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The Maternal Lifestyle Study: Cognitive, Motor, and Behavioral Outcomes of Cocaine-Exposed and Opiate-Exposed Infants Through Three Years of Age

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ABSTRACT. *Objective.* To evaluate the direct effects of prenatal cocaine exposure and prenatal opiate exposure on infant mental, motor, and behavioral outcomes longitudinally between 1 and 3 years old.

Methods. As part of a prospective, longitudinal, multisite study, the Bayley Scales of Infant Development II were administered to 1227 infants who were exposed to cocaine ($n = 474$), opiates ($n = 50$), cocaine and opiates ($n = 48$), and neither substance ($n = 655$) at 1, 2, and 3 years of corrected age by certified, masked examiners. Hierarchic linear modeling of the 1-, 2-, and 3-year scores was conducted using cocaine and opiate exposure as predictors with and without controlling for covariates.

Results. Overall retention was 88.4% and did not differ by cocaine or opiate exposure. Overall (at 1, 2, and 3 years), cocaine-exposed infants scored 1.6 Mental Development Index points below infants who were not exposed to cocaine. Opiate-exposed infants scored 3.8 Psychomotor Development Index points below infants who were not exposed to opiates. Neither the cocaine nor the opiate effect remained significant after controlling for covariates. Neither cocaine nor opiate exposure was associated with the Behavioral Record Score during the examination. Low birth weight and indices of nonoptimal caregiving were associated with lower Mental Development Index, Psychomotor Development Index, and Behavioral Record Score scores for all groups of infants.

Conclusions. In the largest at-risk sample observed longitudinally to date, infant prenatal exposure to cocaine and to opiates was not associated with mental, motor, or behavioral deficits after controlling for birth weight and environmental risks. *Pediatrics* 2004;113:

1677–1685; cocaine, opiates, prenatal exposure, BSID-II, outcome.

ABBREVIATIONS. BSID-II, Bayley Scales of Infant Development II; MDI, Mental Development Index; PDI, Psychomotor Development Index; SES, socioeconomic status; MLS, Maternal Lifestyle Study; EMIT, enzyme-multiplied immunoassay technique; MISU, Maternal Inventory of Substance Use; BE, benzoylecgonine; HOME, Home Observation for Measurement of the Environment; PPVT-R, Peabody Picture Vocabulary Test-Revised; BRS, Behavioral Rating Scale; HIV, human immunodeficiency virus.

Illicit drug use by pregnant women constitutes a widespread public health problem. Analyses¹ of the National Household Survey on Drug Abuse,² a nationally representative sample survey, indicated that 2.8% of pregnant women reported using illicit drugs. Estimates based on first-trimester use indicated that 202 000 pregnancies involved illicit drug use, 1 203 000 involved cigarette use, and 823 000 involved alcohol use. Cocaine accounted for 10% of reported illicit drug use. Illicit drug use continues to be^{2,3} higher among nonwhite than white women and higher among women who had not finished high school than among those who had finished high school.

Both cocaine and opiate exposures are associated with premature birth and lower birth weight,^{4–7} but their impact on later development is less clear. Early suggestions that exposure invariably led to substantial deficits in multiple areas of functioning have been supplanted by reports indicating that the impact of exposure is subtle.^{8,9} Some reports using broad measures of developmentally appropriate performance, such as the Bayley Scales of Infant Development (BSID),^{10,11} indicate that prenatal cocaine exposure is associated with modest decrements on the Bayley Mental Development Index (MDI),¹² whereas other reports do not show significant effects.¹³ Cocaine-exposure deficits in motor functioning have been reported using standardized assessments,¹⁴ including the Bayley Psychomotor Development Index (PDI).^{12,15} However, a substantial number of studies report no deficits in motor functioning as assessed with the PDI.^{13,16–20} It is also not clear whether cocaine exposure is associated with behavior difficulties on tasks such as the original BSID, with reports

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of behavioral deficits^{17,21} balanced by reports of no effects in a large-scale longitudinal study.²⁰

Longitudinal modeling of assessments—in which scores at multiple time points are analyzed simultaneously—provides for stable measures of performance and of development that may enable detection of subtle effects. Two longitudinal reports^{16,19} indicated that higher levels of cocaine exposure were associated with decrements in mental performance in the second year of life that were significant after controlling for potential confounders. A third study reported no significant MDI differences between unexposed, lightly exposed, and heavily exposed infants on the MDI at 6, 12, and 24 months old either with or without covariate control.²⁰ Opiate exposure has been associated with deficits in mental and motor performance over the first 2 years of life^{22,23} and with deficits in focused attention at age 2.²⁴ There have not been large-scale reports of the longitudinal impact of prenatal cocaine or opiate exposure on mental, motor, or behavioral development in infants older than 2 years.

The objective of this study was to evaluate the direct impact of prenatal cocaine and opiate exposure on infant mental, motor, and behavioral outcomes at 1, 2, and 3 years of age. For minimizing indirect exposure effects mediated by maturity at birth, exposed and nonexposed infants were matched on gestational age. Infants in exposed and nonexposed groups had a broad range of gestational ages and were from multiple geographic sites. They were assessed by masked examiners on the Mental, Psychomotor, and Behavioral Record Scales of the BSID-II.

