Early fluid retention and severe acute mountain sickness

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NUMEROUS REPORTS HAVE NOTED a direct association between fluid retention and acute mountain sickness (AMS). Many have been from field studies (5, 6) or a combination of field and laboratory studies (3), with few taking place solely in altitude chambers where the environment and activity are continuously controlled. Most studies have taken place over a period of days to weeks and usually lack these controls because of the variability of rate and mode of ascent (amount of exercise), diet, and environmental temperature. As a result, findings have not been consistent and not always reported in clear association with AMS severity because of the time it took to develop in susceptible individuals and the complications of the more severe conditions of pulmonary and cerebral edema.

Because fluid balance is altered by hypoxia per se, inducing an acute diuresis (9, 20), the subsequent secondary relationship between AMS and fluid retention is closely related to experimental protocol, especially the severity and duration of hypoxia, leading to inconsistent results. However, there is evidence that the occurrence of acute AMS during a 9-h exposure to simulated altitude in a decompression chamber bears a close relationship to the AMS severity experienced during longer field exposures (19); thus our model seems relevant to the development of AMS in the field.

This report describes a study in which human subjects were exposed to simulated altitude at rest over a period of 12 h, with chamber temperature, diet, and initial fluid intake regulated. Periodic measurements of fluid balance and variables associated with its physiological modulation were subsequently compared between subjects who developed severe AMS and those who did not become ill, with the elimination of equivocal data from subjects between these extremes. This approach allowed for an evaluation of the relationship between fluid balance, AMS, and other measurements during acute altitude exposure to differentiate responses by these two groups of individuals.

MATERIALS AND METHODS

Subjects. The main overall objectives of this study were to compare AMS and other responses to 12 h of acute simulated altitude in a decompression chamber at 426 mmHg (~4,880 m = 16,000 ft., according to West (23)) by gender and menstrual cycle phase and oral contraceptive use in women. A total of 99 exposures were performed on 51 individuals, with some findings previously reported (13, 14). The study logistics and subjects have been previously described, as well as the selection of AMS and non-AMS groups of 16 subjects each after completion of the study (12). These two groups were chosen on the basis of a ranking of AMS scores from highest to lowest and included two-thirds of all of the experiments. The AMS symptoms were quantified by the average of the Lake Louise (LL) score (16) and the AMS-C score from the Environmental Symptoms Questionnaire (18) given during the baseline control period and after 1 h, after 6 h, and during the last hour at altitude. In summary, subject subgroups were selected post hoc from all of those studied, on the basis of the score obtained during the last hour at altitude, the “non-AMS” group being most tolerant (mean LL = 1.0, range 0–2.5; mean AMS-C = 0.2, range 0–0.9) and the “AMS” group being most susceptible to altitude hypoxia (mean LL = 7.4, range 5–11; mean AMS-C = 2.7, range 1.5–3.7). Nine subjects of the non-AMS group
and 7 of the AMS group had been exposed to simulated altitude for 6–10 h in the same chamber at least once before this study. Informed consent was obtained from all subjects, as reviewed and approved by the local Institutional Review Board and the US Army. Other group characteristics are summarized in Table 1.

**Protocol.** Subjects were provided food matched to their own prior average intake and preferences in regards to carbohydrates, fat, protein, fiber, calories, and Na⁺ on the control day preceding the altitude day and at altitude. Because of the constraints of the study and the fact that many subjects had to be run on short notice, depending on changing hormone levels (women), an ideal extended baseline control of a week or more at desired electrolyte intake levels was impossible. The original, overall objective of the study was to compare AMS severity between men and women, comparable to “field conditions.” We felt that strict Na⁺ diets (whether restricted or increased) would be unusual for many subjects and might by themselves induce variability into the occurrence of AMS from that which they might experience with an unrestricted diet. It is possible that the higher-than-average Na⁺ intake observed in these subjects from their excretion rates and intake might alter the AMS occurrence and severity that resulted, compared with other studies wherein Na⁺ intake was more tightly controlled or restricted. Be that as it may, the average preferred and actual Na⁺ intake levels turned out to be the same for both groups when the diet records and intakes were retrospectively analyzed after the study.

