Significance of systemic inflammatory markers in patients with systemic diseases

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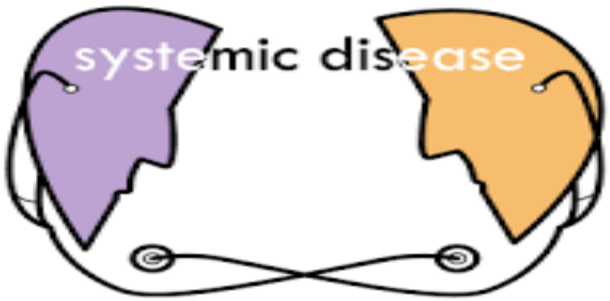
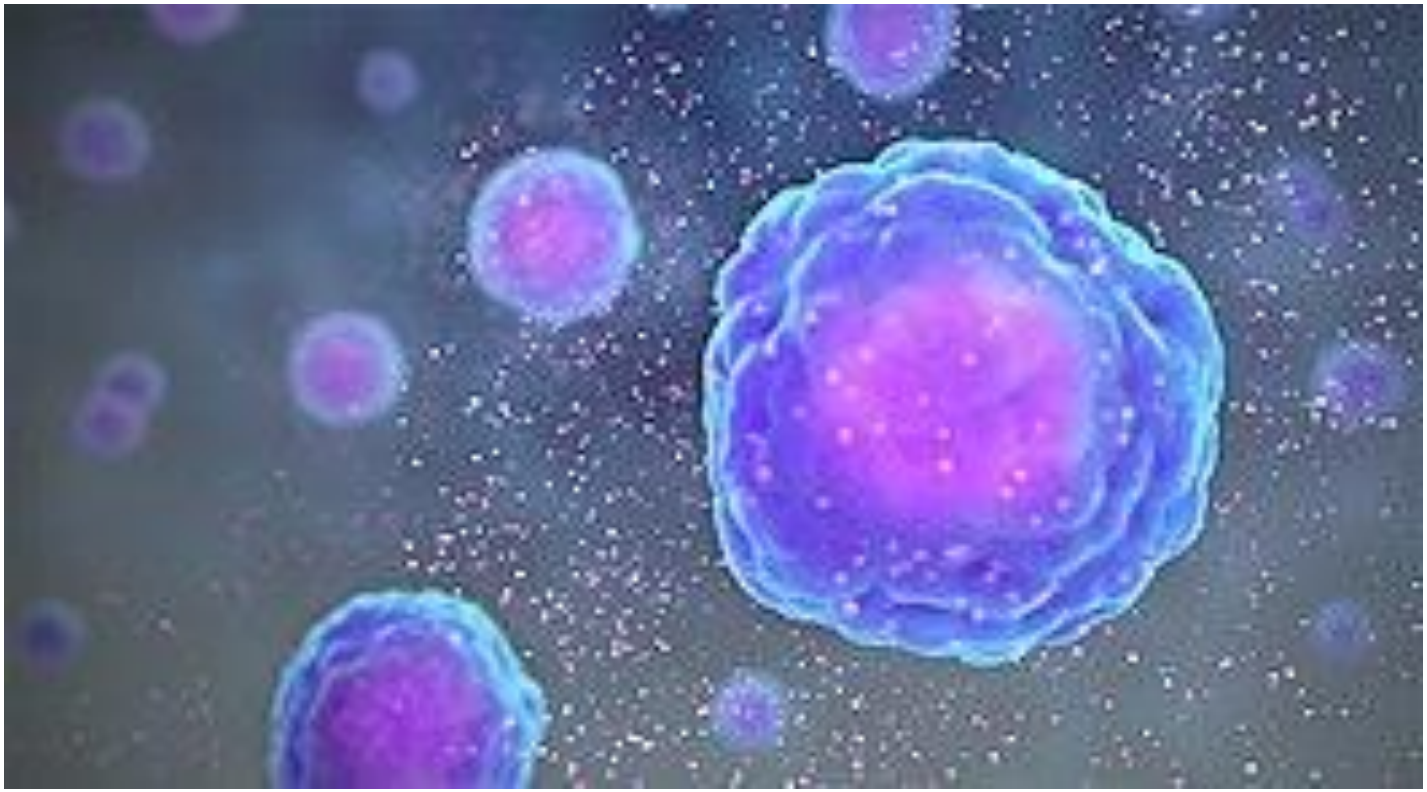
Systemic diseases

