Opioid Detection in Maternal and Neonatal Hair and Meconium: Characterization of an At-Risk Population and Implications to Fetal Toxicology

Monique Moller, BMSc,† Tatyana Karaskov, MD,* and Gideon Koren, MD, FRCP*†*

Abstract: Identification of maternal opioid abuse in pregnancy is often difficult to ascertain in the absence of a reliable self-report. We aimed to characterize an at-risk neonatal population for opioid exposures as well as other drugs of abuse and alcohol. From June 2007 to January 2009, 563 neonatal hair and 1318 meconium specimens were assessed for opioids and were positive in 11.4% and 17.0%, respectively. Neonates testing positive for opioids in hair or meconium analysis were also more likely to test positive for other licit and illicit substances (odds ratio$_{hair}$, 1.75; 95% confidence interval, 1.03–2.97; odds ratio$_{meconium}$, 1.61; 95% confidence interval, 1.16–2.22). Specifically, a positive neonatal hair test for opioids also predicted a positive result for oxycodone. In addition, a positive meconium test result for opioids was associated with positive results for cocaine, oxycodone, methadone, benzodiazepines, and fatty acid ethyl esters (alcohol). Finally, there was a significant correlation between maternal and neonatal hair test results for opioids (Spearman rank rho = 0.657, P = 0.03). Understanding the addiction profiles of these women may lead to better clinical and social management and may largely benefit an at-risk population.

Key Words: opioid, intrauterine exposure, placental transfer, hair detection, meconium, drugs of abuse, alcohol

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INTRODUCTION

Opiates are naturally occurring alkaloids derived from the poppy seed and have been used for thousands of years for the treatment of pain.[1] Opioids (the term used to refer to any compound acting at the mu receptor) provide their analgesic effects through opioid receptors located on nociceptive C and delta-A fibers; this indirectly inhibits the release of pain neurotransmitters such as glutamate and substance P.[2] Additionally, opioids cause disinhibition of dopaminergic neurons, resulting in increased concentrations of dopamine in the nucleus accumbens and thus an intense feeling of pleasure.[1]

Opiates are widely used and typically abused for their outlined sedative, analgesic, and euphoric properties.[3–6] Consumption of opioid-containing medications in Canada is on the rise as 230%, 159%, and 28% increases for oxycodone, fentanyl, and morphine, respectively, were recorded from 2001 to 2005.[7] The identification of opioid abuse, however, is often very difficult to ascertain, especially in pregnancy, as a result of unreliable self-reporting.[8–11]

Although it is largely known that opioids do cross the placenta,[12–14] therapeutic use of these medications in pregnancy is not necessarily contraindicated for several reasons. For example, the treatment for illicit opioid use with a prescribed methadone maintenance program has been shown to decrease maternal and fetal morbidity and mortality and promote fetal stability and growth.[15]

Pharmacovigilance is warranted when treating the pregnant mother with opioid-containing medications. This is because maternal fluctuations of opioids may lead to fetal withdrawal or overdose. Furthermore, infants born to opioid-dependent mothers are frequently faced with significant postnatal problems, including jaundice, aspiration pneumonia, transient tachypnea, infection, and most notably, neonatal abstinence syndrome or withdrawal.[16,17] It has been estimated that neonatal abstinence syndrome occurs in approximately 55% to 94% of in utero opioid-exposed neonates and frequently requires supportive care.[18] Maternal characteristics of the opioid-abusing pregnant woman may also be cause for concern; substance-abusing pregnant women are typically at high risk for malnourishment,[16] lack adequate obstetric care, and these individuals typically reside in incompatible and often violent environments.[19] Therefore, it is important to monitor opioid use in pregnancy and identify potential drug abuse if possible. As such, testing has played a considerable role in the evaluation of maternal and neonatal opioid exposures.[20–23]

Testing for drugs of abuse and alcohol in biologic fluids or matrices offers many advantages, most important of which is objectivity. Although blood and urine are typically used for toxicologic screening, the presence of drugs (and specifically opioids) in these fluids is generally short-lived; thus, detection

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From the *Motherisk Program, Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada; and †Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

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Correspondence: Gideon Koren, MD, FRCP, Motherisk Program, Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G1X8 (e-mail: gidiup_2000@yahoo.com).

