

THE CUMULATIVE EFFECTS OF BUPIVACAINE
EPIDURAL ANESTHESIA AND OBSTETRIC
VARIABLES ON NEONATAL BEHAVIOR

By

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TABLE OF CONTENTS

ACKNOWLEDGMENTS.....	ii
ABSTRACT.....	ix
INTRODUCTION.....	1
Types of Obstetric Medication.....	6
Perinatal Pharmacology.....	9
Empirical Studies of the Behavioral Effects of Obstetric Medication.....	14
Lack of Significant Behavioral Effects.....	45
Methodological Considerations.....	54
Purpose of the Study.....	65
METHODS.....	72
Study Site.....	72
Subject Recruitment.....	72
Sample.....	75
Instruments.....	76
Procedure.....	82
RESULTS.....	85
Characteristics of the Sample.....	85
Relationship Among Variables: Bivariate Correlations.....	94
Cumulative Effects of Bupivacaine and Obstetric Variables: Multiple Regression.....	96
Comparisons of Epidural and Nonmedicated Groups.....	102
DISCUSSION.....	109
Cumulative Effects of Bupivacaine and Other Obstetric Variables.....	109
Comparison of Bupivacaine Epidural and Nonmedicated Groups.....	118
Comparisons with other Bupivacaine Epidural Studies.....	120
Conclusions.....	123
Implications.....	129
REFERENCES.....	134

APPENDICES

1	SUMMARY OF OBSTETRICIANS.....	152
2	PARENTAL CONSENT FORM.....	153
3	BRAZELTON NEONATAL BEHAVIORAL ASSESSMENT SCALE ITEMS.....	156
4	CATEGORIZATION SYSTEMS FOR SIX STATES ASSESSED DURING BRAZELTON EXAM.....	157
5	BRAZELTON SCALE SEVEN CLUSTER SCORING CRITERIA.....	158
6	MATERNAL INTERVIEW.....	159
7	OBSTETRIC COMPLICATION SCALE.....	163
8	MEAN CLUSTER SCORES FOR EPIDURAL AND NONMEDICATED GROUPS WITH VARIANCE DUE TO LENGTH OF LABOR REMOVED.....	165
9	MEAN CLUSTER SCORES FOR EPIDURAL AND NONMEDICATED GROUPS WITHOUT VARIANCE DUE TO LENGTH OF LABOR REMOVED.....	166
	BIOGRAPHICAL SKETCH.....	167

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by

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This study was designed to investigate the cumulative behavioral effects of maternal epidural anesthesia with bupivacaine and the constellation of nonoptimal obstetric conditions found in a relatively healthy sample of newborns with varying birth histories. It was hypothesized that obstetric variables which may influence the rate of placental transfer of local anesthetics potentiate the effects of bupivacaine on behavior over the first month of life.

The sample was 60 healthy fullterm infants selected randomly from a population of mothers delivering without pain-relieving medication or with bupivacaine epidural anesthesia only. The Brazelton Neonatal Behavioral Assessment Scale was administered by trained examiners at 3 hours and at 3, 7, and 28 days after birth.

The variables entered as predictors into stepwise multiple regressions performed on six Brazelton clusters were dose of bupivacaine, hours of administration of oxytocin, umbilical arterial pH, ponderal index, maternal weight:height ratio, lengths of the first and second stages of labor and Obstetric Complication Scale score. Eleven of 24 multiple correlations were significant. More behavioral clusters were predicted on the first day than on any other testing day. The motor and autonomic regulation clusters were predicted more frequently than the other clusters over the entire month.

All independent variables contributed to some of the regressions. Dose of bupivacaine was the most important predictor followed by hours of oxytocin. Comparisons of multiple and bivariate correlations indicated that the effects of bupivacaine on behavior were potentiated by the other nonoptimal obstetric conditions.

The sample was divided into epidural and nonmedicated groups matched on obstetric variables. Analyses of variance indicated that the two groups differed in Brazelton performance on each testing day and on six of seven clusters. Although all babies performed within a normal range of behavior, the nonmedicated group consistently performed better than the epidural group.

Post hoc analyses illustrated possible indirect effects of bupivacaine. The epidural group had more forcep

deliveries, longer labors and more oxytocin than the nonmedicated group. Also, these mothers spent significantly less time with their infants while in the hospital. Limitations of the study design and recommendations for future research were discussed.

INTRODUCTION

Over the past twenty-five years, a new picture of the capabilities of the newborn has emerged. With this, the neonatal period has become a focus of developmental research.

During the first half of this century, the neonate was conceptualized as a passive and helpless organism who could not see or hear (Kessen, 1963). It was thought that newly born babies could not learn and that their behavior was totally reflexive. Scientists and physicians thought that infants were born essentially alike, having been immune to environmental forces in utero. After birth, the infant was considered to be a behavioral tabula rasa, ready to be completely shaped by the outside world.

The focus of the earliest infant research was to document normative behavioral development (Bayley, 1933; Buhler & Hetzer, 1935; Gesell, 1928). Illuminating the abilities of the baby led to an explosion of research in the area and thus, the newly emerging picture of the newborn. Scientists discovered that neonates could not only see and hear but that they could actively select input from the environment by the mechanisms of habituation and orientation (Tronick, Als, & Brazelton, 1979). They seemed to prefer and respond differently to animate stimuli such as the human face and voice than to inanimate stimuli (Brazelton,

Koslowski, & Main, 1974; Carpenter & Stechler, 1967; Condon & Sander, 1974; Eimas, Sigueland, Juzczyk, & Vigorito, 1971). It was also discovered that newborns could be conditioned not only to modify their sucking in response to stimuli (Kron, 1966; Lipsitt & Kaye, 1964) but that they could condition adults to modify responses to their sucking. Kaye and Brazelton (1971) investigated the effects of mothers' jiggling behavior on infants' sucking responses during feeding. They found that the jiggling did not stimulate infants to resume sucking but that the infants stopped sucking to provoke the stimulation from their mothers. Blauvelt and McKenna (1961) found that rooting is not merely a reflexive action of the infant's but that it is used to change or to control the mother's activity in order to elicit help attaining the nipple. Thus, the picture of the normal newborn which has emerged from this research is one of a competent organism who is skilled, selective, socially influential and capable of actively interacting with and making demands on its environment (Lester, 1979).

Standardized assessment tools which were developed with the growth in understanding of the complexity of the behavioral repertoire of the neonate have led to the recognition of the existence of individual differences in behavior at birth. The present task of developmental research is to investigate the origins of these differences and their effect on developmental outcome (Kopp & Parmalee, 1979).

The study of the relationship between perinatal events and behavioral outcome has become a major area of importance in developmental research. The individual goes through more physiological, behavioral and environmental changes during the perinatal period than at any other time in life. Since the neonate is still morphologically and functionally immature, it is especially vulnerable to insult from the host of variables surrounding the birth process. Advances in perinatal technology have reduced the mortality rate for mothers and babies so that now it has become increasingly important to investigate the perinatal conditions which may be related to morbidity and poor developmental prognosis (Lipsitt & Field, 1982).

One variable introduced into the delivery room with medical technology was pain relieving medication. Although various forms of analgesia had been used for centuries, anesthesia was first used during labor and delivery by Simpson, a Scottish obstetrician, in 1847 (Brackbill, 1979). Childbirth without pain was such an attractive option that the use of obstetric medication spread rapidly. Today, its use is so widespread that it is considered part of routine medical practice.

When Simpson first introduced the use of anesthesia to obstetrics, scientific opinion still promoted the idea that the uterus and placental barrier protected the fetus from foreign substances. However, as early as 1889, Hirsh had discovered that many substances, including opiates and

ether, flow from the mother's bloodstream through the placenta and into the baby (MacFarlane, 1977). It was not until the thalidomide tragedy of the early 1960's that the potential consequences of placental transfer of drugs were fully recognized. The use of this tranquilizer during the second month of pregnancy was implicated as the cause of severe deformities of infants' limbs (Moya & Thorndike, 1963). Since this finding, the teratogenic effects of many pharmacologic agents have been studied. The exposure of rodents to inhalant anesthesia early in gestation has been related to degeneration of the liver (Chang, Dudley, Lee, & Katz, 1975), pathological development of the central nervous system (Chang, Dudley, Lee, & Katz, 1974; Quimby, Aschkenase, Bowman, Katz, & Chang, 1974), morphologic changes (Lund, Owen, & Linde, 1981; Smith, Gaub, & Moya, 1965) and fetal death (Corbett, Cornell, Endres, & Millard, 1973). Studies of teratogenic action in humans are limited by ethical considerations to naturally occurring situations. Several investigators have found a higher incidence of birth defects among children of operating room personnel (Cohen, Brown, Bruce, Cascorbi, Corbett, Jones, & Whitcher, 1974; Corbett, Cornell, Endres, & Lieding, 1974; Knill-Jones, Newman, & Spence, 1975). Chronic exposure to low levels of inhalation anesthesia has also been related to infertility and miscarriage (Cohen, Bellville, & Brown, 1971; Knill-Jones, Moir, Rodriguez, & Spence, 1972).

Coyle, Wayner and Singer (1975) have suggested that behavioral changes in the offspring of exposed mothers might be a more sensitive indicator of the teratogenic action of drugs. Behavioral teratogenic deficits may be induced by smaller doses of a drug than those necessary to produce morphological abnormalities. These effects may be further mediated through the developing relationship between the mother and baby, both of whom are recipients of the medication (Brazelton, 1971; Coyle et al., 1975).

Unlike most other perinatal variables or potential teratogens, exposure to drugs during delivery is under the direct control of the obstetrician and/or anesthesiologist. The safety of differing agents can be monitored and if harmful effects are found, their use can be discontinued or their dosage decreased (Scanlon & Hollenbeck, 1982). With this in mind, the assessment of the neonatal effects of drugs used routinely during labor and delivery deserves special attention. The present study focuses on the potential behavioral effects of obstetric medication on the newborn. Before reviewing the literature which has investigated these effects, I will first briefly discuss the types and routes of parturitional medicine and the principles of perinatal pharmacology.

Types of Obstetric Medication

Medications given to relieve pain or anxiety during labor are divided into two general categories: premedication and anesthesia. Either may be given alone or in conjunction with a drug(s) from the other general category.

Premedication is usually administered early in labor before anesthesia. It includes the narcotic-analgesics, sedative-hypnotics and tranquilizers. These medications may be administered orally, intravenously or intramuscularly.

Narcotics include both the opium alkaloids such as morphine and codeine and their synthetic analogues such as meperidine and alphaprodine. They are used as analgesics to reduce the sensation of pain and work by depressing central nervous system (CNS). When taken in large doses, they also produce euphoria and drowsiness. Narcotics are commonly administered intramuscularly early in labor and may be used as the only form of analgesic or, more frequently, in conjunction with anesthesia.

Sedatives include the barbiturates such as pentobarbital and secobarbital and nonbarbiturates such as scopolamine and diazepam (Valium). They are given to calm the parturient and may induce drowsiness or sleep. Diazepam is typically given to relax muscles. High doses of some sedatives will produce general anesthesia. Like narcotics, sedatives work by depressing the CNS. They are used much less frequently today in obstetric practices than they were in the past.

Tranquilizers most commonly used during parturition include the phenothiazine derivatives: chlorpromazine, promazine and promethazine, and the benzodiazepines. They are given to relieve anxiety, prevent nausea and vomiting during labor, and provide sedation. When given in small doses, tranquilizers do not work as general CNS depressants. They produce an alpha-adrenergic blockade leading to an epinephrine reversal and norepinephrine unresponsiveness (Cohen & Olsen, 1970). Tranquilizers are frequently used today both in early and later stages of labor.

Anesthesia is the second major category of medication commonly used during childbirth. It produces not only relief from pain, but a loss of sensation. General anesthesia depresses the CNS and produces unconsciousness. The agents used to produce this effect include inhalants such as nitrous oxide, enflurane, isoflurane and methoxyflurane and intravenous agents such as thiopental and ketamine. Ketamine has also been found to produce hallucinations (Meer, Downing, & Colman, 1973). General anesthesia is used today mainly for cesarean deliveries. A combination of an intravenous drug with an inhalant is often used so that the required dose of each can be reduced. The use of this type of anesthesia in vaginal deliveries is reserved for emergencies and for women who desire to be unconscious during the delivery.

Local anesthetics are being used more and more frequently in obstetric practices. They work by blocking the transmission of sensory impulses along nerve fibers. Local anesthetic agents include the ester compounds such as procaine, tetracaine and chlorprocaine and the amide compounds such as bupivacaine, lidocaine, mepivacaine and etidocaine. These drugs are administered via different routes to provide either numbness at the site of injection or regional analgesia. For local infiltration, the agent is injected directly into the area to be anesthetized. During vaginal deliveries, this area is the perineum. A local is injected into this site immediately before delivery in preparation for an episiotomy or immediately after for repair of a tear or of the episiotomy.

Local anesthetic agents are also administered regionally to block nerve impulses leading to the lower part of the body. They are used in this way for both vaginal and cesarean deliveries. Regional anesthesia is classified according to the space in the woman's back into which the agent is injected and at which point the nerve impulses are blocked. This includes epidural, or caudal, spinal, or saddle, pudendal and paracervical blocks. These injection sites differ in the amount and concentration of the local anesthetic agent which is needed to provide effective analgesia, in the amount of time it takes for the agent to be effective and in the region of the body which becomes anesthetized. Therefore, the route chosen for the

administration of the drug depends in part on the time during labor at which pain relief is desired and how quickly it is needed.

Medication used during parturition for purposes other than pain relief includes oxytoxics, to induce or augment labor, vasopressors and vasoconstrictors, to retard absorption of local anesthetics and prevent hypotension, and narcotic antagonists, to avoid respiratory depression associated with narcotics. These are typically given in addition to analgesics and/or anesthetics.

Perinatal Pharmacology

The dose and route of administration of a drug, the time it is given and the properties of the agent all affect the amount of drug that circulates in the mother and crosses the placenta, the duration of fetal exposure to the drug and its concentration in the newborn at delivery. Any drug administered to the mother by any route eventually enters her bloodstream. The rate at which it enters specific tissues depends on the rate of blood flowing through the tissues and the ease at which the drug molecules pass through the capillary membranes (Julien, 1978). The brain receives a greater amount of blood flow than any other organ. Thus, drugs which can bypass the blood brain barrier have a sufficient chance to exert their effect on the CNS.

Any substance which is given to affect the CNS will readily cross the placenta. The placental barrier is similar to the blood brain barrier. Passage through these

membranes is accessible only to the free unbound form of the drug. The concentration of free drug in the maternal plasma is affected by the rate of absorption from the site of administration, the protein binding capacity of the drug and its distribution through various tissues. It is also affected by the rate of uptake by the liver, subsequent biotransformation and, finally, excretion from the kidneys.

Most drugs enter the placenta passively by simple diffusion. In other words, they flow from an area of high concentration to one of low concentration. The rate at which they pass depends on several properties of the specific agent: its molecular weight, spatial configuration, lipid solubility, protein binding capacity and degree of ionization. Small nonionized molecules which are fat soluble cross placental membranes most quickly. Theoretically, increasing the protein binding capacities of molecules should decrease the amount of free drug available for placental transport. However, drugs with higher protein binding capacities are also more lipid soluble. The solubility counteracts the binding capacity making much of the drug readily available to pass directly into the placenta (Ostheimer, 1977).

Another variable which affects the rate of drug transfer is the difference between maternal and fetal acid-base statuses. According to the law of mass action, ionized molecules accumulate on the side with the lower pH (Brown, Bell, & Alper, 1976). Normally fetal blood is slightly more

alkaline than maternal blood. However, local anesthetics have a depressant effect on the heart and blood vessels and may cause maternal hypotension (de Jong, 1970). This drop in maternal blood pressure reduces the oxygen content of the fetal blood which lowers the pH and causes acidosis. The alkaline drugs such as local anesthetics become trapped in fetal circulation after crossing the placental barrier. The increased acidity of the fetal blood leads to increased ionic dissociation which reduces the drug's diffusibility through the placenta and back into maternal circulation. Since local anesthetics are myocardial depressants, a vicious cycle is established with the increased drug concentration causing further acidosis and the acidosis causing a further increase of the drug in the fetal blood stream, etc. (Brown et al., 1976).

Several other maternal conditions may influence the rate of transfer of drugs to the baby. Hypoproteinemia allows a greater amount of drugs which normally bind to maternal protein to cross the placenta. Liver diseases reduce the capacity of the mother to metabolize drugs. This results in an increased concentration of the drug in the maternal bloodstream and, thus, the transfer of a greater amount of the drug to the fetus. Obesity creates a condition in which lipid soluble drugs which cross into the fetal bloodstream quickly return to the mother. This occurs because fat molecules absorb these lipid soluble drugs leaving the concentration of free drug circulating in the

mother lower than that in the fetus (Cohen & Olsen, 1970; Ralston & Shnider, 1978).

The placenta itself may have a role in altering the rate of drug transfer. Although little is known about changes which take place within this organ, it is possible that some compounds are metabolized there. This would cause a change in the structure of the drug molecule and, consequently, in its rate of entry into fetal circulation (Cohen & Olsen, 1970). The placental vasculature and metabolic capacities may also be directly altered by the drug. This could, in turn, further affect the rate of drug transfer. It could also affect fetal functions, thereby lowering the nutritional status of the neonate (Dubowitz, 1975; Scanlon, 1974).

Maternal diseases which may affect the rate of drug transfer by altering the placental vascular bed are toxemia, diabetes, eclampsia and chronic hypertension. The increased permeability of the placenta caused by these illnesses may speed up the exchange of drugs with the fetus.

The amniotic fluid has been suggested to be another likely route of drug transfer (Cohen & Olsen, 1970). Since the pH of the amniotic fluid is significantly lower than the pH of maternal or fetal blood, high concentrations of some drugs may pass into the fluid and subsequently be ingested by the fetus. However, very little is known about this process as a possible means of drug exchange.

Once the drug has entered the fetal bloodstream, the inherent vulnerability of the immature organism makes both the fetus and the neonate more susceptible than the adult to the effects of the drug. Their immature livers lack many of the enzymes which are necessary for the metabolism of drug molecules. Also, their kidneys are not fully functional so that their ability to excrete drugs is limited. The elimination of drugs in the newborn is further slowed down by hypothermia. The common difficulty neonates have with temperature regulation is exacerbated in the presence of acidosis. Hypothermia is also pronounced in premature and malnourished infants (Morishima, Mueller-Heubach, & Shnider, 1974).

Fetuses and neonates also have different membrane permeabilities, regional circulation, tissue affinities and plasma protein binding capacities than adults (Alper, 1979). The brain is the area most vulnerable to these factors. The blood brain barrier of the young organism is poorly developed allowing for greater diffusion of drugs into the CNS. Additionally, there is more blood flow to the brain during labor and delivery than at other times because of the decrease in fetal PO₂ and the increase in PCO₂ (Julien, 1978). The use of anesthesia has been related to an increase in the length of labor (Berges, 1971). Increasing the length of labor to the point where it becomes dysfunctional can lead to fetal asphyxia (Aleksandrowicz, 1974). Fetal asphyxia produces a release of catecholamine

which causes a shunting of blood to the brain in an effort to increase its oxygenation. Asphyxia also aggravates acidosis thereby causing a further accumulation of the anesthetic in the bloodstream. The protein binding capacity of the drug is disrupted by the asphyxia and the vascular permeability of the brain is increased.

In summary, the immaturity of the brain at birth makes the neonate especially vulnerable to the effects of any substance entering its bloodstream in utero. Vulnerability is increased by an insufficient ability to metabolize and excrete drug molecules, by a more permeable blood brain barrier and by a greater blood flow to the brain during gestation and parturition. Susceptibility to obstetric medication is further increased by common complications of labor and delivery such as asphyxia, acidosis and hypothermia.

Empirical Studies of the Behavioral Effects of Obstetric Medication

Awareness of the morphological and functional immaturity of the neonate as well as of the remarkable capabilities of the neonate has led to research focusing on the behavioral effects of obstetric medication. Over the past ten years, there have been fifty studies published in the child development, pediatric and anesthesiology literature relating the effects of drugs used during labor and delivery to infant behavior. Although medication has been used to relieve the pain of childbirth since the mid

1800's, there are only nine studies about its effect on infant behavior reported prior to 1971 and none before 1948.

The literature on the effects of maternal medication has varied in both the independent and dependent parameters under investigation. The drugs, doses and routes of administration which are popular to use in obstetric practices today have changed over the years as a result of dispelling the myth that drugs do not cross the placenta and the increasing focus on neonatal outcome. New technology to measure the concentration of drugs in the bloodstream and the development of different drugs have also contributed to the changes. In general, there has been a decrease in the use of centrally depressant narcotics, sedatives and general anesthesia and an increased use of local or regional anesthesia so that the mother can remain alert and aware during labor and delivery (American Academy of Pediatrics Committee on Drugs, 1978). However, overall, the use of medication to relieve anxiety and pain during labor is on the increase (Brackbill, 1979).

Some of the earliest literature investigated the behavioral effects of heavier doses of sedatives than are typically used today (Brazelton, 1961; Hughes, Ehemann, & Brown, 1948; Hughes, Hill, Green, & Davis, 1950). More recently, varying agents frequently used for epidural anesthesia such as mepivacaine, lidocaine and bupivacaine have been studied. As the rate of cesarean section deliveries has increased, so have investigations of

different agents and routes of administration used to alleviate pain during surgery. Premedication has continued to be used and studied in both vaginal and cesarean deliveries over the years, especially meperidine. Another common parameter in the behavioral studies of obstetric medication has been the potency score. Many studies have not differentiated routes and agents of premedication or of anesthesia in their analyses but have lumped them together and given them a clinical rating from high to low depending on the dose and/or characteristics of the drugs and routes of administration.