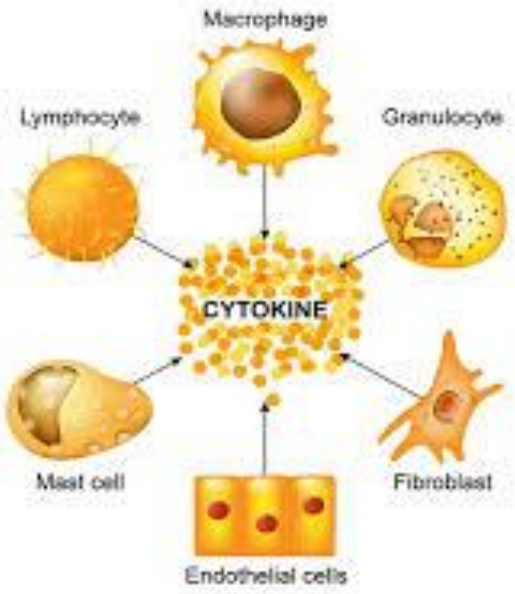
- Systemic diseases are generally an interdisciplinary challenge in clinical practice.
- Systemic diseases are able to induce tissue damage in different organs with ongoing duration of the illness.



Cytokines are peptides, and they include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factor.

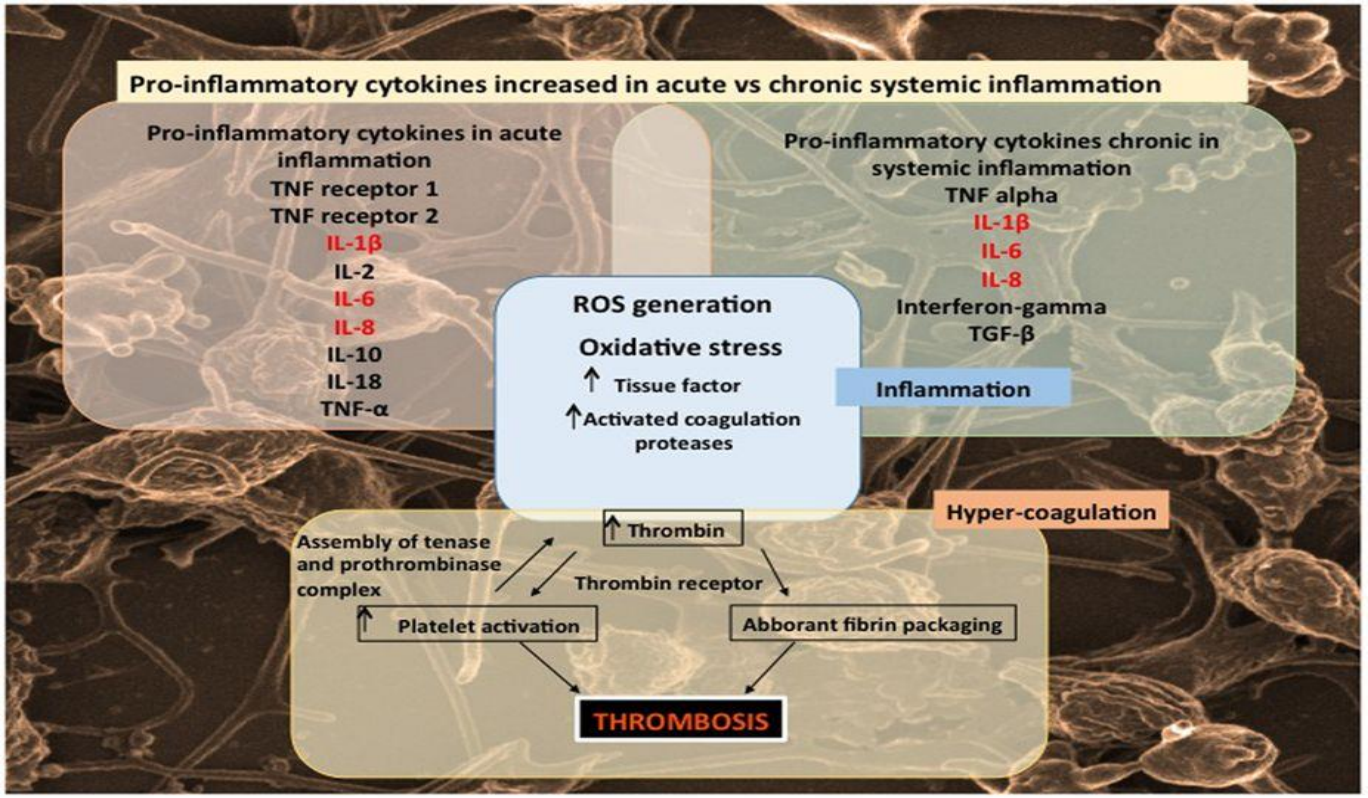


- Complex interactions exist between cytokines and inflammation, and specifically the interleukin family plays a fundamental role in systemic inflammation. Particularly IL-1β, IL-6 and IL-8 are present in whole blood, and measurable (in pg.mL−1) in most systemic inflammatory conditions.



- Bacteria and their metabolic by-products stimulate a local cellular immune response represented by a dense infiltration of neutrophils, macrophages and other lymphoid cells, resulting in the synthesis and release of the following proinflammatory cytokines and prostanoids.

