Enhanced Parathyroid Function in Essential Hypertension: A Homeostatic Response to a Urinary Calcium Leak

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SUMMARY   Disorders of calcium metabolism are not generally considered important either clinically or pathophysiologically in essential hypertension. Recent reports, though, suggest that increased parathyroid gland function may be one of the more common endocrine disturbances associated with hypertension. We measured serum parathyroid hormone (PTH) concentrations as well as routine blood and urine chemistries in 34 hypertensives. Their mean PTH, 79.1 ± 3.1 μliter Eq/μliter, was significantly higher ($p < 0.025$) than the mean PTH, 66.9 ± 3.3, of an age- and sex-matched normotensive control population. The mean serum calcium, 9.5 ± 0.1 mg%, was identical in the two populations. Compared to a second age- and sex-matched normotensive population, the hypertensives demonstrated a significant ($p < 0.005$) relative hypercalciuria. For any level of urinary sodium, hypertensives excreted more calcium. These preliminary data suggest that parathyroid gland function may be enhanced in essential hypertension. This increased gland activity appears, in part, to be an appropriate, physiologic response to a previously unrecognized relative hypercalciuria, or renal calcium leak, associated with essential hypertension. We conclude that the increased prevalence of hypertension in subjects with hyperparathyroidism probably represents the final event in a continuum that begins with obligatory urinary calcium losses in hypertensives, but whose pathological presentation is hyperparathyroidism. The results of this pilot study indicate a need for derivative experiments directed at defining the importance of our preliminary findings in the pathogenesis of human and experimental hypertension. (Hypertension 2: 162–168, 1980)

KEY WORDS • parathyroid hormone • serum calcium • urinary calcium •
urinary calcium and sodium excretion • urinary cyclic AMP/creatinine

PRIMARY hyperparathyroidism has been associated with an increased prevalence of hypertension (35% to 70% in most series).[1-3] Conversely, the prevalence of hyperparathyroidism may be two to eight times greater in hypertensive than in normotensive subjects.[4, 5] In addition, thiazide diuretics cause overt hypercalcemia in certain hypertensives.[6] Published evidence indicates that the hypercalcemic effect of thiazides is, in part, related to the level of endogenous parathyroid hormone activity.[7, 8] These observations, viewed together, suggest that altered parathyroid gland function may be one of the more common perturbations of normal endocrine physiology encountered in subjects with essential hypertension.

There is, however, no systematic study of parathyroid function in hypertensive patients. For this reason, we initiated this pilot study to investigate whether PTH concentrations of untreated hypertensive subjects are increased compared to those of normotensive subjects. In addition, we sought to establish what might be the stimulus for increased parathyroid activity in the hypertensive state; specifically, how parathyroid function relates to sodium intake and calcium homeostasis in hypertensive patients.

Materials and Methods

Subjects

We studied 34 hypertensive subjects, mean arterial pressure (diastolic + 1/3 pulse pressure) > 105 mm

Hg and/or diastolic blood pressure > 95 mm Hg, who had been evaluated and followed in the Hypertension Clinic at Tufts-New England Medical Center. All subjects had been off all medications for at least 4 weeks. Eleven had received thiazide diuretics in the past. Renal function was known to be normal in all the subjects. Before entry into the study, these subjects had been screened for secondary causes of hypertension and were all categorized as having essential hypertension. Two age- and sex-matched control populations were used. The first was selected from normotensive (blood pressure < 140/90) blood donors. They were studied concurrently with the hypertensive subjects. Subsequently, a second control group was recruited from normotensive healthy volunteers at the University of Oregon Health Sciences Center. This second control population was necessary to provide comparison data on renal function, serum phosphorus, and urinary electrolyte excretion as these were not obtained at the time the original normotensive controls were screened for serum PTH and calcium values.