Both prenatal cocaine and opiate exposure index multiple co-occurring risk factors of clinical relevance.²⁵ For determining how exposed infants presented clinically, the impact of cocaine exposure and opiate exposure on mental, motor, and behavioral outcomes was initially examined without additional covariates. The unique impact of cocaine and of opiate exposure was then assessed by adjusting for covariates including birth weight, socioeconomic status (SES), maternal education, vocabulary size, race, and psychopathology, as well as prenatal exposure to alcohol, cigarettes, and marijuana.

METHODS

Study Design

The Maternal Lifestyle Study (MLS) is a large, multisite, longitudinal investigation of cocaine and opiate exposure using a matched comparison cohort that is being conducted at 4 geographically diverse, collaborating university centers (Brown University, Providence, RI; University of Miami, Miami, FL; University of Tennessee at Memphis, Memphis, TN; and Wayne State University, Detroit, MI).^{26,27} Between May 1993 and May 1995, mothers who delivered at these centers were screened for eligibility (18 years or older, without psychiatric disorders, developmental delay, or language barriers to informed consent), as were their neonates (inborn, likely to survive, singleton, gestational age <43 weeks). Because prenatal cocaine and opiate exposure are associated with low birth weight deliveries, all neonates with birth weights ≤1500 g were screened. Infants with birth weights >1500 g were screened when their births occurred during routine, daytime working hours. Of the 19 079 subjects screened in the acute phase of the study, 16 988 met the eligibility criteria and 11 811

mothers consented to participate in the acute phase of the study.²⁶ The study was approved by the institutional review board at each site, and signed informed consent was obtained from all participants.

Exposure was determined separately for cocaine and opiates by maternal admission of use during pregnancy and/or a positive screen for meconium metabolites confirmed with gas chromatography/mass spectroscopy.²⁸ For the longitudinal phase of the study, recruitment of all infants who were exposed to cocaine and/or opiates was attempted. Potential comparison infants obtained a negative enzyme-multiplied immunoassay technique (EMIT) screen for cocaine and opiate metabolites, and their mothers denied cocaine and opiate use during the pregnancy. A list of possible comparison infants from this “unexposed” group within each center that matched an infant in the exposed group on ethnicity (black, white, Hispanic, or other), gender (male or female), and gestational age (±2 weeks) was established. Mothers were called on the list in sequence to confirm consent for follow-up and to schedule the 1-month visit. When an infant in the comparison group did not attend the 1-month visit, another match was generated for each exposed infant until a comparison infant was enrolled successfully in the longitudinal phase of the study. This procedure minimized differences in race, gender, and gestational age between infants who were exposed to cocaine and/or opiates and infants who were exposed to neither of these substances. It was possible, however, for either an exposed or a comparison infant to be in the longitudinal phase of the study without a match. Because of low exposure rates to amphetamines (no confirmed positive screens) and PCP (3% positive screen, 4% of which were confirmed positive by gas chromatography/mass spectroscopy), there was no additional examination of exposure to these substances. Prenatal exposure to alcohol, tobacco, and marijuana existed in both groups and was treated as a background measure.

Participants

The longitudinal phase of the study began at the infant's first follow-up visit at 1 month (age corrected for prematurity). The 1388 mother–infant dyads (658 in the cocaine/opiate-exposed group and 730 in the comparison group) who came to the 1-month visit were enrolled in the longitudinal study. One or more BSID-II scores were obtained from 1227 of those infants, which is the final sample in this study. This sample had different rates of cocaine exposure (522 exposed and 705 not exposed) and opiate exposure (98 exposed and 1129 not exposed). Overall, 572 infants were exposed to cocaine and/or opiates, 48 of whom were exposed to both cocaine and opiates.

The 1-month Maternal Interview of Substance Use (MISU), a perinatal maternal interview, and the meconium metabolite benzoylecgonine (BE) were used to determine level of cocaine exposure. Infants were assigned to the high-use group when their mothers reported cocaine use of at least 3 times a week in the first trimester or when the infants had BE concentrations greater than the 75th percentile (1097 ng/g). Infants were assigned to the some-use group when they did not meet the criteria for heavy exposure and either their mothers reported any nonhigh pattern of cocaine use or the infants had BE concentrations >0 but less than the 75th percentile. Infants were assigned to the no-use group when their mothers reported no cocaine use on the MISU (if available) and in the perinatal interview and the infants did not have a positive EMIT screen for cocaine. Information on level of cocaine exposure was not available for 90 subjects who were excluded from analyses involving level of cocaine exposure. These mothers denied use on the MISU or did not complete a MISU; they were cocaine positive by perinatal interview or positive cocaine EMIT, but a BE level could not be established.

