

Assessment of Behavior during Labor in Rats and Effect of Intrathecal Morphine

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Background: Efficacy of analgesics varies with the type of pain. Little is known in this regard concerning labor pain, given the ethical barriers to study in humans and the lack of surrogate animal models. To address this, the authors classified and quantified spontaneous behaviors during labor and delivery in rats and examined the effects of a known analgesic, intrathecal morphine.

Methods: Pregnant rats were video recorded for 72 h surrounding the time of anticipated labor and delivery. Specific behaviors were identified and classified into general activities, phasic stretching behaviors, and maternal attention activities. Rats received intrathecal infusion of saline or morphine, 0.035–3.5 µg/h, beginning approximately 1 day before delivery, and effects on behaviors and response to noxious heating of the paw were quantified.

Results: Phasic stretching behaviors occurred with high frequency before delivery of the first pup and were rare after delivery of the last pup. Intrathecal morphine at infusion rates greater than 0.035 µg/h abolished these behaviors without affecting general or maternal behaviors or the timing or duration of labor and delivery. Morphine was also antinociceptive to noxious heat, but only at infusion rates of 1.0 µg/h or higher.

Conclusions: Phasic stretching behaviors are observed after distension or inflammation of pelvic viscera in rats, and similar behaviors occur during labor and delivery. Selective and dose-related blockade by intrathecal morphine of only these behaviors suggests that they reflect nociception and that this simple monitoring method can be used to study therapies for the pain of labor and delivery.

MOST women experience moderate to severe pain during labor and delivery, and a majority of women in many countries, including the United States, receive epidural or spinal injections for its treatment. Although these analgesic methods are effective, they are costly, produce significant side effects, and are not readily available in many institutions. Systemic opioids or nitrous oxide, in restricted doses that do not affect the fetus, provide mediocre analgesia.^{1,2} As such, there is an unmet need

for effective systemic analgesic therapy for the pain of labor and delivery.

A better understanding of nociception during labor in animals may result in new hypotheses regarding its physiology and new pharmacologic treatments. The first stage of labor involves primarily visceral pain, and visceral pain differs from somatic pain in many aspects.³ The study of pain from the gastrointestinal and genitourinary tract has been aided by description of specific behaviors in conscious rats induced by distension of these structures.^{4,5} In contrast to the obvious abdominal guarding reflex and stretching induced by distension of those structures, distension of the uterus in the nonpregnant rat produces minimal changes in behavior, restricted primarily to subtle reductions in exploration of a novel environment.⁶ We previously showed that distension of the uterine cervix in the lightly anesthetized rat results in reflex contraction of the abdominal musculature, neuronal activation in the dorsal horn of the thoracolumbar spinal cord, and, after discontinuation of the anesthetic, specific stretching behaviors in the postoperative period that are sensitive to opioids.^{7–10} A similar pattern of neuronal activation also occurs in the dorsal horn of the thoracolumbar spinal cord after labor and delivery in rats,¹¹ suggesting that labor and delivery produce nociception by stimulation of afferents to the uterine cervix. That study¹¹ quantified stretching behaviors during the last 75 min before delivery of the first pup but did not assess other behaviors. The primary purpose of the current study was to codify and quantify spontaneous behaviors during labor and delivery in the rat in addition to stretching behaviors thought related to uterine contractions.

Intrathecal injection of opioids without local anesthetic produce dose-dependent analgesia in women during the first stage of labor,¹² presumably by a direct spinal action. Although intrathecal morphine was previously reported not to alter duration of labor, viability of the newborns, or attention to the newborns in rats,¹³ the effect of intrathecal morphine on spontaneous behaviors in rats during labor and delivery has not been examined. A secondary purpose of the current study was to determine the effect of a range of intrathecal morphine doses on rat behavior during labor and delivery. Epidural morphine reduces stretching behavior during labor in rats,¹¹ but whether this is a general depression of behavior or specific to this presumed response to a noxious stimulus has not been examined. We reasoned that a specific

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effect of intrathecal morphine in low doses on behaviors that were only present during labor would further validate the use of such behaviors as a model for nociception during labor in this species.