Protocol

Blood was withdrawn from the hypertensive subjects between 10 a.m. and noon on 2 days and analyzed for PTH, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, uric acid, albumin, and creatinine concentrations. The subjects were fasting and had completed a 24-hour urine collection immediately prior to the phlebotomy. The 24-hour urine was analyzed for sodium, potassium, calcium, magnesium, phosphorus, uric acid, creatinine, epinephrine, and norepinephrine excretion. A cAMP/creatinine ratio was measured on a spot urine sample obtained at the time of the blood drawing. For the 34 age- and sex-matched normotensive blood donors, a blood specimen for PTH and total serum calcium was collected between 9 a.m. and noon prior to the donation of blood. The second control group, also matched for sex and age, provided timed a.m. urine collections. These volunteers had voided upon arising, recorded the time, and then reported to the Clinical Research Center at the University of Oregon Health Sciences Center between 8 and 9 a.m. While still fasting, the volunteers voided again and the time was noted. These timed urine collections were analyzed for sodium and calcium. In addition, blood was obtained for serum creatinine, calcium, and phosphorus determinations.

Analytical Methods

The serum sodium, potassium, chloride, bicarbonate, phosphorus, uric acid, albumin, and creatinine concentrations were determined by an autoanalyzer technique. Serum calcium and magnesium were measured by atomic absorption spectrophotometry. The 24-hour urines and timed urine collections were analyzed by identical methods.

Parathyroid hormone was measured by radioimmunoassay with a guinea pig (GP101) antibovine antiserum with approximately 50% amino- and 50% carboxy-terminal specificity. The technical details of this assay have been previously reported.[8-11] Previously unthawed serum was used to measure the PTH. Specimens from the control and hypertensive subjects were placed in the same assay run in order to control for interassay variation. All samples were assayed in duplicate. The mean of these two determinations was the PTH value used for statistical analysis. Urinary catecholamine excretions were determined by a column technique (Bio-Rad Laboratories). A competitive binding assay (Amersham-Searle) was used to measure cAMP.

The blood pressures of all subjects but the blood donors were measured on 3 separate days by the same observer utilizing a mercury sphygmomanometer. The blood donors had one measurement prior to the phlebotomy. The criteria of the American Heart Association were used for recording of blood pressure in the recumbent and standing positions. Unpaired t tests, linear regression analyses, and F tests were used for statistical analysis.

Results

Subjects

Table 1 describes the mean age and sex distribution of the hypertensive subjects and the initial normotensive controls. Racial distribution was comparable in the two populations. The second control group has a similar age, sex, and racial distribution.

Parathyroid Hormone Levels

The mean PTH and serum calcium values for the hypertensive subjects and normotensive controls are also shown in table I. While the mean serum calcium concentrations were identical in the two populations, the PTH concentration was significantly higher ($p < 0.025$) in the hypertensive individuals, though the mean value of 79 μliter Eq/mliter is within the normal range for the parathyroid hormone assay.

Blood and Urine Chemistries

The mean ($\pm$ SD) of the individual blood and urine chemistry tests are listed in table 2. The hypertensives'

TABLE 1. *Comparison of Serum Parathyroid Hormone and Calcium Concentrations (Mean $\pm$ SE) in 34 Hypertensive and 34 Normotensive Subjects*

	Normotensives	Hypertensives
Age	44.6 $\pm$ 1.9	44.9 $\pm$ 1.8
Sex	9 F, 25 M	9 F, 25 M
PTH (μliter Eq/mliter)	67 $\pm$ 3.3	79 $\pm$ 3.1*
Ca++ (mg%)	9.5 $\pm$ 0.1	9.5 $\pm$ 0.1
n	34	34

*$p < 0.025$.

TABLE 2. *Mean (± SD) Blood Chemistries and 24-Hour Urine Chemistries in 34 Hypertensive Subjects*

Blood chemistries		24-Hour urine chemistries	
Sodium (mEq/liter)	140.5 ± 1.7	Sodium (mEq/24°)	147 ± 57
Potassium (mEq/liter)	4.1 ± 0.4	Potassium (mEq/24°)	56 ± 21
Chloride (mEq/liter)	102.5 ± 1.8	Calcium (mg/24°)	169 ± 93
Bicarbonate (mEq/liter)	25.6 ± 1.8	Phosphorous (mg/24°)	864 ± 326
Calcium (mg%)	9.5 ± 0.4	Magnesium (mg/24°)	92 ± 45
Phosphorus (mg%)	3.0 ± 0.4	Uric acid (mg/24°)	405 ± 187
Magnesium (mg%)	1.9 ± 0.2	Creatinine (mg/24°)	1527 ± 406
Uric acid (mg%)	6.1 ± 0.3	cAMP/creatinine (nmol/mg)	4.1 ± 1.8
Albumin (g%)	4.6 ± 0.5	Norepinephrine (μg/24°)	39.8 ± 25.5
Creatinine (mg%)	1.0 ± 0.2	Epinephrine (μg/24°)	16.5 ± 7.8

