Smoking During Pregnancy and Newborn Neurobehavior

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ABSTRACT. *Objective.* **This was a prospective study of the effects of maternal smoking during pregnancy on newborn neurobehavior, including dose-response relationships using self-report and a bioassay of nicotine exposure.**

Methods. **The sample included 27 nicotine exposed and 29 unexposed full-term newborn infants with no medical problems from comparable social class backgrounds. Mothers were excluded for using illegal drugs during pregnancy, using antidepressant medication, or if they consumed >3 alcoholic drinks per month. Nicotine exposure was determined by maternal self-report and cotinine in maternal saliva. The NICU Network Neurobehavioral Scale (NNNS) was administered by masked examiners in hospital to measure neurobehavioral function. NNNS scores were compared between nicotine-exposed and -unexposed groups including adjustment for covariates. Dose-response relationships with NNNS scores were computed for maternal salivary cotinine and maternal report of number of cigarettes per day during pregnancy.**

Results. **After adjustment for covariates, the tobacco-exposed infants were more excitable and hypertonic, required more handling and showed more stress/abstinence signs, specifically in the central nervous system (CNS), gastrointestinal, and visual areas. Dose-response relationships showed higher maternal salivary cotinine values related to more stress/abstinence signs ($r = .530$) including CNS ($r = .532$) and visual stress ($r = .688$) and higher excitability scores ($r = .617$). Cigarettes per day during pregnancy was related to more stress/abstinence signs ($r = .582$) including CNS ($r = .561$) and visual stress ($r = .640$).**

Conclusions. **These findings suggest neurotoxic effects of prenatal tobacco exposure on newborn neurobehavior. Dose-response relationships could indicate neonatal withdrawal from nicotine. Research directed at understanding the effects of cigarette smoking during pregnancy on infants can lead to improved public health outcome.** ***Pediatrics*** **2003;111:1318–1323;** ***smoking, pregnancy, neurobehavior, cotinine, dose-response.***

ABBREVIATIONS. LBW, low birth weight; NBAS, Neonatal Behavioral Assessment Scale; NICU, Neonatal Intensive Care Unit; NNNS, NICU Network Neurobehavioral Scale; TLFB, Timeline Follow Back; SES, socioeconomic status; CNS, central nervous system, SD, standard deviation.

Cigarette smoking during pregnancy continues to be a significant public health concern.[1] Despite declines in the percentage of women who smoked during pregnancy during the 1990s, the Centers for Disease Control and Prevention reported that 12.3% of mothers who gave birth during 1999 smoked.[2] The most recent report from the National Household Survey on Drug Abuse estimated that 30.5% of nonpregnant women between the ages of 15 and 44 smoked. For pregnant women in this age range, the rates were 17.6% for tobacco use during pregnancy in contrast to rates of 13.8% for alcohol and 3.4% for illicit drugs.[3] Furthermore, unlike other substances of abuse, cigarettes are typically used on a daily basis while for other drugs such as cocaine, 3 days a week is considered heavy use during pregnancy.[4]

Maternal smoking during pregnancy is a well-known risk factor for low birth weight ([LBW], <2500 g) infants. LBW infants account for 7.6% of all live born infants, and 65% of deaths in the United States occur among LBW infants.[5] Mothers who smoke during pregnancy are nearly twice as likely to have a LBW infant, and smoking during pregnancy is responsible for 20% to 30% of all LBW infants. LBW infants born to smoking mothers weigh an average of 150 to 250 g less than infants born to nonsmoking mothers.[6]

Maternal smoking during pregnancy produces adverse effects for the fetus through several pathways. First, cigarette smoke interferes with normal placental function. As metabolites of cigarette smoke pass through the placenta from mother to fetus, they act as vasoconstrictors reducing uterine blood flow by up to 38%.[7] The fetus is deprived of nutrients and oxygen, resulting in episodic fetal hypoxia-ischemia and malnutrition.[8] This is the basis for the fetal intrauterine growth retardation seen in many infants born to smoking mothers.

