Wing patterns with broad contrasting vertical stripes occur in most families of butterflies (Fig. 1A) and in some diurnal moths. They are rare or absent among chemically "protected," unpalatable species. Such patterns have frequently been cited as examples of disruptive coloration (for example, in *Limenitis a. arthemis*) [(*13*) and Fig. 1A]. Yet *A. fatima* does not appear to be protected from visually oriented predators by its striped coloration (*14, 15*).

Few concepts in the theory of adaptive coloration are as well accepted, but as poorly documented, as that of disruptive coloration. No direct experimental tests demonstrating its efficacy have yet been performed. We are reluctant to cast doubt on this logical general concept from the results of a single experiment, but consider it important to point to the need for caution in interpreting animal coloration from untested hypotheses.

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6. Age is determined by subtracting the date on which a butterfly was first captured from the date in question. Longevity is the difference between the dates of the first and last captures. Both age and longevity really refer to residence time in the population, since it is not possible to distinguish emigration from death as causes of disappearance.
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8. General condition refers to the overall extent of wear on individuals; it is a subjective measure of how old a butterfly looks, taking both scale loss and marginal fraying into account. Four states are recognized: excellent (no evident wear), good (slight wear), fair (considerable wear), and poor (extensive wear and fraying). General condition is estimated independent of wing damage.
9. *Anartia fatima* has brittle wings that break and tear upon seizure. Bill marks, scars in the uniform ordering of wing scales characteristic of other butterflies, are not produced; the wing membrane is notched or clipped instead. Symmetrical notching or clipping of the left and right wings is the most common general category of damage; it occurs suddenly and is not due to gradual wing wear. Damage was coded separately for each of the four wings, with a system that described both location and type of damage.
10. We are confident that none of the animals chosen for the experiment were more than 1 week old when first captured. The greatest extent of wing damage, in an experimental or control animal at first capture, was one slight nick in one wing margin (three individuals).
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14. Alternative roles for the bands of *A. fatima*, not exclusive of a protective role, include that of a social signal used during courtship (*3*). The light bands vary from yellow to white and change color with age [O. R. Taylor, Jr., *Evolution* **27**, 161 (1973)]. Further experiments on color change and courtship will be reported elsewhere.
15. Five (5.2 percent) experimental and five control individuals were captured by a nonvisual predator, a strategically located female orb-weaving spider (*Argiope argentata*, Araneae), during the course of the study.
16. We thank W. H. Bossert, W. J. Glynn, D. K. Pickard, R. Robbins, and J. M. Sigda for statistical advice, numerous colleagues for helpful suggestions, and the Smithsonian Tropical Research Institute for support and the use of facilities.
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Fetal Exposure to Narcotics: Neonatal Sleep as a Measure of Nervous System Disturbance

Abstract. *Newborn infants, chronically exposed in utero to low doses of methadone with or without concomitant heroin, display more rapid eye movement sleep and less quiet sleep than control infants, while babies fetally exposed to both opiates and nonopiates have less organization of sleep states. Other perinatal factors, such as birth weight and gestational age, are related more to the amount of fetal drug exposure than to the type.*

Since 1965, when the synthetic opioid methadone became an accepted treatment for heroin addiction, thousands of methadone-treated, heroin-dependent women have given birth. Evidence that opioids such as heroin and methadone cross the placental barrier suggests that chronic use of narcotics by women during pregnancy increases the probability that the fetus will become physically dependent (*1*). Soon after birth, the neonate is likely to display clinical symptoms of opiate withdrawal, including agitated behavioral states, hypertonicity, tremors, and irritability. Studies of this narcotic abstinence syndrome in neonates have generally focused on its clinical characteristics and management, finding considerable individual differences in the onset, variety, intensity, and duration of the behavioral symptoms (*2*).

Psychophysiological assessment of sleep states is an objective measure of nervous system disturbance, offering a potentially useful index of the severity and time course of narcotic withdrawal in neonates. It has not, however, been commonly employed in studies of neonatal withdrawal, despite reports that heroin- and methadone-dependent adults undergoing withdrawal have increased amounts of rapid eye movement (REM) sleep (*3*). Although a similar finding has been confirmed for newborns of untreated heroin-addicted women (*4*), and claimed for newborns of women maintained on methadone (*5*), a recent study reported a decrease in REM in newborns exposed to heroin and methadone in utero (*6*). Consequently, the precise nature of sleep disturbance during narcotic withdrawal in neonates remains unclear; there is no information on whether neonates have different sleep state alterations after fetal exposure to low doses of methadone or various doses of opiates and other drugs. Nor is it known how the degree of sleep state disturbance is related to other perinatal outcomes. We sought to clarify the nature of sleep states and perinatal outcomes during narcotic withdrawal in neonates by taking into account the actual fetal drug exposure resulting from various drug-intake patterns in methadone-treated, heroin-dependent women.

