Effects of Smoking Exposure in Infants on Gastroesophageal Reflux as a Function of the Sleep–Wakefulness State

Djamal Djeddi, MD, PhD1,2, Erwan Stephan-Blanchard, PhD1, André Léké, MD, PhD1,2,3, Mohamed Ammari, PhD1, Stephane Delanaud, Ing1, Anne-Sophie Lemaire-Hurtel, PharmD, PhD4, Véronique Bach, PhD1, and Frédéric Telliez, PhD1

Objective To determine whether perinatal smoking exposure is associated with gastroesophageal reflux (GER)-related changes in sleep-wakefulness states in neonates.

Study design Thirty-one neonates, referred for the investigation of suspected GER, were recruited and underwent multichannel impedance–pH monitoring and synchronized 8- to 12-hour polysomnography. The infants’ exposure to tobacco smoke was estimated by means of a urine cotinine assay. The total number, frequency (h⁻¹), and mean duration (minutes) of GER-pH (reflux events detected by the pH electrode only) and GER-imp (reflux events with bolus movement detected by impedance) events were determined. Intergroup differences (smoking-exposed group vs nonexposed group) were probed with nonparametric, unpaired Mann–Whitney U tests. A χ² test was used to assess a possible intergroup difference in bolus retrograde migration during GER-imp events.

Results According to the urine cotinine assay, 21 of the 31 neonates had been exposed to cigarette smoke during the perinatal period. The number (and frequency) of GER-imp was significantly greater (P = .016) in the exposed group (29 [0-90]) than in the nonexposed group (12 [2-35]). Migration of the esophageal bolus from the distal segment to the most proximal segment was significantly more frequent (P = .016) in the exposed group (83% of GER) than in the nonexposed group (41%). The GER pattern associated with smoking exposure was particularly obvious during Rapid eye movement sleep.

Conclusions The more frequent occurrence and greater proximal migration of GER-imp in the smoking-exposed group (especially during rapid eye movement sleep) may have clinical relevance. Smoking exposure is a preventable risk factor for limiting the occurrence of GER in neonates. (J Pediatr 2018;201:147-53).

Gastroesophageal reflux (GER) is a physiological phenomenon that occurs in more than two-thirds of infants. In contrast, GER disease is characterized by harmful symptoms and/or complications associated with GER. Between 10% and 35% of women smoke during pregnancy. Smoking is still the most important preventable risk factor for complicated pregnancies in all developed countries and an increasing number of developing countries.

It has been shown in adults that smoking increases the frequency of GER events and prolongs esophageal acid clearance and that cessation of tobacco smoking is associated with a reduction in severe GER symptoms. Pre- and postnatal smoke exposure is associated with health problems (including neurologic, respiratory, and cardiovascular disorders) in the neonate. The effects of tobacco smoke exposure on GER patterns in neonates have been investigated in 1 published study. In that study, GER was not investigated with combined multichannel intraluminal impedance and pH monitoring (MII-pH). In addition, tobacco smoke exposure was established subjectively on the basis of the mother’s response to a questionnaire. The study was restricted to the specific context of apparently life-threatening events. These limitations highlight the lack of comprehensive data on the influence of perinatal exposure to tobacco smoke on GER in the infant.

In the present study, we used MII-pH monitoring (now the gold standard for assessing GER in infants) to classify the reflux as acid, weakly acid, or alkaline and monitor distal to proximal migration of the esophageal bolus. We also assessed vigilance states (sleep states and wakefulness) because of their well-known influence on GER distribution, acid exposure, numbers of acid/nonacid refluxes, and retrograde bolus migration in particular. Furthermore, the reflexes that protect the airways against aspiration depend on the vigilance state.

We hypothesized that perinatal smoking exposure (as determined by a urine cotinine assay) would be associated with a greater frequency and duration of GER events and that this relationship would depend on the sleep–wakefulness state.
We also reasoned that the identification of modifiable environmental risk factors and GER-related mechanisms is important for understanding the underlying pathophysiologic processes and developing early prevention and health management strategies in exposed subpopulations of neonates.