becomes limited to recent exposure.[24] Hair is an attractive matrix for assessing chronic exposures for reasons such as ease of collection, stability of the specimen, and a protracted window of detection. Drugs of abuse are incorporated into the adult hair shaft at the time of its formation in the follicle; the majority of incorporated drug remains in the shaft indefinitely and may be subject to analysis.[25] Hair grows at an internationally accepted rate of 1 cm/month[25] and through the use of segmental analysis, hair can provide a detailed account of drug exposures over time. Neonatal hair begins to form at approximately 20 weeks gestation[26] and, similar to adult hair, incorporates drugs of abuse present in fetal circulation.[27] Meconium is comprised of the first few bowel movements of the neonate and begins to form at approximately 12 weeks gestation on initiation of fetal swallowing.[28] Like hair, it is also a matrix by which toxicologic testing may be performed. Therefore, through the exploitation of maternal and neonatal hair and meconium specimens, the detection of maternal opioid use and abuse in pregnancy and subsequent in utero fetal exposures is possible.

This study aimed to identify trends in neonatal opioid exposure and coexposure by other drugs of abuse and alcohol through hair and meconium test results. In addition, the characterization of maternal–fetal passage of opioids by the placenta was assessed using hair test results of mother–infant dyads tested for opioids.

SUBJECTS AND METHODS

The Motherisk Program in the Division of Clinical Pharmacology and Toxicology at the Hospital for Sick Children receives thousands of hair and meconium specimens from across Canada for illicit and licit drug testing each year. Requisition of specimen analysis usually comes from child protection authorities (Children's Aid Societies) or healthcare providers and follows suspicion of parental substance abuse. The tested population primarily includes women and their children, although many paternal samples are also tested as required by authorities. Between June 2007 and January 2009, nearly 9000 specimens were received for analysis, and of these, over 1500 neonates were assessed for opiate drug exposure through hair and/or meconium; 396 neonates were tested using both hair and meconium.

The analyses for alcohol and drugs of abuse are routinely performed in the Motherisk Laboratory by established methods.[29–31] For hair analysis of drugs of abuse, hair was first finely cut in 1 mL methanol and incubated overnight on agitation at 56°C. The next day, the methanol extract was decanted and dried under N_2 at 40°C. Next, 400 μL of phosphate buffer saline (PBS; pH 7.4) was added and the individual drugs were analyzed by enzyme-linked immunosorbent assay using their respective kits manufactured by Immunalysis (San Diego, CA). For meconium testing, approximately 0.5 to 1.0 g was extracted with methanol, centrifuged, and the supernatant diluted 1:5 with PBS. The PBS extract was analyzed using the enzyme-linked immunosorbent assay kits previously described. Fatty acid ethyl esters (FAEE) analysis in meconium first required 50 mg of the specimen to be mixed with 1 mL PBS, transferred to headspace solid phase microextraction autosampler vials, and subject to gas chromatography/mass spectroscopy analysis for four-principle FAEE, namely ethyl palmitate, ethyl linolate, ethyl oleate, and ethyl stearate. Results for FAEE concentration are recorded as a sum of these FAEE.

The opiate enzyme-linked immunosorbent assay kit detects primarily morphine, codeine, hydrocodone, hydromorphone, 6-acetylmorphine, and 6-acetylcodeine; has limited crossreactivity to oxycodone, oxymorphone, normorphone, norcodeine, noroxycodone, noroxymorphone, and nalorphine; and no crossreactivity to other synthetic opioids such as methadone, meperidine, fentanyl, and buprenorphine.

Hair and meconium drug test results are available in electronic (database) and hardcopy form in the laboratory. Ethics approval was obtained from the Research Ethics Board at the Hospital for Sick Children for the study of these results to identify trends of in utero drug exposure. Neonatal hair and meconium sample results (for all drugs/alcohol) were recorded/included if the specimen was tested for opiates. If the sample was not tested for opiates, the data were excluded. Additionally, hardcopy records of tests conducted between June 2007 and January 2009 were examined for potential mother–infant pairs.