renal function, as determined by serum creatinine, was identical to that documented in the second normotensive control group (1.0 ± 0.2 mg%). Of note is the mean serum phosphorus ($\pm$ SD) concentration, which was significantly ($p < 0.001$) lower than that found in the second control group (3.4 ± 0.5 mg%). The mean sodium excretion of 147 mEq/day supports a normal sodium intake in our patients.

Electrolyte Excretion Relationships

The hypertensives' 24-hour urinary excretion of calcium ($r = + 0.42$, $p < 0.001$), phosphorus ($r = + 0.50, p < 0.001$), and magnesium ($r = + 0.55$, $p < 0.001$) were all correlated with their daily sodium excretion. Calcium and phosphorus excretion were positively correlated ($r = + 0.44 < 0.001$) with one another.

For purposes of comparison, the urinary excretion rates for the 24-hour collections and the timed a.m. urine collections were standardized to a per hour basis, i.e., for calcium, mg/hr and sodium, mEq/hr. Table 3 compares the equations relating urinary sodium excretion per hour to urinary calcium excretion per hour for the hypertensive subjects and the second age- and sex-matched control population. It is important to note that on either an adjusted hourly basis (6.05 mEq vs 6.94 mEq) or a calculated 24-hour basis (147 mEq vs 167 mEq), the sodium excretion was similar in the two groups. Calcium excretion was related to sodium excretion for both groups as tested by an F statistic. The slopes of these two equations

were not different from one another, which is evident in figure 1. However, an F test of the adjusted means for the two populations indicates that the "y" intercepts are significantly ($p < 0.005$) different from one another. At any level of sodium excretion, the hypertensives had significantly greater quantities of calcium in their urine.

Since the slopes do not differ, a pooled estimate of a common slope ($b = 0.52$) was used to calculate average differences in calcium excretion at various levels of sodium excretion per 24 hours (table 4). For example, at 150 mEq/24 hours of sodium, the calcium excretion of the hypertensives would be approximately 1.7 times that of the normals (167 mg vs 97 mg).

### Parathormone, Blood, and Urine Chemistries

While PTH levels failed to correlate with any of the serum electrolyte concentrations or individual excretion rates, including catecholamines, there was a significant ($p < 0.01$, $r = 0.436$) inverse relationship between PTH and the serum creatinine. In addition, the serum PTH was positively correlated with the ratio of urinary sodium excretion to urinary calcium excretion ($p < 0.05$) (fig. 2), and also with the spot urine cAMP/creatinine ratio ($p < 0.001$) (fig. 3).

Calcium, Phosphorus, and Blood Pressure

The serum calcium ($p < 0.05$) and phosphorus ($p < 0.02$) were inversely related to the mean arterial pressure and systolic blood pressures; for each

TABLE 3. *Comparison of Equations Relating Hourly U_{Na}^+ to U_{Ca}^{++} for Hypertensive Patients and Normal Volunteers*

