DOUBLE-BLIND COMPARISON OF THE NEUROBEHAVIOUR OF NEONATES FOLLOWING THE ADMINISTRATION OF DIFFERENT DOSES OF MEPERIDINE TO THE MOTHER*

ROBERT HODGKINSON, M. BHATT, AND C.N. WANG

IN THE RECENT PAST, neonatal central nervous system depression produced by narcotics, tranquillizers and anaesthetic agents has been measured by depression in the Apgar score. Depression of the Apgar score by drugs in the presence of the intense sensory stimulation of birth means that the dose was too large, the baby unduly sensitive or the dose was given too close to delivery. The limitations of the score were recognized by Apgar who stated that "... it is no substitute for a careful physical examination or serial observation over the first few hours of life".[2] Following the work of Prechtl and Beintema,[3] Brazelton,[4] and Scanlon,[1] a large number of neurobehavioral tests have been devised for the neonate which can be repeated throughout the neonatal period.

Meperidine administered to the mother has been shown to depress the Apgar score and the effect is time and dose related.[5] Respiratory function is also depressed. The oxygen saturation is lowered in the first 20 minutes of life following the intravenous administration of meperidine 100 mg to the mother within 60 to 90 minutes of delivery.[7] There is a significant increase in carbon dioxide retention and respiratory acidosis in babies whose mothers have received meperidine 100 mg within three and a half hours of delivery.[8] Thermoregulation is also depressed following large doses.[9]

In view of the effect of meperidine on the Apgar score and the respiratory and thermal regulatory function in a minority of infants, it was felt of importance to study the effects of meperidine on neonatal neurobehaviour in normal term babies delivered from healthy women after a normal labour and showing no clinical evidence of respiratory depression or a reduced Apgar score. To make such an evaluation the Early Neonatal Neurobehaviour Scale (E.N.N.S.) tests described by Scanlon, *et al.*[1] were administered to 920 neonates on the first and second days of life.

Robert Hodgkinson, M.A., M.D., M. Bhatt, M.D., and C.N. Wang, M.D. Obstetrical Anaesthesia Units, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, 78207, and Albert Einstein College of Medicine, Bronx, New York, 10461.

*Abstract read at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, October 1976.

METHOD

The 920 neonates were delivered under four different anaesthetic techniques. Table I lists the percentage of mothers in each group who were treated with oxytocin or were delivered by forceps. Table II further describes the mothers and babies in terms of drugs received, length of labour, age, weight and height of the mother and weight of the baby.

The first group consisted of 280 babies whose mothers received epidural anaesthesia with a mean dose of chloroprocaine 510 (±225) mg given over 2.3 (±1.1) hours. One hundred and seventy-seven of the mothers did not receive meperidine, while 81 received 50 mg and 22 received 75 to 150 mg. The second group consisted of 180 babies whose mothers had induction of anaesthesia with a mean dose of ketamine 0.7 mg/kg intravenously, followed by 6 litres/min of each of nitrous oxide and oxygen until delivery. Forty-five of these mothers did not receive meperidine, 88 received 50 mg intravenously within four hours of birth and 47 received 75 to 150 mg. The third group consisted of 180 babies whose mothers were induced with a mean dose of thiopentone 3.2 (±0.1) mg followed by 6 litres per minute each of nitrous oxide and oxygen until delivery. Fifty-two of these mothers did not receive meperidine, 72 received 50 mg intravenously within four hours of delivery and 56 received 75 to 150 mg. The induction to delivery interval was 3.9 (±1.1) minutes for the thiopentone and 3.8 (±1.2) minutes for the ketamine group. The fourth group consisted of 280 babies whose mothers had a pudendal block with lidocaine 200 to 400 mg. One hundred and fifteen of the mothers did not receive meperidine, 117 received 50 mg and 48 between 175 to 150 mg. All the mothers receiving meperidine also received promethazine (Table II).