Methods

The study protocol was approved by the regional investigational review board (Comité de Protection des Personnes Nord Ouest II). All parents gave their written, informed consent to their respective infant’s participation before inclusion in the study.

Thirty-one neonates underwent synchronized MII-pH monitoring and polysomnography (PSG) after referral for the investigation of suspected GER in the Department of Pediatrics at Amiens University Medical Center (Amiens, France). They were referred for MII-pH monitoring by their family pediatrician because of GER-related clinical symptoms (recurrent regurgitation and/or vomiting and/or belching at least 5 times per day for a week associated with significant irritability—ie, potential warning signs for GER disease). The main exclusion criteria included the presence of major gastrointestinal diseases, signs of esophagitis, congenital anomalies, neurologic impairments, or cardiorespiratory problems.

None of the enrolled neonates had been treated with medications known to influence gastrointestinal motility or gastric pH. All the neonates were formula-fed, which therefore rules out tobacco exposure via the mother’s milk. None of the mothers had undergone nicotine-replacement therapy, which is known to increase the risk of gastrointestinal dysregulation in the neonate.21

Evaluation of Smoking Exposure

The infants’ exposure to tobacco smoke was estimated by means of a urine cotinine assay. Samples of urine were collected in sterile bags on the day of the MII-pH analysis, immediately frozen, and stored at −20°C until analysis. Urine cotinine was assayed in duplicate using a gas chromatography-mass spectrometry protocol (detection threshold: 1 ng·mL−1). Two groups of neonates were constituted: those with a urine cotinine level greater than 1 ng·mL−1 (constituting the smoking-exposed group), and those with urine cotinine level less than 1 ng·mL−1 (constituting the nonexposed control group). This cut-off has been used in previous studies148 of the cardiovascular effects of secondhand tobacco smoke on neonates were constituted: those with a urine cotinine level greater than 1 ng·mL−1 (constituting the smoking-exposed group), and those with urine cotinine level less than 1 ng·mL−1 (constituting the nonexposed control group), and those with urine cotinine level greater than 1 ng·mL−1 (constituting the smoking-exposed group). This cut-off has been used in previous studies148 of the cardiovascular effects of secondhand tobacco smoke on neonates.

Multichannel Intraluminal Impedance and pH Monitoring

MII-pH monitoring (obtained with the Ohmega system from Medical Measurement Systems, Enschede, The Netherlands) was performed in compliance with current European guidelines.24 The neonatal impedance-pH catheter (with an outer diameter of 8 French; Unisensor, Attikon, Switzerland) contained 7 impedance rings (constituting 6 dipolar impedance channels) and an antimony electrode for pH detection (located in the middle of the distal impedance dipole). The distance between adjacent impedance rings was 15 mm.

The pH electrode was calibrated with standard buffers before the clinical procedure. The MII-pH catheter was introduced nasally, positioned according to the Strobel equation,25 and then checked radiographically. The tip was fixed around 1 cm above the lower esophageal sphincter. MII-pH plots were analyzed automatically with dedicated software (MMS Database, version 8.9a; Medical Measurement Systems BV, Enschede, The Netherlands) and visually checked by a specialist in pediatric gastroenterology.

Feeding periods were excluded from the analysis. All reflux events with bolus movement detected by impedance (defined as a 50% decrease on at least 2 of the distal channels) were referred to as “GER-imp” events (ie, GER detected by impedance monitoring) and (depending on the characteristics of the impedance signal) defined as liquid, gaseous, or mixed. Depending on the characteristics of the concomitant pH changes, GER-imp events were further classified as acid reflux (pH <4), weakly acid reflux (4 < pH < 7,) or alkaline reflux (pH >7). Reflux events detected by the pH electrode only (ie, in the absence of bolus retrograde migration) were referred to as “GER-pH” events (ie, GER detected by pH monitoring only).

The proximal nature of each reflux event was evaluated according to the time course of the change in impedance (ie, propagation from the distal channel to more proximal channels). We considered all GER events in our analysis and did not solely analyze gaseous reflux. The total number, frequency (h−1), and mean duration (minutes) of GER-pH and GER-imp events were determined. The reflux index (RI) was defined as the percentage of the total recording time with pH <4, and the bolus exposure index was defined as the percentage of the total recording time with GER-imp events.