	Normotensives	Hypertensives
Equations ·	$U_{Ca}^{++} = 4.49 + 0.49 (U_{Na}^+ - 6.94)$	$U_{Ca}^{++} = 6.98 + 0.77 (U_{Na}^+ - 6.05)$
	$r = 0.52$	$r = 0.42$
	$p < 0.001$	$p < 0.01$
$H_0: b = 0$	$F'_{33} = 11.72$	$F'_{33} = 6.80$
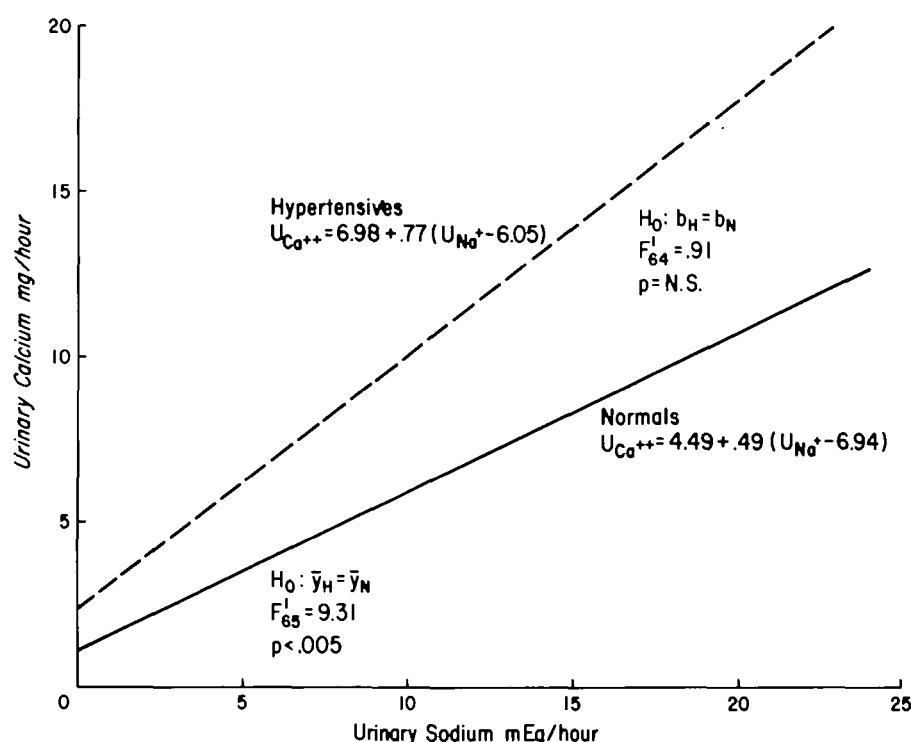
FIGURE 1. *Comparison of equations relating U_{Na+} to U_{Ca++} for normal and hypertensive subjects.*

TABLE 4. *Estimated Mean 24-Hour U_{Ca}^{++} at Various Levels of U_{Na}^{+} for Normals (NL) Versus Hypertensives (HTN)*

U_{Na}^{+}/24 hr (mEq)	U_{Ca}^{++}/24 hr (mg) — NL	U_{Ca}^{++}/24 hr (mg) — HTN	Ratio: HTN/NL
10	27	97	3.6
50	47	117	2.5
100	72	142	2.0
150	97	167	1.7
200	126	196	1.6
300	177	247	1.4

hypertensive subject the lower the serum calcium and phosphorus, the higher the blood pressure. Parathyroid hormone concentrations were not related to observed blood pressures.

Discussion

While these results are preliminary, they suggest that mean basal parathyroid function is enhanced in untreated, hypertensive subjects and that hypertensives have a previously unrecognized relative hypercalciuria or urinary calcium leak. The former finding appears to be an appropriate, homeostatic response to the latter, as serum calcium concentrations were identical to those measured in the control subjects. The negative correlation of our hypertensive subjects'

serum calcium concentrations with their blood pressures is consistent with such a homeostatic mechanism. This relationship has not been previously reported. The inverse correlation of serum phosphorus and blood pressure has been noted by other investigators.[12]