An assessment of neurobehaviour was made on the 920 neonates on the first and second day of

TABLE I

PATIENT DESCRIPTION: PERCENTAGE OF ALL MOTHERS IN EACH OF THE TWELVE GROUPS DELIVERED BY FORCEPS OR RECEIVING OXYTOCIN

	Epidural			Ketamine			Thiopentone			Pudendal block		
Meperidine (n)	0 (177)	50 (81)	75–150 (22)	0 (45)	50 (88)	75–150 (47)	0 (52)	50 (72)	75–150 (56)	0 (115)	50 (117)	75–150 (48)
Forceps	38	51	45	27	23	40	40	25	36	10	8	10
Oxytocin	34	40	45	20	20	31	17	29	30	17	10	17

TABLE II

PATIENT DESCRIPTION MEAN ± SD OF BABIES' BIRTH WEIGHT, LENGTH OF LABOUR AND MOTHERS' DESCRIPTION

	Epidural (n = 280)			Ketamine (n = 180)			Thiopentone (n = 180)			Pudendal (n = 280)		
Dose: meperidine (mg)	0	50	75–150	0	50	75–150	0	50	75–150	0	50	75–150
Dose: promethazine (mg)	0	25	50–100	0	25	50–100	0	25	50–100	0	25	50–100
No. of patients	177	81	22	45	88	47	52	72	56	115	117	48
Birth weight (kg)	3.3 (±4)	3.4 (±3)	3.4 (±4)	3.4 (±4)	3.4 (±5)	3.3 (±4)	3.4 (±5)	3.4 (±5)	3.5 (±4)	3.4 (±4)	3.5 (±4)	3.4 (±5)
Duration: 1st stage	9.7 (±4)	10.6 (±3)	7.5 (±4)	7.1 (±3)	8.9 (±2)	7.3 (±3)	6.1 (±3)	6.8 (±4)	7.6 (±2)	6.8 (±3)	7.2 (±3)	9.2 (±2)
Duration: 2nd Stage	0.9 (±5)	0.9 (±6)	1.0 (±5)	0.7 (±6)	0.7 (±7)	0.8 (±5)	0.6 (±6)	0.7 (±6)	0.7 (±6)	0.7 (±5)	0.8 (±3)	0.9 (±5)
Mother's age	25 (±4)	26 (±3)	25 (±3)	27 (±4)	25 (±3)	25 (±4)	26 (±3)	27 (±4)	26 (±5)	27 (±4)	27 (±5)	25 (±3)
Mother's weight (kg)	73 (±12)	73 (±10)	77 (±9)	71 (±9)	74 (±8)	71 (±8)	76 (±13)	71 (±12)	72 (±9)	70 (±10)	78 (±8)	77 (±7)
Mother's height (cm)	161 (±5)	162 (±6)	161 (±3)	162 (±7)	161 (±4)	160 (±6)	160 (±6)	159 (±9)	161 (±8)	161 (±6)	162 (±8)	159 (±7)

life, during the hour before feeding, by one investigator unaware of the anaesthetic management, method of delivery or perinatal risk factors. Testing was done in a quiet constant temperature environment, with the baby awake or in a light sleep. To obtain similar groups for comparison only babies from spontaneous or low forceps deliveries resulting in a normal baby of over 2500 grams in weight with an Apgar score of at least 8 at one minute and 10 at five minutes were tested. On the first day of testing the babies were between 4 and 24 hours of age when examined (a mean of 9.2 hours for the thiopentone group, 8.6 for the ketamine, 8.2 for the epidural and 8.7 for the pudendal block groups). The second examination was performed 24 hours later.

