Late Preterm Infants: Near Term But Still in a Critical Developmental Time Period
Amir Kugelman and Andrew A. Colin

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Late Preterm Infants: Near Term But Still in a Critical Developmental Time Period

abstract

Late preterm (LP) infants are defined as those born at 34-0/7 to 36-6/7 weeks’ gestational age. LP infants were previously referred to as near term infants. The change in terminology resulted from the understanding that these infants are not fully mature and that the last 6 weeks of gestation represent a critical period of growth and development of the fetal brain and lungs, and of other systems. There is accumulating evidence of higher risks for health complications in these infants, including serious morbidity and a threefold higher infant mortality rate compared with term infants. This information is of critical importance because of its scientific merits and practical implications. However, it warrants a critical and balanced review, given the apparent overall uncomplicated outcome for the majority of LP infants.

Others reviewed the characteristics of LP infants that predispose them to a higher risk of morbidity at the neonatal period. This review focuses on the long-term neurodevelopmental and respiratory outcomes, with the main aim to suggest putative prenatal, neonatal, developmental, and environmental causes for these increased morbidities. It demonstrates parallelism in the trajectories of pulmonary and neurologic development and evolution as a model for fetal and neonatal maturation. These may suggest the critical developmental time period as the common pathway that leads to the outcomes. Disruption in this pathway with potential long-term consequences in both systems may occur if the intrauterine milieu is disturbed. Finally, the review addresses the practical implications on perinatal and neonatal care during infancy and childhood. Pediatrics 2013;132:741–751
INTRODUCTION

Late preterm (LP) infants are defined as those born at 34-0/7 to 36-6/7 weeks gestational age (GA).1 LP infants are born near term, but are immature.2 3 The late premature birth interrupts normal in utero fetal development during the last 6 weeks of gestation that represents a critical period of growth and development of the fetal brain and lungs. Kinney defined a critical period as a time-sensitive, irreversible decision point in the development of a neural structure or system in which deprivation of the normal environment interrupts the maturational trajectory of the structure/system.4 We find this definition attractive and applicable also to the respiratory system and likely to other systems as well. This review will focus on the neurodevelopmental and the respiratory systems as models for fetal and neonatal maturation.

LATE PREMATURITY: SCOPE OF THE PHENOMENON, MORTALITY, AND NEONATAL MORBIDITY

LP newborns comprise the fastest growing subset of neonates, accounting for ~74% of all preterm births and ~8% to 9% of total births in the United States.5 There is accumulating evidence that during infancy LP infants were more vulnerable to death likely varying with circumstances and are hard to deduce from existing epidemiologic studies.

Despite the low absolute risk for death and other complications in LP infants, factoring in their large numbers compared with more extreme preterm infants, the relative risk translates into significant medical, emotional, and economic impact at the population level.12,22

Most LP infants (~80%) will have a neonatal course with no significant complications.23 However, compared with term neonates, LP newborns are at increased risk for the following: respiratory distress syndrome, jaundice, hypoglycemia, temperature instability, apnea, and respiratory distress.2,3,6,12,16,24,25 These morbidities variably result in workup for sepsis evaluations and antibiotic therapy, intravenous fluid administration, ventilatory support, and increased length of stay (~30%).2,12,25 Predisposing factors to these morbidities were reviewed by Engle et al.2 LP infants were also found to have increased readmission rate2,6,7,24,26 and more use of medical resources during their first year of life, such as respiratory syncytial virus (RSV) prophylaxis.27

The rate of complications decreases with progression of gestational age through the LP period.6 Shapiro-Mendoza et al compellingly demonstrated the relationship between advancing age and morbidity, reporting a sevenfold increase (22.2% vs 3.0%) in neonatal morbidities in LP infants compared with term infants.23 Respiratory complications are the prime morbidities of LP infants.10,12,16,24,25 A large retrospective study found that the odds of respiratory distress syndrome decreased significantly with each advancing week of gestation up to 38 weeks compared with 39 to 40 weeks.28 Despite a relatively low absolute risk for RDS (10.5%) or transient tachypnea of the newborn (TTN) (6.4%) at 34 weeks compared with more premature infants, this rate poses an increased risk for LP infants when

...
compared with term infants (0.3% for RDS and TTN).29

LONG-TERM MORBIDITY OF LP INFANTS

Neurodevelopmental Long-Term Outcome

Neurodevelopmental Outcome: Clinical Evidence

LP infants are often perceived to have similar risks for developmental problems as neonates born at term. Because the rate of intraventricular hemorrhage is low (0.2% to 1.4%),10,29,30 albeit higher than in term infants10 and their rate of periventricular leukomalacia (PVL) is low although practically unknown,4,31 they do not undergo routine brain ultrasonography. Furthermore, the common practice is not to follow them in neurodevelopmental centers.