Materials and Methods

Animals

The study protocol was approved by the Animal Care and Use Committee of Wake Forest University School of Medicine, Winston-Salem, North Carolina. A total of 25 primigravid pregnant Sprague-Dawley rats (Taconic, Hudson, NY) were studied. Animals were housed individually with free access to the standard food and water and a 12:12 h light-dark cycle.

Surgical Procedures

For all surgical procedures, animals were anesthetized using isoflurane (1-5%) in oxygen with spontaneous ventilation. Sterile preparation of the surgical site was performed with povidone-iodine solution followed by a sterile drape. On day 15 of pregnancy, animals were anesthetized, and after sterile preparation, an incision was made at the dorsal region of neck to expose the dura mater. Under direct vision, a 32-gauge polyethylene catheter (ReCathCo, Allison Park, PA) was inserted caudally through the cisternal membrane and advanced for 6.5 cm such that the tip was located in the thoracolumbar region. The other end of the catheter was connected to a piece of Tygon tubing (Saint-Gobain Performance Plastics, Akron, OH) and was secured in the neck. All incision layers were closed with 4-0 silk. After the surgery, rats with any sign of sensory or motor deficit were killed immediately and excluded from the study.

For intrathecal therapy, a 7-day continuous infusion pump (delivery rate at 1 $\mu\text{l}/\text{h}$, Alzet; Durect Corporation, Cupertino, CA) was filled with solution containing either saline or preservative-free morphine (0.035, 0.35, 1.0, or 3.5 $\mu\text{g}/\mu\text{l}$) and placed into an incubator overnight (37°C) for activation. The next morning, on day 21 of pregnancy, animals were anesthetized and a sterile field was prepared. The previous incision was reopened, and the extension tubing from the pump was connected to the intrathecal catheter. Care was taken to visually inspect the catheter and pump to assure the absence of any air bubbles. The pump was implanted subcutaneously and secured on the side of the back. The incision was closed with 4-0 silk suture, and the animal was placed in the cage for recovery. One hour later, the rat was placed in a chamber with clear plastic walls for behavioral observation.

Behavioral Testing

To determine the effect of intrathecal morphine on acute somatic nociception, we determined latency to withdrawal from a heat stimulus to the paw as previ-

ously described.¹⁴ Briefly, on days 15, 16, 17, and 23 or, in one case, 24, from the onset of pregnancy, animals were placed in a study room for 30 min for acclimation. Thermal testing was conducted by focusing a heated light beam to the hind paw, and the time was recorded until paw withdrawal. A cutoff of 30 s was used to avoid tissue damage, although in no case in the current study was withdrawal latency this long. An average of three tests was used for data analysis.

To determine spontaneous behavior during labor and delivery, animals were placed in individual chambers with clear plastic walls in an isolated study room. Usually, behavior from two to four animals was recorded simultaneously, using separate digital cameras, for 72 h continuously. Animals had free access to food and water and a normal light-dark cycle throughout the entire experimental period.

At the end of experiment, the video recording was stopped, and the number of pups and their viability were recorded. The video recordings were manually reviewed, and rat behaviors were analyzed by one investigator (D.R.C.) blinded to group assignment, using Noldus Observation 5.0 Pro (Noldus Information Technology, Wageningen, The Netherlands). This software allows the investigator to mark the start and stop time of each predefined behavior and provides summary analysis as well as time-specific data. Behaviors were coded beginning 2 h from the time of delivery of the first pup until 30 min after the delivery of the last pup. Specific behaviors quantified were those identified in a previous study in nonpregnant rats that had undergone distension of the uterine cervix¹⁰ as well as behaviors observed in a preliminary assessment of four rats during labor and delivery (data were not included in the analysis). Three classes of behaviors were observed and quantified. General activities included eating food pellets, drinking water, rearing (vertical exploration), and grooming of the thorax and head. Phasic stretching behavior during labor included squashing (symmetrical contraction of the lower body and extremities), lateral contraction (asymmetrical contraction of the lower body and extremities), elongation (stretching of the abdomen and all four extremities), and phasic humped back posture. Maternal attention activities included nest building, licking pups, and eating the placenta. Within each general class, behaviors were assessed separately, and a composite score of the sum of behaviors was also calculated. In addition to these three classes of behaviors, we quantified expulsive, pushing efforts, which were very brief (<2 s) and resulted within seconds to minutes in the delivery of a pup. Behaviors were quantified beginning 2 h before delivery of the first pup until 30 min after delivery of the last pup. Both the incidence and the duration spent in each behavior were determined.