The neurobehavioural scale used was that of Scanlon, *et al.*[1] whose paper should be consulted for details. It consists of a description of the baby's state of activity followed by 13 assessments, including four decrement responses performed in a set sequence selected to rouse the baby to maximal activity. The state is described as deep sleep, light (R.E.M.) sleep, drowsy, little activity, bright and alert, and intense crying. Apart from the habituation (decrement) tests, scoring is on a four-point ranking (ordinal) scale. The response was recorded as 1 for absence, 2 for weak or delayed, 3 when intermediate and 4 when strong or full. Pin-prick response measures the withdrawal reaction to a blunt pin applied to the sole of the foot. Tone is judged by pulling the infant gently to a sitting position, by arm recoil on gently extending the forearm, by suspending the baby horizontally with the hand under the abdomen and by a general impression of body tone. Rooting is graded by the vigour of the response to gently strokes at the corner of the mouth. Sucking is scored from no response to long periods of vigourous sucking to the distal joint of the index finger. The Moro response is assessed by the extent of the embracing reaction following a twenty-five-degree head-drop in the supine position. Decrement response to light, pin-prick, Moro response and the sound of a bell is the number of stimuli up to 12 that have to be applied before the infant first decreases its response. To judge placing, the baby is suspended in an upright position and the dorsum of the foot allowed to touch the protruding edge of the bassinet. Scoring is based upon the degree of flexion and extension of the stimulated leg until the placement of the foot on the edge is obtained. Alertness is judged from dull or absent response to response to all stimuli. The overall score forces the examiner to judge the infant's overall performance.

Results

The "Early Neonatal Neurobehavioural Scale" is a four-point ordinal (ranking) scale and statistical significance is assessed by a non-parametric test, chi-square. To obtain sufficient numbers in the cells of the contingency table, scores were divided into "high" and "low" scores and the results of tests following meperidine 75 to 150 mg were combined.

Comparison of the neonatal neurobehavioural scores showed marked differences between groups of patients when these were compared for the anaesthetic and the amount of meperidine administered. No significant differences were found in regard to the age of the patient, the duration of labour or the use of forceps or oxytocin.

Differences between meperidine dose groups

The percentage of high scores for overall response, tone, rooting, sucking, Moro response, placing, alertness and decremental scores to light, sound and pinprick were progressively lower with each increment of the dose of meperidine on both the first- and second-day examinations regardless of the anaesthetic used. For most tests, statistical significance was reached with the probability ranging from $p < 0.05$ to $p < 0.001$ (Figures 1, 2, 3 and 4).

Difference between anaesthetic groups when meperidine had not been used

General and regional anaesthesia

The combined epidural and pudendal groups showed a greater percentage of high scores than the two general anaesthesia groups on both day one and day two for overall assessment ($p < 0.001$), rooting ($p < 0.01$), sucking ($p < 0.001$), Moro response ($p < 0.001$), placing ($p < 0.01$), alertness ($p < 0.001$) and total decrement score ($p < 0.01$). On day two the score for tone was also significantly higher after regional anaesthesia ($p < 0.01$).

Epidural and Pudendal Block

On day one a greater percentage of high scores were found with chloroprocaine epidural block as compared to lidocaine pudendal block ($p < 0.001$). Otherwise, there were no significant differences.

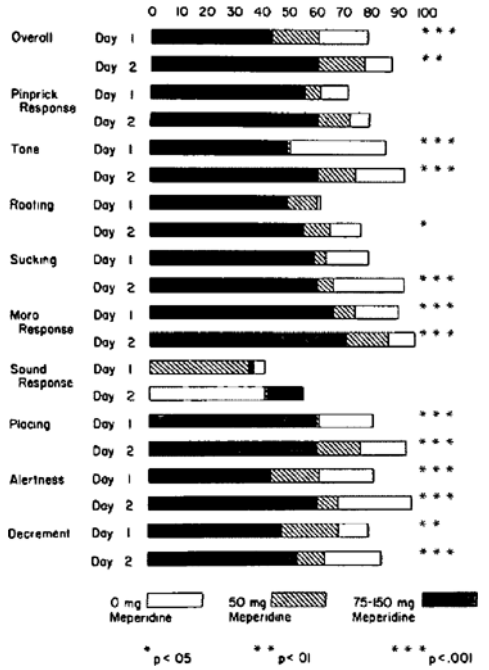

FIGURE 1. Percentage of high neurobehavioural scores in neonates whose mothers received no meperidine (n = 177), meperidine 50 mg and meperidine 75 to 150 mg within four hours of delivery and who also had chloroprocaine epidural anaesthesia.