Polysomnography

The following noninvasive signals were recorded continuously (via the Brainnet–Morpheus system from Medical Data Technology, Brussels, Belgium): (1) 2 electroencephalograms, from the right and left centro-occipital leads; (2) 2 electro-oculograms; (3) an electrocardiogram; (4) chest and abdominal wall motion (using respiratory inductance...
Table I. General characteristics of the 2 groups of neonates

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nonexposed group</th>
<th>Smoking-exposed group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Urine cotinine level, ng·mL⁻¹</td>
<td>0</td>
<td>12 (2-243)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38.5 (25-41)</td>
<td>38.2 (29-42)</td>
<td>.83</td>
</tr>
<tr>
<td>Postnatal age, d</td>
<td>32 (2-124)</td>
<td>36 (3-125)</td>
<td>.55</td>
</tr>
<tr>
<td>Postconceptional age, wk</td>
<td>40.0 (32-59)</td>
<td>42.5 (37-57)</td>
<td>.83</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>2.8 (0.9-3.8)</td>
<td>2.8 (1.0-3.8)</td>
<td>.72</td>
</tr>
<tr>
<td>Weight at the time of the study, kg</td>
<td>3.6 (2.5-7.8)</td>
<td>3.3 (2.0-4.8)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Statistically significant values are indicated in bold. Values are quoted as the median (min-max).

Table II. GER data (detected by MII-pH monitoring) for the 2 groups of neonates

<table>
<thead>
<tr>
<th>Data</th>
<th>Nonexposed group</th>
<th>Smoking-exposed group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Recording time, min</td>
<td>749 (502-828)</td>
<td>782 (462-868)</td>
<td>.58</td>
</tr>
<tr>
<td>GER-pH + GER-imp events</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total events, n</td>
<td>152</td>
<td>771</td>
<td>—</td>
</tr>
<tr>
<td>GER-pH events</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total events, n</td>
<td>44 (29%)</td>
<td>188 (24%)</td>
<td>—</td>
</tr>
<tr>
<td>RI, % of total time</td>
<td>0.4 (0-7.0)</td>
<td>1.2 (0-11.5)</td>
<td>.36</td>
</tr>
<tr>
<td>Time spent with reflux, min</td>
<td>0.1 (0-16.7)</td>
<td>5.2 (0-64.7)</td>
<td>.31</td>
</tr>
<tr>
<td>Number of reflux events, n</td>
<td>0.5 (0-17)</td>
<td>6.5 (0-50)</td>
<td>.25</td>
</tr>
<tr>
<td>Frequency of reflux, events, h⁻¹</td>
<td>0.1 (0-1.6)</td>
<td>0.5 (0-4)</td>
<td>.26</td>
</tr>
<tr>
<td>Duration of reflux events, min</td>
<td>0.9 (0-1.1)</td>
<td>1.0 (0-1.3-3.8)</td>
<td>.65</td>
</tr>
<tr>
<td>GER-imp events</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total events, n</td>
<td>108 (71%)</td>
<td>583 (76%)</td>
<td>—</td>
</tr>
<tr>
<td>Bolus exposure index, % of total time</td>
<td>0.3 (0.1-1.4)</td>
<td>0.8 (0-2.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Acid</td>
<td>0.02 (0-0.3)</td>
<td>0.07 (0-1.3)</td>
<td>.40</td>
</tr>
<tr>
<td>Weakly acid</td>
<td>0.2 (0.1-0.8)</td>
<td>0.2 (0-1.3)</td>
<td>.42</td>
</tr>
<tr>
<td>Time spent with reflux, min</td>
<td>2.1 (0.4-6.5)</td>
<td>5.7 (0-18.3)</td>
<td>.10</td>
</tr>
<tr>
<td>Acid</td>
<td>0.2 (0-1.9)</td>
<td>0.5 (0-10.9)</td>
<td>.51</td>
</tr>
<tr>
<td>Weakly acid</td>
<td>1.7 (0.3-3.5)</td>
<td>1.8 (0-9.7)</td>
<td>.43</td>
</tr>
<tr>
<td>Number of reflux events, n</td>
<td>12 (2-35)</td>
<td>29 (0-90)</td>
<td>.016</td>
</tr>
<tr>
<td>Acid</td>
<td>1.5 (0-8)</td>
<td>4.0 (0-35)</td>
<td>.41</td>
</tr>
<tr>
<td>Weakly acid</td>
<td>8.0 (2-28)</td>
<td>15.0 (0-57)</td>
<td>.28</td>
</tr>
<tr>
<td>Frequency of reflux events, h⁻¹</td>
<td>1.0 (0.2-3.8)</td>
<td>2.6 (0-9.8)</td>
<td>.017</td>
</tr>
</tbody>
</table>