Behavior data were generally not normally distributed and are expressed as median (25th, 75th percentiles).

Table 1. Labor Characteristics and Withdrawal Latency to Noxious Heat

Group	Time from First to Last Pup, min	No. of Pups	Day of Delivery	Withdrawal Latency, s	
				Days 15–17	Days 23–24
Saline	76 ± 34	14 (10, 15)	23 (23, 23)	15.8 ± 1.7	10.3 ± 0.7
Morphine					
0.035 µg/h	65 ± 15	12 (12, 13)	23 (23, 23)	13.0 ± 1.0	14.0 ± 1.3
0.35 µg/h	65 ± 29	11 (10, 12)	22 (22, 23)	13.9 ± 0.8	14.0 ± 2.3
1.0 µg/h	73 ± 24	11 (11, 12)	23 (23, 23)	13.7 ± 0.8	18.8 ± 3.3*
3.5 µg/h	89 ± 27	11 (10, 15)	22 (22, 23)	12.3 ± 2.3	18.4 ± 2.9*

* $P < 0.05$ compared with saline.

Thermal withdrawal latency data were normally distributed and are expressed as mean ± SEM. Treatment groups were compared for behavioral data using non-parametric analysis of variance followed by the Dunn test, using saline as the comparator, and for thermal withdrawal latency by one-way analysis of variance followed by the Dunnett test, using saline as the comparator. $P < 0.05$ was considered significant.

Results

General Observations

Twenty-four of the 25 animals in this study completed delivery of all pups on day 22 or 23 of pregnancy. One animal in the saline group successfully completed delivery on day 24 of pregnancy. Saline and morphine treated groups did not differ in the day of delivery of first pup, the duration from first to last pup delivered, or the number of pups delivered (table 1). Similarly, treatment groups did not differ in the percentage of viable pups (data not shown).

Acute Somatic Nociception

The average thermal withdrawal latency in the hind paw on days 15–17 of pregnancy was 13.9 s (SD, 2.4 s) and was similar among groups. Withdrawal latency numerically decreased in the saline group after delivery and numerically increased in all morphine groups. Compared with saline, withdrawal latency after delivery was significantly increased in the two highest infusion rates of morphine, 1.0 and 3.5 µg/h (table 1).

Spontaneous Behavior during Labor and Delivery

Time Course of Behaviors. For this description, behaviors were divided into times of labor (beginning 2 h before delivery of the first pup until delivery of the first pup), delivery (interval between delivery of the first and last pup), and postdelivery (from delivery of the last pup until 30 min later). As shown in figure 1, for animals treated with intrathecal saline, general activities were present throughout all observation periods but declined through this time period. Phasic stretching and expulsive efforts were seen only during labor and delivery.

Expulsive efforts during the labor time period typically occurred in the last 5–10 min before delivery of the first pup. Maternal attention activities remained high throughout all three phases, dominated by nesting behavior before delivery and attention to the pups thereafter. Similar patterns of behavior were observed with total duration of time spent in each of these categories (data not shown) as with the incidence data shown in figure 1. The subsequent discussion reflects a sum of the incidence and duration of behaviors during the labor, delivery, and postdelivery periods.

General Activities. Rats were actively eating, drinking, and grooming before the birth of first pup, with the highest incidence and duration of activity associated with grooming. Vertical exploratory behavior (rearing) was less frequently observed. The continuous infusion of morphine had no effect at any infusion rate on the incidence or duration of these behaviors (table 2).

Phasic Stretching Behavior. Squashing and lateral contractions were frequently observed in the period before the delivery of first pup, occurred regularly between deliveries, and were rare after the delivery of the last pup. Elongation posture occurred with much less frequency and duration than these other phasic behav-