Recently, however, there is growing concern that these infants are more vulnerable to brain injury than previously appreciated. PVL is not restricted to the very prematurely born infant, and occurs in the LP (and term) infants as well.32–35 Some studies reported a threefold increased risk for developing cerebral palsy in LP infants compared with term infants.10,36

There is mounting evidence that LP infants have more subtle neurodevelopmental issues such as inferior academic performance or behavioral problems.37–45 McGowan et al reviewed the literature relating to early childhood development of LP infants born at 34 to 36 weeks’ gestation at 1 to 7 years of age.45 Of 4581 studies, 10 (3 prospective and 7 retrospective cohorts) were included. They concluded that LP infants compared with term infants were at increased risk for adverse developmental outcomes and academic difficulties up to 7 years of age, but that a systematic measurement of early childhood outcomes was lacking. We tabulated the results of the recent literature (Table 1) supporting higher risk for decreased developmental and school performance and academic abilities of LP infants.37–44 Notably, the results of other studies were less conclusive.46,47

The available data are weighted toward a concern regarding the long-term neurodevelopmental outcome of LP infants. Given, however, that the data rely mostly on retrospective studies, and that not all studies focused on healthy LP infants, a need for prospective large studies is obvious.

Mechanisms of Neurologic Effects of LP Birth

A number of possibilities could be postulated as playing a role in the causation of long-term neurodevelopmental abnormalities in LP infants and include: (1) prematurity itself leading to maturation outside the uterine milieu, (2) the morbidity associated with LP, and (3) the primary cause of premature labor.

The last half of gestation (including the late prematurity period) was described as a “critical period” for brain development and characterized by rapid and/or dramatic changes in 1 or more molecular, neurochemical, and/or structural parameters (Fig 1).4 Brain development is not a linear process, and the critical development changes that occur in the brain in the last weeks of gestation can easily be underappreciated. To what extent the extraterine milieu affects the process is not well studied. Brain weight at 34 weeks is only 65% of that of the term brain and gyral and sulcal formation is incomplete. Cortical volume increases by 50% between 34 and 40 weeks’ gestation, and 25% of cerebellar development occurs during this time period (Fig 1).48–50 Therefore, in the LP infant, the period between 34 and 40 weeks’ gestation is critical, because the relative percentage of both gray