Descriptive statistics were used to illustrate the trends of in utero exposure to drugs of abuse and alcohol. Logistic regression analysis was used to determine the likelihood of the presence of other drugs of abuse in conjunction with opiates in neonatal hair and meconium specimens. Odds ratios and their 95% confidence intervals (95% CI) were calculated using SigmaStat 3.11 for Windows (SPSS Inc., Chicago, IL). For some drugs of abuse that did not coexist with opiates in any samples, the odds ratios could not be calculated (eg, benzodiazepines in neonatal hair).

RESULTS

A total of 1515 neonates were tested for opiates in hair and meconium from June 2007 to January 2009 of which 563 hair and 1318 meconium specimens were assessed. Of these, 64 of 563 (11.4%) and 224 of 1318 (17.0%) tested positive for opiates in hair and meconium, respectively. Additionally, 396 neonates were tested for opiates using both hair and meconium specimens; 37 of 396 (9.3%) infants tested positive in both hair and meconium, 36 of 396 (9.1%) tested positive only in the meconium but not in hair, and 10 (2.5%) tested positive in the hair and not meconium.

Of the available 563 neonatal hair specimens tested for opiates, 550 were also tested for other drugs of abuse. Thirty-two of 550 (5.8%) tested positive for opiates and one or more other substances, 30 of 550 (5.4%) tested positive for opiates but negative for other substances, and 185 (33.6%) tested negative for opiates but positive for other substances (Table 1). The odds ratio calculated for testing positive for other drugs of abuse if testing positive for opiates was significant at 1.75 (95% CI, 1.03–2.97). Hence, infants were more likely to be coexposed to other drugs of abuse if testing positive for opiates as determined by neonatal hair testing.

Evidently, many other drugs of abuse are frequently tested for alongside opiates, the most common being cocaine

TABLE 1. Drug Coexposures Among Positive and Negative Opiate Hair Tests

Drug Coexposure Frequency in Hair	Opiate-Positive		Opiate-Negative	
No. of different drugs	No.	Percent	No.	Percent
1	30	48.4	171	92.5
2	30	48.4	13	7.0
3	2	3.2	1	0.5
Total	62	100	185	100

(558 of 563 [99.1%]) and cannabinoids (504 [89.5%]) followed by barbiturates (163 or 29%), amphetamine and methamphetamine (161 and 148 [28.6% and 26.3%], respectively), benzodiazepines (94 [16.7%]), oxycodone (50 [8.9%]), and methadone (45 [8.0%]). Among neonates tested positive for opiates, the odds ratios for testing positive for cocaine/benzoylecgonine (BE) were calculated to be 1.58 (95% $CI_{cocaine}$, 0.90–2.76) and 1.61 (95% CI_{BE}, 0.92–2.82). For marijuana, the odds ratio was 0.97 (95% CI, 0.44–2.16), for methadone the odds ratio was 5.5 (95% CI, 0.89–33.99), and for oxycodone the odds ratio was 66 (95% CI, 4.57–953.28). Positive benzodiazepines, barbiturate, amphetamine, methamphetamine, and nicotine, hair tests did not coincide with positive opiate hair tests, precluding the calculation of odds ratios for these drugs. Additionally, there were no positive results for phencyclidine and meperidine in this neonatal study population. FAEE cannot currently be detected in neonatal hair in any laboratory, but an effort is underway to develop methods suitable for this analysis. The statistics described above are summarized in Table 2.

Of the 1318 meconium specimens analyzed for opiates, 1304 were tested for other drugs of abuse or alcohol (FAEEs) as well. Among these tests, 62 (4.8%) tested positive for opiates only, 129 (9.9%) tested positive for opiates and one or more other substances, and 628 (48.2%) tested negative for opiates but positive for another substance in meconium. The frequency of coexposures to other drugs of abuse as determined by meconium testing is outlined in Table 3. If testing positive for opiates in meconium, the odds ratio for testing positive for other drugs was calculated to be 1.61 (95% CI, 1.16–2.22). Hence, infants testing positive for opiates were more likely to be coexposed to other substances as determined by meconium test results and coinciding with odds ratios determined using neonatal hair specimens as well.