In the hour preceding chamber entry at 0700, the morning urine volume was measured and fluid equilibration was approximated by the subject drinking a fluid volume equal to 1,000 minus the morning urine volume (ml). Then, as part of breakfast, an additional 300–400 ml were taken in to ensure an adequate urine volume during altitude exposure. Cumulative fluid intake and urine volume were measured at 3-h intervals. After subjects entered the altitude chamber, the fluid intake was matched to urine output for each interval. During altitude exposure, the subjects rested while sitting upright or semirecumbent while reading or watching television. The chamber temperature was maintained at levels requested by the subjects (24–27°C). Twenty percent of exposures were curtailed, from 12 to a minimum of 8 h, by severe AMS symptoms.

**Water compartments.** Total body water (TBW) was estimated from the plasma enrichment of D₂O and extracellular water (ECW) from NaBr enrichment sampled 2 and 3 h after an oral dose given at 1600 on the control day and at the same time at altitude. Intracellular water was obtained by subtraction. Plasma samples were analyzed for NaBr and D₂O by a commercial laboratory (Metabolic Solutions, Nashua, NH). The value of the two samples that gave the highest plasma concentration (lowest TBW or ECW) from these subjects, due to AMS, prevented oral administration, absorption, or equilibration of the D₂O and NaBr.

**Plasma volume.** Plasma volume (PV) was measured with Evans blue dye as described previously (13) at late afternoon–early evening of the control day (C12) and over the last 3 h at altitude. Transcapillary escape rate (TCER) was computed from the decay curve of Evans blue dye and expressed as the percentage change in concentration per hour, which is representative of the rate of albumin loss from the vascular space. A greater TCER is indicated by a larger negative number. Serial estimates of PV change (∆PV) at altitude (a) after exposure for 1, 6, 9, and 12 h were based on measured changes in hemoglobin (Hb) and hematocrit (Hct) relative to the baseline, control (c) measurements as follows (22): ∆PV = [(Hb/Hbc) × (100 – Hctc/100 – Hct)] – 1] × 100. Hct was measured by the microhematocrit method with no corrections for trapped plasma in the calculation of ∆PV.

**Measurement of blood and urine constituents.** Free water clearance (CH₂O) was calculated as urine flow minus osmolar clearance. Plasma and urine osmolality were estimated from freezing point depression, measured by osmometer (Advanced Instruments, Norwood, MA). Glomerular filtration rate (GFR) was estimated from creatinine clearance. Plasma and urine creatinine and electrolytes, Na⁺ and K⁺, were measured by utilizing dry chemistry with a Vitros 950 analyzer (Ortho Clinical Diagnostics, Rochester, NY). Four fluid-regulating hormones were measured in plasma. Antidiuretic hormone (ADH), as arginine vasopressin, was determined in ethanol-extracted plasma by RIA (Nichols Institute, Diagnostics BV) with [1²⁵I]-vasopressin as the labeled compound. Atrial natriuretic peptide (ANP) was determined with an RIA kit without prior extraction (Nichols Institute, Diagnostics BV). Aldosterone (Aldo) measurements were done via modified RIA (AldoCTK-2, Sorin Biomedica). Plasma renin activity (PRA) was determined by quantitative measurement of angiotensin-I (RENCTK, Sorin Biomedica). The principle of the RIA was based on the competition between labeled angiotensin-I and angiotensin-I contained in probes to be assayed for a fixed number of antibody binding sites. PRA was expressed as the number of nanograms of angiotensin-I formed per milliliter of plasma after a 1-h incubation period.

The blood samples were obtained via indwelling venous cannula, previously placed in an arm vein and maintained patent by periodic infusion of physiological saline and heparin solution. Samples were drawn after a minimum of 30 min of complete semirecumbent rest, with noise and light minimized and eyes closed. Blood was drawn by syringe and placed in glass tubes containing EDTA. Samples were then placed on iced water and centrifuged within 10 min at 4°C for 20 min. Separated plasma was placed in cryotubes, placed on dry ice, and transferred to a freezer at −80°C until analyses. Arterial blood samples were obtained during the first and last hour at altitude, as previously described (14). Plasma HCO₃⁻ was calculated from arterial PCO₂ (PaCO₂) and pH from these samples to estimate renal compensation for the hypocapnia.