Second, the nicotine in cigarette smoke acts as a neuroteratogen that interferes with fetal development, specifically the developing nervous system.[9] In utero, nicotine targets nicotinic acetylcholine receptors in the fetal brain to change the pattern of cell proliferation and differentiation. Fetal nicotine exposure upregulates nicotinic cholinergic receptor binding sites, causing abnormalities in the development of synaptic activity.[10] The end result is cell loss and ultimately, neuronal damage. Furthermore, because

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concentrations of nicotine on the fetal side of the placenta generally reach levels 15% higher than maternal levels, even low levels of cigarette smoking may expose the fetus to harmful amounts of nicotine.[11,12] As preclinical studies have shown, fetal doses of nicotine that do not result in LBW still produce deficits in fetal brain development.[12]

Despite how much is known about the effects of maternal smoking during pregnancy, surprisingly little is known about how such effects impact newborn neurobehavior. In previous works, maternal smoking during pregnancy and newborn behavior has been studied using the Neonatal Behavioral Assessment Scale (NBAS),[13,14–17] neuromotor assessment,[18] and acoustic cry analysis.[19] In the current study we provide the first evidence for newborn neurobehavioral effects of prenatal cigarette smoking using a bioassay (maternal salivary cotinine), including dose-response relationships and a neurobehavioral examination specifically designed to measure drug effects (NICU Network Neurobehavioral Scale [NNNS]).[20] This study provides an important link between preclinical and human data, and examines the short-term neurobehavioral mechanisms that may underlie long-term behavioral differences associated with prenatal smoking exposure.

METHODS

Participants

The study included 56 postpartum mothers 18 to 35 years of age and their 1- to 2-day-old newborns recruited at Women and Infants Hospital in Providence, Rhode Island. The research protocol was approved by the hospital's institutional review board. Mothers were recruited within 2 to 3 days after delivery.

Eligibility was determined through maternal self-report and a review of medical records. The self-report interview was administered in a checklist format that the mother completed on her own. Interviewers then asked if the mother admitted to any of the behaviors on the checklist, allowing the mother to openly admit to any exclusionary criteria without specifying exactly which behaviors she had engaged in. Mothers were excluded if any illicit drugs, antidepressants, thyroid or steroid medications were used during pregnancy, or if >3 alcoholic drinks per month were consumed during pregnancy. Mothers who experienced either psychiatric or serious physical illness during pregnancy were also excluded.

Healthy newborns (gestational age: 36–41 weeks) with appropriate weight for gestational age were recruited into the study. Gestational age in weeks was determined using the best obstetric estimate from medical records. Infants who had congenital anomalies, jaundice, or serious medical complications were excluded from the study. Only spontaneous vaginal deliveries were included.

A total of 135 mothers were approached. Of these, 62 women refused participation; 2 were smokers. An additional 15 women could not participate because of language barriers ($N = 8$) or they did not meet the inclusion criteria ($N = 7$).

Exposure Classification

A combination of self-report and biological markers were used to identify tobacco exposure during pregnancy. Participants were assigned to the smoking or nonsmoking group based on self-report of cigarette use during the maternal interview or a positive cotinine bioassay (>10 ng/mL) of maternal saliva. Both procedures are detailed below. There were 27 participants in the smoking group. Of these, 25 were identified based on maternal report and 2 denied smoking during pregnancy but had a positive cotinine assay. Valid cotinine assays were available for 16 of the participants in the smoking group. Three of these participants had a 0 (zero) cotinine value. The 29 participants in the nonsmoking group denied use; 26 had valid cotinine assays and they were all negative (cotinine = 0.0).

Procedures

Maternal Interview

After completing a brief medical history questionnaire, mothers completed the Timeline Follow Back (TLFB) interview of smoking and alcohol use during pregnancy.[21] The calendar-based TLFB is a clinical protocol designed to gather detailed information on substance use using anchor points to facilitate recall. The TLFB was adapted to cover the 3 trimesters of pregnancy as well as the 3 months before conception (prerecognition period). Information from the TLFB was summarized as the mean number of cigarettes and alcoholic drinks per day during prerecognition and the 3 pregnancy trimesters. The mean cigarette use and mean alcohol use for the 4 time periods was used for data analysis. Mothers also completed a socioeconomic status (SES) interview from which the Hollingshead Four-Factor Index of Socioeconomic Status was derived.[22] The Hollingshead Index evaluates the mother's education, occupation, and financial contributions from other household members to measure SES. Participants were categorized by low or high SES as determined by Hollingshead indices.