Ketamine-Nitrous Oxide and Thiopentone-Nitrous Oxide

The percentage of high scores was greater following ketamine-nitrous oxide on day one for overall score ($p < 0.05$), total habituation score ($p < 0.05$), and alertness ($p < 0.05$). The only significant difference on day two was for rooting ($p < 0.05$).

DISCUSSION

Since a neurobehavioural assessment is evaluated on a ranking (ordinal) scale which is equivalent to classifying the response as superior, better than average, average, worse than average, etc., two points regarding the analysis of results deserve emphasis. The first is that parametric statistical manipulations such as means and standard deviations on numbers used merely as short-hand symbols for a description are not appropriate forms of statistical analysis. Results should preferably be analyzed in terms of frequency of a given response and not the mean score of the response.[16] The second point is that the definition of normal, better than normal, etc., can never be precise and the assessment will vary from observer to observer. In such a situation, the assessor should be "blind" to the perinatal risk factors, preferably "naive" to the purpose of the trial and only one evaluator should be used, to eliminate differences between observers. In this trial the smallest detectable difference from normal was given a one-point difference either upward or downwards.

The effect of drugs may be considered against the background of the physiological capabilities of the neonates at birth. At birth all the sensory systems are functional, although there are differences in the threshold to response as compared to the adult. Memory and learning ability are shown by habituation, classical Pavlovian conditioning and operant conditioning. A neonate should therefore be considered a responsive human capable of receiving sensory in-put, reacting to it and learning from the experience. Any drug altering this active, sensitive mental activity has a potential for disrupting normal neonatal activity and parent-child relationships. Neonatal neurobehavioural tests administered by a standardized

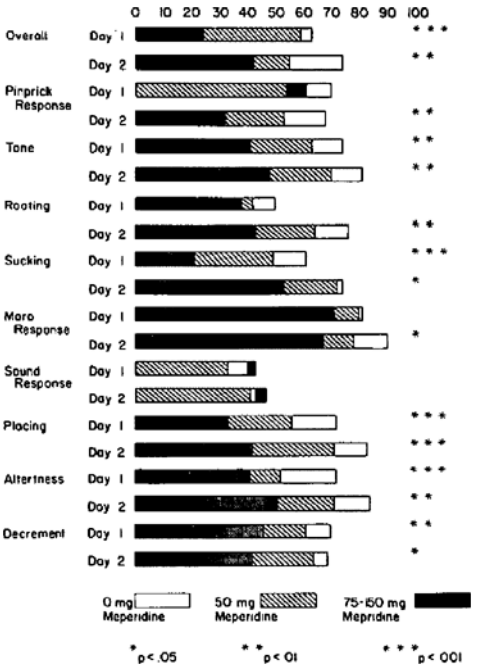

FIGURE 2. Percentage of high neurobehavioural scores in neonates whose mothers received no meperidine (n = 45) meperidine 50 mg (n = 88) and meperidine 75 to 150 mg (n = 47) and who also had general anaesthesia induced with ketamine.

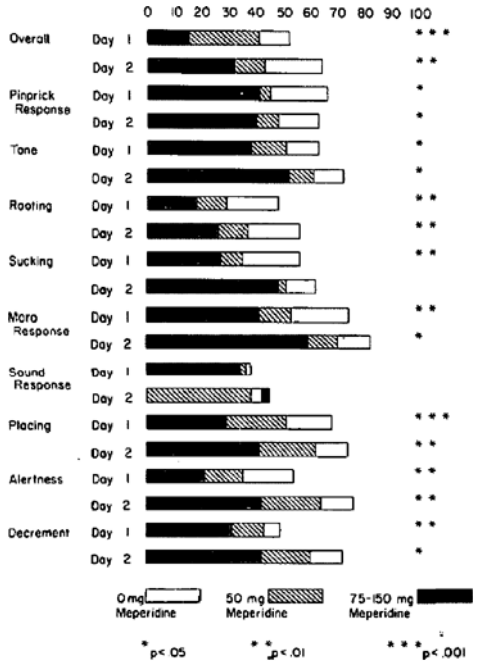

FIGURE 3. Percentage of high neurobehavioural scores in neonates whose mothers received no meperidine (n = 52), meperidine 50 mg (n = 72) and meperidine 75 to 150 mg (n = 56) and who also had general anaesthesia induced with thiopentone.