The findings of our study were perhaps predictable as disorders of calcium, phosphorus, and parathyroid hormone homeostasis are being recognized with increasing frequency in hypertensive populations. The hypertension generally has been attributed directly to hyperparathyroidism, associated hypercalcemia and/or renal function impairment.[2] Recent reports, though, have provided evidence that hypertension itself may predispose an individual to the development of hyperparathyroidism.[5, 13] Prior to the ready
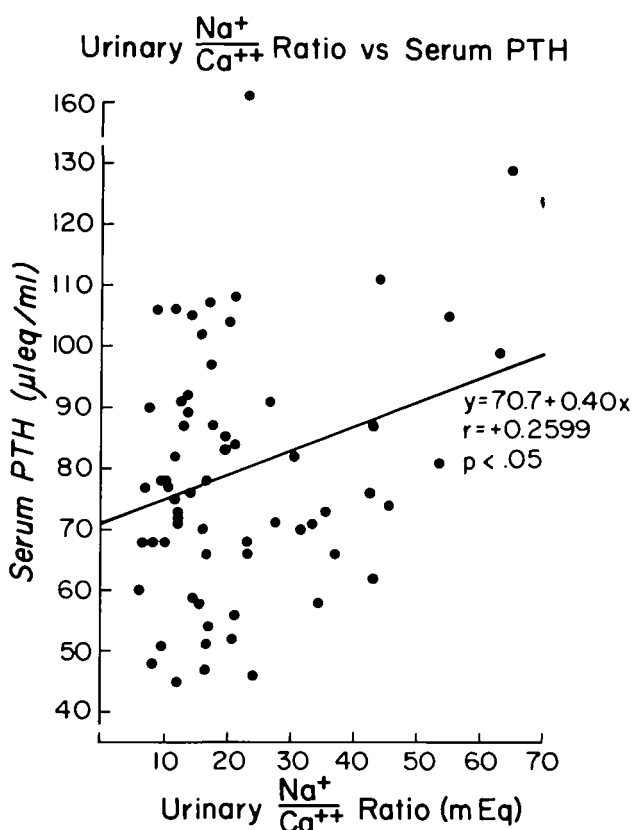
FIGURE 2. Correlation between the ratio of urinary Na^+ to urinary Ca^{++} excretion per 24 hours vs serum PTH.
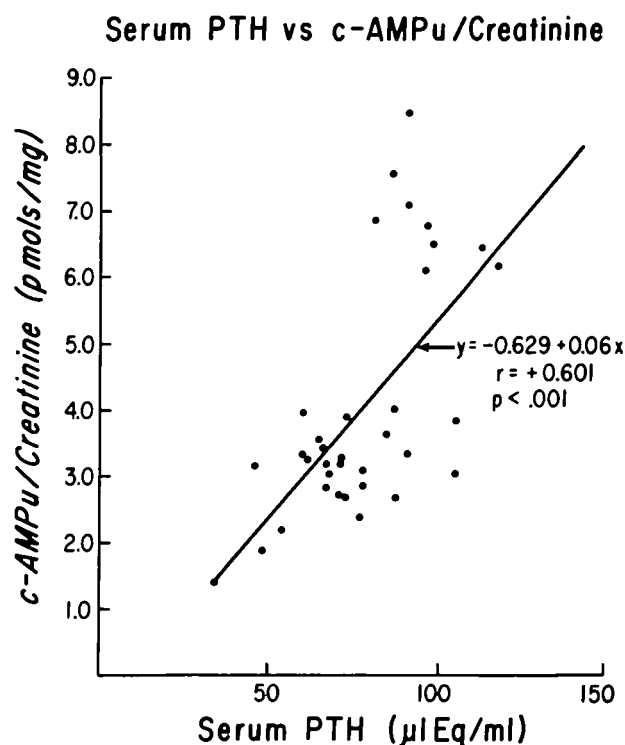

FIGURE 3. Correlation between serum PTH and simultaneously measured spot urinary $cAMP\mu/creatinine$ ratio.

availability of PTH and calcium and phosphorus measurements, the diagnosis of hyperparathyroidism depended primarily upon the recognition of the serious clinical manifestation of the disease. Where hyperparathyroidism has been looked for in a hypertensive population, the prevalence has been two to eight times greater than that found in the general population.[4, 5] Reliance solely upon the serum calcium as a screening criterion is likely to significantly underestimate the true prevalence of parathyroid disorders in any population. Measurements of multiple indicators of parathyroid function (PTH, nephrogenous cAMP, ionized calcium and phosphorus) is necessary to accurately define the frequency of parathyroid gland overactivity.[14] Our data indicate that the cAMP/creatinine ratio may be an additional simple screening test for the presence of increased parathyroid activity in hypertensive patients.

While our findings suggest that mean parathyroid hormone levels are increased in hypertensive patients secondary to a urinary leak of calcium, there are other possible etiologies to consider. These hypothetical explanations would include early impairment of the glomerular filtration rate from chronic hypertension with a secondary increase in PTH, increased sympathetic nervous system stimulation of PTH release, renal tubular resistance to PTH action, impaired

vitamin D metabolism, and/or inadequate dietary calcium intake.