Akin to the neonatal hair data, when testing for opiates, the most frequently cotested drugs were cocaine (1283 of 1304 [98.4%]) and marijuana (1250 [95.9%]). These substances were followed by, in descending order, amphetamine (344 [26.4%]), methamphetamine (340 [26.1%]), FAEE (325 [24.9%]), oxycodone (228 [17.5%]), BE (227 [17.4%]), and lastly methadone (149 [11.4%]).

Among neonates testing positive for opiates in meconium, the odds ratios calculated for testing positive for cocaine/BE were 1.51 (95% $CI_{cocaine}$, 1.11–2.07) and 1.69, respectively (95% CI_{BE}, 1.25–2.28). For cannabinoids, the odds ratio was 0.77 (95% CI, 0.56–1.06), for benzodiazepines the odds ratio was 1.72 (95% CI, 1.17–20.56), and for amphetamine and methamphetamine the odds were 2.54 and 1.72, respectively (95% CI_{amph}, 0.62–10.49, 95% CI_{meth}, 0.34–8.73). Lastly, the odds ratios calculated for methadone, oxycodone, and FAEE were 3.9 (95% CI, 1.63–9.35), 8.05 (95% CI, 3.01–21.5), and 2.35 (95% CI, 1.13–4.9), respectively. There were no positive meconium test results for barbiturates, phencyclidine, or meperidine in this study population. Collectively, these data suggest that neonates testing positive for opiates in meconium are significantly more likely to test positive for cocaine, benzodiazepines, methadone, oxycodone, and FAEE. This is summarized in Table 4.

Maternal–Neonatal Opioid Correlations

In total, 18 mother–infant dyads tested for opiates were identified from our database. Ten pairs were tested for opiates in maternal and neonatal hair and 14 pairs consisted of maternal hair and neonatal meconium; of these, six

TABLE 2. Itemized Drug Coexposures as Determined by Neonatal Hair Testing and the Corresponding Odds Ratios

Drugs	Tested (opiate tested) Population		Positive†		Simultaneous Positive‡		Odds Ratio (95% confidence interval)
	n^a	Percent	n^b	Percent	n^c	Percent	
Cocaine	558	99.1	150	26.9	22	3.9	1.58 (0.90–2.76)
Cannabinoids	504	89.5	76	15.1	8	1.6	0.97 (0.44–2.16)
Barbiturates	163	29	1	0.6	0	0	—
Amphetamine	161	28.6	1	0.6	0	0	—
Methamphetamine	148	26.3	3	2.0	0	0	—
Benzodiazepines	94	16.7	1	1.1	0	0	—
Oxycodone	50	8.9	4	8.0	3	6.0	*66 (4.57–953.28)
Methadone	45	8.0	9	20.0	3	6.7	5.5 (0.89–33.99)
Phencyclidine	45	8.0	0	0	0	0	—
Meperidine	23	4.1	0	0	0	0	—
Nicotine	8	1.4	3	37.5	0	0	—

*Odds ratio is significant.
†Percent positive describes those tested for individual drug (ie, n^b/n^a).
‡Drug tested positive simultaneously with positive opiate result; of percentage of tests conducted for individual drug (ie, n^c/n^a).

TABLE 3. Drug Coexposures Among Positive and Negative Opiate Meconium Tests

Drug Coexposure Frequency in Meconium	Opiate-Positive		Opiate-Negative	
No. of different drugs	No.	Percent	No.	Percent
1	62	32.5	463	73.8
2	81	42.5	149	23.7
3	36	18.8	16	25.5
4	10	5.2	0	0
5	1	0.5	0	0
6	1	0.5	0	0
Total	191	100	628	100

mother–infant dyads had both neonatal hair and meconium test results (Table 5). Among these six mother–infant pairs, four tested positive in all three specimens (maternal hair, neonatal hair, and meconium), one pair tested positive in maternal and neonatal hair only, and one pair tested positive in maternal hair and meconium only.

Results for the 10 maternal–infant hair tests for opiates showed positive maternal hair tests in 100% of the pairs. Two neonatal hair tests (two of [20%]) were negative for opiates despite a positive maternal result, thereby having 80% concordance between the tests. Alternatively, of the 14 maternal hair test and neonatal meconium test pairs, only nine of 14 (64%) demonstrated concordance, because two maternal hair specimens and three meconium specimens were negative for opiates (mutually exclusive).