Statistically significant values are indicated in bold. Values in italics represent the subtype of GER events. Values are quoted as the median (min-max).

Results

On the basis of the urine cotinine assay results, 10 neonates constituted the nonexposed group (urine cotinine: < 1 ng·mL⁻¹) and 21 constituted the smoking-exposed group (urine cotinine: 2-243 ng·mL⁻¹) (Table I). According to the health questionnaire answers and the date of hospitalization for delivery, 6 of the neonates in the smoking-exposed group had been exposed in utero only. It was not possible to discriminate between in utero and postnatal smoking exposure for the other 15 neonates in the group. The smoking-exposed and nonexposed groups did not differ significantly in terms of other clinical characteristics (Table I). Eight of the 21 neonates in the smoking-exposed group and 3 of the 10 neonates in the nonexposed group were born preterm.

In the smoking-exposed group, only 10 mothers stated that they had smoked during pregnancy, with a median (min-max) of 10 (6-40) cigarettes per day. Four smoked 5-9 cigarettes per day, 5 smoked 10-20 cigarettes per day, and 1 smoked more than 20 cigarettes per day. Only 1 mother stated having ceased smoking during pregnancy (after the first trimester). All the mothers in the smoking-exposed group continued to smoke or started smoking again after giving birth. Regular smoking by the mother’s partner during and after pregnancy was reported in 6 of the 21 cases. In the nonexposed group, there were no reports of maternal smoking and/or exposure to passive smoking in the household.

MII-pH Data

A total of 923 GER events during 304 hours of recording time were analyzed. The total recording time was similar in the 2 groups (Table II). All the GER variables were greater in the smoking-exposed group than in the nonexposed group; however, only the differences in the median number (29 vs 12, respectively) and frequency (2.6 vs 1.0 h⁻¹, respectively) of GER-imp events were statistically significant. These differences were mainly due to greater number of both acid and weakly acid GER-imp events in smoking-exposed group. Alkaline reflux was detected in 1 subject only and thus was not analyzed. No significant correlations between cotinine urinary levels and GER-pH or GER-imp variables were observed in the smoking-exposed group.

Retrograde Migration of Esophageal Content during GER-imp Events

The percentage of GER-imp events with retrograde bolus migration to the most proximal segment was significantly higher
P = .032) in the smoking-exposed group (83%) than in the nonexposed group (41%).

Interaction with Vigilance States
No intergroup differences in the PSG data (neither the duration of vigilance states nor the sleep episode frequency) were observed (Table III). A relationship between smoking exposure and more frequent GER-imp was observed in all vigilance states but was only statistically significant for REM sleep (Figure). During REM sleep, the time spent in GER-imp and median number of GER-imp were 2-fold greater in the smoking-exposed group than in the nonexposed group (P = .045 and P = .039 for the 2 variables, respectively) (Figure). This difference was mainly due to a 3-fold greater frequency of weakly acid events in the smoking-exposed group (2.3 h⁻¹ [0-6.7]), relative to the nonexposed group (0.71 h⁻¹ [0-1.1]; P = .050).

Preterm vs Term Neonates
There were no differences between infants born preterm (n = 11) and infants born at term (n = 20) with regard to the number and characteristics of GER events.

