mechanisms of cocaine induced teratogenesis. *Res Comm Subst Abuse* 5(4):279-303, 1984.

Mayes, L.C.; Granger, R.H.; Bornstein, M.H.; and Zuckerman, B. The problem of prenatal cocaine exposure: A rush to judgment. *JAMA* 267:406-408, 1992.

Mirochnick, M.; Meyer, J.; Cole, J.; Herren, T.; and Zuckerman, B. Circulating catecholamine concentrations in cocaine-exposed neonates: A pilot study. *Pediatrics* 88(3):481-485, 1991.

Mullen, M.K.; Garcia-Coll, C.T.; Vohr, B.R.; and Oh, W. Mother-infant feeding interaction in full-term small for gestational age infants. *Pediatrics* 112:143-148, 1988.

Niswander, K.R., and Gordon, M., eds. The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. In: *The Women and Their Pregnancies.* Philadelphia: W.B. Saunders, 1972.

Pasamanick, B., and Knobloch, H. Retrospective studies on the epidemi-ology of reproductive causality: Old and new. *Merrill-PalmerQ* 12:7-26, 1966.

Porges, S.W. Vagal tone: A mediator of affect. In: Garber, J.A., and Dodge, K.A., eds. *The Development of Affect Regulation and Dysregulation*. New York: Cambridge University Press, 1991.

Ritchie, J.M., and Greene, N.M. Local anesthetics. In: Gillman, A.G.; Goodman, L.S.; Rall, T.W.; and Murad, F., eds. *The Pharmacological Basis of Therapeutics.* 7th ed. New York: Macmillan, 1985. pp.309-310.

Rosenberg, N.M.; Meert, K.L.; Knazik, S.R.; Yee, H.; and Kauffman,-R.E. Occult cocaine exposure in children. *Am J Dis Child* 145:1430-1432, 1991.

Sameroff, A.J., and Chandler, J.J. Reproductive risk and the continuum of caretaking casualty. In: Horowitz, F.D., ed. *Review of Child Development.* Vol. 4. Chicago: University of Chicago Press, 1975.

Sameroff, A.J.; Seifer, R.; Barocas, R.; Zax, M.; and Greenspan, S. Intelligence quotient scores of 4-year-old children: Social environmental risk factors. *Pediatrics* 79:343-350, 1987.

Shaul, P.W.; Cha, C.M.; and Oh, W. Neonatal sympathoadrenal response to acute hypoxia: Impairment after experimental intrauterine growth retardation. *Pediatr Res* 24:472-477, 1989.

Tarr, J.E., and Macklin, M. Cocaine. *Pediatr Clin North Am* 34:319-331, 1987.

Tronick, E.Z.; Frank, D.A.; Cabral, H.; and Zuckerman, B.S. A dose-response effect of in utero cocaine exposure on infant neurobehavioral functioning. *Pediatr Res* 35(4):28A, 1994.

Volpe, J.J. Effect of cocaine use on the fetus. *Mechanisms Dis* 327(6):399-407, 1992.

Waddington, C.H. *Principles of Development and Differentiation*. New York: Macmillan, 1966.

Werner, E.E.; Bierman, J.M.; and French, F.E. *The Children of Kauai*. Honolulu: University of Hawaii Press, 1971.

Wise, R. Neural mechanisms of the reinforcing action of cocaine. In: Grabowski,J., ed. *Cocaine: Pharmacology, Effects, and Treatment of Abuse*. National Institute of Drug Abuse Monograph 50. DHHS Pub. No.(ADM)84-1326. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984.

Yoon, J.J.; Kim, T.; MacHee, K.; Checola, R.T.; and Noble, L.M. Maternal cocaine abuse and microcephaly. *Pediatr Res* 25:79A, 1989.

APPENDIX 1. List of included articles (N = 50).

Anday, E.K.; Cohen, M.E.; Kelley, N.E.; and Leitner, D.S. Effect of in utero cocaine exposure on startle and its modification. Dev Pharmacol Ther 12:137-145, 1989.

Barabach, L.M.; Glazer, G.; and Norris, S.C. Maternal perception and parent-infant interaction of vulnerable cocaine-exposed couplets. J-Perinat Neonat Nurs 6(3): 76-84, 1992.

Calhoun, B.C., and Watson, P.T. The cost of maternal cocaine abuse: I.Perinatal cost. Obstet Gynecol 78(5):731-734, 1991.

Carzoli, R.P.; Murphy, S.P.; Hammer-Knisely, J.; and Houy, J. Evaluation of auditory brain-stem response in full-term infants of cocaine-abusing mothers. Am J Dis Child 145:1013-1016, 1991.

Chasnoff, I.J.; Burns, W.J.; Schnoll, S.H.; and Burns, K.A. Cocaine use in pregnancy. N Eng J Med 313(11):15-18, 1985.