Because the data were not normally distributed, we used a Spearman rank test to determine if there was any significant correlation between mother–infant concentrations of opiates in these specimens. There was a significant correlation between maternal and neonatal hair concentrations for opiates (Spearmans rank rho = 0.657, $P = 0.03$) (Fig. 1); maternal hair and neonatal meconium opiate concentrations were not significantly correlated.

DISCUSSION

Hair and meconium analysis are increasingly being used by child welfare authorities and legal services for the accurate and objective determination of drug abuse.[32] This is not only beneficial for children potentially at risk, but also for parents mislabeled as drug abusers.[31] Thus, characterization of abuse and exposures by these susceptible populations is warranted for improved clinical and social care.

Because opioids are widely prescribed to and used by women of reproductive age and are not absolutely contraindicated in pregnancy, the assessment of fetal exposures to such compounds and other drugs of abuse using these alternative matrices deserves consideration. It has been estimated that between 5% and 10% of pregnancies are affected by drug abuse.[33,34] Specifically, opiate exposures in pregnancy vary from 1.2% to 8.7% as estimated by meconium analyses.[35,36] Our results indicate a higher than previously estimated rate of opioid exposures; we detected 17% opioid exposures by meconium analysis and 11.4% by neonatal hair analysis. This elevation in exposures was intuitively expected because the population tested was that of high risk and sent to us on suspicion by child welfare authorities. Additionally, the higher rate of detected exposures through meconium versus hair is in agreement with previous literature investigating prenatal cocaine exposures; the authors found that meconium had nearly a 10% greater diagnostic sensitivity than neonatal hair.[37] Therefore, opioid use in this population appears to be greater than that of the general population by approximately 10% and should be flagged as a potential public health concern.

In assessing polydrug exposures among the infants tested for opioids, we found that if the infant tested positive for opioids in both hair and meconium, they were more likely to test positive for other drugs of abuse as well. Specifically, in neonatal hair, oxycodone was found more likely to test positive with a positive opioid result; in meconium, cocaine, benzodiazepines, methadone, oxycodone, and FAEE were

TABLE 4. Itemized Drug Coexposures as Determined by Meconium Testing and the Corresponding Odds Ratios

Drugs	Tested§		Positive		Simultaneous Positive‡		Odds Ratio (95% confidence interval)
	n^a	Percent	n^b	Percent	n^c	Percent	
Cocaine	1283	98.4	356	27.7	75	5.8	*1.51 (1.11–2.07)
Cannabinoids	1250	95.9	467	37.4	64	5.1	0.77 (0.56–1.06)
Amphetamine	344	26.4	9	2.6	3	0.9	2.54 (0.62–10.49)
Methamphetamine	340	26.1	8	2.3	2	0.6	1.72 (0.34–8.73)
FAEE	325	24.9	65	20.0	13	4.0	*2.35 (1.13–4.9)
Oxycodone	228	17.5	20	8.8	13	5.7	*8.05 (3.01–21.5)
Benzodiazepines	227	17.4	8	3.5	4	1.75	*1.72 (1.17–20.56)
Barbiturates	224	17.2	0	0	0	0	—
Methadone	149	11.4	35	23.5	13	8.7	*3.9 (1.63–9.35)
Phencyclidine	84	6.4	0	0	0	0	—
Meperidine	52	4.0	0	0	0	0	—

*Odds ratio is significant.
†Percent positive describes those tested for individual drug (ie, n^b/n^a).
‡Drug tested positive simultaneously with positive opiate result; of percentage of tests conducted for individual drug (ie, n^c/n^a).
§n value and respective percentage tested for indicated drug among opiate tested population.
FAEE, fatty acid ethyl esters.