Discussion
We investigated the effects of perinatal smoking exposure on GER in infants by using MII-pH monitoring and by taking account of the vigilance state. We found that almost 68% of the neonates enrolled in the present study for GER had been exposed to tobacco smoke. The number and frequency of GER-imp events and the frequency of retrograde bolus migration from the distal esophageal segment to the most proximal segment were significantly greater in the smoking-exposed group than in the nonexposed group.

The proportion of neonates with perinatal tobacco smoking exposure in the present study (68%) is much greater than that reported in a French epidemiologic study of healthy neonates.27 In the latter study (based solely on a questionnaire completed by the mother), 31% of the women reported smoking at the beginning of their pregnancy and 17% reported smoking throughout their pregnancy. A direct comparison with our study is difficult because both the study population and the method used to evaluate smoking exposure differed. However, the fact that 32% (10 of 31) of the mothers in our study admitted to having smoked during their pregnancy (according to our questionnaire) is in line with the literature data. The present study shows that direct or indirect perinatal exposure to tobacco can provoke or exacerbate GER events. The frequency of GER events observed in the present study was similar to that reported by Van Wijk et al in neonates with frequent regurgitation (between 1.6 and 6 GER events per hour, as detected with MII-pH monitoring).28

The median RI recorded in the present study was lower than the “abnormal” threshold of 7%.2 Only 4 neonates (3 infants in the smoking-exposed and 1 control infant) had an RI greater than 7. In the study by Corvaglia et al of symptomatic infants born premature, the RI (8.35%) and the bolus exposure index (1.31%) were greater than the values observed here in the smoking-exposed group (1.0% and 0.7%, respectively).29 Neither of these 2 studies investigated smoke exposure as a possible explanatory factor in the occurrence of GER. Accordingly, we consider that our results are valid for this population but need to be studied further—notably to confirm the specific impact of smoke exposure on a population of newborns with GER disease.

Our results are in line with literature data on pH monitoring in neonates.1 In the study by Alaswad et al, the esophageal pH measures (RI and reflux frequency) were greater in a

<table>
<thead>
<tr>
<th>Table III. Sleep data in the 2 groups of neonates</th>
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<tbody>
<tr>
<td>Sleep measures</td>
</tr>
<tr>
<td>Wakefulness, min</td>
</tr>
<tr>
<td>REM sleep, min</td>
</tr>
<tr>
<td>NREM sleep, min</td>
</tr>
<tr>
<td>Frequency of sleep state changes, h⁻¹</td>
</tr>
</tbody>
</table>

NREM, nonrapid eye movement sleep. Values are quoted as the median (min-max).

Figure. Median number of GER-imp events (n) and the time spent with GER-imp (minutes) as a function of the vigilance state in the nonexposed (□) and smoking-exposed (■) groups. *P < .05. NREM, nonrapid eye movement sleep.
smoking-exposed group than in a nonexposed group. In our study, the frequency of GER-pH events and the RI also were greater in the smoking-exposed group than in the nonexposed group, although these differences were not statistically significant.

Our most striking result was the significantly greater frequency of GER-imp events in smoking-exposed neonates. This result is important because GER-imp typically accounts for two-thirds of all reflux events (71% and 76% for our nonexposed and smoking-exposed groups, respectively). Interestingly, we did not observe an intergroup difference in the median duration of a GER event, which suggests that smoking exposure does not have a significant effect on the clearance of impedance-detected reflux (such as saliva production, swallowing, and secondary peristalsis). The same observation has been made in adult active smokers and in newborn lambs exposed postnatally to environmental tobacco smoke.

There are several possible mechanistic explanations for the association between tobacco smoke exposure and an elevated frequency of GER. In infants, transient relaxation of the lower esophageal sphincter is the predominant mechanism for GER. In adult smokers, an increase in the number of reflux events might be due to a reduction in lower esophageal sphincter pressure. This effect is probably related to nicotine—the main neurotoxic effecter of smoking. As has been demonstrated by esophageal manometry, the transdermal delivery of nicotine is associated with a significant reduction in lower esophageal sphincter pressure. In vitro studies also have found an increased, nicotine-induced relaxant response in isolated gastric fundus smooth muscle strips and in human clasp and sling fibers from the proximal stomach.