Salivary Cotinine

Nicotine exposure was measured using a saliva bioassay for cotinine, nicotine's primary metabolite. Cotinine has been established as a reliable biomarker for nicotine levels (sensitivity: 96%–97%; specificity: 99%–100%).[23] Cotinine is also readily passed from mother to infant, with fetal cotinine concentrations in pregnant smokers reaching ~90% of maternal values during pregnancy.[24] The saliva sample for cotinine determination was obtained from the mother in her hospital room after delivery. Saliva samples were collected, sealed, and stored at −20°C within 1 hour. The samples were assayed using gas chromatography-mass spectrometry techniques at the Clinical Pharmacology Laboratories at the University of California, San Francisco, California. To minimize interassay variation, the samples were analyzed in shipment batches.

NNNS Examination

The NNNS was developed for the National Institutes of Health to study prenatal drug exposure[25,26] and is sensitive to the effects of intrauterine exposure to cocaine[27,28] and opiates.[29,30] The examination provides an assessment of neurologic, behavioral, and stress/abstinence neurobehavioral function. The neurologic component includes active and passive tone, primitive reflexes, and items that reflect the integrity of the central nervous system (CNS) and maturity of the infant. The behavioral component includes items from the NBAS[31] modified to be sensitive to putative drug effects. The stress/abstinence component is a checklist of 50 yes or no items based primarily on the work of Finnegan.[32] The NNNS follows a fixed sequence of administration that starts with a preexamination observation, followed by the neurologic and behavioral components. The stress/abstinence scale is based on signs of stress observed throughout the examination. The NNNS items are scored using the following summary scales: Habituation, Attention, Arousal, Regulation, Number of Handling Procedures, Quality of Movement, Excitability, Lethargy, Number of Nonoptimal Reflexes, Number of Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence. The Stress/Abstinence scale is further divided into the following subscores: physiologic, autonomic, CNS, skin, visual, gastrointestinal, and state. Psychometric properties of the summary scales were evaluated with coefficient alphas ranging from .56 to .85.

The NNNS was administered within 48 hours after birth by a certified examiner masked to the exposure status of the newborn. All examinations took place in a quiet examination room under similar lighting and temperature conditions.

Statistical Analysis

Analysis of variance was used to compare differences between the smoking and nonsmoking groups on maternal and infant characteristics and on the NNNS summary scores. We also used analysis of covariance to adjust for covariates. Potential covariates were selected from demographic and medical characteristics (Ta-

TABLE 1. Demographic and Medical Characteristics

	Smoking (N = 27) Mean (SD) or Percent	Nonsmoking (N = 29) Mean (SD) or Percent	P
Maternal demographics			
Maternal age	24.2 (5.3)	30.1 (5.7)	<.000
Gravida	2.52 (1.4)	2.31 (1.4)	.58
Parity	1.22 (1.1)	1.86 (1.1)	.03
High school education, %	70.4	82.8	.35
Employed, %	44.4	69	.1
Low SES, %*	11.1	3.4	.34
Alcohol use during pregnancy, %	44.4	51.7	.61
Amount of alcohol†	1.41	1.24	.19
Newborn medical characteristics			
Gestational age, wk	38.9 (1.60)	39.4 (1.30)	.20
Birth weight, g	3335 (544)	3445 (348)	.38
Apgar, 1 min	6.92 (2.20)	7.85 (1.10)	.06
Apgar, 5 min	8.73 (0.83)	9.00 (2.90)	.12

* Based on the Hollingshead Index.
† Based on the following 3 point scale: 1, <1 drink per month; 2, 1 to 3 drinks per month; 3, 1 or more drinks per week.

ble 1) and were included based on previously established criteria,[28] that the covariates were correlated (r = >.10) with smoking or NNNS scores and were not highly correlated (r = <.7) with each other. Based on these criteria the covariates used were parity, 5-minute Apgar score, and birth weight. The habituation data were not used because of missing data (infants were not asleep at the beginning of the examination). Pearson correlation coefficients were used to determine dose-response relationships between measures of smoking exposure (cotinine or self-report) and NNNS scores.

RESULTS

Demographic and Medical Characteristics

Mothers in the smoking group were younger and had fewer previous pregnancies than mothers in the nonsmoking group (Table 1). Infant characteristics did not differ between the 2 groups (Table 1).