**Statistics.** Probabilities of significant differences (P < 0.05) between high AMS and non-AMS subject groups were obtained by t-tests and multiple-classification ANOVA. Standard least squares

| Table 1. Measurements of 16 subjects in each group |
|----------------|----------------|----------------|---------------|----------------|----------------|----------------|----------------|----------------|
|                 | AMS            | Non-AMS        |                |                |                |                |                |                |
|                 | LL scale       | Range          | Gender        | Age, yr        | Ht, cm         | Wt, kg         | BMI, kg/m²    | V̇O₂max, mL/min⁻¹/kg⁻¹-wt | %Fat          | V̇O₂max, mL/min⁻¹/kg⁻¹-LBM |
| Non-AMS         |                |                | 7 men         | 27.6           | 170.2          | 67.5           | 23.2          | 40.1            | 21.1           | 50.2               |
| SE              | 0.1            |                | 3.0           | 0.8            | 2.7            | 3.0            | 0.8           | 2.7             | 2.6            | 2.2                |
| AMS             |                | 4 men          | 27.4          | 169.7          | 72.8           | 25.1           | 34.1          | 27.3            | 46.9           |                   |
| SE              | 1.4            |                | 3.7           | 1.2            | 2.7            | 3.7            | 0.9           | 1.3             | 2.1            | 1.4                |
| P diff          | <0.001         |                | 0.28          | 0.90           | 0.90           | 0.14           | 0.06          | 0.07            | 0.20           |                   |

Values are means ± SE. AMS, acute mountain sickness; Ht, height; Wt, weight; BMI, body mass index; V̇O₂max, maximal O₂ uptake; LL, Lake Louise AMS score; LBM, lean body mass estimated by D₂O. P diff, statistical probability of the means being significantly different.
linear regression equations were used to determine relationships between measured variables.

RESULTS

As previously stated, at altitude, the subjects were encouraged to maintain a fluid intake approximating the cumulative volume of the previous 3-h interval’s urine flow, after beginning the chamber exposure with an extra intake volume of 0.5% of body weight (~300 ml). The results of fluid intake, urine volume, and net fluid balance for both groups are shown in Fig. 1. Multiple classification ANOVA analyses for all subjects’ measurements combined gave a significant decrease in fluid intake and urine volume over the time at altitude ($P < 0.001$) but no significant change in net balance. Comparison between groups indicated a slightly greater reduction (~119 ml) in intake at altitude and a significantly smaller urine volume (1,802 ml) over the total time at altitude in AMS than non-AMS. This resulted in a positive fluid balance of 1.2 liters in AMS ($P = 0.004$) that was 1.9 liters greater than the insignificant negative value of 0.7 liters in non-AMS ($P = 0.13$). Over the first 3 h at altitude the positive balance of 147 ml in AMS was significantly higher than the negative balance of 46 ml in non-AMS.

Figure 2 shows that plasma Na$^+$ in AMS declined progressively while at altitude, with K$^+$ showing an early but insignificant ($P = 0.13$) rise. For plasma K$^+$ and GFR, the changes with time at altitude and differences between groups were not significant, except for the transiently lower value in GFR at 9 h of altitude exposure. The excretion of these electrolytes and their ratio in the urine are shown in Fig. 3. The excretion rates of both electrolytes significantly decreased at altitude with no overall significant differences between groups. However, at 9 h of altitude exposure, the excretion rates of both transiently dropped in AMS, corresponding to the drop in GFR (Fig. 2). The ratio of urine Na$^+$ to K$^+$ was not different overall while at altitude but showed a clear and significant separation between the two groups after 6 h at altitude, with non-AMS showing an increase due to an equivalent increase in Na$^+$ and reduction in K$^+$ of 14%. In AMS, the urine concentrations of both Na$^+$ and K$^+$ rose significantly by 75 and 94%, respectively, to account for their fall in the ratio.