Perinatal smoking exposure also may be involved in the pathophysiologic mechanisms of GER because it affects the maturation of the central nervous system during a critical period of development. The main effect of perinatal smoking exposure has been ascribed to nicotine. By providing excessive cholinergic stimulation throughout pre- and/or postnatal life, nicotine can alter the control of autonomic functions. It has been shown that neonatal smoking exposure decreases parasympathetic tone. Moreover, studies of neonates have suggested that decreased vagal activity could reduce the myogenic control of the lower esophageal sphincter and thus induce relaxation.

The involvement of other mechanisms cannot be ruled out. Prenatal smoking exposure significantly increases the frequency and duration of body movements and the frequency of obstructive apnea and central apnea—especially during REM sleep, which may favor the occurrence of reflux.

Proximal migration of the GER-imp reflux was twice as frequent in the smoking-exposed group than in the nonexposed group. Perinatal smoking exposure might therefore expose infants to a greater clinical risk. Due to anatomic contiguity, distal retrograde migration of the gastric content exposes the body to a risk of aspiration into the airways. This risk could be exacerbated in infants exposed to tobacco smoke, because the latter decreases aerodigestive reflexes (such as reflexive pharyngeal swallowing) in adults. If gastric reflux reaches the upper airway, it might trigger upper airway reflexes (such as laryngeal chemoreflexes, which can cause major cardiorespiratory inhibition). In newborn lambs, postnatal exposure to environmental tobacco smoke increases cardiorespiratory inhibition and decreases protective mechanisms during laryngeal chemoreflexes. Exposure to cigarette smoke during gestation also was reported to accentuate the laryngeal chemoreflex in rat pups.

The effect of perinatal smoking on GER patterns was significant during REM sleep. This may have clinical relevance. Not only REM sleep is the main vigilance state in the neonate, but also, the reflexes that protect the respiratory tract against pulmonary aspiration are depressed during this sleep state. Smoking exposure could strengthen this deleterious effect because this decreases the stimulus-induced arousal process during REM sleep; the latter process is required to prevent adverse cardiorespiratory events in response to laryngeal stimulation by gastric contents.

The study had several limitations. The small number of included infants may have prevented some intergroup differences (particularly those concerning GER-pH events) from achieving statistical significance. Smoking during pregnancy is associated with an increased risk of preterm birth; the latter might represent a major confounding factor for the occurrence of GER. Our results should therefore be interpreted with caution, because infants born premature are more prone to GER. A synergistic effect of smoking exposure and prematurity cannot be ruled out when considering our results. Nevertheless, we did not find any difference between infants born preterm and infants born full term with regard to the number and characteristics of GER-pH and GER-imp (as also found in a recent study).

Cotinine levels do not provide a detailed history of exposure to tobacco smoke throughout pregnancy and after birth. We were thus not able to differentiate between pre- and postnatal effects of smoking. At birth, a newborn’s urine cotinine level reflects in utero exposure to tobacco smoke at the end of pregnancy. Urine cotinine is also a biomarker of second-hand exposure in infants. In a study of prenatally exposed newborns, Mansi et al showed that neonatal urinary cotinine was significantly associated with the mother’s daily nicotine intake. In infants from nonsmoking mothers, paternal smoking was the most significantly related determinant of measurable levels of urinary cotinine.

In neonates, Etzel et al found an averaged cotinine half-life of 68 hours (range: 37–160 hours), whereas Leong et al found a median half-life of 28.3 hours (range: 6–259 hours) in infants. In the present study, our assay’s limit of detection (1 ng/mL) enabled us to measure any exposure to nicotine. In view of our study’s objectives and procedures, urinary cotinine was measured on the day of MII-pH monitoring (the GER investigation) between 2 and 125 days after birth. Therefore, with the exception of 6 neonates exposed only during the in utero period, the observed urinary cotinine concentration can result from in utero smoke exposure and/or from second-hand smoke exposure at home after birth.
We thank David Fraser, PhD (Biotech Communication SARL, Ploudalmézeau, France) for co-copying support. We also thank the staff in the Department of Pediatrics at Amiens University Medical Center for assistance with the experiments.

References


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