The literature also varies in the measures of behavior used to investigate the effects of obstetric medication and in the age of testing. Most studies have examined behavior over the first three days of life. Many of them have followed subjects to seven or ten days of life but only a few have gone beyond this age. The standardized exams which have been used most frequently as the dependent parameters in these studies are the Brazelton Neonatal Behavioral Assessment Scale (Brazelton, 1973) and the Scanlon Early Neonatal Neurobehavioral Scale (Scanlon, 1974). The Brazelton Scale was designed to measure the capabilities the infant has for interacting with a caregiver over the first month of life. It consists of 27 behavioral items and 17 reflexive items administered in an order determined by the individual infant's state patterns. Special care is taken by the examiner to elicit the best performance the baby is

capable of (for a more complete description of the Brazelton Scale, see the Methodology chapter). The literature on obstetric medication has summarized Brazelton items in several different ways for the purpose of data analyses. These include using item-by-item analysis, factor analysis, "marker" variables, elicited and emitted item summary scores, the four a priori summary scores of Als, Tronick, Lester, and Brazelton (1977) and the seven conceptual clusters of Lester, Als and Brazelton (1982). Some studies have included modifications of the Brazelton Scale, e.g., the Kansas version (Horowitz, Sullivan, & Linn, 1978) which scores both the infant's best and average performance on several items. It also includes six additional summary scores. The Mother's Assessment of the Behavior of her Infant (Field, Dempsey, Hallock, & Shuman 1978) which includes the mother's scores of her baby's performance during the administration of the Brazelton exam has also been used in some studies.

The Scanlon Scale has been the exam used most frequently in studies of obstetric medication, particularly among those appearing in the journals of anesthesiology. It consists of ten items taken from the Brazelton Scale but administered in a predetermined order. The Scanlon Scale was designed to be a short and easily administered exam which could be used by physicians in the first few hours of life. The items were chosen to screen specifically for the effects of obstetric medication on higher CNS functioning.

Standardized assessment scales which have been used less frequently are the Graham (Graham, Matarazzo, & Caldwell, 1956) and the Graham/Rosenblith (Rosenblith, 1961; 1975) Behavioral Examination of the Neonate and Prechtl and Beintema's (1964) and Parmalee's (1974) neurological exams. Most recently, the Neurologic and Adaptive Capacity Score (Amiel-Tison, Barrier, Shnider, Levinson, Hughes, & Stefani, 1982) has been designed as a screening exam to look for the effects of obstetric medication. It is quicker to administer than the Scanlon exam, taking 4 minutes to administer as opposed to 7 minutes for the Scanlon exam, and focuses on the muscle tone of the newborn.

After the neonatal period, the Bayley Scales of Infant Development (Bayley, 1969) and the Denver Developmental Screening Test (Frankenburg & Dodds, 1967) have been used to evaluate mental and motor development during the first year. The Carey Infant Temperament Questionnaire (Carey, 1970) has also been used during this time period to assess maternal perception of infant temperament. At one year of age, the Catell Infant Intelligence Scale (Catell, 1960) has been used.

Other measures of behavioral outcome which have been investigated include habituation to visual and auditory stimuli, visual fixation, sucking, electroencephalographic patterns (EEGs), organization of sleep states and measures of mother-infant and father-infant interaction.

In order to summarize the findings of the literature and examine what aspects of a baby's behavior may be affected by obstetric medication, it is possible to group most of the behavioral measures studied into the seven conceptual clusters described by Lester, Als and Brazelton (1982). These clusters were designed to summarize the Brazelton Scale items. They include habituation, orientation, motor performance, range of state, regulation of state, autonomic regulation and reflexes. Although the behavioral measures described previously often differ from each other in their administration and scoring of particular items, they can generally be grouped into these seven areas of behavioral functioning. It is important to remember that not every study has assessed behaviors which fall into all seven clusters. For instance, the Scanlon exam does not assess autonomic functioning or state dimensions. Even studies using the Brazelton exam frequently do not assess habituation due to babies beginning the exam in an inappropriate state for the administration of the habituation items. Also, the reflex scores are frequently not reported because they are not included in the Als et al. (1977) four a priori dimensions.

A summary of the studies which have found significant effects of obstetric medication on behaviors which fit into the seven clusters can be seen in Table 1.

Table 1. Summary of Studies Finding Significant Effects of Obstetric Medication on Behaviors Fitting into Seven Clusters.

Study	Clusters						
	III*	I	II	VII	VI	IV	V
Aleksandrowicz & Aleksandrowicz 1974		d+	d		d		d
Belsey et al. 1981	a		a			a	a
Bonta et al. 1979	a		a				
Borgstedt & Rosen 1968						a	
Brackbill et al. 1974	a	a	a	a	a	a	a
Brackbill 1976		d					
Brazelton et al. 1979	d		d		d		d
Brown et al. 1975			a				
Clark et al. 1976	a						
Conway & Brackbill 1970	d	d	d				
Corke 1977	a	a		a			
Friedman et al. 1978		d					
Hodgkinson et al. 1976	c	c	c	c			
Hodgkinson et al. 1977	d	d	d	d			
Hodgkinson et al. 1978a	d	d	d	d			
Hodgkinson et al. 1978b	d	a	d	d			
Hodgkinson et al. 1978c	c	c	c	c			
Hollmen et al. 1978	d			d		d	
Horowitz et al. 1977	d	a	a,d		d	d	d
McGuinness et al. 1978	b						
Meis et al. 1978		b	b	b			
Merkow et al. 1980		b					
Moreau & Birch 1974		c					
Murray et al. 1981	b		b		b	b	b
Nesheim et al. 1979	d	b					
Palahniuk et al. 1977	d		c	d			
Richards & Bernal 1972	a			a	a		
Rosenblatt et al. 1981	b		b		b	b	b
Scanlon et al. 1974	b	b		b			
Scanlon et al. 1976							
Standley et al. 1974	d				d	d	
Stechler 1964			d				
Tronick et al. 1976	b	a,b	a,b		b		a
VanderMaelen et al. 1975		d					
Wiener et al. 1979	d	a		d			
Woodson & DaCosta-Woodson 1980						a	

* Clusters: III=Motor; I=Habituation; II=Orientation; VII=Reflexes; VI=Autonomic Regulation; IV=State Range; V=State Regulation.

+ Obstetric Medication: a=premedication; b=local anesthesia; c=general anesthesia; d=mixed analgesia and anesthesia.

Motoric Functioning

Significant effects of maternal medication have been found most frequently on neonatal motoric functioning. In general, babies of medicated deliveries seen to be more hypotonic, less active, less able to lift their heads and have less control over their movements. Motoric behaviors have been found to be depressed up to 6 weeks of age.

Brackbill, Kane, Manniello and Abramson (1974a; 1974b) found that infants whose mothers had received meperidine were less able to swipe at a cloth placed over their eyes on the second day of life than a group whose mothers had not had meperidine. Also using the Brazelton scale, Belsey, Rosenblatt, Lieberman, Redshaw, Caldwell, Notariani, Smith and Beard (1981) found that the greater the exposure of the infant to meperidine as determined by the umbilical cord blood concentration and the time before delivery that the drug was administered, the more depressed motoric behaviors were at 3 days and 1, 3 and 6 weeks of life. Spontaneous motor activity during the Prechtl exam was also depressed on the first day. Decreased motor tone shortly after birth was observed by Richards and Bernal (1972) in babies whose mothers received a compound which included both meperidine and an antihypotensive and by Corke (1977) in babies of meperidine and promethazine deliveries.

Effects of meperidine on motor functioning have also been found by examining the reversal of effects when naloxone is administered to the baby or mother. Naloxone is

a narcotic antagonist given to reverse depression caused by meperidine or other narcotics. Using the Scanlon exam at varying times over the first day of life Clark, Beard, Griefenstein and Barclay (1976) and Bonta, Gagliardi, Williams and Warshaw (1979) found a meperidine group of babies without naloxone to have lower tone than a group receiving naloxone. However, both groups had lower tone than a group without meperidine. Hodgkinson, Bhatt, Grewal and Marx (1978a) found that the administration of naloxone improved motor scores at 2 hours after birth but not at 4 or 24 hours, due to the fact that length of time the narcotics were active exceeded the effectiveness of the short acting antagonist.

Local anesthetics have also been found to depress motor behavior. This may be due to the direct action of the drug on the neuromuscular function itself. Several experimental studies have shown that local anesthetics influence neuromuscular transmission and function (Bianchi & Bolton, 1967; Usubiaga & Standaert, 1968).

Effects of bupivacaine epidurals were found on motoric items of the Brazelton exam by Murray, Dolby, Nation and Thomas (1981) on day 1, Wiener, Hogg and Rosen (1979) on days 1 and 2 and Rosenblatt, Belsey, Lieberman, Redshaw, Caldwell, Notarianni, Smith and Beard (1981) up to 6 weeks. Tronick, Wise, Als, Adamson, Scanlon and Brazelton (1976) and Scanlon, Brown, Weiss and Alper (1974) found that motor performance on the Scanlon exam was depressed more during

the first half day of life by mepivacaine and lidocaine epidurals than by spinals, locals or no medication. Tronick et al. also found decreased activity during the Brazelton exam on day 10.

Nesheim, Lindbaek, Storm-Mathisen and Jenssen (1979) found low tonus over the first three days in lidocaine and bupivacaine paracervical block groups and in a lidocaine local group. Both groups had also received diazepam and nitrous oxide.

General anesthetics used during vaginal deliveries or cesarian sections have also been found to depress motor performance on the Scanlon exam. In separate studies, Hodgkinson, Wang, and Marx (1976), Hodgkinson, Marx, Kim and Miclat (1977) and Hodgkinson, Bhatt, Kim, Grewal and Marx (1978b) found that infants of mothers anesthetized with thiopental had lower scores on days 1 and 2 than those of deliveries using ketamine. Both drugs depressed motoric scores more than chloroprocaine epidurals or tetracaine spinals. Palahniuk, Scatcliff, Biehl, Wiebe and Sankaran (1977) compared thiopental generals combined with either methoxyflurane or nitrous oxide to lidocaine epidurals and found that tone was depressed in both the nitrous oxide and lidocaine epidural groups. However, Hollmen, Jouppila, Koivisto, Maatta, Pihlaniemi, Puukka and Rantakyla (1978) found hypotonia on the Prechtl-Beintema exam with lidocaine epidurals only when hypotension occurred following the initiation of anesthesia. They also found low tone up to

one week among babies whose mothers received intravenous thiopental and had hypertension during labor. Bupivacaine epidurals and tetracaine spinals have also been related to depressed tonus at four hours among cesarian section infants (McGuinness, Merkow, & Kennedy, 1978). Conway and Brackbill (1970) found a decrease in muscle tension with increasing potency of medication on the Graham scale on days 2 and 5 and on the Bayley Motor Index at one month. Standley, Soule, Copans, and Duchowny (1974) found that poorer motor performance on the Brazelton exam on day 3 was related to a greater potency score. The Brazelton motor cluster was found to be lower up to day 10 among a group of infants of Greek middle-class mothers who had received varying obstetric medication than among a lower-class group that had received no medication (Brazelton, Tryphonopoulou, & Lester, 1979). In another cross-cultural study of the effects of obstetric medication, Horowitz, Ashton, Culp, Gaddis, Levin, and Reichmann (1977) found babies of light to moderately medicated mothers in Israel and Uruguay to be poorer on defensive performance and lower on activity level on day 3 than nonmedicated babies. An American sample which was more heavily medicated did poorly on several motor items up to one month of age.

Habituation

Significant effects of obstetric medication have been found almost as frequently on the infant's rate of habituation as on motoric functioning. Dependent measures

which have been used to determine habituation are, most commonly, a decrement in motoric responses to repeated presentations of auditory, visual or tactile stimuli, a decrement of eye blinks, and a change in heart rate responses. Both the Brazelton and the Scanlon exams include items which assess the infant's ability to habituate to repetitive stimuli.

Brackbill et al. (1974a;1974b) premedication during labor was more closely related to neonates' ability to inhibit responding than to their ability to respond to stimuli. The authors investigated the effects of meperidine on the infant's ability to inhibit motoric responses to white noise on days 2 and 3. They found that infants whose mothers did not take meperidine during labor habituated twice as fast as those who had taken the medication. The dose and timing of the administration of the drug and the birthweight of the baby were found to be related to the rate of habituation. Wiener et al. (1979) found that slower inhibition of responses to repeated presentations of a rattle and bell on the Brazelton exam on days 1 and 2 was related to meperidine usage. Also, Corke (1977) found that both meperidine and promazine affected rate of habituation to a pinprick in the the first four hours on the Scanlon exam. In a sample of infants of cesarean section deliveries with general anesthesia, Hodgkinson et al. (1978a) found that meperidine was the variable related to a slower rate of habituation on the first day. As with the motor items,

naloxine improved habituation at two hours but not later in the day.

A higher portion of infants in a group with an obstetric history of maternal epidural anesthesia with mepivacaine or lidocaine could not inhibit their responses to a pinprick over the first six hours of life than a mixed group with either alphaprodine, secobarbital, local or spinal anesthesia or no medication at all (Scanlon et al., 1974). However, Tronick et al. (1976) found that groups of infants with histories of lidocaine locals or alphaprodine and/or promazine were slower to habituate at 3 days to a pinprick than a mepivacaine or lidocaine epidural group. The mean umbilical cord blood concentration of mepivacaine reported in the Scanlon et al. study was slightly higher than that in the Tronick et al. study (1.68 vs. 1.58 ug/ml) but mean concentration of lidocaine in the epidural group was slightly lower (.48 vs. .55 ug/ml). The actual doses of maternal drug intake were reported in neither study.

Habituation to items on the Scanlon exam have been examined with respect to the effects of paracervical blocks. Nesheim et al. (1979) found decrement to the light, pinprick and Moro was slower up to 3 days with both bupivacaine and lidocaine paracervicals than with lidocaine locals. Randomly assigning mothers who desired paracervicals to differing agents, Merkow, McGuinness, Erenberg and Kennedy (1980) found that infants from bupivacaine or chloroprocaine groups habituated slower at four hours than those from the

mepivacaine group. However, Meis, Reisner, Payne and Hobel (1978) found decrement to presentations of the light was faster at 2 hours in a bupivacaine paracervical block group than in a group with locals, spinals or pudendal blocks.

Infants delivered with general anesthesia were found to habituate more slowly on day 2 to white noise and to a somesthetic stimulus than infants delivered without general anesthesia regardless of what other medication was used (Moreau and Birch, 1974). Hodgkinson et al. (1976; 1977; 1978b) found that general anesthesia with thiopental among cesarean sectioned babies was related to slower habituation on the Scanlon exam on the first two days of life than was general anesthesia with ketamine. Both agents were related to worse performance than chloroprocaine epidurals or tetracaine spinals. The authors found similar results among infants delivered vaginally, with meperidine further lowering the scores of babies delivered with general anesthesia (Hodgkinson et al., 1978c).

Assigning potency scores to varying combinations of obstetric medication, Conway and Brackbill (1970) found that habituation of the orienting reflex to white noise was correlated .66 with potency at 2 days, .64 at 5 days and .61 at one month. They also found that babies delivered with general anesthesia took over two and one-half times as long to habituate as babies of nonanesthetized deliveries. Using the same paradigm, VanderMaelen, Strauss and Starr (1975) also found that a slower rate of habituation at 3 days was

related to an increased level of obstetric medication.

In a study by Aleksandrowicz and Aleksandrowicz (1974), obstetric medication accounted for 9 to 21 percent of the variance among scores on response decrement to the pinprick on the Brazelton exam over the first month of life.

Horowitz et al. (1977) found that a group of light to moderately medicated babies in their Uruguyan sample were slower to habituate to the light on the Brazelton exam at 3 days than a group of nonmedicated babies.

Friedman, Brackbill, Caron and Caron (1978) investigated longer term effects of obstetric medication on the habituation process by having 4 and 5 month olds view slides of regular or distorted faces and measuring the amount of time they fixated on the stimuli. They found that premedication, oxytocin and general anesthesia were related to slower rates of habituation. At eight months of age, Brackbill (1976) found that the potency of anesthesia continued to be correlated with the rate of habituation as defined by a shift in heart rate response to white noise from deceleration to acceleration.

Orientation

Performance on the orientation cluster has also been frequently related to the effects of obstetric medication. This cluster assesses the infant's ability to orient to visual and auditory stimuli and his or her overall quality of alertness. This dimension of behavior is especially important to the parent-infant relationship as it reflects

some of the infant's capabilities for interacting with his or her parents.

The dose of meperidine has been correlated with orientation and alertness scores on the Brazelton exam on day 2 (Brackbill et al., 1974a,b). Hodgkinson et al. (1978a, c) also found decreased alertness and responsiveness to sound on the Scanlon exam on days 1 and 2 in a group of babies exposed to meperidine in utero. They (1978a) found that naloxone improved orientation scores at 2 hours of age, but that the improvement was temporary. However, Bonta et al. (1979) found that naloxone improved alertness at 1 and 4 hours, and responsiveness to sound at 24 hours. Although meperidine doses were similar in the two studies, .4 mg. of naloxone was administered intravenously to the mother 15 minutes prior to delivery in the Hodgkinson et al. study and in the Banta et al. study, 20 mcg. per kilogram of body weight was injected intramuscularly into the baby a few minutes after birth. The brief reversal of behavioral depression in the Hodgkinson et al. study may be due to the small amount of naloxone given to the mother and to its short acting duration.

Rosenblatt et al. (1981) found that the greater the exposure to bupivacaine as epidural anesthesia, the poorer the performance on Brazelton orientation items up to six weeks of life. Comparing a group of babies from bupivacaine epidural deliveries to a minimally or nonmedicated group, Murray et al. (1981) found no differences over the first

month of life on the interactive Brazelton dimension which assesses the orientation items. However, only 45% of the mothers in the bupivacaine group reported that their babies' interactive performance at one month was exceptional, compared to 85% of the mothers in the control group. Bupivacaine paracervical blocks have also been related to decreased alertness on the Scanlon exam at 6 hours (Meis et al., 1978).

Infants of cesarean deliveries with general anesthesia have been found to be less alert on days 1 and 2 than those of deliveries with regional anesthesia (Hodgkinson et al., 1976; 1977; 1978b; 1978c). Again, thiopental has been related to more depressive effects than ketamine. Furthermore, Palahniuk et al. (1977) found that within a thiopental group, nitrous oxide was related to less alertness on day 1 than methoxyflurane.

In one of the earliest studies on the effects of obstetric medication on infant behavior Stechler (1964) examined the relationship between analgesics and attention. He weighted varying agents according to their dose and time of administration. Findings indicated that the greater the dosage and the closer to delivery the drugs were administered, the less attentive the baby was to different visual stimuli. Brown, Bakeman, Snyder, Fredrickson, Morgan and Hepler (1975) also investigated the effects of analgesics and found that doses greater than 52 mg. were associated with less responsiveness to auditory stimulation

and less overall alertness during a feeding observation than were smaller doses.

In the Tronick et al. (1976) study, analgesics were related to a decreased ability to orient to the voice during the Brazelton exam on day 3. Poor performance on orientation to inanimate auditory stimulation was associated with local anesthesia. Aleksandrowicz and Aleksandrowicz (1974) found that combination of analgesics and anesthetics accounted for 24% of the variance among Brazelton orientation scores on day 1, 13% on day 2, 11% at a week and 28% at a month. Also, the medicated Greek sample in the Brazelton et al. (1979) study did poorer on Brazelton orientation items over the first 10 days than the nonmedicated group. In the Horowitz et al. study (1977), medicated Israeli babies had difficulties with orientation items during the first four days of life and the highly medicated American group had difficulties up to 10 days.

Lastly, Conway and Brackbill (1970) found a correlation of .51 between a potency of medication score and the vision subscale of the Graham exam on day 5. They found that the performance of babies from deliveries with general anesthesia was worse than that of babies from deliveries with local anesthesia which, in turn, was worse than performance of babies from nonmedicated deliveries.

Reflexes

The most comprehensive assessments of infant reflexes are found with neurological exams such as the Prechtl-Beintema. Standardized behavioral and pediatric exams also include the assessment of several reflexes, most notably, sucking, rooting and the Moro. Reflexive responses have been related to maternal obstetric medication, although not as frequently as the three previously mentioned clusters.

Meperidine has been related to depressed reflexes more than any other medication. Brackbill et al. (1974a; 1974b) found that on day 2, babies exposed to meperidine in utero scored less optimally on a cluster of reflex items from the Brazelton exam than those who were not exposed. Wiener et al. (1979) reported similar findings. They also found that naloxone significantly improved reflex scores. Several studies have found that the four reflexes assessed by the Scanlon exam, i.e., rooting, sucking, placing and the Moro, are lower among meperidine groups on days 1 and/or 2 than among non-meperidine groups (Corke, 1977; Hodgkinson et al., 1976; 1978a; 1978b; 1978c). Hodgkinson et al. (1978a) also found that naloxone improved reflex scores, but only at 2 hours of age. Using a short screening exam at birth and the Prechtl-Beintema exam at 8 days, Richards and Bernal (1972) found that several reflexes were depressed among a group of babies whose mothers received a compound including meperidine and a hypotensive medication.

The Wiener et al. (1979) study found that reflex scores on the Brazelton exam over the first 2 days were as low among a group of bupivacaine epidural babies as they were among a meperidine without naloxone group. The intramuscular administration of 200 mcg. of naloxone at delivery to the mother seemed to improve scores among a meperidine group for the 2 days. Scanlon et al. (1974, 1976) found reflexes to be depressed during the first 8 hours of life among a mepivacaine or lidocaine epidural group but not among a bupivacaine group. Reflex scores on the Prechtl-Beintema exam were also found to be low among a group of babies born by cesarean section with lidocaine epidural anesthesia (Hollmen et al., 1978). Weak reflexes were significantly correlated with maternal hypotension within this group.

Babies who are the products of deliveries with paracervical blocks with bupivacaine have been found to have a weaker sucking reflex at 24 hours of age than babies of local, pudendal or spinal deliveries (Meis et al., 1978). Hodgkinson et al. (1978c) found that epidural babies had a higher percentage of good reflex scores than pudendal block babies. They also found along with Hollmen et al. (1978) and Palahniuk et al. (1977) that babies born by cesarean section with general anesthesia have lower reflex scores on the first two days than cesarean babies delivered with epidural anesthesia. Hodgkinson et al. (1976; 1977; 1978b; 1978c) found that thiopental was related to weaker reflexes

than ketamine. Palahniuk et al. found that within a thiopental group, nitrous oxide seemed to be more depressive than methoxyflurane.

Autonomic Regulation

The autonomic regulation cluster assesses the infant's ability to control physiological responses to stress, i.e., startles, tremors and changes of skin color such as flushing or cyanosis. Several investigators have found a relationship between these responses as measured by the Brazelton Scale and the use of obstetric medication.