Chasnoff, I.J.; Griffith, D.R.; Freier, C.; and Murray, J. Cocaine/polydrug use in pregnancy: Two year followup. Pediatrics 89(2):284-289, 1992.

Chasnoff, I.J.; Griffith, D.R.; MacGregor, S.; Dirkes, K.; and Burns, K.A. Temporal patterns of cocaine use in pregnancy: Perinatal outcome. JAMA 261(12):1741-1744, 1989.

Chasnoff, I.J.; Lewis, D.E.; Griffith, D.R.; and Willey, S. Cocaine and pregnancy: Clinical and toxicological implications for the neonate. Clin Chem 35(7):1276-1278, 1989.

Chen, C.; Duara, S.; Netro, G.S.; Tan, S.; Bandstra, E.S.; Gerhardt, T.; and Bancalari, E. Respiratory instability in neonates with in utero exposure to cocaine. J Pediatr 119(1):111-113, 1991.

Cohen, H.R.; Green, J.R.; and Crombleholme, W.R. Peripartum cocaine use: Estimating risk of adverse pregnancy outcome. Int J Gynecol Obstet 35:51-54, 1991.

Cohen, M.E.; Anday, E.K.; and Leitner, D.S. Effects of in utero cocaine exposure on sensorinoural reactivity. Ann NY Acad Sci 562:344-345, 1989.

Coles, C.D.; Platzman, K.A.; Smith, I.; James, M.A.; and Falek, A. Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. Neurotoxicol Teratol 14:23-33, 1992.

Cordero, L., and Custard, M. Effects of maternal cocaine abuse on perinatal and infant outcome. Ohio Med May: 410-412, 1990.

Corwin, M.J.; Lester, B.M.; Sepkoski, C.; McLaughlin, S.; Kayne, H.; and Golub, H.L. Effects of in utero cocaine exposure on newborn acoustical cry characteristics. Pediatrics 89(6):1199-1203, 1992.

Davidson-Ward, S.L.; Bautista, D.B.; Buckley, S.; Schuetz, S.; Wachsman, L.; Bean, X.; and Warburton, D. Circulating catecholamines and andrenoreceptors in infants of cocaine-abusing mothers. Ann NY Acad Sci 563:349-351, 1989a.

Davidson-Ward, S.L.; Bautista, D.B.; Schuetz, S.; Wachsman, L.; Bean,-X.; and Keens, T.G. Abnormal hypoxic arousal responses in infants of cocaine-abusing mothers. Ann NY Acad Sci 562:347-348, 1989b.

Dixon, S.D., and Bejar, R. Encephalographic findings in neonates associated with maternal cocaine and methamphetamic use: Incidence and clinical correlates. J Pediatr 115(5):770-778, 1989.

Eisen, L.N.; Field, T.M.; Bandstra, E.S.; Roberts, J.P.; Morrow, C.; Larson, S.K.; and Steele, B.M. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton scale. Pediatrics 88(3):477-480, 1991.

Fulroth, R.; Phillips, B.; and Durand, D.J. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. Am J Dis Child 143:905-910, 1989.

Gillogley, K.M.; Evans, A.T.; Hansen, R.L.; Samuels, S.J.; and Batra,-K.K. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. Am J Obstet Gynecol 163:1535-1542, 1990.

Hadeed, A.J., and Seigel, S.R. Maternal cocaine use during pregnancy: Effect on the newborn infant. Pediatrics 84(2):205-210, 1989.

Hume, R.F.; O'Donnel, K.J.; Stanger, C.L.; Killam, A.P.; and Gingras,-J.L. In utero cocaine exposure: Observations of fetal behavioral state may predict neonatal outcome. *Am J Obstet Gynecol* 161:685-690, 1989.

Legido, A.; Clancy, R.; Spitzer, A.R.; and Finnegan, L.P. Electroenceph-alographic and behavioral-state studies in infants of cocaine-addicted mothers. Am J Dis Child 146:748-752, 1992.

Lester, B.M.; Corwin, M.J.; Sepkoski, C.; Seifer, R.; Peucker, M.; McLaughlin, S.; and Golub, H.L. Neurobehavioral syndromes in cocaine-exposed newborn infants. Child Dev 62:694-705, 1991.

Link, E.A.; Weese-Mayer, D.W.; and Byrd, S.E. Magnetic resonance imaging in infants exposed to cocaine prenatally: A preliminary report. Clin Pediatr 30(8):506-508, 1991.

MacGregor, S.N.; Keith, L.G.; Bachicha, J.A.; and Chasnoff, I.J. Cocaine abuse during pregnancy: Correlation between prenatal care and prenatal outcome. Obstet Gynecol 74:882-885, 1989.

MacGregor, S.N.; Keith, L.G.; Chasnoff, I.J.; Rosner, M.A.; Chisum,-G.M.; Shaw, P.; and Minogue, J.P. Cocaine use during pregnancy: Adverse perinatal outcome. Am J Obstet Gynecol 157:686-690, 1987.