Patterns of Maternal Smoking

As shown in Table 2, the mean number of cigarettes per day averaged over the pregnancy, including prerecognition was 6.7 (standard deviation [SD]: 5.25). The heaviest smoking occurred during prerecognition, in which a mean of 12.9 cigarettes were smoked per day (SD: 7.9). Quitting was defined as complete termination of smoking for the remainder of the pregnancy with no relapse. No mothers in this sample terminated smoking at one point and resumed smoking later on during pregnancy. Cotinine results from bioassay of maternal saliva were obtained for 42 participants (16 in the smoking group and 26 in the control group). The remaining participants lacked reportable results because of cotinine values below the limit of quantification or inadequate saliva to perform the assay. The mean maternal cotinine value in the smoking group was 32.9 ng/mL (SD: 48.4). The mean maternal cotinine value in the control group was 0.0 ng/mL. For mothers in the smoking group, self-report of cigarette use was significantly correlated with salivary cotinine values (r = 0.624; $P < .01$).

TABLE 2. Patterns of Maternal Smoking

	Number (%) in Smoking Group Who Quit (N = 25)	Mean (SD) Number of Cigarettes per Day
Prerecognition	0 (100)	12.9 (7.9)
First trimester	2 (8)	7.52 (6.1)
Second trimester	3 (20)	3.76 (3.8)
Third trimester	2 (28)	2.8 (3.2)

NNNS Outcome

Smokers Versus Nonsmokers

Analysis of the unadjusted mean NNNS scores in Table 3 indicates that infants in the smoking group showed more excitability, a greater number of asymmetrical reflexes, and more hypertonia than infants in the nonsmoking group. The total stress/abstinence score was higher in the smoking group with subscale effects showing more stress/abstinence signs in 5 of the 7 areas; autonomic, CNS, gastrointestinal, visual, and state.

Analysis of the adjusted scores showed that the effects on excitability, hypertonia, total stress/abstinence and the CNS, gastrointestinal, and visual subscales were still statistically significant with covariates controlled. Effects on asymmetrical reflexes and on the autonomic and state subscales were no longer significant with adjustment for covariates. An additional effect showed that, with adjustment for covariates, infants in the smoking group required more handling to keep them in a quiet alert state than infants in the nonsmoking group.

Dose-Response Relationships

Correlations between cotinine values and NNNS scores were computed for 13 of the 16 participants in the smoking group (3 participants were deleted because they had 0 [zero] cotinine values). Higher cotinine values were related to a higher total stress/abstinence score (r = .530l $P < .05$), more CNS stress (r = .532; $P < .05$), more visual stress (r =. 688; $P <$. 05), and a higher score on the excitability summary scale (r =. 617; $P < .05$).

We also found similar relationships with correlations between mean number of cigarettes per day and NNNS scores for 11 of these 13 participants (2 were deleted because they reported 0 [zero] cigarette use during pregnancy). A greater number of ciga-