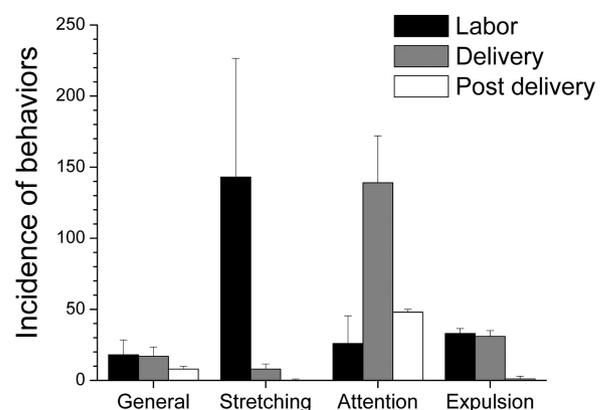


Fig. 1. Incidence of behaviors observed in the 2-h period before delivery of the first pup (Labor), during the time between delivery of the first and last pup (Delivery), and for 30 min after delivery of the last pup (Postdelivery) in rats receiving continuous intrathecal saline. Behaviors were divided as indicated in the text into general activities, phasic stretching activities, maternal attention activities, and expulsive efforts. Data are presented as median + 75th percentile.

Table 2. General Activities during Labor and Delivery

Group	Grooming		Eating		Drinking		Rearing	
	Incidence	Duration	Incidence	Duration	Incidence	Duration	Incidence	Duration
Saline	25 (20, 36)	203 (113, 258)	0 (0, 7)	0 (0, 277)	3 (0, 5)	46 (0, 85)	0 (0, 0)	0 (0, 0)
Morphine								
0.035 $\mu\text{g}/\text{h}$	27 (20, 29)	193 (177, 194)	0 (0, 2)	0 (0, 35)	3 (0, 4)	74 (0, 76)	0 (0, 2)	0 (0, 4)
0.35 $\mu\text{g}/\text{h}$	24 (14, 27)	146 (111, 178)	3 (0, 4)	39 (0, 89)	6 (0, 10)	11 (0, 152)	1 (0, 3)	3 (0, 20)
1.0 $\mu\text{g}/\text{h}$	18 (18, 26)	130 (115, 162)	0 (0, 6)	0 (0, 340)	11 (11, 14)	148 (139, 199)	2 (0, 4)	4 (0, 4)
3.5 $\mu\text{g}/\text{h}$	27 (18, 39)	265 (108, 272)	1 (0, 7)	380 (0, 332)	1 (0, 5)	8 (0, 54)	0 (0, 0)	0 (0, 0)

Duration in seconds. No significant differences.

iors (table 3), and humped back posture was rarely observed, regardless of treatment (data not shown). The infusion of intrathecal morphine reduced phasic stretching behavior during labor in a dose-related fashion, with all but the lowest infusion rate of morphine differing significantly from saline (table 3).

Maternal Attention Activities. Nest-building behaviors were observed primarily in the period preceding the delivery of the first pup. Infusion of intrathecal morphine had no effect on the incidence or duration of maternal attention activities before or after delivery (table 4).

Expulsive Efforts. Expulsive efforts immediately preceded delivery of each pup. Intrathecal morphine did not affect the total incidence of expulsive efforts to deliver all pups (saline: 48 [34, 61]; 0.035 $\mu\text{g}/\text{ml}$: 51 [50, 76]; 0.35 $\mu\text{g}/\text{ml}$: 72 [48, 143]; 1.0 $\mu\text{g}/\text{ml}$: 91 [68, 94]; 3.5 $\mu\text{g}/\text{ml}$: 54 [47, 84] expulsive efforts; $P > 0.7$). Similarly, intrathecal morphine did not affect the total duration of expulsive efforts (data not shown).

Composite Summary. Behaviors classified as maternal activities (nesting, interacting with pups and the placenta) dominated the period of labor and delivery, in terms of both incidence and duration spent in these activities (figs. 2A and B, respectively). In saline-treated animals, phasic stretching behaviors were the next most common set of activities and coincided with labor, because they were never observed after the delivery of the last pup. Morphine did not affect general behaviors or maternal activities but produced a dose-related reduction in the composite score of phasic stretching behav-

iors, with all morphine infusion rates except the lowest, 0.035 $\mu\text{g}/\text{h}$, significantly different from saline (figs. 2A and B). In fact, these behaviors were nearly abolished by all doses greater than 0.035 $\mu\text{g}/\text{h}$.