Brackbill et al. (1974a; 1974b) found that infants whose mothers took meperidine during labor startled more frequently on the second day of life than infants whose mothers took no meperidine. Using a screening tool which they devised, Richards and Bernal (1972) found that use of meperidine with an antihypotensive was related to poor skin color shortly after birth.

Infants with more exposure to bupivacaine epidural anesthesia had a greater number of tremors and startles over the first 6 weeks of life in the Rosenblatt et al. study (1981). Murray et al. (1981) also found poorer performance on physiological response to stress among a bupivacaine group, but only on day 1. On day 3, Standley et al. (1974) found that an increase in tremulousness and startles was related to use of anesthesia. Tronick et al. (1976) found poorer skin color on day 10 among a group of infants delivered with lidocaine or mepivacaine epidural anesthesia.

Horowitz et al. (1977) found poorer skin color over the first month of life among their American sample of babies from deliveries with general anesthesia than among those from moderately medicated deliveries. A heavier amount of obstetric medication was also related to a greater number of tremors and startles at one month in the Standley et al. (1974) study. Finally, Brazelton et al. (1979) found poor performance on the autonomic regulation cluster on days 1, 5, and 10 among the Greek neonates whose mothers were medicated during delivery than among those whose mothers were unmedicated.

Range of State

Clusters of behavior assessing the infant's state patterns have been related to obstetric medication less frequently than the other clusters. As noted previously, this may be because the Scanlon exam, which has been used most frequently in these studies, omits state-related items. Another reason for the lack of significant state-related effects may be that different medications have opposite effects on the infant's states so that they may tend to cancel out the effects of each other. The range of state cluster assesses the predominant states the baby is in during an examination period, the number of state changes, how irritable the baby is and the amount of stimulation it takes to make the baby cry. The results of the literature seem to indicate that analgesics are related to drowsiness during the first few days of life and to irritability later

on while anesthetics are related to increased irritability immediately after birth. Oxytocin may also be related to drowsiness. Therefore, studies in which mothers have received both premedication and anesthesia may find no significant effects on items assessing to state patterns (e.g., Brazelton et al., 1979).

Brackbill et al. (1974a; 1974b) found that babies whose mothers took 50 to 100 mg. of meperidine during labor were drowsier and had fewer state changes at 2 days of age on the Brazelton exam than infants whose mothers had no meperidine. Using the Brazelton on day 1 in Malaysia, Woodson and DaCosta-Woodson (1980) found that when the effects of parity, length of labor, maternal blood pressure and ethnic group were controlled for, use of meperidine and promazine was related to a decrease in an irritability factor. The factor included the item assessing frequency of fussing, time to buildup to the initial cry, general state of arousal, number of state changes, ability to self-quiet or be consoled and muscle tonus. Additionally, in an investigation of the effects of meperidine and promethazine, Borgstedt and Rosen (1968) had a pediatric neurologist rate the baby's states and activity levels during the Prechtl-Beintema exam on days 2 and 4 as "impaired" or not. The use of the analgesics was related to drowsier babies with less labile state patterns. Belsey et al. (1981) found that during the first twenty minutes after birth, a greater concentration of meperidine in cord blood was correlated

with a longer latency to cry and more intervals spent in a drowsy state. A greater exposure to meperidine in utero was correlated with less intervals in a crying state. The authors also examined infants using the Brazelton exam on days 1, 3, 7, 21 and 42. Although no significant relationship between meperidine and range of state was found during the first few days of life, a greater dose and/or exposure level to meperidine was related to an increased number of state changes and irritability from 1 through 6 weeks of age. Horowitz et al. (1977) also found that the Israeli analgesic group was less irritable than a nonmedicated group on the Brazelton over the first 3 days of life and more irritable at one month. The analgesic group also had fewer state changes and a lower peak of excitement during the first few days and the opposite at one month.

Anesthesia seems to be more generally related to increased irritability. Rosenblatt et al. (1981) found that the greater the exposure to bupivacaine epidural anesthesia in utero, the greater the irritability, peak of excitement and number of state changes during the Brazelton exam on days 1 and 3. The anesthesia was also related to increased irritability at 6 weeks. Murray et al. (1981) found more labile state patterns in a bupivacaine epidural group on days 1 and 5 than in a minimally or nonmedicated group. However, an epidural group whose mothers had also received oxytocin for induction or augmentation of labor exhibited the opposite state pattern, i.e., flat with few state

changes. Although no significant differences were found in Brazelton performance at one month, mothers assessed their infants at one month as continuing to exhibit the same state patterns that were seen on days 1 and 5. Standley et al. (1974) also found that the use of anesthesia for delivery was related to increased irritability and state changes on day 3. The agent and route used for the anesthesia were not reported. Hollmen et al. (1978) assessed infants' states of arousal during the Prechtl-Beintema exam in the first week of life. They found no differences comparing groups of cesarean section babies delivered with epidural or general anesthesia. However, infants in the epidural group whose mothers were hypotensive during labor and delivery were found to be listless for the first week of life. Comparing the state-related performance on the Brazelton exam of the moderately and heavily medicated American infants, Horowitz et al. (1977) related general anesthesia to an increased peak of excitement and a greater number of state changes over the first month of life. Infants delivered with general anesthesia were also found to be less irritable on the first day of life than other infants but more irritable over the rest of the month.

Regulation of State

The regulation of state cluster is defined by items assessing the infant's abilities to modulate his or her states of consciousness. This includes the infant's capabilities for self-quieting, sucking on his or her

fingers, quieting with help from the examiner or caregiver and adapting to cuddling maneuvers. The Brazelton Scale is the only standardized exam which assesses regulation of state. Thus, all studies finding differences related to obstetric medication have used this exam.

The dose of meperidine has been related to a decreased ability to self-quiet at 3, 14 and 42 days, to decreased hand-to-mouth ability at 3 and 42 days and to more difficulty consoling at 42 days (Belsey et al., 1981). Brackbill et al. (1974a; 1974b) found that infants whose mothers had taken meperidine meperidine were more difficult to console at 2 days and were less able to cuddle or to relax and mould to the examiner's body when being held. Tronick et al. (1976) also found more difficulty consoling at 3 days among babies whose mothers took some type of analgesic.

Exposure to bupivacaine was related to a decreased ability to self-quiet on days 3 and 42 by Rosenblatt et al. (1981). Murray et al. (1981) also found that babies in a bupivacaine group had less control over their states on days 1 and 5 than a group of minimally or nonmedicated babies. The mothers in the bupivacaine group also reported that their babies had difficulties controlling their states at one month of age. Tronick et al. (1976) reported decreased hand-to-mouth ability on day 10 among a group of infants delivered with lidocaine or mepivacaine epidural anesthesia.

Cuddliness has been found to be lower at one month of age among groups of babies from highly medicated deliveries (Aleksandrowicz and Aleksandrowicz, 1974). Horowitz et al. (1977) also found that infants from the highly medicated American sample scored lower than moderately medicated Israeli or Uruguayan infants on day 3. Investigating the behavior of Greek neonates, Brazelton et al. (1979) found that babies of middle class mothers medicated with analgesia and anesthesia performed worse on the state regulation cluster over the first 10 days of life than babies of lower class mothers who received no medication during labor and delivery.

Other Behaviors

Several behavioral measures which have been investigated in relation to obstetric medication did not fit into the clustering system previously described. These behaviors are changes in electroencephalogram pattern, sleep states, sucking, feeding and weight gain and parent-infant interaction.

Electroencephalogram patterns (EEGs)

In one of the earliest studies on the behavioral effects of obstetric medication on the neonate, Hughes, Hill, Green and Davis (1950) examined EEG patterns at 1 and 2 days in infants whose mothers received large doses of meperidine (100-300 mg.), vinabarbital (5-10 grains), or morphine (10-15 mg.). They found that dose was correlated

with a clinical picture of drowsiness and that EEGs in these babies were typically of low amplitude and high frequency, consistent with pictures of cortical depression. In another study, Hughes, Ehemann and Brown (1948) found that infants whose mothers had taken varying doses of secobarbital during labor were drowsy for the first two days of life but that their EEGs continued to be of low amplitude and high frequency on the third day. Borgstedt and Rosen (1968) related similar EEG patterns between 2 and 4 days to the effects of obstetric medication. Most of the mothers in their medicated group received meperidine and either promethazine or phenobarbital. Differences in EEGs during auditory stimulation at 48 hours have also been related to meperidine intake in a study by Brower, Crowell, Leung and Cashman (1978).

Sleep states

Observing newborns for the first ten hours of life, Emde, Swedberg and Suzuki (1975) found that a group of infants born to mothers who had received low levels of meperidine, diazepam or secobarbital during labor had 400% more quiet sleep in the first 2 hours and 50% more in the next 8 hours than a group who had received no premedication. A decrease in amount of time awake was correlated with an increase in dose. The group born to mothers who had taken meperidine had less than half the amount of wakefulness as the unexposed group in the first 8 hours. Yang, Zweig, Douthitt and Federman (1976) found that a greater amount of

quiet sleep and less active sleep during the third day of life was correlated with an earlier administration and a greater amount of analgesia and anesthesia during labor.

Feeding and interactive behaviors

Several studies have associated the effects of obstetric medication to differences in neonatal feeding behavior or sucking times and to differences in parental responses to the infants. Studies relating the following drugs to a weaker sucking reflex over the first 2 days of life have been reviewed previously: meperidine, mepivacaine and lidocaine epidurals, paracervical blocks with bupivacaine and general anesthesia.

Dubignon, Campbell, Curtis and Partington (1969) found that with length and type of labor covaried, nutritive sucking was influenced by obstetric medication but nonnutritive sucking was not. A decrease in sucking time was related to general and epidural anesthesia despite exposure to sedatives. Although sucking time was not found to be influenced by sedatives, babies of mothers who had been sedated were found to have a lower food intake when calories and ounces were measured. Kron, Stein and Goddard (1966) randomly assigned women to receive 200 mg. of secobarbital during labor or no medication at all. They found that on days 2, 3 and 4, sucking rate, pressure and amount consumed was impaired in the barbiturate group. Observing feedings on day 2 to 10, Richards and Bernal (1972) found that infants of mothers premedicated with the

compound of meperidine and an antihypotensive fed for shorter periods of time and needed more stimulation from their mothers to suck than a group that had no history of premedication. They did not find statistically significant differences between groups on a measure of nonnutritive sucking but there was a trend toward a reduced amount of sucking and less responsiveness to the removal of a nipple among the meperidine group.

Brazelton (1961) assessed the effects of obstetric medication on the infant's ability to establish a normal breast feeding pattern as reported by the mother over the first six days of life. Effective nursing was defined as no more than 5 minutes of stimulation needed from the mother to get the baby to feed and being able to establish a continuous feeding period of at least 3 minutes on the first 2 days and 5 minutes on the next 4 days. High doses of barbiturates and general anesthesia were found to impair the infants' ability to nurse effectively over the first 4 days. There was also a 24 hour delay in effective weight gain among infants in the highly medicated groups.

Kraemer, Korner, and Thoman (1972) studied a sample of babies whose mothers had received any of 12 drugs during labor in any of 41 combinations. These were classified into four drug groups according to the type of anesthesia administered and whether or not analgesia was administered in addition to the anesthesia. They observed the first feeding by a nurse at 12 hours of age. Results indicated

that before length of labor and parity were covaried, there was a significant difference between the four groups in the number of feed intervals. However, when the effects of these two variables were removed, only exposure to analgesia was related to a decrement in the number of feed intervals.

Brown et al. (1975) observed a feeding by mothers on the third day of life. Their sample had received various combinations of analgesics and tranquilizers not greater than 150 mg. one to six hours prior to delivery. They found that infants whose mothers received more than 52 mg. of the drugs were more passive during the feeding. They were held, fed and stimulated more by their mothers than the group with less premedication.

Murray et al. (1981) also found that epidural anesthesia was related to the number of times mothers had to stimulate their babies to suck during a feed at 5 days and one month. Mothers in bupivacaine groups with or without oxytocin had to stimulate their infants more frequently than those from the control group. There was also less affectionate handling and less eye contact during the feeding in these groups. According to diaries kept by the mothers, infants in the bupivacaine with oxytocin group fed less frequently than infants from the other two groups.

Observing mother-infant interactive behavior in the first 20 minutes after birth, Lieberman, Rosenblatt, Belsey, Packer, Mills, Caldwell, Notarianni, Smith, William and Beard (1979) found that mothers in a bupivacaine epidural

group spent less time talking to their infants than mothers in a control group without obstetric medication. Parke, O'Leary and West (1972) found that when the effects of length of labor were removed, a higher potency of obstetric medication was correlated with a greater amount of maternal stimulation in the form of rocking and vocalizations during interactions between 6 and 42 hours after birth. There was a trend toward a decreased amount of paternal stimulation with increased medication.

Lack of Significant Behavioral Effects

The majority of the investigations into the effects of obstetric medication have shown a substantial negative relationship with the behavioral outcome for the infant, and no study has shown a positive relationship. However, several studies have found little or no effects of varying drugs used during labor and delivery on infant behavior. Ten of these studies have compared the effects of varying agents on behavior and four have compared the effects of no medication to varying agents. Four other studies for which significant findings have been previously reported are considered to have shown minimal effects of obstetric medication when the total number of nonsignificant findings are taken into account.

Most of the studies which have found no differences between drugs have used the Scanlon exam as the measure of behavioral outcome. Baraka, Noueihid and Hajj (1981) investigated the effects of 1 vs. 2 mg. of intrathecal

morphine as parturitional medication and simply reported that at 24 hours, the Scanlon scores in both groups were normal. In another study, Baraka, Maktabi and Noueihid (1982) compared 6 to 12 hour Scanlon scores between a group of babies whose mothers received meperidine injected epidurally followed by bupivacaine supplementation and a group receiving bupivacaine only. Again, they merely reported that all scores were normal. Writer, James and Wheeler (1981) compared bupivacaine epidurals to morphine epidurals. They found no significant differences between the groups at 3 or 24 hours in Scanlon scores. However, at three hours, three-quarters of the babies in the morphine group were classified as "borderline" with respect to the normalcy of their behavior.

In a recent study, Stefani, Hughes, Shnyder, Levinson, Abboud, Henriksen, William and Johnson (1982) randomly assigned 61 women to receive either enflurane, nitrous oxide or no inhalation agent during labor. Sixty-five percent of the entire sample had also received local infiltration and/or pudendal block and 40% had received meperidine or alphaprodine. They compared group performance on the Amiel-Tison exam at 15 minutes after birth and on both this exam and the Scanlon exam at 2 and 24 hours. They reported finding no significant differences in behavioral performance between the drug groups on either of the exams. They compared performance on the two exams by devising a summary score for the Scanlon and comparing it to the Amiel-Tison,

which concludes with a summary score. No significant differences were found. However, examining scores on the individual Scanlon items which are presented in their paper, it appears that infants from the control group did significantly better than the inhalation analgesic groups on head control during pull-to-sit and on alertness. It is difficult to interpret these findings though since a varying number of infants within each group received local anesthetics and/or narcotics.

Shnider, Abboud, Levinson, Wright, Kim, Henrikson, Hughes, Roizen and Johnson (1979) compared infants whose mothers had received either halothane or .5 or 1% enflurane in addition to thiopental induction for cesarean delivery. They found no differences in Scanlon scores at 2 or 24 hours between any of the groups. Also examining cesarean section babies, Lund, Cwik, Gannon and Vassallo (1977) reported that 2 to 4 hour Scanlon scores were normal among babies whose mothers received etidocaine epidurals with or without adrenaline. No differences in performance were attributed to the use of adrenaline. Datta, Corke, Alper, Brown, Ostheimer and Weiss (1980) compared the use of etidocaine, bupivacaine and chloroprocaine as epidural anesthesia for elective cesarean sections. They found no differences in Scanlon scores at 2 to 4 hours.

Scanlon, Ostheimer, Lurie, Brown, Weiss and Alper (1976) studied the behavior of 20 infants delivered vaginally with bupivacaine epidural anesthesia. They

reported that all 2 to 4 hour Scanlon scores were normal. Comparing this group to a group of infants from a previous study who had been exposed to mepivacaine or lidocaine epidural anesthesia (Scanlon et al., 1974), they concluded that there were no "appreciable" differences between the groups but that the bupivacaine group did not have the motoric depression or slow rate of habituation noted in the previous sample.

In the study in which Corke (1977) compared Scanlon performance between a meperidine-promethazine and an unmedicated control group as described earlier, he also included a group of bupivacaine epidural babies. No significant differences were found in Scanlon scores at approximately 4 hours of age between the bupivacaine and the control groups. Abboud, Khoo, Miller, Doan and Henriksen (1982) compared the use of varying agents for epidural anesthesia during labor and delivery to the use of no medication. They found no significant differences in 2 or 24 hour Scanlon scores between babies in a bupivacaine, chloroprocaine, lidocaine or control group. Investigating weight gain over the first 5 days of life, Abouleish, Van der Donck, Meeuwris, and Taylor (1978) found no significant differences between babies exposed to spinal, epidural or general anesthesia or to no obstetric medication. In a study designed to compare different methods of induction during labor, Ounsted, Boyd, Hendrick, Mutch, Simons and Good (1978) also compared the results of babies delivered

spontaneously with epidural anesthesia and/or meperidine or no medication at all. They found no significant differences between these groups on a composite neurobehavioral score given on the first day of life and at 2 months, or on the Denver test given at 18 months. However, they did find that babies from a group induced with oxytocin performed worse at 2 months and had lower fine motor scores at 18 months than groups induced with prostaglandin E2.

A longitudinal study by Field and Widmayer (1980) investigating the effects of cesarean section deliveries with general anesthesia on infant development reported few significant findings. Since this was a comprehensive study and the results were unexpected, I will discuss it in more detail than the other studies. The authors sampled a group of infants of lower class black mothers, 20 who delivered by emergency section with thiopental and nitrous oxide and 20 who delivered vaginally with lidocaine local, pudendal, saddle back or without anesthesia. Each subject was given a drug score according to the dose of obstetric medication (anesthesia, narcotics, sedatives, tranquilizers and/or oxytocin) multiplied by the time of administration. The cesarean group had a significantly higher drug score than the vaginal group. They also had a less optimal obstetric complication score and higher pre- and postpartum maternal blood pressure.

Infants were assessed at 2 days with the Brazelton Scale, during the first month with the Mother's Assessment

of her Infant's Behavior, at 4 months with the Denver Developmental Screening Test and the Carey Infant Temperament Questionnaire and at 8 months with the Bayley Scales of Infant Development and the Carey Questionnaire. At 4 months, a feeding and play interaction with the mother was also observed.

Very few significant differences were found. The only measure on which the cesarean section infants performed less optimally was on the Denver adaptability items (tracking, reaching and grasping) at 4 months. Otherwise, cesarean babies were rated more optimally on the temperament questionnaires and both mothers and babies in this group received better ratings on the interactional observations.

The authors offered several hypotheses for these curious findings. They suggested that the stresses of passage through the birth canal and the depressive effects of local anesthesia may be greater in the case of the vaginally delivered infant. Also, subjects in most studies on the effects of general anesthesia have received intravenous anesthetics as well as various inhalation anesthetics. They suggested that the nitrous oxide may provide an antagonistic effect against the effects of the other medications given. However, as noted previously, comparing groups receiving thiopental plus an inhalation agent, Palahniuk et al. (1977) found that nitrous oxide depressed scores on the Scanlon exams over the first day of life more than methoxyflurane. Both groups performed worse than an epidural group.

Field and Widmayer (1980) also suggested that the high blood pressure among many of the cesarean mothers may have decreased the rate of placental transfer of the medications since hypertension has been found to alter the placental vascular bed and possibly inhibit the passage of some drug compounds (Cohen and Olsen, 1970). However, as previously discussed, Hollmen et al. (1978) found that mothers who received general anesthesia with thiopental for cesarean section and who were hypertensive had infants who were drowsy and hypotonic for the first week of life. Field and Widmayer neglected to report if any of the mothers in the vaginal group were hypotensive.

Lastly, the authors of this study suggest that the special nature of the emergency cesarean section among a lower class population may require more support from family members than is typical for a natural delivery. Thus, the mother may be especially attuned to her baby which would in turn yield better temperament ratings and more optimal interactions.

One final comment on this study which the authors failed to note is that an almost equal number of mothers in both groups received meperidine (11 section and 8 vaginal), promethazine (2 and 2) and oxytocin (20 section and 16 vaginal). One additional interpretation of the results would be that the effects of cesarean section delivery were masked by the more powerful depressive effects of these

drugs as reported in previous studies. Additionally, varying extremes in the lengths of labor could have potentially influenced the neonatal outcome. The authors failed to report the lengths of labor in either group. Thus, the results of this research are not easily interpretable because of the nature of the sample and the possibility of many confounding variables.

Several of the studies which have been reported previously should be mentioned in this section because the findings of significant effects of maternal medication on infant behavior were relatively minimal when the total number of dependent measures in these studies are taken into consideration. For example, after covarying the length of labor, Kraemer et al. (1972) found that drugs had no effect on a visual pursuit score, irritability, state changes or duration of sleep and wakefulness on the third day of life. Although Brackbill (1976) found that a drug potency score was related to habituation at 8 and 12 months as indicated by heart rate responses to auditory stimulation, she found no significant relationship at one and four months. Brackbill postulated that the delayed effect of the obstetric medication may be due to the immaturity of the cardiovascular function in the first few months of life and to the more stressful nature of the testing situation at the later age. Thus, the effects of drugs may manifest themselves only when the infant is mature enough to perceive the event as being stressful.

In the Horowitz et al. (1977) study of Brazelton performance among three populations, they found few significant differences between the light to moderately medicated and the unmedicated Israeli or Uruguyan samples. However, comparing a moderately to highly medicated American sample to the unmedicated samples of the Standley et al. (1974) and Tronick et al. (1976) studies, they found many behavioral differences. The authors suggested that a combination of genetic, biological and attitudinal factors may have contributed to the differences among the different groups.