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Participants</th>
<th>Main Outcomes</th>
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<tbody>
<tr>
<td>Chyi et al37</td>
<td>Retrospective</td>
<td>767 LP/13 671 term</td>
<td>Increased risk for below-average reading competence at all grade levels, increased need for individualized education programs at early school ages, and increased need of special education.</td>
</tr>
<tr>
<td>Gray et al38</td>
<td>Prospective</td>
<td>260 LP /General population</td>
<td>Increased rate of behavior problems at age 8 yr</td>
</tr>
<tr>
<td>Huddy et al39</td>
<td>Retrospective</td>
<td>83 LP</td>
<td>Increased rate of hyperactivity, behavioral, or emotional problems</td>
</tr>
<tr>
<td>Woythalier et al40</td>
<td>Prospective</td>
<td>1200 LP/6300 term</td>
<td>Increased risk for mental or physical developmental delay at age 24 mo</td>
</tr>
<tr>
<td>Morse et al41</td>
<td>Prospective</td>
<td>7152 LP/152 661 term</td>
<td>Increased risk for developmental delay or school-related problems through age 5 yr</td>
</tr>
<tr>
<td>Lipkind et al42</td>
<td>Retrospective</td>
<td>13 207 LP/199 589 term</td>
<td>Increased need for special education and lower adjusted math and English scores at school age. Linear association between GA and test scores through 39 wk gestation</td>
</tr>
<tr>
<td>Quigley et al43</td>
<td>Retrospective</td>
<td>537 LP/6159 term</td>
<td>Increased risk for poorer educational achievement at age 5 yr</td>
</tr>
<tr>
<td>Talge et al44</td>
<td>Retrospective</td>
<td>168 LP/168 term</td>
<td>Increased risk for behavioral problems and lower IQ at age 8 yr</td>
</tr>
<tr>
<td>Odd et al46</td>
<td>Prospective</td>
<td>741 (32–36 wk)/13 102 term</td>
<td>Despite an increased risk for special educational needs, there was little evidence of a reduction in IQ, memory, or attention measures at school age</td>
</tr>
<tr>
<td>Gurka et al47</td>
<td>Prospective</td>
<td>53 LP/1245 term</td>
<td>No difference regarding cognition, achievement, behavior, and socioemotional development through childhood</td>
</tr>
</tbody>
</table>
matter and myelinated white matter to total brain volume increases exponentially. The LP infant is at risk for white matter injury through multiple potential mechanisms, including developmental vulnerability of the oligodendrocyte, glutamate-induced injury, cytokine- and free radical-mediated injury, and the absence of maturation-dependent antioxidant enzymes that regulate oxidative stress. Synaptogenesis and dendritic arborization are occurring, and are likewise incomplete in the LP brain compared with the term brain, albeit not to the degree seen in the very premature brain.

Beyond the question of whether the extraterine environment would be an inherently inhospitable milieu to normal development, multiple compounding factors in the extraterine environment could be related to the developmental immaturity of LP infants and amplify the risk for brain injury and subsequent neurologic sequelae. These include the risk for development of intraventricular hemorrhage and PVL, hypoxic respiratory failure, hypoglycemia, hyperbilirubinemia, infection, and chorioamnionitis. The LP neonate has a two- to fivefold increased risk for developing significant hyperbilirubinemia. When compared with term newborns with similar bilirubin levels, LP infants are more likely to have severe neurologic sequelae and neurotoxicity at earlier postnatal ages. This most likely is secondary to a combination of factors, including immaturity of conjugation and enzymatic pathways, immature feeding patterns, and the age-dependent susceptibility of developing neurons and astrocytes to bilirubin-induced injury. On the reassuring side, a recent prospective study reported that there were no significant differences in early childhood development (at 3 years of age) between LP infants who received neonatal intensive or high-dependency care and those who did not. This study did not have a control group of term infants, but as is, it may be pointing toward factors other than short-term morbidities as playing a role in the long-term outcomes. The primary cause of premature labor might also impair neurodevelopmental outcome. LP infants compared with term infants have higher rates of congenital malformations, IUGR, high-risk pregnancies (preeclampsia, hypertension, diabetes), chorioamnionitis, and maternal smoking. Each of these factors, although not specific to LP infants, could potentially be associated with poor neurodevelopmental outcome or behavioral problems. For example, SGA was associated with poor outcome in extremely low birth weight infants and in term infants, but the few studies that assessed the correlation between SGA and poor long-term neurodevelopmental outcome were negative for LP infants. Although intuitively correct, larger, prospective studies focusing on LP infants are needed to assess whether findings from very preterm or term infants are generalizable to this subgroup of infants.

To summarize, LP infants are at risk for long-term neurodevelopmental morbidities. The primary causes of late prematurity and prenatal factors as well as congenital malformations and IUGR may expose the LP infant to short-
long-term sequelae (Fig 2A). The late prematurity itself puts the LP infant at risk for neonatal morbidities, which are usually of modest severity compared with more extreme premature infants, but may contribute to the insult. The interruption of the in utero maturational process of the brain, which is in a critical period, is probably the main reason for the long-term neurodevelopmental outcomes.