Maone, T.R.; Mattes, R.D.; and Beauchamp, G.K. Cocaine exposed infants show an exaggerated sucking response to sucrose. Physiol Behav 51(3):487-491, 1992.

Mastrogiannis, D.S.; Decavalas, G.O.; Verma, U.; and Tejani, N. Perinatal outcome after recent cocaine usage. Obstet Gynecol 76(1):8-11, 1990.

Mayes, L.C.; Granger, R.H.; Frank, M.; Schottenfeld, R.; and Bornsteirn,M.H. Neurobehavioral profiles of neonates exposed to cocaine prenatally. Pediatrics 91(4):778-783, 1993.

McCalla, S.; Minkoff, H.L.; Feldman, J.; Delke, I.; Salwin, M.; Valencia,G.; and Glass, L. The biological and social consequences of perinatal cocaine use in an inner-city population: Results of an anonymous cross-sectional study. Am J Obstet Gynecol 164:625-630, 1991.

McCann, E.M., and Lewis, K. Control of breathing in babies of narcotic- and cocaine-abusing mothers. Early Hum Dev 27:175-186, 1991.

Mehta, S.K.; Finkelhor, R.S.; and Anderson, R.L. Transient myocardial ischemia in infants prenatally exposed to cocaine. J Pediatr 122:945-949, 1993.

Mirochnick, M.; Meyer, J.; Cole, J.; Herron, T.; and Zuckerman,B. Circulating catecholamine concentrations in cocaine-exposed neonates: A pilot study. Pediatrics 88:481-485, 1991.

National Institute on Drug Abuse. *National Household Survey on Drug Abuse: Main Findings, 1990.* Rockville, MD: National Institute on Drug Abuse, 1992.

Neerhof, M.G.; MacGregor, S.N.; Retzky, S.S.; and Sullivan, T.P. Cocaine abuse during pregnancy: Peripartum prevalence and perinatal outcome. Am J Obstet Gynecol 161(3):633-638, 1989.

Neuspiel, D.R.; Hamel, S.C.; Hochberg, E.; Greene, J.; and Campbell,-D. Maternal cocaine use and infant behavior. Neurotoxicol Teratol 13:229-233, 1991.

Oro, A.S., and Dixon, S.D. Perinatal cocaine and methamphetamine exposure: Maternal and neonatal correlates. J Pediatr 111(4):571-578, 1987.

Ostrea, E.M.; Brady, M.; Gause, S.; Raymundo, A.L.; and Stevens,M. Drug screening of newborns by meconium analysis: A large scale, prospective, epidemiologic study. Pediatrics 89(1):107-113, 1992.

Parker, S.; Zuckerman, B.; and Bauchner, H. Jitteriness in full-term neonates: Prevalance and correlates. Pediatrics 85:17-33, 1990.

Rodning, C.; Beckwith, L.; and Howard, J. Characteristics of attachment organization and play organization in prenatally drug-exposed toddlers. Dev Psychopath 1:277-289, 1990.

Rodning, C.; Beckwith, L.; and Howard, J. Prenatal exposure to drugs: Behavioral distortions reflecting CNS impairment? Neurotoxicology 10:629-634, 1989.

Ryan, L.; Ehrlich, S.; and Finnegan, L. Cocaine abuse in pregnancy: Effects on the fetus and newborn. Neurotoxicology 9:295-299, 1987.

Salamy, A.; Eldredge, L.; Anderson, J.; and Bull, D. Brain-stem transmission time in infants exposed to cocaine in utero. J Pediatr 117(4):627-629, 1990.

Schneider, J.W., and Chasnoff, I.J. Motor assessment of cocaine/polydrug exposed infants at age 4 months. Neurotoxicol Teratol 14(2):97-101, 1992.

Shih, L.; Cone-Wesson, B.; and Reddix, B. Effects of maternal cocaine abuse on the neonatal auditory system. Int J Pediatr Otorhinolaryngol 15:245-251, 1988.

Stein, J.A.; Newcomb, M.D.; and Bentler, P.M. Differential effects of parents and grandparents drug use on behavior problems of male and female children. Dev Psychol 29(1):31-43, 1993.

Struthers, J.M., and Hansen , R.L. Visual recognition memory in drug-exposed infants. Dev Behav Pediatr 13(2):108-111, 1992.

Tabor, B.L.; Smith-Wallace, T.; and Yonekura, M.L. Perinatal outcome associated with PCP versus cocaine use. Am J Drug Alcohol Abuse 16(3 and 4):337-348, 1990.

Van de Bor, M.; Walther, F.J.; and Sims, M.E. Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. Pediatrics 85(5):733-736, 1990.

Zuckerman, B.; Frank, D.A.; Hingson, R.; and Amaro, H. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 320:762-768, 1989.

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