Finally, in the Tronick et al. (1976) study, only thirteen significant differences were found comparing 54 subjects in 8 drug groups on 26 Brazelton items on each of 7 days. They found no significant differences between a group of infants of epidural deliveries and a group with premedication. This study has been criticized for excluding babies with Apgar scores less than 7 and, therefore, possibly excluding those babies who were most affected by obstetric medication (Fanaroff, Kennell, McClelland and Mortimer, 1977). Lester, Als and Brazelton (1982) recently reanalyzed the Tronick et al. data and found a significant relationship between medication and behavior in this sample when the effects of other nonoptimal obstetric variables were taken into account. This study will be reported later in the next section.

Methodological Considerations

The literature on the behavioral effects of obstetric medication on the infant has generated considerable controversy within the scientific community. This is due to the clinical importance of the area since approximately 95% of the deliveries in this country are medicated (Brackbill, 1979), to the interdisciplinary nature of the subject and frequent naivete of authors not thoroughly investigating disciplines other than their own, to the diversity of findings and to methodological problems within the literature. Several of the studies which have been reported in the previous section were accompanied by critical editorials. Criticisms have covered study designs, subject criteria, analyses of the drugs, appropriateness and reliability of the dependent measures, use of blind observers and the adequacy of data analyses. Psychologists have been criticized for naivete regarding the principles of perinatal pharmacology and anesthesiologists, obstetricians and pediatricians, for naivete regarding the complexities of behavior and statistical procedures.

The study of the effects of obstetric medication on infants is severely limited by ethical considerations regarding random assignment of women to drug groups. Although the experimental method was used in an early study by Kron et al. (1966) in which they randomly assigned subjects to receive either 200 mg. secobarbital or nothing during labor, there has been enough evidence since then to

indicate that medication administered perinatally may not be completely safe for the baby. Therefore, the experimental design may no longer be used in this type of research which necessitates the use of correlational designs. The only exceptions have been studies comparing similar agents and routes of administration. Merkow et al. (1980) randomly assigned subjects who were to receive a pudendal block during labor to receive bupivacaine, mepivacaine or chloroprocaine as the agent. Nesheim et al. (1979) randomly assigned women to a bupivacaine paracervical block group or a lidocaine local group. Additionally, Hodgkinson et al. (1978a) randomly assigned some women who had received meperidine during labor to receive the antagonist naloxone in addition to the meperidine. As more is known about the differing effects of agents, this type of random assignment will also become unfeasible.

Most of the literature on obstetric medication has used two types of designs to correlate drugs with behavior. One design is to choose subjects from the medical records who fit the selection criteria, i.e., after receiving the medication under investigation. The problem with this design is that data such as blood samples normally collected at the time of delivery cannot be obtained. Also, medical records omit many variables crucial to studies of this nature. The second design which is used frequently is to recruit subjects who fit selection criteria prior to delivery and to study the drugs which they end up receiving.

This method is fraught with problems in interpretation. When a variety of medications have been administered obstetrically, it is difficult to tease out the agents and routes of administration which are having the major effect on behavioral outcome. The dose and timing of the medication have also been found to be important to consider. Most studies have either ignored one or more of these variables or have used a drug-weighting system which attempts to combine some or all of these variables. This latter approach may be inappropriate when assessing the effects of more than one drug type and/or route because not enough evidence exists to be able to rank-order different drugs and routes of administration or to weight them quantitatively. Most of the studies which have used this approach ignore principles of perinatal pharmacology (Scanlon and Hollenbeck, 1982). According to pharmaceuticals, it is unreasonable to equate the potential effects of varying drugs or routes of administration on the baby because of differences in the rate of placental transfer of various agents, the time of maximum effectiveness as determined by the agent, route and time of administration and the varying doses used for different agents. One study which has been highly criticized for using this approach is that of Standley et al. (1974). For the purpose of analyses, they lumped the use of narcotics and tranquilizers together as analgesics and varying agents used as pudendal, paracervical, spinal and epidural blocks as anesthesia.

Comparisons were made between groups receiving analgesia, anesthesia and various combinations of the two. Hodgkinson, Marx and Kaiser (1975), Ostheimer (1981) and Scanlon and Sostek (1979) have argued that the groups are incomparable. For example, spinals are put in the same group as epidurals and compared to pudendal and paracervical blocks and locals. The differing doses and metabolic rates of the various local anesthetics make the comparisons meaningless.

Another deficiency of most obstetric medication studies is that they lack samples of "clean" nonmedicated controls. Studies in the anesthesiology literature typically compare the effects of different drugs, often comparing newly developed agents to older ones. When no differences are found, they have concluded that the null hypothesis was proven, i.e., that there are no differences between the drugs. Use of the newly developed agents may therefore be considered safe. In order to estimate potential effects of drugs on behavior, it is important to examine the behavior of infants delivered without medication. Since most births are medicated, these subjects may be very difficult to find. Murray et al. (1981) thought that they had recruited a "clean" control group until analyzing cord blood samples and discovering lidocaine in the plasma of over half of this sample. The drug had been given for local infiltration of the perineum but the hospital records had not reported whether the drug had been administered before or after delivery. Half of the "unmedicated" group had also briefly inhaled nitrous oxide.

Major criticisms of the sampling procedures may be made of most studies. Selection criteria generally include only the "clinically accepted ideal" or a population described as healthy fullterms with no complications of pregnancy and delivery. Optimal birthweights, maternal ages and other variables are often specified. Infants with histories of common nonoptimal pre- and perinatal conditions are not included in an attempt to exclude variables other than drugs which may affect behavior. However, the practice of using strict subject selection criteria makes it difficult to generalize from the "superbaby" samples which are recruited to a typical population. Additionally, the exclusion of subjects with conditions which may have been caused by the drugs such as long labors, fetal heart rate variability, acidosis and low Apgar scores make conclusions about the safety of drugs negligible. Alper (1978) has noted that complications arise in at least thirty percent of all births which appear to be following normal progressions. It is, therefore, very difficult, if not impossible, to control for every nonoptimal condition that may occur during pregnancy and delivery. These conditions may either mask drug effects or interact with drugs to affect behavior. Most investigators have ignored the variables which are not controlled for in their studies. However, a few have recognized the influence of variables other than drugs on their findings and have either conducted post hoc analyses

on their cumulative effects, have excluded their effects or have examined them individually. For example, Brackbill et al. (1974a; 1974b) regressed scores on a habituation paradigm and on a revised Brazelton exam using birthweight, length of the first stage of labor, mother's age, parity, low forceps and timing and dose of meperidine as predictors. They found that birthweight and length of labor significantly increased the predictability of the infants' performance. The combination of these variables with the dose of meperidine accounted for more of the variance in scores than did dose alone.

Hollmen et al. (1978) investigated the effects of maternal blood pressure within groups of infants delivered by cesarean section with epidural or general anesthesia. They found that the longer the hypotension within the epidural group, the more depressed activity and neurologic scores were. Also, hypertension had a cumulative effect on behavior within the general anesthesia group. One problem with this study is that their conclusions were based on clinical findings among a small number of subjects within their sample.

After finding significant differences with analysis of variance between drug groups in feeding behaviors, Kraemer et al. (1972) used analysis of covariance to eliminate the effects of length of labor, parity, sex, birthweight and maternal age from their results. They found fewer differences in behavior between drug groups after covarying

length of labor. No further significant effects on behavior were found with removal of the other variables although drug use was found to be significantly related to both length of labor and parity.

Woodson and DaCosta-Woodson (1980) also investigated covariates of obstetric medication. They sampled a group of babies in Malaysia and found that parity, ethnic group, duration of the second stage of labor, gestational age and maternal blood pressure during labor influenced the relationship between analgesia and a Brazelton irritability factor. When the effects of these variables were controlled, infants from a group delivered with analgesia were found to be less irritable than those from an unmedicated group. This lends support to the Horowitz et al. (1977) hypothesis that genetic, biological and attitudinal factors may contribute to differences in drug effects among different cultures.

Investigating the effects of several variables on mother-infant interaction, Brown et al. (1975) found that parity was the best predictor of behavior followed by dose of analgesics and length of labor. However, more than two-thirds of the variance associated with parity was confounded with amount of analgesic taken and length of labor. In separate analyses, the authors found that birthweight and sex also had a significant effect on interactive behaviors. These authors concluded their study with the following recommendations:

In future studies, investigators might consider selecting a large number of mothers and infants at random and extracting the effects of background variables through statistical analyses rather than attempting to increase the homogeneity of their sample through the imposition of stringent selection criteria. At the present time not enough is known about the importance of even the most common background variables to enable researchers to choose selection criteria without introducing possible biases. (Brown et al., 1975, p. 686)

With this recommendation in mind, if variables which have not been controlled for by selection criteria act in concert with obstetric medication to stress the infant, the best way to examine the relationship is with multivariate analysis as in the Brackbill et al. (1974a; 1974b) study. This allows us to examine the predictive power of related variables and to estimate the relative contribution of each variable to the prediction of behavior. A recent reanalysis of the Tronick et al. (1976) data by Lester, Als and Brazelton (1982) using stepwise multiple regression serves as a good illustration of the power of this method. This analysis shows the cumulative effects of drug and nondrug variables on behavior where few effects were found in the Tronick et al. study as a function of drugs alone within a sample of "superbabies" whose mothers received relatively low doses of obstetric medication.

The sample was 54 infants more highly selected for obstetric and pediatric well-being than in most studies. Selection criteria are shown in Table 2. The Brazelton exam was administered to each infant on days 1 through 5, 7, and

Table 2. Selection Criteria for Tronick et al. (1977) Study

Infant Was Excluded if Mother Had

Toxemia

Threatened Abortion

Diabetes mellitus

Chronic disease (renal, hyperthyroidism,
neurological disorders)

Age < 18 yr or > 35 yr

Prolonged first-stage labor > 24 hr

Prolonged second-stage labor > 6 hr

Rupture membranes > 24 hr

Hemorrhage or shock

Precipitous labor < 3 hr

Any abnormal delivery (breech, Caesarian section,
shoulder, brow, head presentation,
high, mid-forceps)

Infant Was Rejected at Delivery or After 24 Hours if

Premature

Gestation was > 41 wk

Birthweight < 2,712 gm or > 4,068 gm

Congenital anomaly

Apgar score < 7 at 1 min and 5 min

Cephalohematoma or other bruising

Development of severe illness during study
(sepsis, seizures, bleeding, etc.)

10. Each of the seven Brazelton clusters previously mentioned on each of the seven testing days plus their slope or rate of behavioral change over the ten days of life were the outcome variables in the regressions. The independent or predictor variables were (1) a drug group score based on the type, route of administration and timing of the medication (drug groups were ranked from 1 to 8 by an anesthesiologist in increasing order according to the magnitude of their expected effects on behavior); (2) a drug factor score based on the amount of time from the first and last drug administration to delivery, the number of different drugs and the number of drug administrations; (3) the ponderal index which is a weight-to-length ratio assessing possible fetal malnutrition; (4) length of labor; and (5) parity. There were few significant individual correlations between any one of these predictor variables and the outcome measures. However, 22 of the 49 multiple correlations were significant. They ranged from .30 to .52, indicating that the linear combination of the 5 predictor variables accounted for 9 to 27% of the variation in the cluster scores over the 10 days. Significant effects were found on 5 of the 7 testing days for the autonomic regulation cluster, 4 days for the range of state cluster and 2 days for the orientation, regulation of state and reflex clusters. The regressions on the rate of behavioral change showed significant effects for the habituation, orientation, motor, autonomic regulation and reflex

clusters. The individual beta weights indicated that worse performance on all clusters was associated with higher drug group and drug factor scores, a lower ponderal index, being firstborn and having a long labor.

The results of this analysis suggest that even with a sample as carefully selected to be low risk as this one was, subtle indications of risk may be present which act in concert with medication to affect behavior. A comparison of the minimal effects found by Tronick et al. with the larger effects found in this reanalysis suggests that the effects of low levels of medication on behavior may be too subtle to be identified when comparing performance between drug groups. It suggests that investigating drugs in combination with perinatal variables that may potentiate their effects may expose the effects of even low levels of medication.

Although this reanalysis is important as an exploratory study, the findings must be considered preliminary since much of the medical information was retrieved retrospectively for the post hoc analyses. The study has been criticized for obtaining data on birthlengths from the medical records (Scanlon, in press). Records of birthlengths are generally considered to be inaccurate because of the varying methods used by physicians to measure babies. This study also suffers from rank-ordering different types of drugs. This detracts from its clinical value because it is impossible to delineate which types and routes of medication are affecting which behaviors.

The Purpose of the Study

The purpose of the present study was to increase our understanding of the effects of one commonly used type of obstetric medication on early behavior by examining the constellation of nonoptimal obstetric conditions found in a relatively healthy sample of newborns with varying birth histories. As in the Brackbill et al. and Lester et al. studies, a multiple regression design was used to tease out the interaction of the variables and to investigate the variables which contributed to different behaviors. In order to avoid the problems of weighting different drugs, no medication for pain relief other than bupivacaine epidural anesthesia was included. The dose and time of administration were the only drug-related variables allowed to vary in the study. This choice of obstetric medication was made because bupivacaine epidurals are the drug and route of administration most commonly used in the Boston maternity hospitals. Statistics for the United States and Great Britain have indicated that it is used in at least 40% of all deliveries (Plumer, 1978; Reynolds, Hargrove & Wyman, 1973).

Bupivacaine has become the agent of choice for epidural deliveries because it has a greater potency and a longer duration of action than other local anesthetics. It also has the greatest plasma protein binding capacity and is highly lipid soluble (Covino, 1971). Bupivacaine has been found to bind more readily to maternal than to fetal plasma

proteins and, therefore, to have a lower maternal/fetal concentration ratio than other agents (Reynolds et al., 1973; Reynolds & Taylor, 1970; Thomas, Long, Moore & Morgan, 1976; Tucker, Boyes, Bridenbaugh & Moore, 1970). The half-life of bupivacaine is estimated to be eight hours and approximately five to seven half-lives are needed to eliminate the drug from the system (Belfrage, Berlin, Raabe & Thalme, 1975). Although we were able to sample maternal and umbilical blood for bupivacaine levels in this study, we were unable to measure bupivacaine after birth because of hospital restrictions on neonatal sampling.

The present study investigated drug-related variables which have been found, in the past, to affect neonatal behavior. They were dose, time of administration and number of topup administrations of bupivacaine. Other obstetric conditions were chosen as predictor variables because of their role in perinatal pharmacology and because of previous research findings. They were the acid-base status of the umbilical arterial blood, neonatal ponderal index, maternal weight-to-height ratio, duration of the administration of oxytocin, length of the first and second stages of labor and number of nonoptimal obstetric conditions.

The relevance of the acid-base status to the study of obstetric medication was discussed previously. Datta, Brown, Ostheimer, Weiss and Alper (1981) found that acidotic infants had higher levels of bupivacaine in their umbilical cord blood samples than infants with normal acid-base

statuses. They also found that acidosis prolonged the half-life of the drug. Maternal blood pressure was found to affect behavioral outcome in the Hollmen et al. (1978) and Woodson and DaCosta-Woodson (1981) studies. In the present study, the acid-base status or pH of the umbilical arterial blood was used because its measurement is more reliable than maternal blood pressure during labor and because the rate of drug transfer is influenced by the fetal pH. It was hypothesized that the combination of drug variables and pH would predict behavior better than the drug alone.

The ponderal index was found to increase the predictability of behavior in the Lester et al. (1982) study. The authors suggested that thin babies respond differently than heavier babies to the same level of medication since the storage of drugs in fatty tissue protects the baby from the influence of circulating drugs. It has also been suggested that a low temperature which is pronounced in thin malnourished babies slows down the elimination of drugs (Aleksandrowicz, 1974; Morishima, Mueller-Heubach and Shnider, 1974). Therefore, in the present study, it was postulated that the addition of the ponderal index to the medication variables would increase the predictability of behavior.

The ratio of the mother's weight-to-height was also investigated because of the role of fatty tissue in drug distribution. The mother's height is typically the only criteria used by physicians to determine the dosage of the

first administration of medication during labor. Dose is not dependent on body mass. It may be expected, as with a low ponderal index, that more drugs will circulate in the baby of a thin mother than in the baby of a heavier mother since drugs bind to fatty tissues. Therefore, use of this variable should increase the predictability of behavior.

Oxytocin is given almost routinely with epidural anesthesia to speed up labor that the anesthesia may slow down especially when the block is given early in labor. Most studies have ignored its use probably because the amount of oxytocin received by the mother is very difficult to estimate. It is typically administered by a manually controlled intravenous drip or infusion pump. Any blockage of the tube caused by a change in the maternal position during labor may stop the flow of the oxytocin. Because the use of this drug could not be omitted in the present study, it was included as a predictor variable. The total amount of time it was administered was used to estimate the quantity of oxytocin. A few studies have related the use of oxytocin to negative results in the baby. Schifrin (1972) found an increase in late decelerations of fetal heart rate with the use of oxytocin and/or epidural anesthesia with lidocaine during labor. He suggested that the late decelerations were a sign of fetal asphyxia. Investigating performance on the Brazelton Scale, Murray et al. (1981) found that a group of Australian babies delivered by bupivacaine epidural anesthesia with oxytocin performed

worse than a group delivered with bupivacaine alone on the motor cluster on day 1 and on state range on day 5. However, Hodgkinson et al. (1977) found no effect of oxytocin augmentation on Scanlon scores over the first 2 days of life. Ounsted et al. (1978) related lower neurological scores at 2 months of age and poorer fine motor performance at 18 months to the use of oxytocin during parturition. Additionally, Friedman et al. (1978) found that infants whose mothers received oxytocin during labor habituated at a slower rate than those not exposed to oxytocin. In the present study, it was hypothesized that use of oxytocin would increase the depressing effects of bupivacaine on behavior.

Length of labor has been shown to interact with drugs in the Lester et al. (1982), Brackbill et al. (1974a; 1974b), Yang et al. (1976) and Kraemer et al. (1972) studies. McGrade, Kessen and Leutzendorff (1965) investigated the relationship between length of labor and activity level, and found that babies of longer labors were less active on days 3 and 4. The findings were interpreted as representing the effects of fatigue after a long labor. In the present study, it was expected that the use of length of labor with the other independent variables would further increase the predictability of behavior.

Previous research has indicated that the physical status of both the mother and the fetus exerts an influence on the pharmacological action of the drug (Covino, 1971;

Scanlon, 1974). Furthermore, numerous prenatal and perinatal risk factors have been related to the behavioral outcome of the infant (Lipsitt & Field, 1982). In order to investigate the cumulative effect of obstetric variables which may influence behavior, a modification of Prechtl's (1968) scale of optimal obstetric conditions was used. Prechtl's technique is a self-weighting one based on the concept that a hazardous obstetric complication will not occur by itself but exists in conjunction with other complications and that multiple events place greater stress on the central nervous system than single events. Parmalee, Kopp and Sigman (1976) used this technique but revised the scale to score the total number of obstetric risk factors. Several studies have found the Parmalee et al. system to be successful in differentiating high and low risk infants on different behaviors (Kittner & Lipsitt, 1976; Field, Dempsey, Hallock, & Shuman, 1978; Sepkoski, Coll, & Lester, 1982; Lester & Zeskind, 1978). In the present study, it was proposed that the use of a cumulative risk score would add to the drug variables in the prediction of behavior.

The Brazelton Neonatal Behavioral Assessment Scale was used in the present study to assess neonatal behavior. This scale was chosen because it is a comprehensive standardized tool useful for assessing behavior over the first month of life. As discussed previously, many studies have found it to be sensitive to the effects of obstetric medication and to perinatal risk. In the present study, it was

hypothesized that newborn behavior as measured by the Brazelton Scale would be sensitive to the combination of anesthesia and obstetric variables. It was further hypothesized that the amount of variance accounted for by these independent variables would differ from day to day and from behavior to behavior.

METHOD

Study Site

The study was begun at the largest maternity hospital in the Boston area, the Boston Hospital for Women, Lying-In Division (BLI). After approximately three-quarters of the sample had been recruited, the BLI moved joining with other hospitals in the area to become the Brigham and Women's (BW) Hospital. The study was completed at this location.

The BLI/Brigham and Women's Hospital is a private maternity hospital staffed by obstetricians and nurses from both individual and group practices. The clientele come from Boston and the surrounding vicinity and are from middle and working class backgrounds. During the two year period of data collection, 13,253 deliveries were performed at this hospital. Seventy-seven percent (n=10,228) of these were vaginal deliveries with 91% (n=9307) receiving some type of anesthesia. Of the vaginal deliveries, 45% (n=4603) received an epidural, 36% (n=3682) a local, 6% (n=614) a spinal, and .3% (n=31) inhalation anesthesia.

Subject Recruitment

After receiving permission from the human subjects' committee to proceed with the study, letters were sent explaining the study to 55 obstetricians who deliver babies at the BLI/BW Hospital. One obstetrician denied permission for his patients' participation in the study; therefore, his

patients were not recruited. (See Appendix 1 for the summary of obstetricians whose patients were recruited.)

Subjects were selected from mothers who delivered in-house and lived within 35 miles of the hospital. Selection criteria included fullterm (38 - 42 weeks gestation) vaginal deliveries with bupivacaine epidural anesthesia or no medication given for pain relief during labor and delivery. Mothers who received any other medication to reduce pain or relieve anxiety were excluded from the study. Infants were selected if they were the product of a singleton birth, had no congenital malformations or disorders and were admitted to the regular newborn nursery. In order to reduce the number of subject variables, only Caucasian infants of English-speaking mothers were included in the study.

A research nurse at the BLI/BW Hospital recruited women who fit the subject selection criteria and who would be delivering during a time when she was available. A maximum of two subjects per day or three per week were recruited. Women were approached for consent while in labor because a maternal blood sample at the time of delivery was requested. The study was explained and written consent was obtained (see Appendix 2). Women were recruited late in labor in order to exclude those who might receive medication other than epidural anesthesia.

A total of 100 women who were patients of 20 different obstetricians were asked to participate in the study. Fifty-six of the women delivered with epidural anesthesia

and 32 delivered without medication. Twelve of the women received a narcotic or local infiltration late in labor. They were, therefore, excluded from the study. Four of the women (2 epidural, 2 nonmedicated) refused consent for the study for the following reasons: being upset by frequent requests during labor to participate in research projects, being upset about receiving intravenous fluid when it was not requested, wanting no intervention with the baby on the first day and being too busy due to a disabled child at home. Because consent was initially obtained during a difficult time, the study was explained again to mothers when they were first seen after delivery and a second verbal consent was requested. One woman (epidural delivery) withdrew consent at this time because her husband did not want her to participate.