technique are very sensitive to the effects of both narcotics and anaesthetic agents. Quimby[11] described them as being "... as sensitive as electromicroscopy for detecting damage from exposure to a trace level of toxicant".

Administration of meperidine to the mother has been shown to depress neurobehaviour in the neonate for up to four days of age. Emde[12] demonstrated that the duration of wakefulness following the administration of meperidine 50 to 75 mg to the mother was less than half that of unexposed neonates in the first eight hours of life. For the first two hours non-R.E.M. sleep was increased by 400 per cent and in the subsequent eight hours by 50 per cent. Attentiveness and visual scanning were evaluated on the second to fourth days of life by Stechler.[13] He found that the mean scanning time of paper marked with simple designs was twice as long for babies unmedicated with narcotics or tranquillizers. Rosen and his colleagues have demonstrated modifications of the foetal electroencephalogram within two minutes of the administration of meperidine to the mother.[14] The effects on the neonatal electroencephalogram persist for at least four days,[15] which correlates well with impairment of waking states, arousal activity and muscle tone. Brackbill[16] has shown that at 46 to 56 hours of age the neonates take twice as long to habituate to noise when their mothers have been exposed to meperidine. Using the Brazelton neonatal neurobehavioural scale Brackbill has also found that the total score, interest in the tester's voice, defense to airblock, consolability, cuddliness and number of states entered were all depressed.

It is not yet possible as a result of neurobehavioural testing to make any dogmatic recommendations for changes in the present intrapartum medication used by obstetricians and the anaesthetists. It would seem advisable to avoid drugs in doses which modify tone and sucking. Although the effect may not be crucial to the normal neonate, a reduced response may become an absent response in the drug-sensitive or may tip the balance of survival in the high risk baby. Work has not yet been done on the effects of drugs on learning and memory, particularly classical and operant conditioning. However, in the first few days of life important new relationships

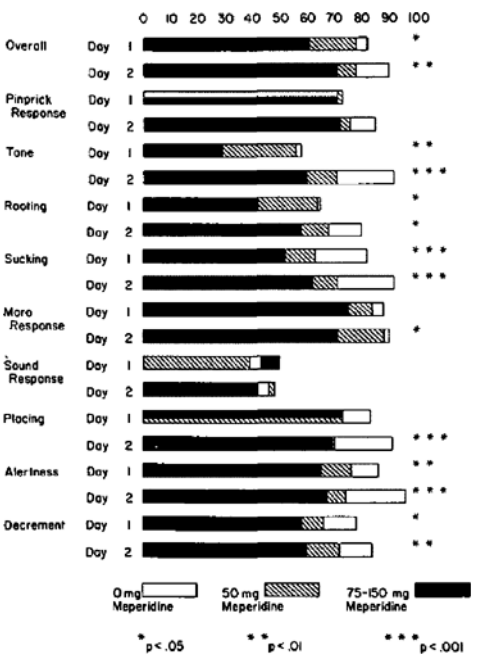

FIGURE 4. Percentage of high neurobehavioural scores in neonates whose mothers received no meperidine (n = 115) meperidine 50 mg (n = 117) and meperidine 75 to 150 mg (n = 48) and who also had an epidural block with lidocaine.

are being established and the effect of drugs on the interacting triad of mother, father and baby is being evaluated. A study[17] of perinatal child behaviour at 6 to 48 hours after delivery found a positive correlation between medication and maternal vocalization and rocking, but a negative correlation to paternal vocalization and rocking. This would suggest that the mother struggles to make the baby respond while the father is "turned off" by a drowsy baby.