Covariates

The MISU provided information about the frequency and quantity of substance use for each trimester during this pregnancy and was administered only to the biological mothers who brought their infant to the 1-month visit ($n = 1119$). MISU reports of the frequency and quantity of their use of alcohol, marijuana, and tobacco per trimester were averaged to produce indices of the number of tobacco cigarettes, the number of drinks (≥0.5 oz absolute alcohol per day), and the number of marijuana cigarettes consumed per day during the pregnancy. For the 108 infants

TABLE 1. Infant Medical Characteristics by Cocaine and Opiate Exposure

	Cocaine Exposed (<i>n</i> = 522) (Mean ± SD or <i>n</i> [%])	Not Cocaine Exposed (<i>n</i> = 705) (Mean ± SD or <i>n</i> [%])	<i>P</i>	Opiate Exposed (<i>n</i> = 98) (Mean ± SD or <i>n</i> [%])	Not Opiate Exposed (<i>n</i> = 1129) (Mean ± SD or <i>n</i> [%])	<i>P</i>
Gestational age, wk	37.1 ± 3.4	37.0 ± 3.7	.531	37.3 ± 3.6	37.0 ± 3.6	.360
Birth weight, g	2546 ± 760	2696 ± 871	.001	2651 ± 821	2631 ± 830	.816
Birth weight <2500 g	231 (44.3%)	277 (39.3%)	.081	41 (41.8%)	467 (41.4%)	.927
Length at birth, cm	46.3 ± 4.9	47.1 ± 5.2	.005	46.6 ± 5.0	46.8 ± 5.1	.796
Small for gestational age	158 (30.3%)	138 (19.6%)	.001	30 (30.6%)	266 (23.6%)	.118
Head circumference, cm	31.9 ± 2.9	32.3 ± 3.2	.034	32.2 ± 3.0	32.1 ± 3.1	.645
Male	270 (51.7%)	382 (54.2%)	.393	46 (46.9%)	606 (53.7%)	.200
HIV exposure	14 (2.7%)	5 (1.0%)	.006	1 (1.0%)	18 (1.6%)	1.00

whose biological mother was not available for the MISU, perinatal in-hospital interviews with the mother were consulted to determine the number of cigarettes smoked daily over the course of the pregnancy and the use of marijuana and alcohol during the pregnancy. Infants whose mother admitted to marijuana and alcohol use in the perinatal maternal interview were assigned the mean quantity of use obtained for the MISU sample.

The number of years of maternal education was recorded in a perinatal interview. At 1 month, SES for all caregivers was determined using the Hollingshead Index of Social Position Score.²⁹ The continuous Social Position Score was used as a covariate in analyses, and low SES (categories IV and V) was identified as a sample descriptor. A dichotomous determination of whether family income fell below or exceeded federal poverty levels in the year of the infant's birth was also calculated at 1 month of infant age.³⁰ The Home Observation for Measurement of the Environment (HOME) Inventory was completed at 10 months of infant age during a home visit.³¹ The child's mother (83.4%) or other primary caregiver (16.6%) was administered the Peabody Picture Vocabulary Test-Revised (PPVT-R) at 30 (89.6%) or 36 (10.4%) months infant age.³² At 4 months (86.8%) or 30 months (13.2%) of infant age, the mothers and caregivers completed the Brief Symptom Inventory from which a Global Severity Index of psychological symptoms was calculated.³³ We also determined whether the infant was in maternal care (ie, whether the biological mother was an in-home caregiver at the 1-, 2-, and 3-year clinic visits when outcomes were assessed).

Outcome Measures

Examiners who were masked to exposure status administered the mental and motor scales of the BSID-II and then rated infant orientation/engagement, emotional regulation, and motor quality on the BRS.¹¹ The BSID-II was administered when infants were 12 ± 0.5, 24 ± 1, and 36 ± 2 months age. Age of administration was corrected for prematurity for infants born at <37 weeks' gestation.³⁴ Examiners were certified annually in their administration and scoring of the examination.

Statistical Procedures

Longitudinal Analyses

Hierarchical linear modeling^{16,35} was conducted separately for the MDI, PDI, and BRS using SAS PROC MIXED (version 8.2; SAS Institute, Cary, NC). A baseline model for all infants was constructed containing an intercept term representing overall performance at 1, 2, and 3 years of age and a linear term representing change with age. The baseline model was used to assess simultaneously the association of cocaine exposure and opiate exposure with overall performance. A cocaine-by-opiate exposure interaction term was also tested in this model but was retained only when significant. Using the baseline model, we also examined any associations of cocaine and opiate exposure with the linear term representing change with age. The identical baseline model with identical follow-up analyses was used to examine associations between level of cocaine exposure and outcome.

Cross-Sectional Analyses

Univariate analyses of variance were conducted to determine whether cocaine and opiate exposures were associated with mean differences in outcome at 1, 2, and 3 years of age. χ^2 analyses were conducted to determine whether cocaine and opiate exposures were associated with a higher percentage of 3-year-olds' scoring in the delayed range (<85) of the mental and motor scales and in the suspect range (<25th percentile) on the Behavioral Record.