The study involved 58 newborns and their mothers. Twenty-eight of the neonates were the offspring of heroin-dependent women participating in an urban methadone treatment program. These mothers received daily a mean methadone dose of 17.7 mg (range, 2.5 to 35.0 mg). The 30 other newborns were the offspring of control mothers; that is, women who were demographically similar to the drug-dependent women but who did not use drugs. All women received prenatal care and gave birth at the same hospital during a 13-month period. (Each mother's informed consent was first obtained for the study.)

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Table 1. Characteristics of the five neonatal subgroups (mean values). See text for abbreviations.

Group	*N* (males/ females)	Maternal methadone (mg/day)	Concomitant use of illicit drugs*	Weight at birth (g)	EGA (weeks)	Apgar scores		Age† (days)	Total sleep time (min)
						1-min	5-min		
OC	9/6			3358	40.1	8.7	9.3	2.5	76.1
NC	11/4			3309	39.1	8.1	8.6	2.8	64.0
LO	7/1	12.1	Opiates	2956	39.1	6.6	7.4	4.8	79.3
HO	2/5	14.3	Opiates	2927	38.9	7.7	8.7	2.2	71.7
HON	7/6	21.7	Opiates, stimulants, others	2783	38.2	8.2	8.9	3.0	64.7
F (4, 53)				2.53	2.43	2.71	3.68	2.30	1.52
P				< .05	< .06	< .04	< .01	< .07	< .21

*For frequency of use, see text. †Postnatal age at testing.

Newborns (2 to 7 days of age) were recorded polygraphically in a sleep laboratory adjacent to the nursery. The recordings were made in the morning between normal feedings and before the administration of any pharmacologic agents (*7*). As each baby arrived at the laboratory, electrodes were applied and it was fed, swaddled, and placed in a crib. Then the lights were dimmed and recording was begun. Measurements included electroencephalogram, electrooculogram, electromyogram, respiration, and behavioral activity. Each 30-second epoch of polygraphic recording was scored by an experimenter (who was blind to the baby's group) as quiet sleep, active REM sleep, indeterminate sleep, or awake, according to standard criteria (*8*). Each sleep state was measured in minutes and calculated as a percentage of total sleep time. Drug-exposed and unexposed newborns did not differ in mean age or total sleep time at the time of recording.

The mean percentages of all three sleep states differed greatly between the two groups. Drug-exposed babies averaged significantly less quiet sleep ($P < .0001$) and significantly more active REM sleep ($P < .01$) and indeterminate sleep ($P < .005$) than their unexposed counterparts. Despite the robustness of these differences, they cannot be attributed to chronic exposure of fetuses to methadone without further analyses in which the actual drug-intake histories are considered.

Throughout their pregnancy, the 28 methadone-maintained women were closely monitored for illicit drug intake by self-report methods and random urine testing once to thrice weekly. It was found that a substantial number were concomitantly using illicit addictive or psychoactive drugs, especially heroin and the stimulant phenmetrazine (Preludin). Therefore the mothers were divided into three subgroups based on the type and frequency of their actual drug intake during pregnancy: (i) women who received methadone daily and never or only rarely abused heroin (less than once a week), (ii) women who received methadone daily and frequently abused heroin (daily to once a week); and (iii) women who frequently abused both illicit opiates and nonopiates while daily receiving methadone. Thus their offspring were classified as having been (i) lightly exposed to opiates (LO); (ii) heavily exposed to opiates (HO); or (iii) heavily exposed to both opiates and nonopiates (HON).

Control newborns were subdivided into optimal (OC) and nonoptimal (NC) groups based on delivery, birth weight, estimated gestational age (EGA), and condition at birth (Apgar scores). The OC neonates had uncomplicated term births and were born in good condition, whereas the NC neonates had at least one major perinatal complication, such as fetal distress or low birth weight. Thus analyses were carried out on the perinatal outcomes of two control groups and three drug-exposed groups.

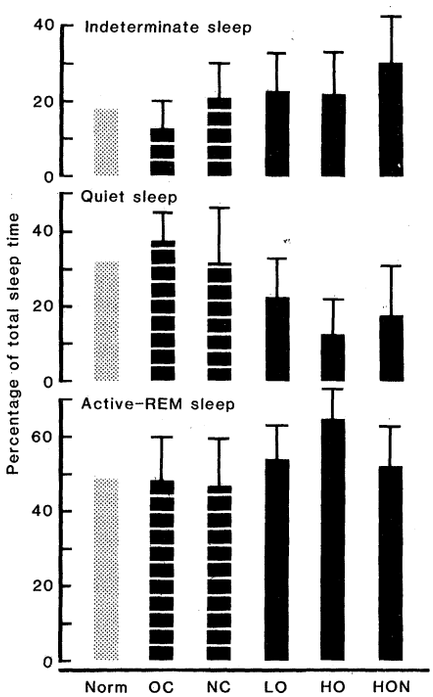

Fig. 1. Mean percentage of time spent in the two sleep states and in indeterminate sleep by the five groups of neonates. Multiple analyses of variance yielded, for indeterminate sleep, F (4, 53) = 4.80 ($P < .003$); for quiet sleep, 7.99 ($P < .001$); and for active REM sleep, 3.24 ($P < .02$). The shaded histograms represent mean values from seven studies on sleep in normal newborns (*13*), and are included to show the similarity of the sleep of OC and NC neonates to the norms.