**Respiratory Long-Term Outcome**

*Respiratory Outcome: Clinical Evidence*

A number of publications attempted to address the question whether late prematurity affects the respiratory system in the long term (Table 2)57–64 Several studies reported an association of preterm birth (30–36 weeks’ GA) without clinical lung disease with altered lung development and function.59,60,62–64 Friedrich et al64 in a longitudinal study found that despite normal lung volume, healthy preterm infants had persistently reduced airflow through the age of 16 months and concluded that preterm birth in itself was associated with altered lung development. A single study showed a potential improvement, especially for large airway function, with advancing age.61

Whether LP birth is associated with airway disease such as asthma in early childhood remains controversial. Abe et al65 did not find an association between LP and physician-diagnosed asthma. Similarly, a Swedish national cohort study failed to find an association between LP birth at 33 to 36 weeks’ gestation and asthma medications in young adults.66 Conversely, Goyal et al67 in a retrospective cohort study using electronic health record data from a primary care network, demonstrated that birth at late-prematurity might be a risk factor for the development of asthma within the first 18 months of life. Escobar et al68 in a retrospective cohort study reported that LP birth was associated with an increased risk for recurrent wheeze in the third year of life. The different findings could result from the different methods of asthma diagnosis, age groups at diagnosis, and from the difficulties in diagnosing asthma in early childhood. A recent large prospective cohort study showed that the number of hospitalizations caused by respiratory problems during the first year of life was doubled in moderately preterm (32–36 weeks’ GA) compared with term infants.69 At preschool age, moderately preterm infants revealed more nocturnal cough or wheeze during or without a cold and increased use of inhaled steroids. At the age of 5 years, rates of respiratory symptoms between moderate and early preterm-born (<32 weeks’ GA) children were similar; both were higher than in term-born children. The most important risk factors for continuing respiratory problems in moderately preterm-born children were eczema, respiratory problems and passive smoking during the first year of life, higher social class, and a positive family history of asthma. Some of the studies reporting on the long-term outcomes of the respiratory system included infants of less than 34 weeks’ GA. Recognizing that the risks are decreasing with advancing age,
caution needs to be exercised when generalizing their findings to the entire group of LP infants.

**Mechanisms of Respiratory Effects of LP Birth**

Three factors play a role in the respiratory vulnerability of LP infants:
(1) prematurity with its inherent developmental and consequently physiologic components, (2) heightened rate of respiratory morbidity in the neonatal period and prenatal factors, and (3) increased susceptibility to RSV.

Lung development occurs mostly in utero. LP infants are born within the final stages of the saccular stage (26–36 weeks of gestation). Premature birth during this critical respiratory maturation period may result in significant alteration in lung function and physiology. Normal in utero lung development occurs according to a highly programmed sequence in a stable milieu, notably and importantly, one that is profoundly more hypoxic relative to the atmosphere. This hypoxic environment represents the norm for lung organogenesis, including vascular development. Early events of trophoblast differentiation are oxygen regulated. It is safe to assume that there is an array of other yet to be determined hormonal and biochemical factors that play a role in regulating the sensitive choreography of lung development and differentiation in utero and are altered or absent after delivery.

To understand the mechanisms that possibly explain the morbidity in LP infants, it is necessary to understand lung physiology at this stage of their development. In early life, the lung-airspace surface area occurs (1 m²). Premature delivery is associated with altered airway development during early infancy (reduced maximal expiratory flow at functional residual capacity up to 12 mo) in healthy preterm infants. Although no difference in PFT between infants with and without RDS, FEV₁ and specific airway conductance were significantly reduced in the premature infants compared with children born at term when studied by spirometry at age 6–9 yr.