Covariate Analyses

Associations between cocaine exposure or opiate exposure and mental, motor, or behavioral performance that were reliable at $P < .1$ were followed up with covariate analyses. Covariates were selected on the basis of empirical and theoretical criteria. Using empirical criteria, variables from Table Tables 1 to 3 were used as covariates in initial models when they differed significantly between exposure groups, were associated with a given outcome at $P \leq .2$, and were not highly correlated ($r > .70$) with other covariates. The baseline hierarchic linear model was used to assess

TABLE 2. Continuous Maternal (Caregiver) Characteristics by Cocaine and Opiate Exposure

	Cocaine Exposed (<i>n</i> = 522) (Mean ± SD [<i>n</i>])	Not Cocaine Exposed (<i>n</i> = 705) (Mean ± SD [<i>n</i>])	<i>P</i>	Opiate Exposed (<i>n</i> = 98) (Mean ± SD [<i>n</i>])	Not Opiate Exposed (<i>n</i> = 1129) (Mean ± SD [<i>n</i>])	<i>P</i>
Maternal age, y	29.88 ± 4.77 (522)	26.41 ± 6.06 (705)	.001	30.35 ± 6.55 (98)	27.67 ± 5.69 (1129)	.001
Maternal education	11.36 ± 1.63 (522)	11.97 ± 2.06 (705)	.001	11.93 ± 1.78 (98)	11.69 ± 1.92 (1129)	.244
Maternal pregnancy drug use (daily)						
Cigarettes	10.33 ± 10.81 (422)	3.51 ± 7.55 (697)	.001	12.26 ± 12.76 (86)	5.57 ± 9.01 (1033)	.001
Drinks	0.57 ± 1.19 (422)	0.10 ± 0.44 (697)	.001	0.33 ± 0.78 (86)	0.28 ± 0.84 (1033)	.599
Marijuana joints	0.16 ± 0.47 (422)	0.04 ± 0.24 (697)	.001	0.06 ± 0.26 (86)	0.085 ± 0.36 (1033)	.390
Maternal (caregiver) characteristics*						
Global Severity Index	0.58 ± .56 (489)	0.59 ± 0.58 (667)	.686	0.67 ± 0.67 (88)	0.58 ± 0.56 (1068)	.194
HOME	33.63 ± 5.54 (433)	33.71 ± 5.98 (591)	.831	35.57 ± 5.55 (77)	33.52 ± 5.79 (947)	.003
PPVT-R	72.78 ± 17.06 (461)	76.81 ± 19.02 (629)	.001	81.26 ± 17.07 (87)	74.57 ± 18.33 (1003)	.001

* Mothers accounted for 82.3% and other caregivers accounted for 17.7% of these data.

TABLE 3. Categorical Maternal (Caregiver) Characteristics by Cocaine and Opiate Exposure

	Cocaine Exposed (<i>n</i> = 522)		Not Cocaine Exposed (<i>n</i> = 705)		<i>P</i>	Opiate Exposed (<i>n</i> = 98)		Not Opiate Exposed (<i>n</i> = 1129)		<i>P</i>
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	
Mother's ethnicity					.654					.001
Black	412	(78.9)	539	(76.5)		52	(53.1)	899	(79.6)	
White	70	(13.4)	113	(16.0)		37	(37.8)	146	(12.9)	
Hispanic	34	(6.5)	45	(6.4)		7	(7.1)	72	(6.4)	
Other	6	(1.2)	8	(1.1)		2	(2.0)	12	(1.1)	
Mother married	51	(9.8)	181	(25.7)	.001	18	(18.6)	214	(19.0)	.164
Poverty status*	330	(70.7)	389	(59.0)	.001	36	(41.9)	683	(65.7)	.001
Low SES†	341	(65.3)	412	(58.4)	.014	60	(61.2)	693	(61.4)	.976
Mother education (categorical)					.001					.135
<12 y	257	(49.3)	220	(31.3)		33	(34.0)	444	(39.4)	
12 y	182	(34.9)	309	(43.9)		36	(37.1)	455	(40.3)	
≥13 y	82	(15.7)	175	(24.9)		28	(28.9)	229	(20.3)	
Maternal care‡	294	(56.4)	657	(93.3)	.001	64	(65.3)	887	(78.7)	.002

* Mothers accounted for 82.3% and other caregivers accounted for 17.7% of these data.

† Defined as Hollingshead categories IV and V.

‡ Indicates whether infant was in maternal care at each 1-, 2-, and 3-year visit attended.

the empirical associations of covariates with overall performance (4). On the basis of theoretical criteria, geographic site; birth weight; and alcohol, marijuana, and tobacco exposure were also used as covariates in initial models. Because of high levels of shared variance between different covariates and outcome, covariates were removed from a model when they did not have a significant association with the outcome. The remaining covariates were included with the exposure effect of interest in a hierarchic linear model to assess the impact of cocaine or opiate exposure on overall mental or motor scores while controlling for covariates. They were also used in analyses of variance and logistic regressions at 3 years to determine whether exposure effects remained significant after covariate control. Finally, covariate analyses were repeated while excluding birth weight to test for the possibility that birth weight was mediating the impact of cocaine exposure.