TABLE 3. NNNS Summary Scores in Nicotine-Exposed and Control Groups

NNNS Score	Smoking ($N = 27$) Unadjusted Mean (SD)	Non-Smoking ($N = 29$) Unadjusted Mean (SD)	$P =$	Smoking ($N = 27$) Adjusted Mean (SD)	Non-Smoking ($N = 29$) Adjusted Mean (SD)	$P =$
Attention	5.82 (1.48)	5.73 (0.81)	.79	5.92 (1.19)	5.72 (1.18)	.56
Arousal	3.85 (0.70)	3.73 (0.69)	.54	3.84 (0.76)	3.72 (0.75)	.57
Regulation	5.64 (0.73)	5.57 (0.44)	.70	5.55 (0.60)	5.61 (0.61)	.73
Handling	0.56 (0.20)	0.46 (0.19)	.07	0.57 (0.21)	0.44 (0.20)	.04
Quality of Movement	4.16 (0.37)	4.25 (0.92)	.61	4.18 (0.74)	4.21 (0.74)	.88
Excitability	3.04 (1.40)	2.00 (1.32)	<.00	3.08 (1.41)	1.91 (1.41)	<.00
Lethargy	4.15 (3.13)	3.21 (1.59)	.16	4.02 (2.62)	3.27 (2.61)	.315
Nonoptimal Reflexes	3.29 (1.40)	3.24 (1.55)	.89	3.33 (1.60)	3.19 (1.59)	.75
Asymmetrical Reflexes	1.59 (1.00)	0.96 (0.90)	.01	1.54 (1.01)	1.02 (1.00)	.07
Hypertonicity	0.37 (0.69)	0.01 (0.01)	<.00	0.37 (0.52)	0.00 (0.52)	.01
Hypotonicity	0.15 (0.36)	0.034 (0.19)	.14	0.14 (0.31)	0.04 (0.31)	.255
Total Stress/Abstinence	0.13 (0.08)	0.04 (0.03)	<.00	0.12 (0.06)	0.05 (0.06)	<.00
Physiological	0.05 (0.16)	0.01 (0.05)	.06	0.04 (0.10)	0.01 (0.11)	.36
Autonomic	0.25 (0.15)	0.16 (0.18)	.043	0.25 (0.18)	0.18 (0.17)	.16
CNS	0.18 (0.13)	0.08 (0.05)	<.00	0.16 (0.09)	0.09 (0.09)	.01
Gastrointestinal	0.16 (0.21)	0.02 (0.86)	<.00	0.16 (0.17)	0.02 (0.17)	<.00
Visual	0.12 (0.12)	0.02 (0.01)	<.00	0.11 (0.09)	0.01 (0.08)	<.00
Skin	0.02 (0.07)	0.05 (0.03)	.22	0.02 (0.06)	0.09 (0.06)	.44
State	0.05 (0.09)	0.01 (0.03)	<.00	0.05 (0.07)	0.01 (0.07)	.08

rettes per day was related to a higher total stress/abstinence score ($r = .582$; $P < .05$), more CNS stress ($r = .561$; $P < .05$), and more visual stress ($r = .640$, $P < .05$).

DISCUSSION

Given the well-documented effects of smoking during pregnancy on LBW, it is surprising that little is known about prenatal cigarette use and newborn neurobehavior. The NBAS[13] has been used in 4 studies.[14–17] In an early study of 15 infants born to mothers who smoked >15 cigarettes per day with 17 control infants,[16] smoking-exposed infants scored higher on auditory habituation, but lower on orientation and consolability items. In a study of 467 women and their newborns, prenatal cigarette smoking was related to lower NBAS orientation scores, but was also related to other potential confounders such as obstetric complications.[17] In the other 2 studies, smoking effects were not found with adjustment for covariates,[14,15] and Espy et al[18] did not find tobacco effects using a neuromotor assessment. There is one report using acoustical cry analysis showing higher-pitched cries related to prenatal tobacco exposure.[19]

An important methodologic difference between our study and previous studies is that our study was specifically designed to study the effects of prenatal tobacco exposure on newborn neurobehavior. Other studies included analysis of tobacco effects as covariates or in the context of other factors such as cocaine, alcohol and marijuana[14,15,18,19,33] or medical factors.[17] By design, our smoking and nonsmoking groups showed fewer demographic and medical differences than are customarily associated with smoking populations. Smoking mothers were of comparable gravida, education, employment, and social class, and displayed similar and low levels of alcohol use. Infants in our sample born to smoking mothers weighed, on average, 110 g less than control infants at birth. This difference was not statistically significant and is small compared with the 200 g difference found by other studies after controlling for differences in social class, parity, education, and maternal alcohol consumption.[34] Thus, the design of our study allowed us to examine the specific effects of tobacco on newborn behavior independent of likely confounds. It will be interesting to see if these effects are replicated in future studies that are specifically designed for this purpose.

The differences we found suggest neurotoxic effects of prenatal tobacco exposure on newborn neurobehavior. After adjustment for covariates, the tobacco-exposed infants were highly aroused and reactive as indicated by the higher excitability and handling scores, and they were more hypertonic. In addition, they showed stress/abstinence signs consistent with what has been reported in other drug-exposed infants and at-risk infants. Indeed, the items on the Stress/Abstinence scale were based on observations of withdrawal signs in opiate-exposed infants and stress behaviors in at-risk infants such as those born preterm. Analysis of the Stress/Abstinence scale by the component subscales revealed that the tobacco effects were specific to the CNS, gastrointestinal, and visual systems. Animal studies have described neuroteratogenic effects of prenatal nicotine exposure that result in altered fetal brain development.[9,10] Our neurobehavioral findings provide an important link between these studies of in utero brain development and the reported long-term outcomes of nicotine-exposed children, because smoking effects at birth could indicate deficits that result in lower IQ and the development of attention-deficit/hyperactivity disorder in later years[35] that are not attributable to postnatal factors such as passive exposure to cigarette smoke, social class, or parenting.