Discussion

Progress in understanding of and development of novel treatment for labor pain has been hindered in part by a lack of an animal model for this class of pain. This statement assumes that labor pain differs in physiology and pharmacology from other types of pain. As investigations in different types of pain progress, it has become clear that pharmacology of analgesia differs significantly from acute noxious stimulation to peripheral inflammation to peripheral nerve injury to acute visceral distension to incisional surgery. The primary contribution of the current study is to define a simple method to examine nociception during labor and delivery in the rat.

Several lines of evidence support our contention that a subset of behaviors observed during labor and delivery in the rat reflect nociception. For one, dilatation of the uterine cervix produces stimulus-dependent increases in nerve activity in the hypogastric nerve, neuronal activation in the dorsal horn of the thoracolumbar spinal cord, guarding reflex of the abdominal musculature, and phasic stretching behaviors after discontinuation of anesthesia after uterine cervical distension.⁷⁻¹⁰ Labor and delivery in the rat are associated with a similar pattern of neuronal activation in the spinal cord dorsal horn¹¹ and,

Table 3. Phasic Stretching Activities during Labor and Delivery

Group	Squashing		Lateral Contractions		Elongation	
	Incidence	Duration	Incidence	Duration	Incidence	Duration
Saline	75 (56, 110)	294 (194, 324)	61 (58, 111)	223 (186, 340)	8 (5, 16)	20 (11, 33)
Morphine						
0.035 $\mu\text{g}/\text{h}$	30 (9, 32)	85 (28, 91)	20 (18, 37)	50 (43, 91)	2 (1, 4)	3 (2, 11)
0.35 $\mu\text{g}/\text{h}$	0 (0, 1)*	0 (0, 2)*	0 (0, 1)*	0 (0, 2)*	0 (1, 3)	0 (0, 4)
1.0 $\mu\text{g}/\text{h}$	5 (0, 7)*	0 (0, 6)*	2 (0, 4)*	2 (0, 5)*	0 (0, 2)	0 (0, 2)
3.5 $\mu\text{g}/\text{h}$	1 (0, 1)*	1 (0, 2)*	1 (0, 4)*	3 (0, 13)*	0 (0, 1)	0 (0, 0)

Duration in seconds.

* $P < 0.05$ compared with saline.

Table 4. Maternal Activities during Labor and Delivery

Group	Nesting		Licking Pups		Eating Placenta	
	Incidence	Duration	Incidence	Duration	Incidence	Duration
Saline	29 (7, 57)	45 (10, 92)	107 (78, 134)	973 (788, 1,164)	62 (52, 85)	998 (727, 1,695)
Morphine						
0.035 $\mu\text{g/h}$	28 (24, 72)	68 (47, 126)	130 (112, 195)	1,126 (948, 1,455)	70 (60, 74)	1,583 (1,382, 1,642)
0.35 $\mu\text{g/h}$	12 (11, 81)	35 (22, 243)	133 (103, 184)	862 (798, 927)	61 (58, 76)	1,192 (824, 1,321)
1.0 $\mu\text{g/h}$	55 (33, 70)	152 (64, 210)	145 (119, 171)	985 (683, 1,156)	78 (59, 81)	1,465 (661, 1,485)
3.5 $\mu\text{g/h}$	37 (16, 62)	115 (54, 117)	110 (97, 130)	895 (493, 999)	62 (61, 107)	1,518 (1,342, 2,298)

Duration in seconds. No significant differences.

in the current study, with similar phasic stretching behaviors. We consider it unlikely that the phasic stretching behaviors observed in the current study represent straining or pushing associated with and important to the delivery of the pups, because these behaviors occurred with high frequency before delivery and were similar to those observed after manual distension of the uterine cervix in the nonpregnant rat.¹⁰ The current study adds importantly to that of Catheline *et al.*¹¹ by quantifying a more complete range of behaviors in these animals, using a software aid to easily summarize their duration and incidence as well as their timing. Using this approach, we extend their observations that one dose of epidural morphine diminished phasic stretching¹¹ by showing that intrathecal morphine abolished these behaviors without influencing the day of delivery or the duration of time from delivery of first to last pup. Finally, similar behaviors are observed after inflammation of the uterus and cervix and during passage of artificial ureteral calculi in rats.^{5,15}

Intrathecal administration of opioids is safe and effective in the treatment of pain during the first stage of

labor in women.¹² This common clinical practice followed safety investigations in rats published more than 25 yr ago, which demonstrated a lack of effect of intermittent injections of morphine on duration of labor or viability of newborns.¹³ Handling of animals to provide those injections precluded observation of spontaneous behaviors. The current study adds to this understanding by extending these observations to continuous morphine infusion and by examining its effects on spontaneous behavior during labor and delivery. We confirmed the lack of effect of intrathecal morphine on the timing and duration of labor and delivery and also observed a lack of effect of intrathecal morphine on general spontaneous behaviors or those associated with interactions with the pups.