The plasma concentrations of fluid-regulating hormones are shown in Fig. 4. The Aldo levels rose significantly overnight in both groups before altitude exposure, more so in AMS, but then declined significantly at a decreasing rate at altitude, with no significant differences between groups. PRA levels showed a downward trend at altitude, but changes over time and group differences were not significant. Concentrations of ANP rose significantly in both groups during the first hour at altitude but then declined with no significant overall change or group differences. The serial changes in Δ%PV from C12 during altitude exposure, estimated from peripheral venous Hb and Hct, demonstrated no significant trends or differences between
groups at altitude, indicating that plasma dilution or concentration over time had no appreciable effect on the hormone concentrations.

However, plasma levels of ADH demonstrated clear group differences, as reported previously (12) and as shown in Fig. 5 in relation to CH2O and the AMS scores. A water diuresis (urine dilution) is characterized by positive values for CH2O, and, when urine is being concentrated to osmolality values higher than the plasma, free water clearance decreases and becomes negative. The ADH level increased significantly in AMS relative to non-AMS during the first 1.5 h at altitude and then continued to rise, remaining significantly elevated above non-AMS for the duration. As expected, trends in CH2O were opposite to those for ADH and strikingly different between groups and very similar to urine volume patterns noted in Fig. 1. By the end of the altitude exposure, CH2O was cumulatively 955 ml below baseline for AMS and 534 ml above baseline for non-AMS, thus accounting for the majority of the difference between groups in net fluid balance noted in Fig. 1. AMS scores generally followed the ADH pattern and continued to climb in the AMS group, even as CH2O differences diminished toward the end of the exposure.

Measurements of body water compartments during the control day are shown in Table 2. The TBW increased by 7.8% in 9 subjects with AMS for whom measurements were available, significantly different from the small decline of −0.7% in all 16 non-AMS subjects. On the basis of the measurements of NaBr, all of the accumulated water in AMS appeared to reside in the extracellular space. However, the 21.6% increase in ECW in AMS (vs. the 0.6% increase in non-AMS) and the large increase in TBW in AMS are clearly too large, being physiologically unreasonable and out of line with the other estimated fluid and electrolyte changes. This appears to be a systematic error that may have been caused by reduced intestinal absorption or altered absorption kinetics of D2O and NaBr in AMS. The Δ%PV estimated by Evans blue was significantly negative (−7.9%, P = 0.013) for non-AMS, but not for AMS (−4.4%, P = 0.22), with the difference not being significant. The corresponding Δ%PV estimates from venous Hb-Hct measurements for the last hour at altitude were slightly smaller for each group, but not significantly so. The two estimates of Δ%PV at the end of altitude relative to baseline were significantly related [Evans blue = −2.88 + 0.99 (Hb-Hct), r = +0.60, n = 31, P < 0.001]. No significant differences were noted in baseline TCER between groups. The TCER tended to increase in non-AMS at altitude and decrease in AMS, although the difference was not significant. The renal compensation for the respiratory alkalosis at altitude is summarized in Table 3. Near the end of altitude exposure, the PaCO2 reduction and the pH increase from the hypoxic ventilatory drive were slightly greater for AMS. The increased bicarbonate excretion was not significantly different between groups, as indicated by the HCO3− being reduced by 2.3 and 1.8 mmol/l in AMS and non-AMS, respectively (P = 0.20). In both groups, this renal compensation served to attenuate the altitude pH rise by 44%
early rise in CH$_2$O and corresponding significant decrease in during the first 3 h by subjects who do not develop AMS. The in contrast to the significant hypoxic diuresis (retention beginning within the first 3 h of exposure. This stands severe AMS during 8 –12 h of simulated altitude have water
trended downward in both groups over time at altitude, but ADH at altitude were reversed in AMS. Electrolyte excretion
took place. This type of water retention is usually associated
time at altitude by AMS compared with non-AMS (P < 0.05). group differences were not consistent. A pronounced diuresis
early in normobaric, poikiloideal hypoxia (90 min) has been
definitively shown as a normal response by Hildebrandt et al. (9) in a well-controlled study. The magnitude of this normal response is apparently not correlated with changes in circulating Aldo, PRA, ANP, or ADH (20). The absence of this response over 3 h in subjects developing early AMS is striking, but the causes remain speculative.