RESULTS

Retention

The complete number of BSID-II examinations at 1, 2, and 3 years by cocaine and opiate exposure is presented in Table 4. Of the 1388 infants (658 cocaine/opiate exposed and 730 comparison) seen at the 1-month visit, 1227 (88.4%) infants had at least 1 MDI and at least 1 PDI. These 1227 infants with outcome

data and the 161 infants without were compared. Availability of outcome data did not distinguish cocaine-exposed infants (87.0% [522]) and infants who were not exposed to cocaine (89.5% [705]; $P = .155$) or distinguish opiate-exposed infants (85.2% [98]) and infants who were not exposed to opiates (88.7% [1129]; $P = .266$). Availability of outcome data also did not differ by level of cocaine, alcohol, tobacco, or marijuana use ($P > .15$); infant gender ($P > .1$); gestational age, birth weight, birth length, or head circumference ($P > .35$); or maternal age, marital status, or educational level ($P > .35$). However, black infants had higher rates of outcome data (89.5% [951]) than other infants (84.9% [276]; $P = .025$). There was no difference in the age of administration of the BSID-II examinations at the 1-, 2-, or 3-year visits by cocaine exposure or opiate exposure ($P > .1$).

Sample Description

Although cocaine exposure was not associated with gestational age in the matched sample, cocaine-

TABLE 4. BSID-II

	No Cocaine	Cocaine	<i>P</i>	No Opiate	Opiate	<i>P</i>
MDI						
1 y	92.1 ± 0.5 (606)	90.3 ± 0.5 (433)	.014	91.6 ± 0.4 (960)	88.5 ± 1.2 (79)	.022
2 y	82.0 ± 0.6 (579)	81.3 ± 0.6 (432)	.382	81.7 ± 0.4 (931)	82.1 ± 1.6 (80)	.748
3 y	83.5 ± 0.6 (562)	81.6 ± 0.6 (434)	.018	82.6 ± 0.4 (918)	83.0 ± 1.6 (78)	.768
Overall			.006			.140
Overall covariate			.992			
PDI						
1 y	89.6 ± 0.6 (600)	90.4 ± 0.6 (418)	.321	90.0 ± 0.4 (939)	88.9 ± 1.6 (79)	.450
2 y	94.6 ± 0.7 (534)	94.9 ± 0.7 (401)	.753	95.2 ± 0.5 (859)	89.0 ± 1.7 (76)	.001
3 y	92.9 ± 0.6 (529)	93.3 ± 0.7 (412)	.649	93.4 ± 0.5 (866)	89.2 ± 1.6 (75)	.016
Overall			.617			.003
Overall covariate						.073
BRS						
1 y	44.4 ± 1.2 (604)	44.0 ± 1.4 (424)	.831	44.3 ± 1.0 (949)	43.8 ± 3.4 (79)	.878
2 y	40.9 ± 1.3 (575)	41.4 ± 1.5 (430)	.581	41.9 ± 1.0 (925)	34.4 ± 3.1 (80)	.031
3 y	56.2 ± 1.4 (564)	55.4 ± 1.6 (435)	.740	56.3 ± 1.1 (921)	50.6 ± 3.6 (78)	.146
Overall			.799			.075
Overall covariate						.634

Data are means ± standard errors and numbers.

All 1-, 2-, and 3-year and overall P values are adjusted for cocaine and for opiate exposure. The overall covariate P was calculated when the overall $P < .1$. The overall covariate P values are adjusted for the covariates described in the text.

exposed infants were more likely to be small for gestational age³⁶ and were of lower birth weight, length, and head circumference than infants who were not exposed to cocaine (Table 1). Although overall human immunodeficiency virus (HIV) exposure was low, HIV exposure was higher among infants who were exposed to cocaine than among infants who were not exposed to cocaine. Mothers who used cocaine during pregnancy had lower levels of education and used cigarettes, alcohol, and marijuana at higher rates than mothers who did not use cocaine (Table 2). Mothers and caregivers of cocaine-exposed infants were of lower SES, were more likely to be below the poverty line, and had lower vocabulary scores than mothers and caregivers of infants who were not exposed to cocaine (Table 3). Cocaine exposure groups did not differ on the HOME scores or on the Global Severity Index of psychological symptoms (Table 2).

Opiate-exposed and nonexposed infants did not differ on anthropometric measures at birth or on infant HIV exposure rates (Table 1). Mothers who used opiates during the pregnancy were less likely to be black and smoked more cigarettes than mothers who did not use opiates (Table 2). Mothers and caregivers of opiate-exposed infants were less likely to live below the poverty line and scored higher on the HOME and on the PPVT-R than mothers and caregivers of infants who were not exposed to opiates (Table 3). These groups did not differ on other measures of SES.

Mental Development

Cocaine-exposed infants scored 1.6 points lower overall on the MDI than infants who were not exposed to cocaine ($P = .006$). Opiate exposure was not associated with the overall MDI level ($P = .140$), and there was no cocaine-by-opiate interaction ($P = .600$). MDI declined after 1 year so that the linear term for age was significant for all infants ($P = .001$; Table 4). Cocaine exposure was not significantly associated with this decline, indicating that the scores of exposed and nonexposed infants did not change at different rates ($P = .973$). At 3 years of age, the mean MDI of cocaine-exposed infants was lower than that of infants who were not exposed to cocaine ($P = .018$; 2.0 point difference), and a higher percentage of cocaine-exposed infants (59.2% vs 51.7%) had an MDI below 85 ($P = .010$).