The intricate relationship between inflammation and hyper-coagulation.

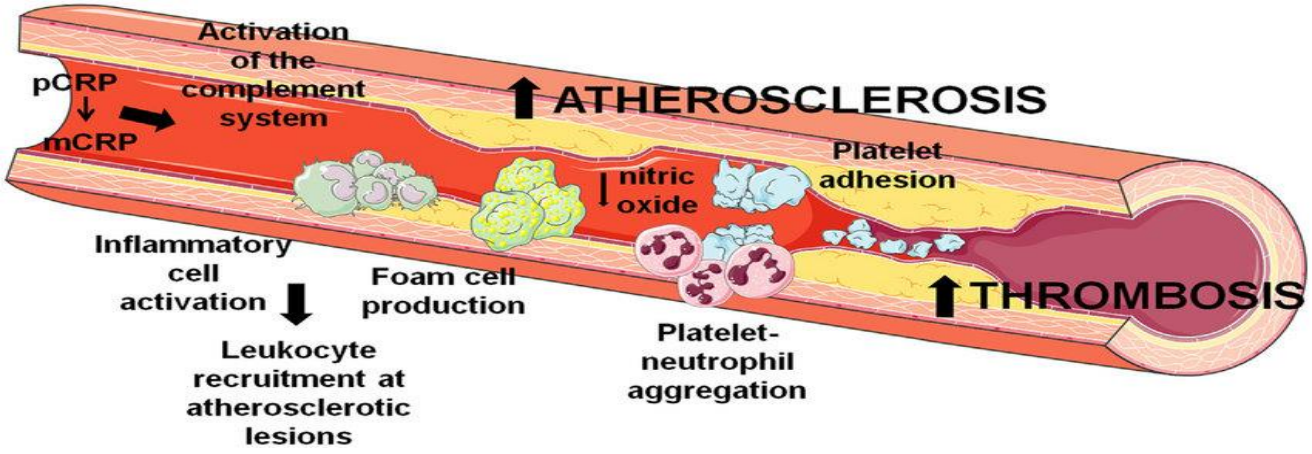


Janette Bester & Etheresia Pretorius. Scientific Reports | 6:32188. Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity

Inflammation and systemic response

- Inflammation and the systemic immune response are believed to play a central role in the initiation and progression of atherosclerosis.
- Inflammatory response and cytokine elaboration are integral components of the host response to the tissue injury and an active role after myocardial infarction.

- Based on a scientific evidence from the last two decades including epidemiological, in vivo and in vitro assays support the notion that the immune system significantly contributes in the development and progression of atherosclerosis.



Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. Circ Res. 2018 Jun 8;122(12):1722-1740.