Intrathecal morphine infusion for several days in the current study inhibited phasic stretching behaviors during labor and delivery as well as increasing the latency of withdrawal to noxious heat to the paw. Although tolerance develops over 3–5 days of intrathecal morphine infusion in rats,¹⁶ the current observations suggest that tolerance development, if it occurred under the condi-

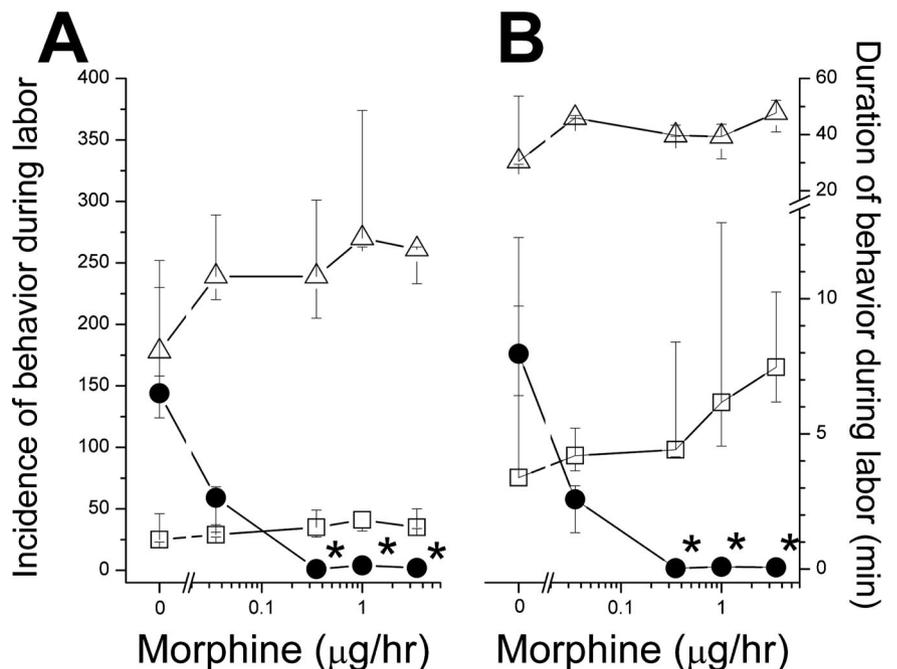


Fig. 2. Cumulative incidence (A) and duration (B) of the sum of general activities (open squares), phasic stretching behaviors (solid circles), and maternal attention activities (open triangles) during labor as a function of infusion rate of intrathecal morphine. * $P < 0.05$ compared with no morphine (saline control).

tions of the current study, was incomplete. Morphine affected labor behaviors at lower infusion rates than those which produced antinociception to heat of a somatic structure. This could reflect a difference in sensitivity to spinal opioid therapy to different stimulus modalities (thermal *vs.* mechanical) or a difference in the relative strengths of the stimuli. Alternatively, this could reflect a difference in sensitivity to spontaneous compared with elicited behaviors. We previously showed that a smaller dose of analgesic is required to block abnormal spontaneous behaviors after incisional surgery than to block hypersensitivity to manually applied stimuli.^{17,18} Those studies showed that doses to block abnormal spontaneous behavior better predicted clinically used doses than those to block elicited behaviors,^{17,18} providing a strong rationale for the use of spontaneous behaviors after nociception in the study of analgesics.

In summary, labor and delivery in rats are associated with a high frequency of the same phasic stretching behaviors observed after other noxious stimuli to pelvic viscera including the uterine cervix. Blockade of these behaviors by intrathecal morphine without affecting other behaviors or duration of labor suggests that these behaviors reflect a noxious stimulus but are not necessary for accomplishment of delivery. These results validate a laboratory model to examine the physiology of labor pain and the pharmacology of its treatment.

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