Covariates for cocaine exposure in the MDI analysis were selected according to empirical criteria (infant age, infant birth weight, infant HIV exposure, maternal care, maternal education, maternal age, poverty status, PPVT-R vocabulary, SES, HOME score, and tobacco exposure) and theoretical criteria (geographic site and opiate, marijuana, and alcohol exposure) outlined in the Methods section. Covariates were entered into an initial model with cocaine exposure to predict overall MDI. After excluding nonsignificant covariates, the prenatal cocaine exposure model was rerun including site, infant age, infant birth weight, infant HIV exposure, maternal care, SES, and PPVT-R score. After controlling for these variables, cocaine exposure was not a signifi-

cant overall predictor of MDI ($P = .843$; 0.1 MDI points). In a similar manner, after controlling for the same variables at 3 years, there was no cocaine exposure difference in mean MDI ($P = .993$) or in the proportions of infants with MDIs in the delayed range ($P = .331$). Cocaine exposure remained nonsignificant in the longitudinal ($P = .780$) and 3-year ($P = .828$) models when birth weight was removed from the covariate set, indicating that birth weight was not mediating the impact of cocaine exposure.

Overall mean MDI differences between the high ($n = 160$), some ($n = 276$), and no cocaine ($n = 701$) groups were significant ($P = .009$). The no-exposure group scored 1.03 MDI points above the high-exposure group, which scored 1.15 points above the some-exposure group. The 2.17-point difference between the some- and no-exposure groups was significant ($P = .003$). Opiate exposure did not have a significant impact on MDI in these analyses ($P = .292$). After controlling for the final set of MDI covariates (site, infant age, infant birth weight, infant HIV exposure, maternal care, SES, and PPVT-R score), there was no overall level of cocaine exposure effect ($P = .352$); neither was the contrast between the some- and no-exposure groups significant ($P = .373$; 0.77 points). Level of cocaine exposure remained nonsignificant when birth weight was removed from this covariate set ($P = .200$).

Motor Development

Opiate-exposed infants scored 3.9 points lower overall on the PDI than infants who were not exposed to opiates ($P = .003$). Presence of cocaine exposure was not associated with the overall PDI level ($P = .617$), and there was no cocaine-by-opiate exposure interaction ($P = .584$). Level of cocaine exposure was also not associated with overall PDI ($P = .470$). The PDI rose after 1 year, and the linear term for age was significant for all infants ($P < .001$). Opiate exposure was not significantly associated with this rise, indicating that the scores of exposed and nonexposed infants did not change at different rates ($P = .635$). At 3 years of age, opiate-exposed infants had a lower mean PDI than infants who were not exposed to opiates ($P = .016$; 4.2-point difference). However, the percentage of 3-year-olds with a PDI below 85 did not differ by opiate exposure status ($P = .218$).

Covariates for opiate exposure in the PDI analyses were selected according to the empirical (infant age, infant birth weight, maternal care, maternal age, HOME score, and ethnicity) and theoretical criteria (geographic site and cocaine, tobacco, marijuana, and alcohol exposure) outlined in the Methods section. After excluding nonsignificant covariates, the impact of opiate exposure on overall PDI was assessed controlling for site, infant age, ethnicity, infant birth weight, maternal care, and HOME score. After controlling for these variables, opiate exposure was not significantly associated with overall PDI ($P = .073$; 2.2 PDI points). In a similar manner, there was no opiate exposure difference in mean PDI at 3 years of age after controlling for the same variables ($P = .337$). Results for overall PDI ($P = .070$) and 3-year

PDI ($P = .352$) were unchanged when birth weight was removed from the covariate set.

BRS

Neither cocaine ($P = .799$; 0.26 percentile difference) nor opiate exposure ($P = .075$; 4.5 percentile difference) was associated with overall differences in BRS ratings. There was no cocaine-by-opiate exposure interaction effect ($P = .733$). Level of cocaine exposure was also not associated with the overall BRS ($P = .219$). The BRS rose after age 2, and the linear term for age was significant for all infants ($P = .001$). Neither opiate exposure ($P = .534$) nor cocaine exposure ($P = .881$) was associated with this increase, indicating that the scores of exposed and nonexposed infants did not change at different rates. At 3 years of age, neither cocaine exposure ($P = .974$; 0.8 percentile difference) nor opiate exposure ($P = .146$; 5.7 percentile difference) was significantly associated with differences in the mean BRS. There were also no cocaine ($P = .982$) or opiate ($P = .354$) exposure differences in the percentages of 3-year-olds with BRS in the suspect range.

Covariates for opiate exposure in the BRS analyses were selected according to the empirical (infant age, infant birth weight, poverty status, maternal education, maternal care, HOME score, and marijuana exposure) and theoretical criteria (geographic site and cocaine, tobacco, marijuana, and alcohol exposure) outlined in the Methods section. After excluding nonsignificant covariates, the impact of opiate exposure on overall BRS percentile was assessed controlling for site, infant age, poverty status, PPVT-R score, infant birth weight, and HOME score. Opiate exposure was not a significant overall predictor of BRS ($P = .634$; 1.1 BRS percentile difference). Opiate exposure remained nonsignificant ($P = .643$; 1.1 BRS percentile difference) when birth weight was removed from the covariate model to test for mediation effects.