Table 1 lists the five groups in the order we hypothesized them to be at risk for sleep disturbance, with OC babies least suspect and HON infants most at risk. If perinatal variables other than sleep psychophysiology are affected by fetal exposure to addictive drugs, as has been reported (*2*), then these parameters should vary significantly across groups. Separate analyses of variance for each variable revealed this to be the case for birth weight, EGA, and neonatal condition 1 and 5 minutes after birth. Although the effects on Apgar scores and age were associated with delivery complications in three of the LO babies (*9*), birth weight and EGA were affected as predicted: both declined as total maternal drug intake during pregnancy increased.

Unlike these perinatal outcomes, sleep state differences between control and drug-exposed infants appeared to be a function of type of fetal drug exposure (*10*). Figure 1 shows the mean sleep state percentages for each group. Compared to the NC neonates, the LO and HO babies averaged significantly less quiet sleep ($P < .05$ and $P < .0005$, respectively) and reciprocally greater amounts of active REM sleep ($P < .08$ and $P < .0005$, respectively). Comparisons of LO and HO babies with OC babies gave similar results (*11*). The increase in REM sleep agrees with findings of REM rebound in adults (*3*) and infants (*4*) undergoing opiate withdrawal, and the data suggest that the effect of opiates on sleep states is dose-related. The HO neonates

experienced greater disturbance of active REM sleep ($P < .025$) and quiet sleep ($P < .05$) than the LO neonates. Moreover, compared to all the other groups, a significantly greater proportion of the HO newborns woke during the recording sessions ($P < .04$). This agrees with both clinical observations and animal studies (*12*) indicating that wakefulness is increased during opiate withdrawal. Given the physiological similarities between wakefulness and active REM sleep, the increase in both states reflects elevated activation of the nervous system in babies born with opiate withdrawal syndrome.

While it seems reasonable to attribute sleep state disturbance in the LO newborns to long-term exposure to methadone, and in the HO infants to both methadone and heroin, HON neonates were fetally exposed to combinations of opiates and other addictive drugs, especially stimulants. In this group there was less quiet sleep ($P < .005$) and more indeterminate sleep ($P < .025$) than in NC babies. Since indeterminate sleep is not a sleep state, but results whenever there is no agreement among at least four of the five sleep parameters, the sleep state pattern of the HON newborns showed less organization than that of the control and opiate-exposed groups. Therefore, from the perspective of the developing nervous system's basic capacity to organize psychophysiological parameters into adaptive states, polydrug exposure is apparently more devastating than exposure to opiates alone. Indeed, 6 of the 13 HON neonates ultimately required pharmacotherapy to control behavioral withdrawal symptoms compared to only 1 of the 13 opiate-exposed infants ($\chi^2 = 3.13$, $P < .10$). Although the multiplicity of drugs taken by the mothers of HON newborns confounds the assessment of specific drug effects, this group represents a not uncommon pattern of fetal drug exposure, and thus is important to study despite the complexity of the exposure.

Insofar as sleep state psychophysiology reflects nervous system integrity, alterations of sleep during neonatal withdrawal from narcotics leave little doubt that long-term exposure to opiates in utero, even in low daily doses, results in abnormalities of brain function that are manifested shortly after birth. These sleep disturbances may continue beyond the newborn period, perhaps long after the behavioral symptoms of withdrawal have subsided. The longitudinal assessment of sleep disturbance and its relation to the child's physical, cognitive, behavioral, and affective development should permit tracking of the long-term effects of prenatal exposure to narcotics.

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References and Notes

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7. Recordings were made during this period, since longer recordings at other times of the day would have been impractical due to the number of newborns being studied, and since there is no evidence suggesting that sleep state distributions in neonates vary diurnally, as in adults. The neonates were on a similar nursery schedule, were recorded at the same time of day, and did not differ in total sleep time, so it is unlikely that sleep state variations that might have been due to time of recording differentially affected any group.
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9. The lower mean Apgar scores and older test ages in the eight LO newborns were associated with the use of general anesthesia during the delivery of three of these babies; it was used in delivering just three of the 15 NC babies, one of the 13 HON babies, and none of the seven HO and 15 OC neonates. Groups did not differ in the frequency of exposure to local anesthesia or to other obstetric medications such as Demerol, Largon, and Vistaril.
10. The younger EGA of the drug-exposed infants was still within the 38- to 40-week range typically considered normal term. Therefore it is unlikely that younger EGA produced sleep state differences between groups, since the increased active REM of prematurity is evident below 38 weeks of EGA. This is further supported by the fact that the HON newborns averaged the youngest EGA and the lowest birth weight, but had no more active REM sleep than control infants.
11. The probability levels are one-tailed since the outcomes were predicted. The findings were further confirmed by (i) comparing sleep states of LO and HO infants to those of NC infants matched for birth weight, EGA, and neonatal condition; (ii) eliminating indeterminate sleep as unscorable and analyzing the percentages of active REM and quiet sleep between groups; and (iii) using minutes of each sleep state rather than percentages to perform the analyses.
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