The extra fluid consumed by both groups just before ascent was rapidly eliminated in non-AMS, as C$_{H_2O}$ increased within 3 h; however, in AMS the elimination of this extra load did not take place. This type of water retention is usually associated with elevated ADH, whereby increased ADH in AMS probably served to increase body fluid volume and reduce urine flow. The ADH levels were about the same and unchanged in both groups at C12 and 30 min before subjects entered the chamber, indicating no overnight change before altitude exposure. The C$_{H_2O}$ response of the two groups was almost identical to that of the divergent urine flow, indicating that the regulation of body fluid osmolality by the loops of Henle, distal tubules, and collecting ducts differed between the non-AMS subjects and those developing AMS. The cumulative reduction in C$_{H_2O}$ over time at altitude by AMS compared with non-AMS (~1,444 ml) accounted for 80% of the difference in urine volume.

The respiratory alkalosis near the end of the altitude exposure was not significantly different between groups and the

Table 2. Body water compartments, plasma volume, and transcapillary escape rate during baseline control and differences from values near the end of exposure

<table>
<thead>
<tr>
<th></th>
<th>TBW base, liters</th>
<th>ECW base, liters</th>
<th>ICW base, liters</th>
<th>Base, mEq/l</th>
<th>Δ</th>
<th>PV Base, ml</th>
<th>Δ%</th>
<th>Hb-Hct Δ%</th>
<th>Base, %/h</th>
<th>Δ, %/h</th>
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<tbody>
<tr>
<td>Non-AMS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>38.6</td>
<td>14.3</td>
<td>24.3</td>
<td>-0.53</td>
<td>-0.41</td>
<td>3,701</td>
<td>-7.9</td>
<td>-2.7</td>
<td>-5.3</td>
<td>-1.9</td>
</tr>
<tr>
<td>SE</td>
<td>2.3</td>
<td>0.7</td>
<td>1.7</td>
<td>0.38</td>
<td>0.21</td>
<td>222</td>
<td>2.8</td>
<td>0.6</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>AMS</td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>(16) 37.9</td>
<td>(16) 14.2</td>
<td>(16) 23.7</td>
<td>(16) -0.74</td>
<td>-0.77</td>
<td>(16) 3,375</td>
<td>-4.4</td>
<td>(16) -3.8</td>
<td>(12) -5.8</td>
<td>2.0</td>
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<tr>
<td>SE</td>
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<td>0.7</td>
<td>1.6</td>
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<td>160</td>
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<tr>
<td>P diff</td>
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<td>0.43</td>
<td>0.67</td>
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</tbody>
</table>

Values are means ± SE; for non-AMS, n = 16 subjects; for AMS, number of subjects is given in parentheses for each measurement. TBW, total body water by D$_2$O; ECW, extracellular water by NaBr; ICW, intracellular water by subtraction; BE, base excess calculated from arterial Pco$_2$, Hb and pH values, and arterial O$_2$ saturation; TCER, transcapillary escape rate from Evans blue decay slope; PV, plasma volume as measured by Evans blue; Hb-Hct, % PV change by hemoglobin and hematocrit; Δ, differences.

Fig. 5. Plasma concentration and log concentration of antidiuretic hormone (ADH), free water clearance (cl.) (urine flow minus osmolar clearance), and serial AMS scores for the 2 groups. See legend to Fig. 1.