Our data would appear to exclude a number of these possible etiologies. Renal function, as measured by serum creatinine, was normal, and higher PTH concentrations were correlated with lower serum creatinine concentrations in our hypertensive subjects. While the former finding does not exclude the possibility that the hypertensives had early impairment of their renal function as a cause of their enhanced parathyroid function, the latter point strongly argues against that possibility. The β-adrenergic nervous system is known to contribute to the regulation of PTH release. In our hhpertensive subjects, however, urinary catecholamine excretion was not related to PTH levels.[15, 16] If increased β-adrenergic nervous system activity was the cause of the elevated PTH levels, one would have anticipated some increase in the serum calcium as is often encountered in subjects with pheochromocytomas independent of a multiple endocrine neoplasis.[17, 18] The low serum phosphorus concentrations suggest an appropriate responsiveness of the renal tubules to PTH. There is no reason to suspect that vitamin D metabolism was impaired, though vitamin D levels were not measured. While it is improbable that dietary calcium intake was inadequate in our patients, this

possibility cannot be excluded as calcium balance studies were not done.

We would hypothesize that the increased parathyroid gland function demonstrated in our hypertensive subjects is, in part, a physiologic response intended to dampen the obligatory urinary calcium losses we characterized in our patients. By minimizing urinary calcium losses, maintenance of a normal serum calcium concentration would be defended. Sodium excretion would be enhanced. The relationship between PTH and the urinary sodium to urinary calcium ratio, which we found in our hypertensives, is in accordance with such a hypothesis.

The magnitude of the hypertensives' calciuria is within the accepted normal range for 24 hours. Indexing the calcium excretion to the simultaneous sodium excretion rate, however, permitted a comparison between the hypertensive and normal subjects that revealed the relative hypercalciuria. In assessing our excretion data, the possible differences between a 24-hour and timed a.m. urine collection must be considered. Since urinary sodium and calcium excretion are closely correlated, referencing calcium excretion to sodium excretion allowed us to control, in part, for the normal fluctuations that occur throughout the day.[19, 20] Excretion of both these ions would be similarly influenced by the normals' fasting state.[21] Finally, mid-morning has been shown to be the time of peak urinary calcium excretion.[22] Possible variations in dietary calcium are not likely to have been of significance in this study, as recent investigations have shown a minimal effect of changes in calcium intake on urinary excretion of the cation.[23]

The renal handling of calcium is influenced by many factors, the major being sodium excretion.[24-26] Throughout the proximal portions of the nephron, calcium and sodium are handled in an identical fashion. Only in the distal tubule, where the final adjustments in calcium excretion occur, does this concordance between calcium and sodium excretion break down.[27, 28] These distal nephron sites are where PTH stimulates calcium reabsorption.[29, 30] Our results combined with these previous studies would suggest that the defect in the hypertensive kidney's handling of calcium is probably a distal tubular one. Confirmation of this hypothesis, though, awaits extensive further testing.

Other reports have speculated that PTH itself might contribute to elevating the blood pressure either directly or via induced changes in serum calcium and/or the renin-angiotensin system.[31-33] Our data do not permit us to draw any definite conclusion as to the net effect of parathyroid hormone in either the genesis or the maintenance of increased arterial pressure. If parathyroid hormone promotes vasodilatation, as other studies have suggested, and it also enhances sodium excretion, then the possibility must be considered that parathyroid hormone is, in fact, protective.[33-38]

The increased parathyroid hormone concentrations may also contribute to the relatively common occurrence (10%–15%) of hypercalcemia encountered when hypertensives are treated with thiazide diuretics.

Popvitzer et al.[8] indirectly demonstrated a synergism between parathyroid hormone and thiazides that further enhances the hypercalcemic effect of these drugs.[8] This interaction is independent of the thiazide-induced changes in proximal tubular sodium and calcium reabsorption. Thus, hypertensive subjects with the higher PTH levels would be expected to be more susceptible to overt hypercalcemia when placed on thiazides. This possibility awaits further investigation.

We have documented the existence of increased concentrations of PTH and a relative hypercalciuria in our hypertensive subjects. Indeed, the increased prevalence of hypertension in patients with hyperparathyroidism may represent the final step in a continuum that begins with hypertension and a renal leak of calcium, but whose pathological presentation is hyperparathyroidism. Conversely, the previously established association between hypertension and hyperparathyroidism may now be more understandable if, in fact, the increases in PTH truly reflect enhanced parathyroid gland function. "Secondary", rather than "primary", may be a more precise descriptive term for the hyperparathyroidism associated with essential hypertension.

Acknowledgments

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