Twenty-three infants were excluded from the study for various reasons other than receiving analgesics or local infiltration. Five were excluded immediately after birth because they were admitted to the special care nursery: four (2 epidural, 2 nonmedicated) had respiratory complications and one had shoulder dystocia (nonmedicated). Four were excluded after the first Brazelton exam: one had a club foot (nonmedicated), one had pneumonia (nonmedicated) and two (epidurals) left the hospital immediately after the first day and could not be contacted. Fourteen infants were excluded after completing the study: the initial ten (epidural) were considered pilot subjects, two subjects (one

epidural, one nonmedicated) received medication for thrush during the first month, and two (nonmedicated) had surgery for pyloric stenosis during the first month. (Both parents of one of the babies with pyloric stenosis were anesthesiologists. The mother of the other baby had a history of infertility, miscarriages and a stillbirth.)

Sample

The final sample consisted of 60 infants, 38 who were products of epidural deliveries and 22 of nonmedicated deliveries. There were 27 girls and 33 boys. The mean birthweight was 3451 grams (SD=388g.) and mean birthlength was 50 cm. (SD=1.9 cm.). One minute Apgar scores ranged from 5 to 9 ($x=8$, $SD=1.0$) and 5 minute Apgar scores ranged from 8 to 10 ($x=9$, $SD=.2$).

The mothers in the sample ranged from 18 to 39 years of age ($x=31$ years, $SD= 3.9$). Thirty-three percent of them were having their first baby. All mothers except for one received prenatal care for all three trimesters of pregnancy. The reported number of prescription and over-the-counter drugs taken during pregnancy ranged from none to 6 and averaged 2 drugs ($SD=1.4$). All mothers were married and of intact families. All fathers were present at delivery. The socioeconomic status of the families according to the Hollingshead Four Factor Index (Hollingshead, 1975) ranged from 20 to 66 indicating that the sample was from middle and working class backgrounds. All parents had completed high school. Sixty-three percent

of the mothers and 68% of the fathers had completed college. Of the parents completing college, 45% of the mothers and 56% of the fathers also had graduate degrees.

Instruments

Brazelton Neonatal Behavioral Assessment Scale

As previously discussed, the Brazelton Neonatal Behavioral Assessment Scale (Brazelton, 1973) is an assessment tool which was designed to measure the behavioral capacities and individual differences of infants during the first month of life. It is based on the concept that the neonate is a complexly organized organism adapted to interact with the environment in such a way to elicit responses that are necessary for future growth and development (Als, Tronick, Lester and Brazelton, 1979). For example, the neonate should be able to elicit attention from a caregiver, control movements and physiological responses which might interfere with interaction with a caregiver, and defend him/herself from negative stimuli in the environment. Thus, the Brazelton Scale goes beyond traditional examinations in its assessment of a range of neonatal behavior which may affect the development of the infant-caregiver relationship.

The Brazelton Scale consists of 27 behavioral and 17 reflexive items (see Appendix 3) and takes approximately 30 minutes to administer. The exam begins with a two minute observation of the infant to assess his or her initial state of consciousness and physical condition. If the baby is

sleeping, the examiner proceeds by repeating presentations of a light, followed by a rattle, bell and tactile stimulation of the heel to look for decrement of responses. These items are excluded if the initial state is not one of sleep or drowsiness. The rest of the exam consists of manipulating the baby with progressively stronger tactile stimulation to observe both elicited and spontaneously emitted responses of the baby. The mild maneuvers include elicitation of reflexes of the hands, feet, arms and legs, the glabella, rooting and sucking. Moderate maneuvers include undressing, pull-to-sit, cuddling, and standing, walking, placing, incurvation, and crawling reflexes. The strongest tactile maneuvers include rotation of the baby to elicit tonic deviation of the head and eyes, elicitation of a defensive reaction to a cloth placed over the eyes, the tonic neck reflex and the Moro. At some point during the exam when the baby is in an alert state, the infant's ability to orient to the examiner's face and voice and to a ball and rattle is observed.

There are several features which distinguish the Brazelton Scale from other assessments of neonatal behavior. The goal of the exam is to bring out the baby's best possible performance, not just the average performance. Thus, an attempt is made to elicit the best capabilities the infant has for interacting with the environment. In order to bring out best performance, it is necessary that the order of administration of the Brazelton Scale be flexible,

or that items be administered when the examiner feels that the best performance can be achieved. In order to do this, it is necessary that the examiner continuously control and monitor the baby's states of consciousness throughout the exam. Prechtl and Beintema's (1964) categorization system for six states is used during the exam (see Appendix 4). The states range from deep sleep to alertness to robust crying. The Brazelton Scale specifies the appropriate state for the administration of each item. It is important that the examiner be familiar with a range of behavior patterns that may be expected during the Brazelton so that he or she can interpret the baby's cues and order the exam to bring out the baby's best performance. The examiner must go through a training procedure of first examining and scoring 30 "pilot" babies to appreciate a range of behavior patterns. He or she then participates in a two day workshop with a qualified trainer. To achieve reliability on the Brazelton Scale, the trainee must be judged reliable on its administration by the trainer, and score within one point on no less than 24 of the 26 behavioral items and within two points on the remaining 2 items. The trainee must also score the 17 reflex items correctly.

Another characteristic which distinguishes the Brazelton Scale from most neonatal assessments is its omission of a single index to summarize the infant's behavior and/or to label the infant's progress. Instead, it provides a profile of the functioning of several systems of

behavioral organization. To obtain this, after the administration of the Brazelton exam, the examiner scores the 17 reflex items on a 4 point scale from absent to extreme. The 26 behavioral items are scored on scales from one to nine. Some of these items are assessed from discreet events during the exam as with the reflexes, i.e., response decrement items, orientation items, pull-to-sit and the defensive response, while other items are monitored continuously and scored during the whole exam, i.e., measures of activity level, motor performance, general tonus, physiological responses, state range and control of states. These scores may then be reduced to the clustering system developed by Lester, Als, and Brazelton (1982) which was discussed in the previous chapter (see Appendix 5). This system consists of one reflex cluster and six behavioral clusters. The reflex cluster is the total number of abnormal reflex scores. To derive the behavioral clusters, the individual items that are curvilinear are rescored so that higher scores in all items of the exam indicate better performance. Six total mean scores are then derived: 1) habituation, which includes items measuring decrement of responses to the light, rattle, bell and touch of the heel; 2) orientation, or responses to the animate and inanimate auditory and visual stimuli, and overall alertness; 3) motor organization, or the items assessing motor maturity and overall muscle tonus; 4) range of state, which examines the rapidity, peak, and lability of state

changes; 5) regulation of state, or the infant's efforts to modulate state; and 6) autonomic regulation, which includes signs of physiological stress, i.e., tremors, startles and changes in skin color.

Interview

A maternal interview was designed to obtain additional information about the mother and baby (see Appendix 6). It was adapted in part from a pregnancy interview by Barnard (1976) and a prenatal drug interview by Doering (1978). Questions were asked concerning decisions made about labor and delivery (e.g., use of anesthesia), the amount of time the mother spent with the baby in the hospital, prenatal drug intake and the mother's and father's occupation and education. Also, information which is often missing in the hospital medical records (e.g., length of labor) was requested.

Obstetric Complications Scale (OCS)

The Obstetric Complication Scale designed by Parmalee, Kopp and Sigman (1976) was used to assess a range of nonoptimal obstetric conditions (see Appendix 7). The OCS was derived from Prechtel's (1968) scale of optimal obstetric conditions. Both scales are self-weighting based on the concept that a hazardous obstetric condition will not occur by itself but exists in conjunction with other complications and that multiple events place greater stress on the central nervous system than single events. Parmalee, Kopp and

Sigman revised Prechtl's scale to score nonoptimal rather than optimal obstetric conditions. This scoring system includes 41 items associated with maternal, parturitional and fetal nonoptimal conditions. The items are scored as present or absent. To obtain an OCS score, the total number of conditions which are absent are divided by the total number of items scored. This percentage of optimal scores is converted to a standardized score based on a mean score of 100 and a standard deviation of 20 (see Manual for Obstetric Complications, Littman and Parmalee, 1974).

The OCS has been found to be a useful technique for discriminating babies according to their risk status. Infants classified as high or low risk according to this system have been found to differ in cries (Lester & Zeskind, 1978) and heart rate (Kittner & Lipsitt, 1976). Additionally, the number of maternal, parturitional and fetal nonoptimal conditions on the OCS, the ponderal index, gestational age and mother's age were found to significantly predict six of the seven Brazelton clusters in a group of Puerto Rican neonates (Sepkoski, Coll, & Lester, 1982). In another study, it was found that a continuum of risk over the first year of life could be predicted by both the OCS and several Brazelton behavioral dimensions (Field, Hallock, Demsey, Dabiri, & Shuman, 1978).

Procedure

Blood Samples

Blood samples were taken at delivery with a heparinized syringe from a vein in the mother's arm and from the vein and artery of a doubly clamped segment of the umbilical cord. Portions of the samples were immediately analyzed using a Radiometer microelectrode to determine acid-base status (pH). The remaining portions were frozen and later analyzed using a gas chromatographic technique to measure the whole blood concentrations of bupivacaine. The maternal blood sample was not obtained if the woman refused consent for it or if it was too difficult to obtain during delivery. A total of 35 maternal blood samples were collected.

Neonatal Assessments

The Brazelton Neonatal Behavioral Assessment Scale was administered by an examiner blind to the obstetric history of the baby on days 1, 3, 7 and 28. The examiners were trained to reliability in both the administration and scoring of the scale according to the procedures outlined in the manual by Brazelton (1973).

The first exam was administered between 3 and 6 hours after birth in an empty postpartum room or in the nursery examining room. The mother was not present for the initial exam since she was generally still in the recovery room. The examining room was darkened due to the sensitivity of the neonate's eyes. (Silver nitrate is administered to the baby's eyes immediately after delivery at the BLI/BW

Hospital). Following the exam the baby was measured as recommended by Miller and Hassanein (1971) by putting him/her in the tonic neck position in an anthropometer (Infa-length, Olympic Surgical Co., Seattle).

The second exam was scheduled between 48 and 72 hours after birth and no less than 4 hours after circumcision. Exams were administered in the mother's hospital room with the exception of one baby who went home early and was examined at home on the fourth day because she left the hospital prior to 48 hours. Mothers were present for these exams. After the exam, the tester discussed with the mother the baby's strongest points, e.g., alertness, activity, ability to calm, etc. The second Brazelton exam was missed for one infant who went home early.

Appointments were made by phone to examine the baby at one week (7 ± 1 day) and one month (28 ± 2 days) of age in the home. Often parents, siblings and grandparents were present for these exams. An effort was made to explain the exam to all of them (this lesson was learned during a visit to one of the pilot subjects' homes when the examiner was punched in the abdomen by a 5 year-old after eliciting a Moro from his baby brother). Often siblings would attempt to get the baby to orient to the rattle or their own voice after the exam was over.

When the examination of the baby at one month was finished, the mother was given the pregnancy and delivery interview. After this home visit, additional medical

information was obtained from the mother's and baby's medical records. Each family was sent a card expressing gratitude for their participation in the study. When the data analyses were completed, abstracts of the study were sent to each family.

RESULTS

Characteristics of the Sample

Bupivacaine Variables

Thirty-eight of the women in the sample received a .5% concentration of bupivacaine (without epinephrine) in an isotonic solution of sodium chloride for relief of pain during labor. The solution was injected at appropriate intervals through a catheter which was inserted into the mother's lumbar epidural space when her cervix was appropriately 5 to 6 cm dilated. As illustrated in Table 3, the first dose of the drug was administered to these women between one and ten hours prior to delivery ($x = 3.5$ hrs., $SD = 2.1$). One to six doses were administered ($x = 2.5$, $SD = 1.2$) with the total amount of bupivacaine received by this sample ranging from 50 to 290 mg. ($x = 112.7$ mg., $SD = 45.6$).

Analyses of the whole blood concentrations of bupivacaine showed that the amount of drug in both the umbilical venous (UV) and umbilical arterial (UA) samples ranged from .04 to .44 ug/ml. The mean UV concentration of bupivacaine was .12 ug/ml ($SD = .07$) and the mean UA concentration was .09 ug/ml ($SD = .09$). The concentration of bupivacaine in the maternal venous (MV) blood samples ranged from .04 to .88 ug/ml and averaged .28 ug/ml ($SD = .2$). The ratio of the UV/MV concentrations ranged from .04 to 1.0 and averaged .33 ($SD = .24$).

Table 3. Descriptive Statistics of Bupivacaine Variables.

	Mean	Standard Deviation	Range
Bupivacaine			
Dose (mg)	112.7	45.6	50-290
Number of Administrations	2.5	1.2	1-6
Time of First Administration (hours prior to delivery)	3.5	2.1	1-10
UV concentration (ug/ml)	0.12	0.07	0.04-0.44
UA concentration (ug/ml)	0.09	0.09	0.04-0.44
MV concentration (ug/ml)	0.28	0.20	0.04-0.44
UV/MV concentration ratio	0.33	0.24	0.04-1.0

As seen in Table 4, Pearson product-moment correlations were run between the following bupivacaine variables which had been preselected as predictors for regressions: total dose, number of administrations, time of administration to delivery and umbilical venous concentration. The intercorrelations were high, ranging from .54 to .91 ($x = .72$). Because of the high correlations among these variables, Fischer Z score transformations were also performed to obtain a mean correlation. The mean result was .746. Thus, because a high portion of the variance was shared by these variables, only the dose of bupivacaine was retained as a predictor variable for the regressions. Dose was chosen over the other variables because it was the single variable most highly correlated with the other three and because it has been related to behavior in studies of the effects of obstetric medication more frequently than the other variables.

Data collected from the maternal interviews indicated that half of the women receiving anesthesia decided on it prior to labor and half decided during labor. Fifty-five percent of these women indicated that they made the decision to have the epidural themselves. Thirteen percent said that their doctors made the decision and 32% said that it was a joint decision between themselves and their doctors. Complete analgesia was achieved in 74% of the medicated

Table 4. Correlations Between Bupivacaine Variables.

	Dose	Number	Time	UV
Dose (mg)	1.0			
Number of Administrations	.91	1.0		
Time of First Administration (hours prior to delivery)	.78	.69	1.0	
UV concentration (ug/ml)	.75	.66	.54	1.0

deliveries and partial analgesia in 18% of the deliveries. Eight percent of the women said that they received no pain relief from the epidural. Regarding plans for future deliveries, 61% of these women said they would want the same medication, 26% would want no medication, 5% would want less medication and 3% would want more.

In contrast, 77% of the 22 women who received no medication for pain relief said that they had decided on this prior to the beginning of labor and 23% decided not to have medication during labor. Seventy-seven percent reported that they made this decision themselves, 5% reported that it was made by their doctors and 18% made the decision with their doctors. Only one of the nonmedicated mothers said that she would like to have medication for the relief of pain in future deliveries.

Predictor Variables

Table 5 illustrates the characteristics of the preselected predictor variables for the entire sample of 60 babies. As determined by analyses of the umbilical arterial blood samples, the neonatal pH ranged from 7.14 to 7.45 ($x = 7.28$, $SD = .07$). Eight babies were mildly acidotic ($pH = 7.2 - 7.24$), and seven were severely acidotic ($pH < 7.19$). One baby had a pH less than 7.14.

The ponderal index of this sample ranged from 2.2 to 3.48 with a mean of 2.72 ($SD = .23$) which falls at approximately the 75th percentile according to Miller and

Table 5. Descriptive Statistics of the Predictor Variables for the Entire Sample (N=60).

Variable	Mean	Standard Deviation	Range
UApH	7.28	.07	7.14-7.45
Ponderal Index	2.72	.23	2.2-3.48
Maternal Weight/Height	2.0	.3	1.6-3.4
Stage 1 Labor (hrs)	8.0	5.4	.6-27
Stage 2 Labor (hrs)	.95	.8	.02-3.3
Obstetric Complication Scale	110	18.8	54-160
Oxytocin (hrs)	2.0	2.4	0-9.3
Bupivacaine Dose (mg)	71.4	65.6	0-290

Hassanein (1971). Only 4 babies in this sample were below the 10th percentile (2.3) with one baby below the 3rd percentile (2.2). However, twenty-one babies fell into the extreme upper range with ponderal indices greater than the 90th percentile (2.85). Seven of these babies were above the 97th percentile (3.00).

The maternal weight-to-height ratio was calculated by dividing the prepregnancy weight of the mother in pounds by her height in inches. Statistics for this variable indicated a range from 1.6 to 3.4 with a mean of 2.0 (SD = .3).

The lengths of first and second stages of labor were recorded in this study, since they have been previously found to have independent effects on behavior. In this sample, the length of the first stage of labor ranged from 36 minutes to 27 hours and averaged 8 hours (SD = 5.4 hrs.). Two mothers had extremely long first stages of labor lasting more than 20 hours and five had extremely short first stages lasting less than 3 hours. The length of the second stage of labor ranged from one minute to 3.3 hours and averaged .95 hours or 57 minutes (SD = .8 hrs.). Five mothers were in the second stage of labor for more than 2 hours and four mothers for less than 10 minutes.

The Obstetric Complication Scale (OCS) scores ranged from 54 to 160. The mean score of 110 (SD = 18.8) was slightly higher than the Parmalee et al. (1976) standardized mean of 100 (SD = 16).

Thirty-eight of the mothers received oxytocin for durations ranging from 35 minutes to 9.3 hours ($x = 3$ hrs., $SD = 2.2$). However, using the duration of the administration of oxytocin as a continuous variable from 0 hours administration to a maximum of 9.3 hours, the mean for the entire sample of 60 was 2 hours ($SD = 2.4$). Also using the amount of bupivacaine as a continuous variable, the total dose for the entire sample ranged from 0 to 290 mg. and averaged 71.4 mg. ($SD = 65.6$).

Relationships Among Variables: Bivariate Correlations

Pearson product-moment correlations were performed among the eight independent variables for the entire sample of 60 babies. As shown in Table 6, the intercorrelations ranged from .004 to .45 and averaged .15, indicating that these variables were relatively orthogonal. Therefore, these eight variables were retained as predictors for the regressions. The analyses which yielded a correlation greater than .4 were the following: dose of bupivacaine with hours of oxytocin (.44) and the first stage (.45) and second stage (.45) of labor and hours of oxytocin with OCS score (-.44).

Pearson product-moment correlations were also performed among the Brazelton clusters. The habituation cluster was omitted from these analyses because 50% of the data was missing on days 1 and 3, 65% was missing on day 7 and 80% was missing on day 28. The data were missing because infants were frequently awake at the beginning of the

Table 6. Correlations Between Predictor Variables

	BP	L1	L2	pH	PI	WH	OC	OX
Bupiva- caine(BP)	1.0							
Labor Stage 1 (L1)	.45	1.0						
Labor Stage 2(L2)	.45	.23	1.0					
UApH(pH)	.25	.15	.08	1.0				
Ponderal Index(PI)	-.10	-.06	.03	-.05	1.0			
Maternal Wt/Ht(WH)	-.03	-.10	-.04	.06	.10	1.0		
OCS(OC)	-.26	.08	.11	-.01	.08	-.01	1.0	
Oxy- tocin(OX)	.44	.10	.07	.07	-.08	.16	-.44	1.0

Brazelton exam. The habituation items can be administered only in sleep states and, therefore, had to be omitted. The intercorrelations among the remaining six clusters on the four testing days were generally low, ranging from .0006 to 0.45 and averaging 0.14, illustrating the relative orthogonality among the clusters. There were only four correlations above .4: day 1 motor with day 1 reflex (-.45) and day 7 autonomic regulation (.42); day 3 motor with day 7 motor (.42); and day 3 reflex with day 7 reflex (.41).

Bivariate Pearson product-moment correlations were also performed between each of the six Brazelton clusters on the four testing days and the eight predictor variables. Of the 192 correlations computed, 13 reached the .05 level of significance. As shown in Table 7, behavior was correlated significantly 4 times with the dose of bupivacaine, 3 times with the length of the second stage of labor, twice with oxytocin and with the first stage of labor and once with the ponderal index and with neonatal pH. The correlations between the clusters and the maternal weight-to-height ratio or the OCS score never reached significance. Using the .05 level of significance, ten of these correlations would have been expected by chance alone. If a more conservative significance level of .01 is used, only one correlation between behavior (motor cluster, day 28) and the dose of bupivacaine was significant.

Table 7. Significant Bivariate Correlations Between Predictor Variables and Brazelton Cluster

<u>Predictor</u>	<u>Day</u>	<u>Cluster</u>	<u>Correlation</u>	<u>p<</u>
Bupivacaine Dose	1	Orientation	-.29	.05
	1	Motor	-.28	.05
	1	Reflex	.28	.05
	28	Motor	-.36	.01
Stage 2 Labor	1	Orientation	-.31	.05
	1	Autonomic Regulation	.30	.05
	3	Autonomic Regulation	.29	.05
Stage 1 Labor	1	Autonomic Regulation	.28	.05
	3	State Range	-.33	.05
Oxytocin	1	Reflexes	.26	.05
	28	Autonomic Regulation	-.26	.05
Ponderal Index	7	State Range	.31	.05
UApH	3	Autonomic Regulation	.29	.05

Cumulative Effects of Bupivacaine and Obstetric Variables:
Multiple Regressions

In order to estimate the cumulative effects of the independent variables on neonatal behavior, a stepwise multiple regression was performed between each of six Brazelton clusters on days 1, 3, 7, and 28 and the eight predictor variables. The habituation cluster was omitted from these analyses because of missing data. The predictor variables were entered one at a time into each regression equation with the order of their entry determined by the amount of variance for which they accounted. The stepwise procedure worked by choosing the variable which accounted for the maximum amount of variance between the dependent variable and all of the independent variables as the first predictor. Then, the variance accounted for by the first predictor was partialled from the dependent variable and all of the remaining independent variables. The independent variable which accounted for the most variance after this step was chosen as the second predictor. This procedure continued until the best linear combination of independent variables which predicted to the dependent variable and accounted for the maximum amount of variance was found. Because the ratio of the number of independent variables to the number of subjects was large, the stepwise procedure permitted the entry of a maximum of six predictors for each regression equation. The relative contribution of each variable to the prediction of behavior was determined both by the order of entry into the regression equations and by

the standardized regression coefficient or Beta weight (B) which expressed the contribution in standard deviation units.