<table>
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<tr>
<th>Reference</th>
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<th>Participants</th>
<th>Main Outcomes</th>
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<tbody>
<tr>
<td>McEvoy et al60</td>
<td>Prospective</td>
<td>31 LP (33–36 wk)/31 term</td>
<td>Healthy LP infants studied at term-corrected age have decreased compliance and increased resistance</td>
</tr>
<tr>
<td>Todisco et al60</td>
<td>Case control, matched siblings</td>
<td>34 LP (34–36 wk)/34 term</td>
<td>Pulmonary functions at age ~11 yr revealed air trapping but no significant difference in bronchial responsiveness in healthy LP</td>
</tr>
<tr>
<td>Kotecha et al61</td>
<td>Prospective</td>
<td>81/48 infants: 33–34 wk, 248/132 infants: 35–36 wk, 6308/4284 infants: term, at 8–9 yr and 14–17 yr, respectively</td>
<td>At 8–9 yr of age, measures of forced expiratory spirometry are lower in children born at 33–34 wk GA compared with children born at term and are of similar magnitude to those in the extremely preterm infants. Infants born at 35–36 wk GA had the same PFTs as term infants. By 14–17 yr, measures of airway function in children born at 33–34 wk GA were similar to those in children born at term with the exception of forced expiratory flow rate between 25% and 75% of exhaled vital capacity</td>
</tr>
<tr>
<td>Hoo et al62</td>
<td>Prospective</td>
<td>24 infants 33.2 ± 2.2 wk</td>
<td>Preterm delivery is associated with altered airway development during early infancy (reduced maximal expiratory flow at functional residual capacity up to 12 mo) in healthy preterm infants</td>
</tr>
<tr>
<td>Mansell et al63</td>
<td>Case control</td>
<td>18 premature infants with RDS/26 premature infants without RDS/18 term</td>
<td>Although no difference in PFT between infants with and without RDS, FEV₁ and specific airway conductance were significantly reduced in the premature infants compared with children born at term when studied by spirometry at age 6–9 yr</td>
</tr>
<tr>
<td>Friedrich et al64</td>
<td>Prospective</td>
<td>26 infants (30–34 wk)/24 infants at term</td>
<td>Healthy infants born prematurely demonstrate decreased forced expiratory flows and normal forced vital capacities in the first and second years of life</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume at 1 s; PFT, pulmonary function tests.
predestined evolution of the matura-
tional process is aborted or altered in
the extraterine milieu.

The morbidities during the neonatal
period could also be affected by prenatal
factors. Epidemiologic studies demon-
strate that IUGR and low birth weight are
associated with impaired lung function
and increased respiratory morbidity
from infancy throughout childhood and
into adulthood. Operative delivery,
maternal diabetes, and chorioamnioni-
tis also increased RDS risk in LP
infants. Gestational hypertension or
preeclampsia appear to protect from
neonatal respiratory morbidity, but
higher rates of cesarean section di-
mish this protective effect, and oth-
er studies reported an opposite effect.

Chorioamnionitis, which is more com-
mon in LP infants, may have a com-
plex effect on the pulmonary system. A
low-grade inflammatory stimulus in
utero may prime the fetal lung for ac-
celerated maturation. Depending on the
severity of inflammatory injury to the
alveolar-capillary unit, however, serum
proteins leak into the airways and in-
duce surfactant inactivation. After this
intrauterine first hit, the immature in-
fant may develop a more severe RDS.
Chorioamnionitis and cytokine ex-
sure in utero, added to neonatal lung
injury because of respiratory morbidity
can lead to a pulmonary inflammatory
response in the immature lungs of very
preterm infants, contributing to the
development of “new BPD.” It has yet
to be determined to what extent these
processes described in very preterm
infants affect LP infants. TTN is more
common in LP infants, is associated
with elective cesarean delivery, and is
associated with childhood wheezing
and asthma. While possible, it is not
known if all these prenatal and neonatal
factors also affect the long-term res-
piratory outcome of LP infants. The
possible mechanism is also obscure;
namely, it is unclear whether this is
a result of a direct injury or a multi-hit
phenomenon on the developing res-
piratory system.

The third factor contributing to the
respiratory vulnerability of LP infants is
increased susceptibility to RSV infection
as a consequence of altered lung de-
velopment. This is thought to be primar-
ily related to the failure to de-
velop an adaptive cytotoxic T-lymphocyte
response and inefficient innate im-
mune responses that clear the virus
from the airways. Non-randomized
trials in preterm infants (~30 ± 2
weeks’ GA) suggested that the pre-
vention of lower respiratory tract
illness caused by RSV reduced sub-
sequent recurrent wheeze in infants
without a family history of atopy, but
showed no effect in infants with a
family history of atopy. In a recent
study in otherwise healthy 33 to
35 weeks’ GA preterm infants, pal-
vizumab treatment resulted in a sig-
mificant reduction in wheezing days
during the first year of life, even after
the end of treatment. These findings
implicate RSV infection as an impor-
tant mechanism of recurrent wheeze
during the first year of life in such
infants.