Results so far would support the anaesthetist's preference for regional over general anaesthesia. Of the regional techniques, epidural anaesthesia gives more pain relief for each mg of local anaesthetic than other regional techniques, with the exception of spinal anaesthesia. Foetal exposure is reduced by the use of chloroprocaine, which is rapidly metabolized and bupivacaine, which is bound to maternal plasma proteins. Limiting the dose of meperidine to the smallest dose needed to control pain in the individual patient is preferable to the routine use of a standardized dose every few hours, a method which is still being used in some obstetrical units. A minimal dose of thiopentone is now widely used. Ketamine may have advantages as an inducing agent but more work is needed comparing minimal doses of ketamine with minimal doses of thiopentone.

Summary

The Early Neonatal Neurobehavioural Scale (E.N.N.S.) tests, first described by Scanlon, *et al.*[1] were administered to 920 neonates on the first and second days of life. Meperidine was not given to 389 mothers, 50 mg was given to 358 mothers and 75 to 150 mg to 173 mothers within four hours of delivery. The delivery was conducted under chloroprocaine epidural anaesthesia in 280, ketamine-nitrous oxide general anaesthesia in 180, thiopentone-nitrous oxide general anaesthesia in 180 and lidocaine pudendal block in 280. All babies were over 2500 grams in weight with an Apgar score of at least 8 at one minute and 10 at five minutes. All were delivered from healthy women 18 to 35 years of age following a normal labour. The evaluator was unaware of the anaesthetic management, the method of delivery or the perinatal risk factors. There was no significant difference between the mothers and babies in the three meperidine dosage groups for maternal parity, maternal age, birth weight, number of forceps deliveries or duration of labour.

Administration of meperidine was associated with a broad spectrum depression of most items on the E.N.N.S. on both the first and second days of life. The depression was greatest with the highest dose of meperidine. The depression produced by anaesthetic agents and meperidine were additive and the highest scores on this scale were obtained in those babies delivered under chloroprocaine epidural anaesthesia without meperidine.

Résumé

Ces dernières années, la dépression produite par les narcotiques, les neuroleptiques et les agents anesthésiques sur la système nerveux central du nouveau-né n'a été mesurée que par l'indice d'Apgar. Cette baisse du résultat de l'Apgar causée par des médicaments malgré la stimulation intense de la naissance signifiait que la dose était trop forte, le bébé susceptible de façon exagérée ou que la dose était administrée trop près de l'accouchement. Les limites inhérentes à l'indice d'Apgar ont été reconnues par Apgar elle-même qui écrivait que l'indice ne pouvait se substituer à un examen physique minutieux ou à l'observation répétée lors des premières heurs de la vie. Avec les travaux de Prechtl et Beintema, Brazelton, et Scanlon, sont apparus plusieurs test du neuro-comportement du nouveau-né, tests qui peuvent être répétés pendant la péiode néonatale.

Les auteurs ont évalué le neuro-comportement précoce de 920 nouveaux-nés en utilisant l'échelle établie par Scanlon et ses collaborateurs à la première et à la deuxième journée de la vie. Un groupe de 389 mères n'avait pas reçu de mépéridine, alors que 358 en avaient reçu 50 mg, 173 de 75 mg à 110 mg dans les quatre heures précédant l'accouchement. L'accouchement fut effectué sous anesthésie péridurale à la chloroprocaine dans 280 cas, sous kétamine associée au protoxyde d'azote dans 180 et sous bloc honteux dans 280 cas. Tous les bébés pesaient plus de 2500 g et avaient un Apgar d'au moins huit à la première minute et de dix à la cinquième minute. Toutes les mères étaient en bonne santé, étaient âgées de 18 à 35 ans et connurent un accouchement normal. L'évaluateur ne connaissait ni l'anesthésie utilisée, ni le mode d'accouchement, ni les facteurs de risque de la période péri-natale. Il n'y eut aucune différence significative pour les trois groupes déterminés par la dose de mépéridine en ce qui concerne la parité, l'âge de la mère, le poids du bébé à la naissance et l'incidence d'applications de forceps ou la durée du travail.