Covariate Effects

Low infant birth weight was associated with lower overall MDI, PDI, and BRS, but birth weight did not moderate cocaine or opiate exposure effects. Indices of higher quality caregiving were also associated with higher BSID-II scores. Higher HOME scores were associated with higher PDI and BRS. Higher mother (caregiver) vocabulary scores were associated with higher MDI and BRS. The consistent presence of the mother in the household was associated with higher MDI and PDI. Poverty level status was associated with lower BRS.

DISCUSSION

Beyond the perinatal period, there is more concern about prenatal exposure to illicit drugs than information about their impact on human development.⁹ Subtle exposure effects that occur in the context of multiple risk factors have obscured a clear understanding of the influence of prenatal exposure on early mental, motor, and behavioral development. The MLS was designed to address the direct impact of prenatal cocaine/opiate exposure in a large mul-

titise sample, group matched on gestational age, gender, and race, by using standardized, masked infant assessments with the power to control statistically for multiple covariates, including prenatal exposure to other drugs. Infant prenatal exposure to cocaine marked deficits in mental performance, and exposure to opiates marked deficits in psychomotor development. However, both sets of deficits were attributable to factors associated with illicit drug exposure rather than to exposure itself.

Retention (defined as contribution of 1 or more mental and motor examinations to the longitudinal data set) was high (88%) for an at-risk sample and did not differ by cocaine exposure or opiate exposure, strengthening confidence in study results. Infants of black mothers did show slightly higher retention rates than other infants and composed 77.5% of the entire sample, suggesting that study results may be most generalizable to this group. Infants were assessed with the BSID-II during standardized assessment windows at 1, 2, and 3 years of age. Hierarchic modeling was used to model these scores longitudinally so that the impact of infant age was controlled both by design and by state-of-the-art statistical techniques.

Cocaine Exposure

A 1.5-point difference in the mental scores of cocaine-exposed infants was no longer significant after controlling for the influence of birth weight and several indices of the caregiving environment. Similar results were obtained when comparing high, some, and no cocaine exposure levels. There was also no evidence that cocaine exposure influenced the decline in mental scores with age. At 3 years of age, cocaine exposure was associated with MDI scores in the delayed range (<85), but this association was not evident after covariate control. Although cocaine-exposed children may present with subtle delays in the first years of life, exposure seems to be a marker for associated risks to development.

In previous longitudinal studies, significant associations between cocaine exposure and MDI were found in samples that included infants who were born before 36 weeks' gestational age^{16,19} but not in samples restricted to infants who were born at 36 weeks' gestation or older.²⁰ The current study included infants who were born at <36 weeks' gestation but used both matching and statistical techniques to ensure that differences in the outcome of exposure groups could not be attributed to maturity at birth. There was no evidence that birth weight was a mediator of cocaine exposure effects within the matched sample. By limiting the impact of maturity at birth, the current results provide an estimate of the direct impact of cocaine exposure on mental performance. The direct impact of cocaine exposure on developing dopaminergic tissue is likely to depend on both the timing and the extent of exposure.³⁷ Cocaine exposure levels in the current study were not high, with substantially lower 75th percentile concentrations of BE (1097 ng/g) than in another recent large-scale study (3314 ng/g).²⁰ Nevertheless, the 1.5-point MDI difference associated with prenatal

cocaine exposure falls within the standard error of the mean IQ difference (3.3 points) identified by a recent meta-analysis of the association between prenatal cocaine exposure and IQ in school-aged children.⁸

The current study showed no significant association between cocaine exposure and psychomotor performance. Although an association between cocaine exposure and psychomotor performance has been reported,^{12,15} recent studies,^{13,19,38} including large-scale longitudinal investigations,^{16,20} have also not shown a significant association of cocaine exposure with psychomotor performance in the first years of life. In fact, subtle effects of cocaine exposure on fine motor functioning detectable with specialized assessments such as the Peabody Development Motor Scales have been detected at 24¹⁵ but not at 36 months of age.³⁸

Although designed to be sensitive to deficits in multiple areas of functioning, broadband developmental assessments such as the Bayley Mental and Motor scales may be relatively insensitive to particular effects of prenatal cocaine exposure even when large samples of infants are assessed longitudinally.^{25,39} It remains to be demonstrated, however, which types of assessments of mental and motor functioning might be consistently more sensitive to exposure effects. With respect to information processing, infants with high levels of cocaine exposure have shown decrements in gazing toward novel stimuli in paired preference tasks¹⁷ but have not shown decrements with sequentially paired stimuli.¹⁹

It has been argued that cocaine exposure effects will be most evident in the domains of attention and affective regulation.^{9,40} Prenatal exposure to cocaine and to opiates have been linked to central nervous system irritability in the first 3 months of life and, less consistently, with other behavioral difficulties.^{27,41–46} Difficulties with self-regulation (both irritability⁴⁷ and low arousal⁴⁸) have been observed among cocaine-exposed infants who performed learning tasks in the first 3 months of life. The current study, however, did not find exposure differences in the BRS. The absence of cocaine effects is striking because of longstanding⁴ and current⁹ concern about the attention, emotion regulation, and motor quality of cocaine-exposed and opiate-exposed²⁴ infants. Although behavioral deficits associated with cocaine exposure have been identified on a precursor of the current BSID-II,¹⁷ a recent report indicated no such effects at 6, 12, or 24 months of age.²⁰ The results suggest that masked examiners' ratings of the test behavior of cocaine-exposed infants are not distinguishable from those of nonexposed infants.