- Elevated values of circulating inflammatory markers such as CRP, serum amyloid A, IL-6, and IL-1 receptor antagonist commonly accompany CAD.
- Such elevations correlate with in-hospital and short-term adverse prognosis and may reflect not only a high prevalence of myocardial necrosis, ischemia-reperfusion damage, or severe coronary atherosclerosis but also a primary inflammatory instigator of coronary instability

Temelli, Başak & Ay, Zuhal & Savaş, Hasan & Aksoy, Fatih & Doguc, Duygu & Uskun, Ersin & Varol, Ercan. (2018). Circulation levels of acute phase proteins pentraxin 3 and serum amyloid A in atherosclerosis have correlations with periodontal inflamed surface area. Journal of Applied Oral Science. 26. 10.1590/1678-7757-2017-0322.

- The acute-phase response is a non-specific process that may occur in the initial host response to injures, infections, ischemic necrosis or malignancy.

Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2017;9(6):7204–7218. Published 2017 Dec 14. doi:10.18632/oncotarget.23208

The literature review

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Front Immunol. 2018 Apr 9;9:586. doi: 10.3389/fimmu.2018.00586. eCollection 2018.

Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines.

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Abstract

Cytokine dysregulation is believed to play a key role in the remodeling of the immune system at older age, with evidence pointing to an inability to fine-control systemic inflammation, which seems to be a marker of unsuccessful aging. This reshaping of cytokine expression pattern, with a progressive tendency toward a pro-inflammatory phenotype has been called "inflamm-aging." Despite research there is no clear understanding about the causes of "inflamm-aging" that underpin most major age-related diseases, including atherosclerosis, diabetes, Alzheimer's disease, rheumatoid arthritis, cancer, and aging itself. While inflammation is part of the normal repair response for healing, and essential in keeping us safe from bacterial and viral infections and noxious environmental agents, not all inflammation is good. When inflammation becomes prolonged and persists, it can become damaging and destructive. Several common molecular pathways have been identified that are associated with both aging and low-grade inflammation. The age-related change in redox balance, the increase in age-related senescent cells, the senescence-associated secretory phenotype (SASP) and the decline in effective autophagy that can trigger the inflammasome, suggest that it may be possible to delay age-related diseases and aging itself by suppressing pro-inflammatory molecular mechanisms or improving the timely resolution of inflammation. Conversely there may be learning from molecular or genetic pathways from long-lived cohorts who exemplify good quality aging. Here, we will discuss some of the current ideas and highlight molecular pathways that appear to contribute to the immune imbalance and the cytokine dysregulation, which is associated with "inflammageing" or parainflammation. Evidence of these findings will be drawn from research in cardiovascular disease, cancer, neurological inflammation and rheumatoid arthritis.

Atherosclerosis. 2009 Jan;202(1):255-62. doi: 10.1016/j.atherosclerosis.2008.04.001. Epub 2008 Apr 11.

The balance between pro- and anti-inflammatory cytokines is associated with platelet aggregability in acute coronary syndrome patients.

Gori AM[1], Cesari F, Marcucci R, Giusti B, Paniccia R, Antonucci E, Gensini GF, Abbate R.

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Abstract

BACKGROUND: Residual platelet reactivity (RPR) on antiplatelet therapy in ischemic heart disease patients is associated with adverse events. Clinical, cellular and pharmacogenetic factors may account for the variable response to antiplatelet treatment.

OBJECTIVE: We sought to explore the interplay of multiple pro-inflammatory and anti-inflammatory cytokines with platelet function in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) on dual antiplatelet therapy.

METHODS: In 208 ACS patients undergoing PCI on dual antiplatelet therapy we measured platelet function by platelet aggregation with two agonists [1mM arachidonic acid (AA) and 10muM ADP]. IL-1beta, IL-1ra, IL-4, IL-6, IL-8, IL-10, IL-12, IP-10, IFN-gamma, MCP-1, MIP-1alpha, MIP-1beta, TNF-alpha, and VEGF levels were determined by using the Bio-Plex cytokine assay (Bio-Rad Laboratories Inc., Hercules, CA, USA). We defined patients with RPR those with platelet aggregation by AA >or=20% and/or ADP (10micromol) >or=70%.