Un abaissement général de tous les paramètres du test de Scanlon fut associé à l'administration de mépéridine pour tous les bébés au premier et au deuxième jour de vie. Cet abaissement fut plus marqué pour la dose la plus élevée de mépéridine. Il fut noté que l'addition d'agents anesthésiques à la mépéridine aggravait cette dépression et que les meilleurs résultats sur l'échelle de Scanlon étaient obtenus lors d'anesthésie péridurale à la chloprocaine sans mépéridine.

REFERENCES

1. Scanlon, J.W., Brown, W.U., Weiss, J.B., & Alper, M.H. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology, *40*: 121 (1974).
2. Apgar, V. & James, L.S. Further observations on the newborn scoring system. Am. J. of Dis. Child. *104*: 419 (1962).
3. Prechtl, J.F.R. & Beintema, D. The neurological examination of the full-term newborn infant. Clin. Dev. Med. No. 12 London, Spastics Int. Med. Publ. (1964).
4. Brazelton, T.B. Neonatal Neurobehavioral Scale. Clin. Dev. Med. No. 50, London & Philadelphia. Heineman & Lippincott (1973).
5. Moya, F. & Thorndike, V. The effects of drugs used in labor on the fetus and newborn. Clin. Pharmacol. Ther. *4*: 628 (1963).
6. Schields, L.V. & Taylor, E.R. Serial oxygen saturation studies of newborn infants following obstetrical complications, difficult deliveries and caesarian section. Am. J. of Obstet. Gynecol. *73*: 1011 (1957).
7. Shnider, S.M. & Moya, F. Effect of meperidine on the newborn infant. Am. J. of Obstet. Gynecol. *89*: 1009 (1964).
8. Koch, G. & Wendel, H. The effect of pethidine on the postnatal adjustment of respirator and acid base balance. Acta. Obstet. Gynecol. Scand. *47*: 27 (1968).
9. Burnard, E.D. & Cross, K.W. Rectal temperature in the newborn after birth asphyxia. Brit. Med. J. *ii*: 1197 (1958).
10. Hodgkinson, R., Marx, G.F., & Kaiser, I.H. Local regional anesthesia during childbirth and newborn behavior. Science *189*: 571 (1976).
11. Quimby, K.L., Aschkenase, L.J., Bowman, R.E., Katz, J., & Chang, L.W. Enduring learning deficits and cerebral synoptic malformation from exposure to 10 parts of halothane per million. Science, *185*: 625 (1974).
12. Emde, R.N., Swedberg, J., & Suzuki, B. Human wakefulness and biological rhythms after birth. Arch. Gen. Psychiatry, *32*: 78 (1975).
13. Stechler, G. Newborn attention as affected by medication during labor. Science, *144*: 315 (1964).
14. Rosen, M.G., Scibetta, J.J., & Hochberg, C. Human fetal electroencephalogram: III. Pattern changes in presence of fetal heart rate alterations and after use of maternal medication. Obstet. Gynecol. *36*: 132 (1970).
15. Hughes, J.G., Hill, F.S., Green, C.R., & Davis, B.C. Electroencephalography of the newborn: V. Brain potentials of the babies born of mothers given meperidine hydrochloride (demerol hydrochloride) vinbarbital sodium. Am. J. of Dis. of Child, *79*: 996 (1950).
16. Brackbill, Y., Kane, J., Maniello, R.L., & Abramson, D. Obstetric Premedication and Infant Outcome. Amer. J. Obstet. Gynecol. *18*: 377–384 (1974).
17. Parke, R.D., O'Leary, S.E., & West, S. Mother-father-newborn interaction: Effects of maternal medication, labor and sex of infant. Proc. Am. Psychopathol. Assoc. (1972).