TABLE 5. Mother–Infant Dyad Test Results for Opiates

Mother–Infant Pair	Mother's Hair Test Result (ng opiate/mg hair)	Neonate's Hair Test Result (ng opiate/mg hair)	Neonate's Meconium Test Result (ng opiate/g meconium)
1	0.51	1.13	1397.19
2	0.37	1.12	296.57
3	0.97	0.85	123.92
4	0.79	2.9	285.8
5	0.58	0	179.91
6	0.09	0.24	0
7	0.31	0.35	—
8	1.38	5.62	—
9	3.91	1.56	—
10	0.36	0	—
11	0.1	—	444.63
12	0.3	—	1155.83
13	0	—	135.13
14	0	—	987.27
15	1.8	—	1419.17
16	3.7	—	855.12
17	0.36	—	0
18	0.63	—	0

more likely to be positive with a positive opioid result. With larger sample sizes, it is possible that the neonatal hair statistics would match that of meconium; however, in our laboratory, the latter matrix is much more common for toxicologic testing simply because it is a discarded material; additionally, neonatal hair is often very scarce. The fact that our results indicate maternal polydrug abuse in this at-risk population is not unanticipated either, as we previously determined maternal cocaine or methamphetamine abuse was associated with such behavior in the same population.[37,38] Moreover, the drugs found to be significantly correlated with positive opioid exposures fit the scenario quite well. Cocaine is the leading choice of stimulant in North America[39] and is commonly abused by high-risk populations. Oxycodone, methadone, and benzodiazepines are all prescribed medications and may be prescribed or abused concurrently with opioids.

Finally, positive alcohol (FAEE) testing was significantly correlated with a positive opioid meconium test. A positive alcohol test in our laboratory indicates chronic/excessive alcohol consumption, which may have significant consequences to the development of the neonate.[40] Alcohol is typically abused by high-risk populations, especially those of low socioeconomic status and/or of minority.[41–44] Because opioids may include legitimately prescribed substances that are not contraindicated in pregnancy, our findings of increased exposure of alcohol to neonates positive for opioids may have great implications on the social, medical, and legal systems alike.[45,46]

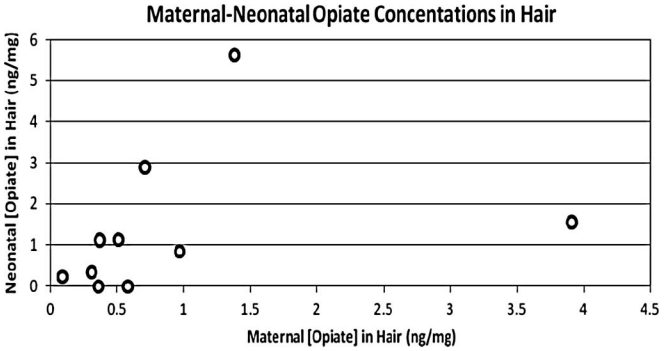

FIGURE 1. Correlation between maternal and neonatal opiate concentrations in hair. Spearman rank rho = 0.657; $P = 0.03$.

Lastly, we assessed the transplacental transfer of opioids as quantified by maternal and neonatal levels in hair. We found that these concentrations were significantly correlated, whereas meconium concentrations did not correlate with maternal hair concentrations. This is not surprising because maternal hair was generally segmented to represent only the final trimester of pregnancy; meconium opioid concentrations represent in utero exposures after approximately 12 weeks gestation and would include second-trimester exposures. These would not be accounted for in the maternal hair segment. Concentrations found in neonatal hair represent in utero exposures after approximately the 20th week of pregnancy (ie, beyond the second trimester) and this corresponds well with the time period that maternal hair segment represents.

A stronger correlation between maternal and neonatal hair concentrations may not have been evident as a result of variation in pharmacokinetic parameters of the maternal–fetal unit, including differences in transplacental transfer/distribution, maternal and fetal opioid metabolism, and maternal–fetal clearance.[47,48] Thus, these results should stimulate further placental research, perhaps in the form of profusion or uptake studies to assist in the mechanistic determination of fetal opioid exposure.

CONCLUSION

Our findings demonstrate the potential for neonatal hair analysis for the determination of in utero exposure to opioids as well as other substances that may have been simultaneously administered or consumed, including benzodiazepines, methadone, cocaine, and/or alcohol. We have also highlighted the increased exposure to opioids in this at-risk population as compared with the general population. Because in utero opioid exposures may predict neonatal abstinence syndrome, and maternal abuse of other drugs and alcohol may precipitate poor neonatal prognoses, our objective assessment of such exposures may lead to improved pediatric clinical care.

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