Long-term persistence of early decrease
in PFT was demonstrated by a longiti-
dinal follow-up into early adulthood for an
unselected random population in the
Tucson Children’s Respiratory Study.
These observations suggest that the
notion of a “critical developmental pe-
riod” for the respiratory system does
exist. Deficits in lung function during
early life, especially if associated with
lower respiratory illnesses (espe-
cially RSV), increase the risk for chronic
obstructive pulmonary disease later in
adult life.

To summarize (Fig 2B), prematurity with
termination of pregnancy is associated
with increased respiratory morbidi-
ty in LP infants. The pernicious combi-
nation of RSV bronchiolitis affecting an a priori
compromised lung/airway of LP infants
may have a lasting effect on respiratory
function and consequent long-term
clinical morbidity.

**PRACTICAL IMPLICATIONS**

The American College of Obstetricians
and Gynecologists has recommended
that elective delivery should only take
place after 39 weeks in well-dated
pregnancies. When feasible, preven-
tion of late prematurity within safety
guidelines for the mother and the fetus
should be the goal. The implementation
of hospital quality improvement pro-
grams has successfully reduced the
occurrence of elective early-term and
late-preterm deliveries, as well as as-
associated neonatal morbidity and mor-
tality.

New approaches to decrease the re-
spiratory morbidity in LP infants are
needed. Antenatal corticosteroids were
shown to significantly reduce admis-
sions to special care units in term infants
delivered by elective cesarean sec-
tion. In LP infants, antenatal steroids
did not lower the rate of either RDS or
TTN and did not affect the need for, type,
and means of ventilatory support. An
NIH study (ClinicalTrials.gov Identifier:
NCT01282287) comparing a single course
of antenatal steroids versus placebo is ongoing.

Once a decision is made to deliver LP infants they should be monitored for the possible complications at an appropriate set-up. No study has determined if this should be done in the nursery, in the intermediate care, or in the NICU according to specific GA groups.

From 1995 to 2000, early discharge (less than 48 hours after vaginal delivery) of LP infants had decreased from 71% to 40% in United States. The AAP published detailed guidelines for the care of LP infants. These guidelines suggest that these infants should not be discharged before 48 hours of birth. Early discharge places these infants at greater risk for complications such as rehospitalization, particularly in breastfed or first-born infants. The AAP recommends a follow-up visit 24 to 48 hours after hospital discharge for LP infants, given their increased risk for rehospitalization secondary to jaundice, feeding difficulties, dehydration, and sepsis. Mothers of LP infants were found to be more likely to smoke, less likely to place the infants in a supine position for sleep, and less likely to initiate as well as continue breastfeeding. Given the increased risk for morbidity and mortality in this population, greater attention needs to be focused not only on their medical care in the hospital but also on engaging families in providing appropriate home care after discharge.

These infants should have closer follow-up during infancy and early childhood with focus on neurodevelopmental and respiratory long-term morbidity. RSV prophylaxis to this large group is difficult to address with equanimity because of the potential staggering cost of immunizing a relatively low-risk population. It needs, however, to be acknowledged that RSV bronchiolitis can be reduced, and that immunizing LP infants can result in protecting susceptible lungs from extra insult. Clearly, immunizing all LP infants is unrealistic because of cost considerations. There have been attempts to define specific risk factors and identify a subset of LP infants at the highest risk to vaccinate in different countries. A Canadian study concluded that a risk-scoring tool they developed was a practical, easy-to-use instrument to guide judicious RSV prophylaxis for moderate to high-risk, 33- to 35-weeks’ GA infants. To summarize, a policy of selective RSV vaccination of LP infants that is tailored to economic realities should be developed.

**SUMMARY**

LP infants are born during a “critical developmental time period” for the brain and the lungs and evidence is growing to show that late prematurity is still a time-sensitive, irreversible “decision point” in development. Although these infants are at higher risk for morbidity and mortality compared with term infants, most of them are expected to do well. Yet, the short- and long-term neurodevelopmental and respiratory consequences, other neonatal morbidities, and the emotional and economic burden associated with LP should have practical implication on the approach to and the care of LP infants.

**ACKNOWLEDGMENT**

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