An evaluation using an F test indicated that 11 of the 24 multiple regressions were significant at the .05 significance level. Table 8 presents a summary of the significant regressions where the multiple correlation includes only those variables which contributed to the regression equation as determined by the stepwise procedure. The significant correlations ranged from .24 to .51 with a mean of .40 suggesting that an average of 20% of the variation in the Brazelton cluster scores over the first month of life was explained by the linear combination of the predictor variables.

Significant effects of the combination of drug and other obstetric variables were found most frequently on the motor and autonomic regulation clusters. The regression equations for the motor cluster on days 1, 7 and 28 were significant. On day 1, better performance was related only to a lower dose of bupivacaine (B = -.28). On day 7, the combination of a lower pH, less oxytocin, a lower OCS score and a larger maternal weight:height ratio (B = -.23, -.26, -.40, and -.08, respectively) combined to predict higher scores. At one month, the cumulative effects of a lower dose of bupivacaine, a higher neonatal pH and a higher OCS score (B = -.36, .10, and .08, respectively) were related to better motor performance.

Table 8. Summary of Multiple Correlations of the Significant Multiple Regressions on the Brazelton Scale Cluster Scores

<u>Cluster and Day of Significant Effect</u>	<u>Multiple Correlation</u>
<u>Orientation</u>	
Day 1	.50*
<u>Motor:</u>	
Day 1	.28*
Day 7	.41*
Day 28	.39*
<u>State Range:</u>	
Day 3	.50*
Day 7	.51*
<u>State Regulation</u>	
Day 1	.24*
<u>Autonomic Regulation:</u>	
Day 1	.47*
Day 3	.39*
Day 28	.41*
<u>Reflex:</u>	
Day 1	.32*

Note: The stepwise procedure chose a maximum of 6 predictor variables.

* $p < .05$

** $p < .01$

The regression equations for the autonomic regulation cluster were also significant on days 1, 7 and 28. On day 1, higher scores were predicted by a lower dose of bupivacaine, more oxytocin, longer durations of both stages of labor, a larger maternal weight:height ratio and a lower ponderal index ($\underline{B} = -.11, .06, .25, .30, .17,$ and $-.23,$ respectively). Day 3 results were due to the combination of a higher pH, lower OCS score and a larger maternal weight:height ratio ($\underline{B} = .28, -.12,$ and $.21,$ respectively). At one month, the effects were related to more bupivacaine, less oxytocin, a better OCS score and a larger maternal weight:height ratio ($\underline{B} = .19, -.18, .34,$ and $.09,$ respectively).

Scores on the range of state cluster were significantly predicted by the independent variables on days 3 and 7. On day 3, a higher score on this cluster was related to the combination of a lower dose of bupivacaine, more oxytocin, a shorter stage 1 labor, a better OCS score, a larger maternal weight:height ratio and a higher ponderal index ($\underline{B} = -.007, .25, -.32, .06, .19,$ and $.21,$ respectively). On day 7, the cluster scores were predicted by a larger dose of bupivacaine, a higher pH, less oxytocin, a shorter stage 2 labor, a lower OCS score and a higher ponderal index ($\underline{B} = .28, .10, -.08, -.34, -.23,$ and $.38,$ respectively).

The remaining clusters, orientation, regulation of state and reflexes, were significantly predicted by the

linear combination of drug and obstetric variables only on day 1. Better performance on the orientation cluster was predicted by less bupivacaine, less oxytocin, a longer stage 1 labor, a shorter stage 2 labor, a lower OCS score and a higher ponderal index ($\underline{B} = -.17, -.22, .17, -.31, -.37, \text{ and } .16$, respectively). A higher score on the regulation of state cluster was related only to a lower dose of bupivacaine ($\underline{B} = -.24$). On the reflex cluster, a greater number of abnormal scores was related to the combination of a larger dose of bupivacaine and a longer duration of the administration of oxytocin ($\underline{B} = .21 \text{ and } .16$, respectively).

In sum, the results of the regression equations showed that the linear combination of drug and other obstetric variables best predicted performance on the Brazelton scale on the first day of life, significantly predicting 5 of the 6 clusters. Examining the results over the entire month, performance on the motor and autonomic clusters was most frequently influenced by the additive effects of the independent variables. All of the variables contributed to some of the variation in cluster scores during the first month. The dose of bupivacaine was entered 9 times into the 11 regressions as a predictor of behavior; duration of oxytocin and OCS score were entered 7 times each; maternal weight:height ratio was entered 5 times; neonatal pH and ponderal index were entered 4 times each; and length of the first and second stages of labor were entered 3 times each. The order of entry of the variables into the 11 significant

regression equations indicated that the dose of bupivacaine was the strongest single predictor of behavior being selected as the first predictor 9 times by the stepwise procedure. The duration of the administration of oxytocin was chosen as the second strongest predictor 7 times. The neonatal pH was selected a total of 4 times as a predictor variable, twice as a primary predictor and twice as a secondary predictor. The 5 remaining independent variables were generally picked by the stepwise procedure as the third through the sixth predictors of behavior after the variance accounted for by the drugs and the pH was removed.

The t tests on the individual Beta weights indicated that the contribution of individual variables accounted for a significant portion of the variance a total of 11 different times given the variance accounted for by all of the other variables. The t tests on the Beta weights for the dose of bupivacaine and the OCS scores were each significant 3 times. Two significant effects were found for the length of the second stage of labor and one significant effect for each of length of the first stage of labor, neonatal pH and ponderal index. The t tests on the Beta weights for oxytocin and maternal weight:height ratio were never significant, suggesting that these variables only made a significant contribution to behavior in combination with the other variables.

Comparisons of Epidural and Nonmedicated Groups of Infants

As noted previously, 22 of the 60 infants, or 37% of the sample were from nonmedicated deliveries. Since the ratio of nonmedicated to epidural deliveries was larger than what would be expected by the norms, it was decided to compare the behavioral performance of subjects from the two groups. First, each nonmedicated infant was matched to an infant from the epidural group on the following variables: a high, low or average ponderal index and neonatal pH, and the presence or absence of fetal distress, maternal illness during pregnancy, and induced delivery. Each subject was also matched on the approximate number of maternal, parturitional and fetal nonoptimal conditions as determined by the Obstetric Complication Scale (OCS) score. The matching procedure resulted in 19 pairs of subjects. An attempt to match subjects on the approximate length of the first and second stages of labor failed. The mean length of the first stage of labor was 6.4 hours ($SD=4.7$) in the nonmedicated group and 10 hours ($SD=6.5$) in the epidural group. The second stage of labor averaged .65 hours ($SD=.53$) in the nonmedicated group and 1.11 hours ($SD=.77$) in the epidural group. Because these group differences could not be excluded by matching subjects, the variance was partialled out of the cluster scores before proceeding with group comparisons.

The overall performance of these 38 infants on all seven clusters of the Brazelton scale over the first month

of life with the variance accounted for by the lengths of the two stages of labor removed was compared using multivariate analysis of variance (MANOVA). The MANOVA tested main effects for drug group (epidural vs. no medication), time effects (4 testing days) and group by time interaction. Results indicated an overall significant main effect for drug group only across the seven clusters ($F(6,31) = 9.17, p < .001$). There was no significant time effect or group by time interaction.

MANOVAs were also performed on Brazelton scale scores on each testing day across all clusters to determine on which days there were differences between the groups in overall performances. Significant effects for the drug group were found all four testing days: day 1 ($F(6, 31) = 5.59, p < .001$), day 3 ($F(6, 31) = 6.85, p < .001$), day 7 ($F(6, 31) = 2.76, p < .05$) and day 28 ($F(6, 31) = 2.59, p < .05$).

The multivariate analyses were followed by a set of univariate analyses to determine which behaviors were accounting for the overall differences in performance. The results of the 2 (drug groups) x 4 (testing days) repeated measures of ANOVA performed on the cluster scores across testing days with length of labor covaried are shown in Table 9. A significant main effect for drug group was found on all clusters with the exception of reflexes. Infants in the nonmedicated group performed better than infants in the epidural group on each of the significant clusters (see Appendices 8 and 9).

Table 9. Summary of the Repeated Measures ANOVAs on the Brazelton Cluster Scores Across Days

<u>Cluster</u>	<u>Effect</u>	<u>F</u>	<u>df</u>	<u>p<</u>
Habituation	drug	5.01	1,61	.05
	drugXtime	3.05	3,61	.05
Orientation	drug	11.55	1,136	.002
Motor	drug	11.16	1,150	.003
	time	4.21	3,150	.01
State Range	drug	5.55	1,150	.05
State Regulation	drug	8.03	1,150	.01
Autonomic Regulation	drug	6.83	1,150	.02
Reflex	time	2.92	3,150	.05

The same set of ANOVAs also resulted in a significant main effect for time on both the motor and reflex clusters. Scores on each of these clusters improved with time. A significant effect of the drug group by time interaction was found only on the habituation cluster indicating that the changes over time in habituation scores differed between the nonmedicated and epidural groups.

A set of post hoc analyses was run on the two groups to determine if they differed on variables not used in the matching procedure other than bupivacaine and length of the two stages of labor. Variables which have been previously related in the literature to the use of anesthesia and/or to behavior were chosen. Information was taken from both the medical records and the maternal interviews. As illustrated in Table 10, t tests were performed on the hours of the administration of oxytocin, number of prenatal drugs, mother's age, socioeconomic status (SES) according to the Hollingshead 4 factor index and the average amount of time the mother reported spending with her baby each day in the hospital. A significant difference between the groups was found in the number of hours of administration of oxytocin, with the epidural group having more than the nonmedicated group. Also, the epidural group reported spending significantly less time with their babies while in the hospital than the nonmedicated group. No significant

Table 10. Post hoc t Tests of Mean Group Differences on Perinatal Variables.

<u>Variable</u>	<u>Epidural Group</u>		<u>Nonmedicated Group</u>		<u>t</u>
	<u>Mean</u>	<u>(SD)</u>	<u>Mean</u>	<u>(SD)</u>	
Oxytocin (hours of administration)	3.4	(2.6)	0.5	(1.2)	4.4**
Prenatal medication (no. of drugs)	1.9	(1.2)	1.8	(1.4)	0.12
Parity	1.1	(1.2)	0.9	(0.8)	0.47
Mother's age (yrs.)	30.4	(3.6)	31.5	(3.4)	1.0
SES (Hollingshead 4 factor index)	52.4	(8.0)	58.5	(10.1)	1.7
Time with baby in hospital (hours per day)	9.5	(3.9)	13.6	(4.7)	2.9*

* p < .01

** p < .001

differences were found between the groups in the number of prenatal drugs, parity, mother's age or SES.

Table 11 shows the results of the chi-square analyses performed on the group differences in the frequencies of hypotension, instrumentation at delivery, hyperbilirubinemia and mother's and father's level of education and attendance of childbirth preparation classes. Significant differences were found between the groups in the frequencies of the use of instrumentation. None of the nonmedicated group needed any form of instrumentation at delivery. Eleven of the epidural group needed low forceps, one needed midforceps and one needed rotation. The groups also differed in the level of maternal education. Eleven mothers in the nonmedicated group had a graduate school education compared to only two in the epidural group. Six of the other nonmedicated mothers had completed college compared to ten of the epidural mothers. Only two of the mothers in the nonmedicated group had completed no more than two years of college compared to seven of the mothers in the epidural group. No significant group differences were found in the fathers' level of education, attendance of childbirth preparation classes or in the occurrence of hypotension or hyperbilirubinemia.

Table 11. Post hoc Chi-Square Analyses of Group Differences In Frequencies of Perinatal Variables.

Variable	Epidural Group	Non-medicated Group	Chi-Square
Hypotension			
Present	5	1	3.2
Absent	14	18	
Instrumentation			
None	6	19	19.00**
Low Forceps	11	0	
Mid Forceps	1	0	
Rotation	1	0	
Hyperbilirubinemia			
Present	3	2	.23
Absent	16	17	
Mother's Education (in years)			
12-14	7	2	11.4*
16	10	6	
17+	2	11	
Father's Education (in years)			
12-14	5	3	5.8
16	9	4	
17+	5	12	

*p<.05

**p<.01

DISCUSSION

Cumulative Effects of Bupivacaine and Other Obstetric Variables

This study was designed to investigate the cumulative effects of bupivacaine epidural anesthesia and other obstetric variables on performance on the Brazelton Scale over the first month of life. The sampling procedure differed from previous obstetric medication studies which have selected only "superbaby" samples with the most optimal pre- and perinatal courses in an attempt to exclude variables other than drugs which may affect behavior. In the present study, the only exclusion criteria were congenital anomalies, admission to the intensive care nursery, premature birth and use of maternal pain relieving medication other than bupivacaine epidural anesthesia. Therefore, we were able to investigate the effects of one drug in a more typical sample of babies varying in obstetric histories. Although the sample did have a range of nonoptimal conditions, the few selection criteria limited the study to a clinically healthy sample. Furthermore, the sample ended up including only intact well-educated families from middle and working class backgrounds. All mothers except for one had a full course of prenatal care. An average of only two drugs were reported to have been

consumed by mothers during pregnancy, a number which is considerably lower than previously reported national averages (Hill, 1973; Hill, Craig, Chaney, Tennyson, & McCulley, 1977; Julien, 1978).

The obstetric variables under investigation in this study were distributed normally among the sample but fell into a generally healthy range. Statistics for the ponderal index indicated that the sample was relatively fat, with a mean ratio of 2.72 which approximates the 75th percentile for neonatal body mass according to Miller and Hassanein (1971). One third of the sample had ponderal indices above the 90th percentile. This differed greatly from the thin sample used in the Lester et al. (1982) reanalysis whose mean ponderal index was 2.35 and of whom 25% were below the 10th percentile.

One quarter of the babies in the present sample were acidotic. Seven were severely acidotic. Statistics for the length of the two stages of labor ranged from extremely short to long with the mean approximating the average reported for healthy samples (Lester et al., 1982; Parmalee et al., 1976). Also, the scores on the Obstetric Complication Scale varied greatly but the mean was higher than the standardized mean calculated by Parmalee et al. (1976), further supporting the evidence that, overall, this was a healthy sample of babies.

Most of the mothers who were medicated during labor in this study received low or moderate doses of bupivacaine. A

few received moderately high doses. The finding of generally low fetal:maternal concentration ratios supports previous research findings for bupivacaine (Reynolds et al., 1973; Reynolds & Taylor, 1970; Thomas et al., 1976; Tucker et al., 1970). However, this ratio must be considered only as a very crude estimate of the placental transfer since it tells us little about the amount of bupivacaine which bound to tissue proteins prior to the blood sampling (Goodman & Gilman, 1975). Recently, Abboud et al. (1982) suggested that the lower fetal blood levels of bupivacaine as compared to lidocaine may actually be due to a higher fetal tissue uptake by the myocardium, liver and brain rather than to a reduced transfer of the drug across the placenta.

In order to investigate the cumulative effect of bupivacaine and the other obstetric variables on behavior, the dose of bupivacaine was treated as a continuous variable, from not receiving any to receiving a moderately high dose. Because dose was so highly correlated with the other drug variables, it was the only drug variable retained for the multiple regression analyses. If the number and timing of the administrations had also been included, it would have been impossible to separate the variance accounted for by each. Several investigators have found that the maternal:fetal concentration of bupivacaine is affected by the dose but not by the number or timing of the administrations (Reynolds & Taylor, 1970; Thomas et al.,

1976). The remaining variables which were selected to be included in the regression analyses were chosen because of their potential role in affecting the placental transfer of bupivacaine and/or because they have been previously found to have an additive effect with drugs on behavior.

The results of the multiple regression showed that the preselected predictor variables potentiated the effects of the anesthesia on behavior. The combination of the dose of bupivacaine and the other obstetric variables significantly predicted 9 of the regressions whereas there were only 4 significant individual correlations between dose alone and behavior. Likewise, each obstetric variable was included as a significant predictor more frequently in the multiple correlations than bivariate correlations, indicating that each obstetric variable had a greater effect on behavior in the presence of other nonoptimal conditions than by itself.

The dose of bupivacaine and the total number of hours that oxytocin was administered were the two most important predictors of neonatal behavior in this study. Dose of bupivacaine emerged as the primary predictor and was most frequently followed by oxytocin. Although all of the other variables emerged as predictors for some of the regressions, their emergence in later steps of the procedure indicated that they were less important. The only exception was the neonatal pH which emerged twice as a primary predictor and twice as a secondary predictor.

The directions of the beta weights indicated that a lower dose of bupivacaine was related to better performance on the Brazelton clusters with the exception of range of state on day 7 and autonomic regulation on day 30. A shorter duration of oxytocin was also related to better performance with the exception of autonomic regulation on day 1 and range of state on day 3. As discussed in the introduction to this study, anesthesia has been found to be associated with irritability and oxytocin with drowsiness. The interaction of the two drugs may be such that on these two clusters the two drugs counterbalance the effects of each other. Additionally, some of the effects of these drugs may reverse with time as in the case of analgesics which are related to drowsiness for the first few days after birth and to irritability later on. The results of the regressions suggest that bupivacaine may have been related to irritability in the first few days and to drowsiness or calmness later on whereas oxytocin may have been related to drowsiness on calmness in the first few days and to irritability later on. The results of the regression on the autonomic regulation cluster on day 1 suggest that babies fatigued by oxytocin, long labors and lower ponderal indices have fewer startles, tremors and changes in skin color. Better scores on this cluster have been previously related to a greater number of fetal complications, prematurity, lower birthweight and a lower ponderal index (Eyler, 1979; Sepkoski, Coll, & Lester, 1982; Werner, Bartlett, &

Siqueland, 1982). Fewer physiological responses to stress may be adaptive when the infant is fatigued by long traumatic labors or by nutritional compromise. This was the only cluster in which a lower ponderal index contributed a better score. On the orientation and range of state clusters, higher ponderal indices were related to better scores. Overall, the ponderal index did not make as large of a contribution to the regressions as in the Lester et al. (1982) study. This may have been due to the difference in the nature of the two samples, i.e., the present sample being fat and the Lester et al. sample being thin. The ponderal index may have a greater effect on behavior when nutritional compromise is an issue. Nonetheless, even though there were few skinny babies in the present sample, the ponderal index did make a significant contribution to the regressions.

The duration of the first and second stages of labor contributed in the direction of shorter labor, better scores on the range of state cluster on days 3 and 7. On day 1, however, longer stages of labor contributed to better scores on the autonomic regulation cluster, as previously discussed, and a longer stage 1 labor and shorter stage 2 labor contributed to better scores on the orientation cluster. These results are similar to the findings of Lester et al. (1982) who found, investigating the total length of labor, that shorter labors were related to better range of state scores and longer labors, to better autonomic

regulation scores. Woodson and DaCosta-Woodson (1980) also found that shorter labors were related to less irritability on the Brazelton Scale.

The maternal weight:height variable accounted for some of the variance in the regressions but not a lot, as indicated by its emergence in later steps. With the exception of the autonomic regulation cluster on day 3, this variable only emerged in regressions when bupivacaine and/or oxytocin were also predictors. A larger maternal weight:height ratio was always related to better performance. This supports the hypothesis that a larger body mass may ameliorate the effects of drugs which bind to fatty tissue.

Neonatal pH did not emerge as a predictor of behavior on day 1. A higher pH was related to better performance on the autonomic regulation cluster on day 3, on the state range cluster on day 7 and on the motor cluster on day 30. However, a lower pH was related to better motor performances on day 7. These results lend little support to the hypothesis that a low pH would potentiate the effects of bupivacaine on behavior due to the ionic trapping of the drug in the acidotic fetus. It is possible that maternal blood pressure or the occurrence of hypotension during labor would have been a better predictor variable. The fetal pH may have been corrected by the time of the blood sampling. Hypotension may occur during labor and cause fetal acidosis and pooling of the local anesthetic. However, it is usually

corrected by changing the maternal position to tilt the uterus laterally in order to increase blood flow. If this does not alleviate the symptom, ephedrine is administered (Ostheimer, 1981). Therefore, the pH at delivery may not be representative of the occurrence of hypotension and increased placental drug transfer during labor.

The Obstetric Complications Scale (OCS) did not work well as a predictor of behavior when added to the other independent variables. Sometimes a lower score was related to better behavioral performance and sometimes a higher score was related to better behavioral performance. As an individual variable in the bivariate correlations, it was never correlated with behavior. The OCS may not be the best summary of nonoptimal conditions to use, especially in a healthy sample. Both Littman (1979) and Sigman and Parmalee (1979) found that the OCS did not predict to later performance on the Bayley Scales in a sample of low or high risk infants. They suggested that a self-weighting scale may not be as useful for identifying infants at risk for behavioral problems as a scale which weights individual complications according to their association with risk.

Overall, the linear combination of the predictor variables had a significant effect on more behavioral clusters on day 1 than on any other day of testing. Since babies were tested approximately three hours after delivery and most of the predictor variables reflected conditions of the delivery process itself, the predictability of day 1 performance over the other days was not surprising.

Examining the findings over the entire month, the motor and autonomic regulation clusters were predicted more frequently by the independent variables than the other four clusters. As discussed in the review of the literature, studies have found effects of obstetric medication most often on motoric behaviors. It has been postulated that the effects may be due to the direct action of local anesthetics on neuromuscular transmission and function (Bianchi & Bolton, 1967; Usubiaga & Standaert, 1968). Behaviors related to autonomic regulation have been studied less frequently. Lester et al. (1982) found that the motor, autonomic regulation and habituation clusters were most sensitive to the combination of drug and obstetric variables. Sepkoski, Coll and Lester (1982) also found that obstetric risk variables accounted for more of the variance in these three clusters over the first few days of life than in the remaining four clusters. Unfortunately, the habituation cluster could not be included in the present regression analyses because of the quantity of missing data.