Opiate Exposure

The 4-point longitudinal deficit in overall psychomotor performance of the current large sample of opiate-exposed infants was not significant after covariate control. There was also no evidence that birth weight mediated opiate exposure effects. At 3 years, opiate exposure was not associated with clinically informative delays in motor performance. The result

is similar to the 4-point longitudinal PDI deficit found in a recent study of opiate-exposed infants over the first 2 years of life that was also not significant after covariate control.²² In the current study, no association was detected between opiate exposure and overall mental performance between 1 and 3 years of age. The presence of a significant association between opiate exposure and MDI scores collected at 5 points in the first 2 years of life as part of a smaller longitudinal study²² suggests that opiate exposure effects on mental performance may be most evident before 2 years of age. Although there was a trend for opiate-exposed infants to receive lower overall mean BRS percentiles than infants who were not exposed to opiates, this tendency was attenuated after covariate control. Opiate exposure was also not associated with an increase in clinically relevant BRS scores.

CONCLUSION

Cocaine and opiate exposures are inextricably associated with other environmental risks, underlining the clinical importance of illicit drug exposure as a marker of environmental risk to individual children.^{27,40} Opiate exposure was a marker for slightly depressed motor performance and a tendency toward behavioral difficulties during the Bayley examination. Opiate exposure was associated with disruptions in maternal care in this sample but was also associated with higher HOME scores and greater maternal (caregiver) vocabulary scores. In covariate analyses, low HOME scores, low vocabulary scores, and low infant birth weight, rather than opiate exposure, were associated with substantial deficits in psychomotor performance and behavioral difficulties.

Cocaine exposure was a marker for subtle decrement in mental performance. It was also associated with low birth weight and disruptions in maternal care, low SES, and low vocabulary scores. These factors, rather than cocaine exposure, were associated with large deficits in mental development. Although infants who were exposed to illicit drugs did not show unique deficits with respect to their peers, all infants in this sample were at risk for poor developmental outcomes. At 3 years of age, both infants who were exposed to cocaine and those who were not exposed had mean mental scores >1 standard deviation (15 points) below the standardized MDI mean of 100.

The largest matched cohort study to date showed no significant covariate-controlled associations between prenatal cocaine or opiate exposure and mental, psychomotor, or behavioral functioning through 3 years of age. Rather, cocaine and opiate exposure marked subtle deficiencies in mental and psychomotor functioning. The effects of prenatal cocaine and opiate exposure may nevertheless become more evident as more advanced motor,¹⁵ cognitive,³⁸ language,⁴⁹ and behavioral skills⁵⁰ develop. Continued longitudinal follow-up will be necessary to determine the degree to which prenatal drug exposure, low birth weight, and environmental risks affect the developmental progress of at-risk children.

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A RESIDENT'S LAMENT

"I was recently informed that as a resident I would be required to log my hours in order to monitor for compliance of national mandates created by the American College of Graduate Medical Education. On the surface this may seem to be a harmless, even well-intentioned measure taken to ensure that every resident is accounted for and has a voice against his/her governing residency program. Good intentions do not always ensure good results.

I entered medical school with the intention of joining a profession of people who dedicate their lives to the care and service of others. I have learned through my limited experience thus far that caring for others is not a 9-to-5 *job*. While having a job has its benefits, with predictable hours and the ability to leave it behind when the clock strikes a certain hour, I do not want a job. I want to be a member of the noble profession I took an oath to serve on my graduation day. Punching a time clock shifts the focus of my work from doing what it takes as a professional to care for a patient, to doing a task for a specified amount of time in anticipation of the final bell. I refuse to be a participant in this degradation of the medical profession.

I learned from my first mentors in medical school that the rewards of a career in medicine are unique. I have begun to understand some of these rewards as I have interacted with families during both tragedies and miracles. Families and patients allow us as physicians into their most private moments because they trust in the medical profession. This trust has been challenged recently with the advent of managed care and explosion of malpractice suits. Teaching young doctors that their job ends at a certain hour will only further the growing mistrust.

One may criticize my stance as hypocritical, as studies have shown that longer work hours and tired residents directly correlate with medical mistakes and harm patient care. By requiring residents to log their hours, the American College of Graduate Medical Education may be able to prevent medical mistakes caused by overworked residents. I agree with the move toward more humane residency work hours to improve patient care. I disagree with the manner proposed to monitor it. I believe the level of regulation should be on the scheduling end. For example, under the current regulations no resident should be scheduled for more than 30 consecutive hours or 80 hours in a week. However, if a patient's condition deteriorates in the 30th hour, or a patient care conference is scheduled in the 82nd hour, young doctors should not be clocked out and taught to abandon their patients.

I have been asked to log my work hours as a resident physician. I refuse and will continue to refuse to do tasks I feel take away from my profession dedicated to the care and service of others."

Submitted by Robert A. Niebler, MD,
3rd-year pediatric resident, University of Arizona

The Maternal Lifestyle Study: Cognitive, Motor, and Behavioral Outcomes of Cocaine-Exposed and Opiate-Exposed Infants Through Three Years of Age

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