DISCUSSION

These results show that subjects who develop significant severe AMS during 8–12 h of simulated altitude have water retention beginning within the first 3 h of exposure. This stands in contrast to the significant hypoxic diuresis (P = 0.005) during the first 3 h by subjects who do not develop AMS. The early rise in C$_{H_2O}$ and corresponding significant decrease in ADH at altitude were reversed in AMS. Electrolyte excretion trended downward in both groups over time at altitude, but
increase in ventilation, indicated by the $P_{\text{CO}_2}$ reduction in Table 3, averaged 27\% in AMS and 20\% in non-AMS, and the renal compensation was insignificantly greater in AMS by 12 h. The $P_{\text{O}_2}$ averaged 43 Torr and was 3–4 Torr lower in AMS throughout the exposure ($P = 0.020$), as previously reported (14). Also, as indicated previously (12), the plasma levels of epinephrine and norepinephrine were higher in AMS while at altitude, suggesting a relatively elevated sympathoad-
reneuric tone in that group that may also have contributed to AMS. A direct correlation between the release of ADH and the degree of hypoxia has been reported in 24-h exposures (4). They also noted a more pronounced ADH response in subjects with AMS symptoms after 3–4 h. An earlier report by Ullmann (21), utilizing 1-h normobaric hypoxic exposures, demonstrated the normal hypoxic diuresis, but in subjects who experi-
enced “malaise, apprehension, excitement, vertigo or nausea” the diuresis was suppressed. A subsequent study by Heyes et al. (8) corroborated these observations in a decompression chamber. Their study also confirmed the relationship between the fluid retention, AMS, and increased ADH.

The retained water was probably distributed throughout the TBW with minimal change in intra- and extracellular osmo-
lality. The addition of 1.2 liters of water to the TBW compart-
ment would reduce by dilution the plasma Na\(^+\) in AMS by approximately the amount shown in Fig. 2. The final concen-
tration is probably attenuated slightly by the reduction in Na\(^+\) excretion after 6 h (Fig. 3).

The pathophysiological mechanism in AMS that would induce these early phenomena must be related to the early increase in ADH. The specific cause for the release of ADH in AMS remains unexplained, but it may be related to the subjects’ early sensation of nausea, as mentioned previously (12, 21). A change at altitude or differences between groups in TCER was not found, suggesting that membrane permeability, at least for small proteins, is not a factor in early AMS, as suggested from previous studies (7, 15), but countered by others (10). The measurement of changes in TBW and ECW (Table 2) in AMS are suspect and do not allow us to draw conclusions about these differences between groups. A signif-
ificant correlation was found between ECW and TBW ($n = 25$, $r = +0.55$, $P < 0.004$), suggesting that there may be a phenomenon associated with AMS that in some way attenuated the absorption, mixing, and equilibration of both indicators within the body. A previous study has noted that subjects developing AMS after 4 days at altitude also showed the largest ECW shifts, but not always in the same direction (25). Seven subjects with severe AMS vomited toward the end of the chamber exposure, and this would also contribute to the poor correlation between $\Delta$PV and AMS severity at altitude. Vomiting would decrease their PV, making their measure-
ments appear to be similar to those in non-AMS subjects, in whom a greater decline in PV was expected.

Prior studies of early AMS mechanisms have often incor-
porated exercise in their protocols, because this mimics prac-
tical climbing scenarios in which AMS and subsequent pul-
monary and cerebral edemas can become life threatening (2). Exercise is known to exacerbate AMS (17), but it also super-
imposes changes in fluid-regulating mechanisms compared with resting studies, notably the elevation of Aldo and ADH, which predispose subjects to AMS (1). The reduction in urine flow and $C_{\text{H}_2\text{O}}$ remain unequivocal, and the measurements support water retention along with reduced Na\(^+\) excretion in AMS as the symptoms develop. Common to both groups is a decrease in Aldo and increase in ANP during the first hour. In normoxia, ANP inhibits Aldo secretion, but hypoxia has been shown to attenuate Aldo secretion (24) and to increase ANP (11), thereby disrupting the normal relationship between these two fluid-regulating hormones. The superimposition of ele-
vated ADH in the AMS subjects apparently serves to inhibit Na\(^+\) and water excretion as time progresses at altitude.

In conclusion, in this resting study of AMS, it appears that susceptible subjects do not show the early hypoxic diuresis exhibited by immune subjects but are triggered to retain water during the early hours of exposure as their AMS severity increases.

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