To summarize, the results of the multiple regressions in the present study indicated that bupivacaine, oxytocin, the ponderal index, maternal weight:height ratio, neonatal pH, length of the two stages of labor and the OCS score had a cumulative effect on behavior. The effects of bupivacaine were potentiated by the other obstetric variables. Although a significant portion of the variance was accounted for by

these predictors in a healthy sample of infants, the results may have been even stronger if a population of infants more at risk for developmental problems had been sampled. However, the present findings are limited by the absence of replication of the multiple regression analyses. The variables which were chosen by the stepwise procedure were selected on a post hoc basis to maximize the amount of variance accounted for in the behavioral clusters. Therefore, the information obtained may not generalize to other healthy or high risk samples. Additionally, the nature of the design limits the interpretations to the associations between variables. In other words, we cannot make statements concerning the cause and effect of the findings or concerning the changes in development over time on the basis of the results of this one set of multiple regression analyses.

Comparisons of Bupivacaine Epidural and Nonmedicated Groups

This study was designed to investigate the behavioral effects of a continuum of bupivacaine, from none to large doses. However, more than one third of the sample received no medication for pain relief. The ratio of nonmedicated to epidural deliveries was probably much higher than indicated by hospital statistics because of the exclusion of premedication from the sample selection criteria. Scanlon and Sostek (1979) have noted that the clinical norm in this country is to use several different agents during labor and delivery. Although the incidence of the use of

premedication is not recorded in the records of hospital statistics, it has been suggested that 50% of the women receiving epidural anesthesia at the BLI/BW Hospital receive either a narcotic or a narcotic-tranquilizer combination in labor (G. W. Ostheimer, anesthesiologist, personal communication, 1982). This would reduce the incidence of pure epidural deliveries to 22.5% of all vaginal deliveries and explain the high ratio of nonmedicated to epidural deliveries found in the present study. Because the groups were large enough to compare, we matched subjects on obstetric variables and investigated group differences in behavior. The variance accounted for by the length of both stages of labor was first eliminated from the behavioral scores since we could not match subjects on these variables.

The multivariate analysis of variance on all Brazelton clusters over the first month of life indicated that the two drug groups differed behaviorally but that there was not a consistent change in scores over time and that changes in scores over time did not differ significantly by drug group. However, the analyses across clusters by day indicated that the drug groups differed behaviorally on all testing days.

The univariate analyses of variance (ANOVA) with repeated measures indicated that the drug groups differed significantly on six of the seven clusters: habituation, orientation, motor, state range, state regulation and autonomic regulation. Investigation of individual cluster scores showed that the nonmedicated group did consistently

better than the epidural group. Performance between groups did not differ significantly on the reflex cluster.

The ANOVAs with repeated measures showed a main effect for time only on the motor cluster only. Both groups improved significantly over the first month. The drug group by time interaction for the habituation cluster indicated that the two groups differed in the changes in their scores over time. The performance of the nonmedicated group improved continuously while the performance of the epidural group decreased on day 3, improved on day 7 and decreased again on day 30.

In summary, these comparisons illustrated that the nonmedicated group of infants performed more optimally on the Brazelton Scale over the first month of life than the epidural group of infants. The results of the group comparisons were more consistently significant than the multiple regressions. This may have been due to differences in the nature of the subsample used for the group comparisons and the complete sample used for the multiple regressions. Additionally, the dose of bupivacaine was ignored in the group comparisons. It is possible that the effect of bupivacaine on some behaviors is not dose-related but depends instead on the presence or absence of the drug and the conditions which are related to its administration.

Comparison with Other Bupivacaine Epidural Studies

All of the studies investigating the behavioral effects of epidural anesthesia with bupivacaine have used samples selected for optimal conditions of labor and delivery. By controlling for variables such as Apgar scores or the use of forceps during delivery, they may have reduced variance in scores associated with the use of anesthesia. Even in the present study, by excluding babies who were sent to the intensive care nursery, we may have omitted subjects with complications caused by the nonoptimal variables during labor that may have been related to the epidural.

Most studies have compared the effects of bupivacaine to other medication. No differences have been found in performance on the Scanlon exam between babies exposed to bupivacaine and those exposed to lidocaine or chloroprocaine (Abboud et al., 1982) or to morphine (Writer et al., 1981). However, as previously mentioned, Scanlon et al. (1976) found that bupivacaine infants did better than lidocaine or mepivacaine infants. Wiener et al. (1979) related exposure to bupivacaine to more depressed muscle tone on the first day of life than exposure to meperidine.

The few studies which have compared a bupivacaine group to a nonmedicated control group are more comparable to the present study. Corke (1977) found no differences in Scanlon performance in the first 4 hours of life. However, the mean total dose of bupivacaine in his study was lower than in the present study. Murray et al. (1981) also investigated the

effects of lower doses of bupivacaine but they found that bupivacaine babies performed worse than a control group on several a priori Brazelton dimensions on the first day of life. Scores on motor performance, state control, physiological response to stress and on overall Brazelton performance were deficient in the bupivacaine group. Use of oxytocin further depressed scores on the motor dimension. On day 5, the bupivacaine group still performed worse on state control and on the total Brazelton score. Although no differences were found by the authors in Brazelton performance at one month, mothers in the bupivacaine group reported that their infants had poorer interactive ability (including items from habituation and orientation clusters), state control and overall performance than infants in the control group. Bivariate correlations were performed between dose, number of administrations, umbilical venous concentration of bupivacaine and the dependent measures. Out of a possible 84 correlations, there were only 9 significant low correlations with behavior. The authors concluded that the amount of medication was not related to the poorer performance of the epidural babies. However, if the dose had been investigated with the other variables that may potentiate its effect as in the present study, they may have found a significant relationship between the amount of bupivacaine and performance on the Brazelton Scale. The fewer differences found in the Murray et al. study than in the present one may be due to the lower doses of bupivacaine

investigated in the former study and/or to its use of a control group which had been lightly medicated.

The findings of Rosenblatt et al. (1981) can be most closely related to the present study. Similar doses of bupivacaine were investigated and the cluster scoring system for the Brazelton Scale developed by Lester et al. (1982) was used. Rosenblatt et al. found that greater drug exposure was related to poorer Brazelton performance on items from the orientation, motor, state range, state regulation and autonomic regulation cluster over the first six weeks of life. The authors did not report whether or not the habituation and reflex clusters were included in the analyses.

Conclusions

In the present study, the use of bupivacaine epidural anesthesia, as a predictor variable in the regressions and as the main variable differentiating groups in the comparisons, was related to poorer behavioral outcome for the baby over the first month of life. Although we were unable to obtain blood or urine samples after delivery, we can deduce from the work of Belfrage et al. (1975) that the drug and its metabolites were still circulating and active in the baby during the first Brazelton exam and, possibly, during the second. The half-life of bupivacaine is estimated to be only 8 hours but 5 to 7 half-lives are needed to totally eliminate it from the body. Thus, the results of the first two exams may have been due to the

direct action of the local anesthetic on the neonatal CNS. However, this cannot be concluded from the present study for the following reasons: (1) the results may be due to the indirect effects of bupivacaine on the delivery process, neonate and mother-infant interaction, and (2) because ethics preclude random assignment of women to drug groups, findings may be attributable to differences between women delivering with anesthesia and those delivering naturally.

Several complications of labor and delivery have been associated with the use of obstetric medication. Local anesthetics have been found to interfere with motor functioning, inhibit uterine contractibility, remove the mother's reflexive urge to bear down and, thereby, to increase the first and second stages of labor (Berges, 1971). McDonald, Bjorkman and Reed (1974), Schifrin (1972) and Wingate (1974) have reported increased incidences of late decelerations of fetal heart rate with even low doses of local anesthetics. Increases in the use of forceps have also been found (Hoult, 1977). Ralston and Shnider (1978) have associated the use of local anesthetics with maternal hypotension, decreased uterine blood flow and fetal acidosis and asphyxia. The product information insert included with Marcaine, the brand of bupivacaine used in the present study, warns physicians of all of these possible side effects. Thus, the associations between bupivacaine and a poorer behavioral outcome in the present study may have been due to the side effects or indirect effects of bupivacaine which would have placed additional stress on the fetus.

Post hoc comparisons were performed on the epidural and nonmedicated groups to see if they differed on variables which may be attributable to the use of bupivacaine and/or to the behavioral outcome for the baby. Potential differences in the groups due to the incidence of fetal distress and acidosis and to the number of parturitional and fetal complications had already been eliminated by the matching procedure. The groups could not be matched on the first and second stages of labor; the epidural group had significantly longer labors. Therefore, the variance due to the two stages of labor was removed from the Brazelton scores. Post hoc analyses were performed to see if there were other differences between the groups which may have accounted for some of the behavioral differences. The groups differed significantly in the number of hours of the administration of oxytocin and in the incidence of instrumental deliveries. The epidural group needed more oxytocin than the nonmedicated group and 70% of the epidural group were delivered by forceps whereas none of the nonmedicated group were. Murray et al. (1981) found similar differences between groups in the incidence of instrumental deliveries and in the length of labor. Additionally, they found that an increase in both of these variables were related to poorer Brazelton scores but that behavioral differences remained between the bupivacaine and control groups even after the variance due to the use of forceps and length of labor were removed.

Obstetric medication may also have an indirect effect on the baby by altering the development of the mother-infant relationship. Behavioral differences between medicated and nonmedicated babies which remain after the first few days of life may be related to differences in mother-infant interactions. Murray et al. (1981) have suggested that the very early critical period for bonding or beginning attachment as described by Klaus and Kennell (1976) may be, instead, a sensitive period for the mother to learn about her baby. Brazelton (1971) has hypothesized that the early encounters a mother has with a newborn whose behavior has been disorganized by a medicated and stressful delivery may create a lasting impression on the mother. This perception of the baby may affect the development of their future relationship. Nisbett and Ross (1980) have found that the first impressions people have of others are very resistant to change. Studies have related decreased reciprocal behaviors between mothers and infants over the first month of life to the use of bupivacaine epidural anesthesia during parturition (Lieberman et al., 1979; Murray et al., 1981). The post hoc analyses between the epidural and nonmedicated groups in the present study resulted in a significant difference in the amount of time mothers in each group reported spending with their infants while in the hospital. The decrease in the amount of time spent together in the epidural group may have been due to difficulties the mothers

had with their medicated babies, to fatigue from difficult labors and deliveries and/or to differences in maternal personality variables. Nonetheless, there is a substantial amount of literature which suggests that this very early period in a baby's life is important to the development of an optimal relationship between the mother and child (Ainsworth, 1973; Bowlby, 1969; de Chateau, 1976; Hales, Lozoff, Sosa, & Kennell, 1977; Klaus, Jerauld, Kreger, McAlpine, Steffa, & Kennell, 1972; Klaus & Kennell, 1976; Ringler, Trausse, Klaus, & Kennell, 1978).

Other variables which may affect neonatal behavior and which may differ between women choosing natural versus medicated deliveries are personality factors. The inclusion of precipitous deliveries in the sample should have reduced personality differences related to the choice of medication. Also, the large number of mothers who made the decision during labor to have an epidural may have been influenced more by the course of their labors than by personality variables. However, the post hoc comparisons indicated that although mothers in both groups were well-educated, mothers in the nonmedicated group were significantly better educated than mothers in the epidural group. No differences were found, though, in their knowledge of parturition as indicated by parity or by attendance in childbirth preparation classes. Brown, Manning and Grodin (1972) followed a sample of primigravidas throughout pregnancy and delivery and the only relationship they found between drug

intake and maternal behavior was that women who did not receive meperidine during labor were, in general, better adapted during pregnancy than those who did. They found no relationship between the amount or variety of drugs administered (meperidine, barbiturates, oxytocin and/or epidurals) and anxiety during labor or reaction to pain. There was also no relationship between the administration of drugs and the time of admission to the hospital, the duration of labor, the type of anesthesia or the standard practice of the obstetrician.

The multiple regressions illustrated that the behavioral effects found in this study were probably caused by the additive effects of many variables, among them, bupivacaine, the complications associated with it and other nonoptimal obstetric conditions. Although this was a healthy sample of babies who performed within a normal range of behavior, the findings supported the hypothesis of Parmalee et al. (1976) that risk does not occur as a single isolated event but only in the presence of several events. The presence of one nonoptimal variable may cause others and the cumulative effects of these variables is what leads to risk. Thus, a low dose of bupivacaine by itself may not harm the baby but when oxytocin, a difficult delivery, and acidosis are present, bupivacaine may have an additive harmful effect. To take this one step further, a continuum of risk may be started by the nonoptimal perinatal conditions which affect neonatal behavior and, thereby,

alter the early mother-infant relationship which in turn, influences later behavioral development (Sameroff & Chandler, 1975). On the other hand, the cycle of risk may be halted and the behavioral outcome ameliorated by an optimally healthy and supportive environment for the baby as well as for the rest of the family.

Implications

One implication of this study is that the use of epidural anesthesia with bupivacaine during labor and delivery should be judicious utilizing as small of a dosage as possible. In this paper, we have discussed the possible effects of anesthesia on the baby. The administration of obstetric anesthesia also carries risks for the mother. Bush and Norman (1977) reported that more than 10% of the maternal deaths during childbirth in England were due to the effects of different types of anesthesia. Obstetricians and anesthesiologists should thoroughly discuss the effects of anesthesia and its possible risks with the mother prior to labor. Women should be fully educated about events taking place during parturition in order to reduce anxiety associated with it. MacFarlane (1977) has noted that the event of childbirth can be enhanced when women are encouraged to feel competent at it and confident in themselves and their bodies. A need exists for more research into different methods of psychoprophylaxis for the relief of pain during labor so that, perhaps, nonmedicated deliveries could replace anesthetized deliveries as the

normal medical routine practice. However, there are some cases in which the use of anesthesia during childbirth may be necessary. Excessive pain and anxiety during labor can cause hyperventilation. This can lead to maternal respiratory alkalosis which reduces the free oxygen available for diffusion to the fetus and results in fetal asphyxia and acidosis (Ahokas & Dilts, 1976). By reducing pain and anxiety, anesthesia reduces the occurrence of hyperventilation. However, the ensuing hypotension associated with local anesthetics also carries the risk of fetal acidosis; therefore, care should be taken to closely monitor the blood pressure of the mother when drugs are administered. Other complications which may require the use of anesthesia during parturition are cardiac disease and other diseases which contraindicate physical exercise (Ostheimer, 1980).

Another implication of the study is that when anesthesia is desired, all variables surrounding the delivery process which may exaggerate the effects of the medication on the newborn should be taken into consideration. The half-lives of local anesthetics have been found to be extended in acidotic (Datta et al., 1981), malnourished (Morishima et al., 1974) and premature neonates (Kuhnert, Kuhnert, Philipson, & Rosen, 1982). Furthermore, it takes longer for infants who are in nonoptimal physical condition to eliminate drugs from their systems. The present study illustrated that the behavioral effects of

bupivacaine were potentiated in the presence of nonoptimal obstetric variables in a sample of healthy babies whose behavior fell within a normal range. The depression of behavior within a normal range by obstetric anesthesia may have a minimal effect on a healthy baby, but it may "tip the balance" for a high risk baby. Future research should investigate the behavioral effects of parturitional medicine in a population of infants at greater risk than those in the present sample. Specifically, to further test the hypothesis of this study, the effects of bupivacaine in a sample with a greater degree of acidosis, lower ponderal indices, thinner mothers and more obstetric complications needs to be examined. The cumulative effects of other types of drugs and perinatal conditions should also be investigated.

As long as the drug industry continues to be a billion dollar business, the market for obstetric medication will remain. Therefore, it is important that research into the development of new drugs that are the most beneficial and the least harmful to the mother and baby continue. Since behavior may be the most sensitive indicator of teratogenic effects, it is imperative that the behavioral effects of all medications used during labor and delivery be thoroughly investigated. Further research into special needs that the mother and baby of medicated deliveries may have should also be done. When anesthesia is used during childbirth, the mother may need additional instruction about the nature of

her baby's early disorganized behavior as well as additional support to deal with difficulties she may encounter. The behavior of infants in the present study may actually have been enhanced by the interventive nature of the research, i.e., that women were taught about their infant's behavior and received support from the examiners. Brazelton (1981) has noted that studying infants in front of their parents automatically changes the study to an intervention study. Several investigators have found that the demonstration of the Brazelton Scale to mothers as an intervention technique has improved mother-infant interactions and the developmental outcome for the baby (Anderson, 1981; Eyler, 1979; Olsen et al., 1981; Widmayer & Field, 1980; Worobey & Belsky, 1982). Mothers in the present study would frequently use the opportunity of the home visits to discuss their concerns about their babies with the examiners, especially regarding techniques used to arouse or to calm their babies that they observed during the administrations of the Brazelton exams. The supportive nature of this work may have accounted for the zero attrition rate in the sample over the entire month of following the infants' development.

This study was the first to use the Brazelton Scale in the first six hours of life. The results suggest that it is a useful tool to assess the effects of perinatal factors at this very early age. However, our clinical impressions indicated that 3 to 6 hour old neonates were more fragile than older infants; therefore, the examiner had to be

extremely sensitive to the physical condition of the newborn and to any signs of stress. It took more care to be able to bring out the baby's best performance at this age than at later ages. Few investigations have also examined infants as late as one month of age using the Brazelton Scale. This study also illustrated the sensitivity of the exam to obstetric factors at this late age. Since the Brazelton Scale was designed to measure neonatal behavior, it should not be used beyond one month of age (Als, Tronick, Lester, & Brazelton, 1979). However, especially in light of our findings relating behavioral differences as late as one month to the use of obstetric bupivacaine, further research needs to be done to investigate the duration of the effects. Additionally, the infant-caregiver relationships should be more closely monitored to determine other potential correlates of behavioral differences which may continue beyond the neonatal period.

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APPENDIX 1

SUMMARY OF OBSTETRICIANS WHOSE PATIENTS WERE RECRUITED

Decision Regarding Medication

Obste- trician	Number of Deliveries		When it was made		By whom it was made		
	Epi- dural	Non- med.	Before Labor	During Labor	Mom	MD	Both
A	1		1		1		
B	1			1		1	
C	2	1	2	1	2		1
D		1	1		1		
E	1	2	3		2		1
F	2	1	2	1	2	1	
G	1	8	5	4	4		5
H	1		1		1		
I		1		1			1
J	5	1	3	3	4	2	
K	1			1	1		
L		1	1				1
M	1			1			1
N	3		3		3		
O	2	1	1	2	1	1	1
P	1	1	1	1	1		1
Q	5		5		3		2
R	6	1	4	3	5		2
S		2		2	2		
T	1	1	2		2		
U	1		1		1		
V	3			3			3

APPENDIX 2

PARENTAL CONSENT FORM
CONSENT TO PARTICIPATE IN BEHAVIORAL STUDY OF THE NEWBORN

Participant's Name: _____ Date: _____

Chart Number: _____ Protocol Pt. Number _____

DESCRIPTION AND EXPLANATION OF PROCEDURE

We are conducting a study of the behavioral development of full-term infants born by vaginal delivery. There is not enough information available as to the effects of the length of labor, various medications used during labor and delivery, maternal blood pressure, and acid content of baby's blood as measured from the umbilical cord, on the baby's future growth and development. During the first thirty days of life, the newborn undergoes many physical and behavioral changes. By observing all the events surrounding labor and delivery and by recording any medications given to you during this time, we hope to be able to evaluate the effects of these factors on your baby. We would like to examine and observe your baby using the Brazelton Neonatal Behavioral Assessment Scale on the first and third day of life in the hospital and on the seventh and thirtieth days of life in your home. The scale will be used in the study to assess both the individual capacities of the infants and the differences among babies and to see whether or not these might be related to the events during labor and delivery. The scale tests a variety of reflexes, such as the hand grasp and walking reflex, as well as more interactive behaviors such as your baby's ability to turn his or her eyes and head to follow the examiner's face and voice, and a ball and rattle. It also examines individual characteristics such as general muscle tone and how your baby sleeps and wakes up. No special equipment is needed for the administration of the exam. As part of our evaluation, we would like to take a small blood sample from your arm and from the umbilical cord at the time of delivery. Also, we would like to interview you during the study period to ask you questions about your pregnancy and delivery and about your baby.

- I. I hereby authorize Carol Sepkoski and her associates
- A. to examine my baby using the Brazelton Neonatal Behavioral Assessment Scale when my baby is 1, 3, 7 and 30 days of age.
 - B. to take a blood sample from a small vein in my arm at the time of delivery

- C. to take a blood sample from the umbilical cord at delivery
 - D. to interview me about my pregnancy and delivery and about my perceptions of my baby. All interviews are private and confidential.
- II. I understand that participation in the study will in no way affect my baby's or my routine hospital care.
- III. Risks and Discomfort
- A. The examination of my baby is unobtrusive and will not in any way harm my baby.
 - B. The amount of blood drawn is not significant to my health. Some discomfort and bruising may result at the needle site.
 - C. My baby will not be attached to its umbilical cord when the blood is drawn from it; therefore, this involves no discomfort.
- IV. Potential Benefits
- A. The immediate benefits of my participation in this study may include an opportunity for me to learn more about my baby's individual characteristics and development.
 - B. If I have concerns about my baby's behavior, with my permission and in consultation with my pediatrician, you may help me find appropriate resources at Children's Hospital or in my community.
 - C. Detection of unsuspected abnormalities in the acid content of my baby's blood as measured from the umbilical cord may require treatment or closer observation.
 - D. Long-range benefits of this research include learning more about early behavioral development which could benefit my baby as well as all children in the future.
- V. I understand that I may terminate my participation in the study at any time.
- VI. The nature and purpose of the above-described procedure with its possible risks and benefits have been

described to me by _____.

Parent's signature:

Investigator's signature:

Witness (not part of the investigating team):

APPENDIX 3

BRAZELTON NEONATAL BEHAVIORAL ASSESSMENT SCALE ITEMS*

I. Reflexes

1. Plantar grasp
2. Hand grasp
3. Ankle clonus
4. Babinski
5. Standing
6. Automatic walking
7. Placing
8. Incurvation
9. Crawling
10. Glabella
11. Tonic deviation of head and eyes
12. Nystagmus
13. Tonic neck reflex
14. Moro
15. Rooting
16. Sucking
17. Passive Movements
 - Arms
 - Legs

II. Behavioral Items

1. Response decrement to light
2. Response decrement to rattle
3. Response decrement to bell
4. Response decrement to pinprick
5. Orientation inanimate visual
6. Orientation inanimate auditory
7. Orientation animate visual
8. Orientation animate auditory
9. Orientation animate visual and auditory
10. Alertness
11. General tonus
12. Motor maturity
13. Pull-to-sit
14. Cuddliness
15. Defensive movements
16. Consolability
17. Peak of excitement
18. Rapidity of buildup
19. Irritability
20. Activity
21. Tremulousness
22. Startle
23. Lability of skin color
24. Lability of states
25. Self-quieting activity
26. Hand-mouth facility

*From Brazelton, T.B. Neonatal Behavioral Assessment Scale. Clinics in developmental medicine, No. 50. London: Heinman, 1973.