We were able to document effects of smoking on neurobehavior at lower levels than has been reported in previous studies. Typically, the threshold for finding effects of prenatal tobacco exposure, including effects on birth weight, is 10 cigarettes per day.[4] Our

mothers smoked an average of 6.7 cigarettes per day, with the heaviest smoking occurring in the prerecognition period. Our ability to detect these subtle effects may have to do with the sensitivity of the NNNS that was specifically designed to measure neurobehavioral effects of prenatal drug exposure.

This is the first study to relate a bioassay of smoking exposure to newborn neurobehavior and to report a dose-response relationship between smoking and newborn neurobehavior. The dose-response relationships were similar for cotinine and cigarettes per day, indicating that more tobacco exposure is related to increasingly negative neurobehavioral effects. The half-life for cotinine in body fluids is 15 to 19 hours.[36] Thus, the saliva cotinine assay only reflects recent cigarette use approximately within 2 days. Although we cannot determine if these dose-response relationships indicate neonatal withdrawal from nicotine, this is a likely possibility.

The use of saliva cotinine in this study was also important because it assisted in confirming maternal self-report of smoking and increased the accuracy of classification of participants into smoking and nonsmoking groups. Smoking mothers who were reluctant to admit smoking were encouraged to do so, knowing that their responses would be compared with a bioassay. Furthermore, 2 mothers would have been misclassified as nonsmokers without the bioassay.

The fact that maternal saliva cotinine only reflects recent cigarette use is a limitation of this study. Measurement of cotinine in meconium would provide both better information about infant exposure as well as exposure during the second half of pregnancy.[37] The meconium assay could also have been useful if there were mothers in our sample who used illegal drugs but denied use.

As mentioned earlier, there are several pathways through which maternal smoking during pregnancy can affect the fetus. Because we controlled for birth weight, we believe that the effects we found on neurobehavior are not attributable to the effects of cigarette smoke on birth weight. In fact, some of the effects that were found in the unadjusted analysis but not in the adjusted analysis could have been attributable to birth weight. Also, because all infants were tested before hospital discharge, we can rule out passive inhalation of second-hand smoke as being responsible for the neurobehavioral effects. Although the teratogenic effects of nicotine in tobacco remain a likely explanation for the effects that we observed, it is also important to acknowledge other factors. Cigarette smoke is a complex mixture of chemicals[38] with ~4000 compounds,[39] including those such as carbon monoxide, that cross the placenta and may also affect the fetus.

Maternal smoking during pregnancy has been identified as the single largest modifiable risk factor affecting intrauterine growth restriction in developed countries.[40,41] The smoking effects observed in our study underscore the importance of smoking cessation programs, particularly for women of childbearing age. This need is further highlighted by existing research on the transmission of nicotine through breast milk and its harmful effects, and the consequences of second-hand smoke exposure on children.[9,15,42–44] At this opportune time in which the harmful effects of cigarette smoke have been subjected to increased scrutiny, including by the American Academy of Pediatrics,[45,46] programs aimed at smoking cessation and addiction treatment, and research directed at understanding the effects of cigarette smoking during pregnancy on infants can lead to improved public health outcome.

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WEST NILE MIMICS POLIO

"When the West Nile virus (WNV) arrived in the United States in 1999, its route of infection was the bite of an infected mosquito. Since then, WNV has proven its versatility: during the 2002 season, delivery came courtesy of transplants, transfusions, and breast milk. Now, the list of symptoms is growing to include a condition reminiscent of paralytic poliomyelitis. In August, the Centers for Disease Control and Prevention (CDC) reported the first 6 cases—3 from Mississippi, 3 from Louisiana. The number is now at least 15."

Lewis R. November 25, 2002

Noted by JFL, MD