APPENDIX 4

CATEGORIZATION SYSTEM FOR SIX STATES ASSESSED DURING THE BRAZELTON EXAM*

Sleep States

- (1) Deep sleep with regular breathing, eyes closed, no spontaneous activity except startles or jerky movements at quite regular intervals; external stimuli produce startles with some delay; suppression of startles is rapid, and state changes are less likely than from other states. No eye movements.
- (2) Light sleep with eyes closed; rapid eye movements can be observed under closed lids; low activity level, with random movements and startles or startle equivalents; movements are likely to be smoother and more monitored than in state 1; responds to internal and external stimuli with startle equivalents, often with a resulting change of state. Respirations are irregular, sucking movements occur off and on.

Awake States

- (3) Drowsy or semi-dozing; eyes may be open or closed, eyelids fluttering; activity level variable, with interspersed, mild startles from time to time; reactive to sensory stimuli, but response often delayed; state change after stimulation frequently noted. Movements are usually smooth.
- (4) Alert, with bright look; seems to focus attention on source of stimulation, such as an object to be sucked, or a visual or auditory stimulus; impinging stimuli may break through, but with some delay in response. Motor activity is at a minimum.
- (5) Eyes open, considerable motor activity, with thrusting movements of the extremities, and even a few spontaneous startles; reactive to external stimulation with increase in startles or motor activity, but discrete reactions to difficult to distinguish because of general high activity level.
- (6) Crying; characterized by intense crying which is difficult to break through with stimulation.

*From Brazelton, T.B. Neonatal Behavioral Assessment Scale. Clinics in developmental medicine, No. 50. London: Heinman, 1973. Brazelton's categorization system was adapted from Prechtl and Beintema (1964).

APPENDIX 5

BRAZELTON NEONATAL BEHAVIORAL ASSESSMENT SCALE
SEVEN CLUSTER CRITERIA*

Criteria for Seven Cluster Scoring			
Cluster	Brazelton Scale Item	Raw Score	Recode
Habituation	Light	1-9	— —
	Rattle	1-9	— —
	Bell	1-9	— —
	Pinprick	1-9	— —
Orientation	Inanimate visual	1-9	— —
	Inanimate auditory	1-9	— —
	Animate visual	1-9	— —
	Animate auditory	1-9	— —
	Visual and auditory	1-9	— —
	Alertness	1-9	— —
Motor Performance	Tonus	1-9	9/1=1;8/2=2;7/3=3;4=4;5=5;6=6
	Maturity	1-9	— —
	Pull-to-Sit	1-9	— —
	Defense	1-9	— —
	Activity	1-9	9/1=1;8/2=2;7/3=3;4/6=4;5=5
Range of State	Peak of Excitement	1-9	9/1=1;8/2=2;4/3=3;7/5=4;6=5
	Rapidity of Buildup	1-9	9/1=1;8/2=2;7/3=3;4=4;5=5;6=6
	Irritability	1-9	9/1=1;8/2=2;7=3;6=4;5=5;2,3,4=6
	Liability of State	1-9	1,7,8,9=1;5,6=2;4=3;3=4;2=5
Regulation of State	Cuddliness	1-9	— —
	Consolability	1-9	— —
	Self-quieting	1-9	— —
	Hand-to-Mouth	1-9	— —
Autonomic Regulation	Tremors	1-9	Invert: 9=1 (1=9); 8=2 (2=8); etc.
	Startles	1-9	if 1, drop; otherwise invert 2=9
	Skin	1-9	on 8-point scale 9,1=1;8=2;7=3;6=4;5=5;4=6;2=7
Reflexes	An abnormal score is defined as 0, 1, or 3 for all reflexes except clonus, nystagmus, or TNR where 0, 1, and 2 are normal and 3 is abnormal. Reflex score=total number of abnormal reflex scores.		

*From Lester, B.M., Als, H., & Brazelton, T.B. Regional obstetric anesthesia and newborn behavior: A reanalysis toward synergistic effects. Child Development, 1982, 53, 687-692.

APPENDIX 6
MATERNAL INTERVIEW

Maternal Interview

One-Month Interview*

Mother's Name: _____ Date: _____ Inter.: _____

Because we are studying differences as well as commonalities among babies, we would like to ask you for some information about you, the baby's father, and your pregnancy and delivery. If there are any questions you can not or would rather not answer, just tell me to skip over them . . .

1. What is your occupation?
2. Your partner's?
3. When did you stop work?
4. When do you plan to return to work?
5. Was your partner given time off from work at and/or around the time of delivery?
6. What level of education have you completed?
7. Your partner?
8. If married, how many years have you been married?
9. Besides you, (your partner), and your baby, are there any other people --adults or children--living in your house?

If yes, relationship to baby: _____ Age? _____ Sex? _____

Now I would like to ask you some questions about you and your pregnancy . . .

10. How tall are you?
11. How much did you weigh when you became pregnant?
12. How much did you weigh at delivery?
13. Have you ever received treatment for infertility or difficulty getting pregnant?

If yes, how long were you treated and type of treatment?

*Adapted in part from interviews by Kathryn Barnard and Paul Doering.

14. Have you had other pregnancies besides this one?
 In what year(s)? _____
15. Did you plan to have this baby? _____
16. When did you think the due date was? _____
17. During what month did you first see a doctor about this pregnancy? _____
18. How many visits did you make to the clinic or doctor about this pregnancy? _____
19. Did you have any illnesses or complications during this pregnancy?
 If _____ yes, _____ please _____ explain _____

20. How many prenatal class sessions did you attend during this pregnancy? _____
21. Were the classes helpful? _____

The following questions concern medication, vitamins, and "social" drugs (e.g., alcohol and smoking) that you may have taken during your pregnancy. I will run through a list of reasons for taking drugs. If you remember the names of the drugs, please tell me. If not, just tell me that you took something for the problem. Also, if you remember the number of different occasions on which you had to take the medication and in what month of pregnancy, that would be helpful . . .

Have you taken medication for:

23. Cold or cough (Contac, Dristan, nose sprays) _____
24. Stomach (Rolaids, Tums, Maalox) _____
25. Nausea and/or vomiting (Dramamine, Peptobismol) _____
26. Constipation (Ex-lax, Feen-a-mint, Milk of Magnesia) _____
27. Diarrhea (Kaopectate, Peptobismol) _____
28. Pain - Headache (Aspirin, Bufferin) _____
 Arthritis _____
 Other _____
29. Eye (Murine) _____
30. Ear (Sweet oil, alcohol) _____
31. Nose (Neo-Dynephrine) _____
32. Weight control - gain or loss (artificial sweeteners, Ayds) _____
-
33. Nerves (Miles Nervine, Cope) _____
34. Vitamins or iron tablets (One-a-Day, Geritol, standard prenatal vitamins) _____
35. What birth control method were you using when you became pregnant? _____
36. Anything to bring on your period when you discovered you were pregnant? _____
37. Asthma or allergy (Allerest, Contac) _____

38. Injections (Insulin, vitamin B-12, liver) _____
 39. Heart medications - high blood pressure _____
 40. Swelling or fluid _____
 41. Antibiotics (for infection), systemic or topical _____
 42. Fever _____
 43. Home remedies _____
 44. Fertility drugs _____
 45. Anticonvulsants _____
 46. Sleep or stay-awake (Nytol, Sleepeze, No-Doz) _____
 47. Coffee (cups per day) _____
 48. Tea (cups per day) _____
 49. Coke (per day) _____
 50. Cigarettes (packs per day) _____
 51. Beer (per week) _____
 52. Wine (per week) _____
 53. Whiskey, gin, etc (per week) _____
 54. Marijuana _____
 55. Other "social" drugs (LSD, speed, depressants, etc.) _____

56. Any drugs I may have missed? _____
 Now

I would like to ask you about your experience in labor and delivery . . .

57. At what time did you begin labor? _____
 58. What time did you arrive at the hospital? _____
 59. When did your membranes rupture? _____
 60. Was this spontaneous or ruptured by the doctor? _____
 61. For how long did you push before delivery? _____
 62. Was your labor and delivery experience satisfactory?

63. Were you satisfied with the hospital experience? _____

64. Did you receive pain relievers or other medication while in labor?

If so, what kind? _____

65. Did you decide on this, your doctor, or both? _____

66. Did you discuss medication before labor? _____

When was the decision to have the _____ made? _____

67. Did the medication help? _____

68. Was your partner and/or a support person with you during labor and delivery? _____

69. Was this helpful? _____

70. How would you want your delivery to be different next time?

Finally, I would like to ask just a few general questions

about your baby . . .

71. When after delivery did you first get to spend time with your baby? _____

72. Did your baby have any complications while in the hospital? _____

If under bilirubin lights, for how long? _____

73. Approximately how much time did you get to spend with your baby while in the hospital? _____

74. How much does your baby weigh now? _____

75. How tall is he/she? _____

76. Has your baby had any illnesses? _____

77. If yes, how did he/she react (fussing, crying, sleeping more or less than usual, change in feeding, etc.) _____

78. Have you had occasion to take him/her to the doctor? _____

79. To the hospital? _____

80. Lastly, is there anything specific that you learned from watching the Brazelton exams or from being in this study? _____

APPENDIX 7

OBSTETRIC COMPLICATION SCALE*

<u>ITEM</u>	<u>Response</u>
1. Gestational Age	> 37 Weeks
2. Birth weight	2500 grams
3. Marital Status	Married
4. Maternal Age	18-30
5. Previous Abortions	2 or less
6. Previous Premature Births	No
7. Previous Stillbirths	No
8. Prolonged Unwanted Sterility	No
9. Length of Time Since Last Pregnancy	>12 mos.
10. Parity	1 to 6
11. Pelvis	No Disproportion
12. Rh Antagonism or Other Blood Group Incompatibility	No
13. Bleeding During Pregnancy	No
14. Infections or Other Acute Medical Problems During Pregnancy	No
15. Drugs Given to Mother During Pregnancy	No
16. Maternal Chronic Diseases	No
17. Chronic Drug Abuse	No
18. Blood Pressure During Pregnancy	<140/90
19. Albuminuria	No
20. Hyperemesis	No
21. Hemoglobin Level at End of Pregnancy	10 or more
22. Twins or Multiple Birth	No
23. Membranes Ruptured Prior to Delivery	0-12 hours
24. Delivery	Spontaneous
25. Forceps	None or Elective, Low Forceps
26. Duration, First Stage	3-20 hours
27. Duration, Second Stage	10-120 mins.
28. Induced Labor	No
29. Drugs During Labor and Delivery	No
30. Amniotic Fluid	Clear
31. Fetal Presentation - Delivery	Vertex
32. Fetal Heart Rate During Labor	100-160/Min.
33. Nuchal or Knotted Cord	No
34. Cord Prolapse	No
35. Placental Infarction	No
36. Placenta Previa or Abruptio	No
37. Onset of Stable Respiration Within 6 minutes	Yes
38. Resuscitation Required	No
39. Prenatal Care During First Half of	

	Pregnancy	Yes
40.	Apgar Score - One minute	7-10
41.	Apgar Score - Five minutes	7-10

- a. Total (Raw Score) _____
- b. Number of Items recorded _____
- c. % Raw Score (a/b) _____
- d. Converted % Raw Score _____

*From Parmalee, Kopp and Sigman (1976) and Precht1 (1968).

APPENDIX 8

MEAN CLUSTER SCORES FOR EPIDURAL AND NONMEDICATED GROUPS WITH
VARIANCE DUE TO LENGTH OF LABOR REMOVED

Cluster and Day of Testing	Epidural Group			Nonmedicated Group		
	N	Mean	SD	N	Mean	SD
<u>Habituation:</u>						
Day 1	10	6.3	(1.2)	12	6.4	(1.7)
Day 3	9	6.0	(2.4)	9	5.5	(1.3)
Day 7	6	5.4	(3.0)	7	6.9	(1.5)
Day 28	7	5.8	(2.2)	2	7.7	(0.9)
<u>Orientation:</u>						
Day 1	15	5.1	(1.0)	16	6.2	(0.9)
Day 3	15	6.0	(1.2)	16	6.9	(0.6)
Day 7	18	6.6	(0.7)	19	5.5	(1.0)
Day 28	19	7.7	(0.9)	19	6.1	(0.6)
<u>Motor:</u>						
Day 1	19	3.8	(0.7)	19	4.5	(0.6)
Day 3	19	4.7	(0.7)	18	5.2	(0.7)
Day 7	19	5.2	(0.6)	19	4.0	(0.7)
Day 28	19	5.6	(0.6)	19	6.3	(0.5)
<u>State Range:</u>						
Day 1	19	4.0	(0.9)	19	4.1	(0.7)
Day 3	19	4.0	(0.5)	18	4.0	(0.4)
Day 7	19	4.1	(0.6)	19	4.0	(0.7)
Day 28	19	4.2	(0.7)	19	4.3	(1.0)
<u>State Regulation:</u>						
Day 1	19	5.7	(1.0)	19	6.2	(0.7)
Day 3	19	6.0	(1.2)	18	5.9	(0.8)
Day 7	19	5.6	(1.1)	19	5.2	(1.2)
Day 28	19	4.8	(1.1)	19	5.4	(1.2)
<u>Autonomic Regulation</u>						
Day 1	19	6.2	(1.0)	19	6.1	(0.9)
Day 3	19	6.4	(0.9)	18	6.2	(0.8)
Day 7	19	6.5	(0.8)	19	6.9	(0.9)
Day 28	19	6.9	(0.9)	19	7.1	(0.9)
<u>Reflex:</u>						
Day 1	19	4.1	(1.8)	19	2.9	(1.2)
Day 3	19	2.4	(1.3)	18	1.9	(0.3)
Day 7	19	1.3	(1.2)	19	.8	(1.2)
Day 28	19	1.3	(1.0)	19	1.5	(1.1)

APPENDIX 9

MEAN CLUSTER SCORES FOR EPIDURAL AND NONMEDICATED GROUPS WITHOUT VARIANCE DUE TO LENGTH OF LABOR REMOVED

Cluster and Day of Testing	Epidural Group			Nonmedicated Group		
	N	Mean	SD	N	Mean	SD
<u>Mobilization:</u>						
Day 1	10	.86	(3.7)	10	2.3	(2.5)
Day 3	9	-.23	(2.4)	9	2.4	(2.1)
Day 7	6	.06	(5.0)	7	3.1	(2.1)
Day 28	7	1.23	(4.3)	2	5.5	(0.6)
<u>Orientation:</u>						
Day 1	15	-.13	(2.8)	16	2.9	(2.5)
Day 3	15	-.06	(3.2)	16	3.0	(2.0)
Day 7	18	.03	(3.4)	19	2.9	(1.9)
Day 28	19	.21	(4.1)	19	3.5	(2.4)
<u>Motor:</u>						
Day 1	19	-.04	(2.5)	19	2.2	(1.2)
Day 3	19	-.08	(2.3)	18	2.3	(1.6)
Day 7	19	.25	(2.9)	19	2.4	(1.5)
Day 28	19	.22	(3.1)	19	2.9	(1.8)
<u>State Range:</u>						
Day 1	19	.23	(2.2)	19	1.7	(1.5)
Day 3	19	.48	(2.2)	18	1.8	(1.4)
Day 7	19	.35	(2.3)	19	1.7	(1.5)
Day 28	19	.32	(2.1)	19	1.9	(1.9)
<u>State Regulation:</u>						
Day 1	19	.52	(3.1)	19	3.0	(1.8)
Day 3	19	.65	(2.9)	18	2.6	(1.6)
Day 7	19	.63	(3.0)	19	2.1	(1.3)
Day 28	19	.17	(2.8)	19	2.5	(1.8)
<u>Autonomic Regulation</u>						
Day 1	19	.41	(3.1)	19	2.5	(1.7)
Day 3	19	.52	(3.5)	18	2.6	(2.0)
Day 7	19	.31	(3.8)	19	3.2	(2.0)
Day 28	19	.44	(3.8)	19	3.1	(2.2)
<u>Relax:</u>						
Day 1	19	.90	(2.0)	19	.63	(2.0)
Day 3	19	.09	(1.4)	18	.16	(0.7)
Day 7	19	.15	(1.2)	19	.17	(1.1)
Day 28	19	.02	(1.4)	19	.65	(1.3)

BIOGRAPHICAL SKETCH

Carol Marie Sepkoski was born at 34 weeks gestation on May 12, 1951, to a 27 year-old mother, gravida 2, parity 1, at Overlook Hospital, Summit, N.J. There were no complications of pregnancy with the exception of a fall which induced premature labor. Labor lasted three hours with ether administered for pain relief. Carol was large-for-gestational age, weighing 2548 grams. She measured 48 cm. and had a low ponderal index of 2.26. Carol would not have met the subject selection criteria for the present study.

Carol's childhood was spent with four siblings in Plainfield, N. J., Muscatine, Iowa, Syracuse, N.Y., and Sparta, N.J. Carol's father, Joseph, is a chemist and her mother, Sally, an assistant librarian. Her older brother, Jack, is an associate professor of paleontology at the U. of Chicago. Diane, a younger sister, is a kindergarten teacher in Glassboro, N.J. The baby of the family, Mary, is an aspiring marine biologist at Rodger Williams College in Rhode Island. Carol's younger brother, Greg, was a classical musician and composer. The family suffered a tragic loss in 1975 with his death at the age of 21.

Carol's fascination with child development began with early summer jobs working with children and with the birth of her youngest sister while Carol was in high school.

Later, at Boston University, Dr. Freda Reber was most instrumental in guiding Carol down the road of developmental psychology. She obtained a grant for Carol to continue with a project she began in her introductory child development course studying children's abilities to discriminate languages. The results suggested that younger children can discriminate languages better than older children. While at Boston U., Carol also coordinated a community playgroup of 4-5 year-olds as part of a federal work-study program. She used this setting along with courses on social interactions to study the developing nature of children's play. In 1973, Carol graduated from Boston U., cum laude with an award of "distinction in psychology."

There have been two experiences other than academic ones that have had a major influence in the development of both Carol's approach to child development and her outlook on life. They are political activities and travels. Carol attended college at a time when the sociopolitical climate of the country demanded obtaining as much of an education of the streets as in the classroom. While at Boston U., Carol became actively opposed to the war in Indochina. This experience furthered the growth of her social awareness which led to her continuing involvement in political activities and ultimately influenced her general approach to child development. Carol's travels have also had an effect on her orientation to psychology. Experiences with other cultures broadened her understanding of human behavior and

helped develop an appreciation of individual differences.

Following graduation from Boston U., Carol worked as a research assistant for two years on a Harvard-Boston U. project studying the mediating effects of nutrition and the social environment on the behavioral development of infant squirrel monkeys. It was here, with monkeys, that Carol was first exposed to the Brazelton Scale. She was fortunate to work for Drs. Patricia Chappell, Freda Rebelsky and Gerald Stechler on this project. Their ideas stimulated her interests in the study of infancy. Dr. Rebelsky recommended that Carol pursue these interests in graduate school, by studying with a former undergraduate student of hers, Dr. Barry Lester.

After 3 months exploring South America, Carol began graduate school at the University of Florida in Gainesville. She became involved in various research projects focusing on the behavior of the human neonate (although her assistantship was in gerontology). Opportunities to do research at the Hospital Municipal de San Juan, Puerto Rico, ensured that Carol never had to spend a hot summer in Florida. The first year's project, which was funded by Sigma Xi, resulted in master's projects for both Carol and her good friend and colleague, Cynthia Garcia Coll. They, along with Dr. Lester, examined the effects of pre- and perinatal influences, cultural differences and teenage pregnancy on neonatal behavioral outcome. The results have been presented at several conferences and

published in several journals. The followup project the next year was funded by the U. of Florida Behavioral Science Foundation and Sigma Xi.

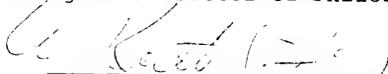
Carol took a two-year leave of absence from graduate school for the next five years to work with Drs. T. Berry Brazelton and Barry Lester at Children's Hospital in Boston. This offered her the opportunity to study a biobehavioral model of child development in an interdisciplinary setting. For the first two years, Carol assisted in a longitudinal study of the preterm infant. Through this project she became competent in the use of many research instruments and gained clinical skills by working with infants and parents in the hospital and home. Later, Carol wrote a proposal to study the cumulative effects of bupivacaine epidural anesthesia and obstetric variables on behavior over the first year of life. The project was funded by the Spencer Foundation of Child Development and the March of Dimes. It was from this project that Carol's dissertation evolved. During this time, Carol also became a trainer of the Brazelton Scale and had the opportunity to teach professionals from varied backgrounds to reliably administer and score the scale.

Carol's graduate committee was most responsive to her unique program of studies. Committee meetings were held during conferences in San Francisco, Providence, New Haven and Boston. Carol's chairperson, Dr. Keith Berg, also visited Boston to help her wrap up the bupivacaine project.

Following the completion of data analyses, Carol retreated to her cabin in the White Mountains of N.H. for three months of the autumn to write.

As winter approached, Carol (and her committee) decided that it was time to return to Florida to finish her degree. She spent the next year and a half enjoying coursework, doing clinical work at Shands Teaching Hospital and teaching a course in infant development. After receiving her Ph.D., Carol plans to return to Boston and continue working in a medical setting investigating the behavioral development of infants.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



W. Keith Berg, Chairman
Associate Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



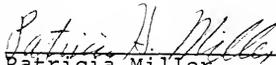
Yvonne Brackbill
Graduate Research Professor of
Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



Jacquelin Goldman
Professor of Clinical Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



Patricia Miller
Associate Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Patricia Ashton

Patricia Ashton
Associate Professor of Foundations
of Education

This dissertation was submitted to the Graduate Faculty of the Department of Psychology in the College of Liberal Arts and Sciences and to the Graduate School, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

April 1984

Dean for Graduate Studies and
Research

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