RESULTS: We documented a significant association between IP-10, IFN-gamma, IL-4 and RPR by both AA- and ADP-induced platelet aggregation after adjustment for age, sex, cardiovascular risk factors, ejection fraction, BMI, vWF and CRP. Patients with pro-inflammatory cytokines not compensated by anti-inflammatory cytokines had higher risk of RPR by both AA and ADP (AA: OR=3.85, 95% CI 1.52-9.74; ADP: OR=2.49, 95% CI 1.33-4.68) with respect to patients with balanced anti-/pro-inflammatory cytokines. Patients with anti-inflammatory response overwhelming pro-inflammatory response have lower risk of RPR (AA: OR=0.55, 95% CI 0.28-1.06; ADP: OR=0.47, 95% CI 0.26-0.87).

CONCLUSION: Our study provides new insights into the interplay of anti-/pro-inflammatory cytokines with platelet hyper-reactivity in high-risk patients.

Clin Oral Investig. 2016 Jul;20(6):1263-9. doi: 10.1007/s00784-015-1621-2. Epub 2015 Oct 5.

Effects of periodontal therapy on serum lipid profile and proinflammatory cytokines in patients with hyperlipidemia: a randomized controlled trial.

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Abstract

OBJECTIVE: The aim of this study was to evaluate whether periodontal treatment in patients with periodontitis and hyperlipidemia may have any influence on plasma lipids and pro-inflammatory cytokine levels.

MATERIAL AND METHODS: We randomly assigned 109 patients with hyperlipidemia and chronic periodontitis into group 1 (n = 55) and group 2 (n = 54). Patients in group 1 underwent a standard cycle of supragingival mechanical scaling and polishing. Patients in group 2 underwent the adjunctive full-mouth intensive removal of subgingival dental plaque biofilms with the use of scaling and root planning. Periodontal parameters, total cholesterol (TC), triglyceride (TRG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), tumor necrosis factor-alpha (TNF-α), interleukin(IL)-1β(IL-1β), and IL-6 were evaluated before treatment and 2 and 6 months after treatment.

RESULTS: Two and 6 months after treatment, TRG levels were significantly lower in group 2 than in group 1 ($P < 0.05$), and the levels of HDL-C were significantly higher ($P < 0.05$). Two and 6 months after therapy, the levels of TNF-α were significantly lower in group 2 than in group 1 ($P < 0.05$), as were the levels of IL-1β ($P < 0.001$) and IL-6 ($P < 0.001$).

CONCLUSIONS: Intensive periodontal treatment of participants with hyperlipidemia and chronic periodontitis improved serum lipid levels and decreased circulating pro-inflammatory cytokine levels.

CLINICAL RELEVANCE: This study showed that intensive treatment of periodontitis results in an improvement in serum lipid levels and a decrease in serum proinflammatory cytokine levels in patients with periodontitis and hyperlipidemia. These findings may contribute to present knowledge that periodontal therapy may be beneficial for individuals with hyperlipidemia.

Open Journal of Stomatology, 2013, 3, 32-38 OJST
doi:10.4236/ojst.2013.31007 Published Online March 2013 (http://www.scirp.org/journal/ojst/)

Elevated levels of inflammatory cytokines and high-sensitivity C-reactive protein in periodontitis patients in Kosovo: A pilot study

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ABSTRACT

High-Sensitivity C Reactive Protein

The aim of this study was to compare the serum levels

Purpose of study

- The purpose of present study was to assess the serum levels of high-sensitivity C reactive protein (hs-CRP), interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) between patients with and without coronary heart disease.

Material and Methods

- Two groups of subjects were included.
- The study group involved a group of 34 patients(21 males; 13 females; ≤49years of age, mean age=60.1) with an initial diagnosis of coronary heart disease admitted to the Coronary Care Unit of the Department of Cardiology of University Clinical Center of Kosovo, Prishtina and control group (n=25).

Material and Methods

- Blood samples were taken from all subjects for measurement of a series of systemic markers of inflammation: hs-CRP, IL-1β, IL-6 and TNF-α using ELISA method.

Statistical Analyses

- The significance - **Student *t* test**.
- Qualitative parameters were compared **x^2 test**.
- For relationship between two quantitative variables - **Pearson correlation coefficient**.
- Data are presented as **mean±SD**

Results

Table 1. Study population demographics, lipid profile

	Control	Study	
	n = 25	n = 34	P-value
Age (years, mean ± SD)	45.4 ± 5.7	60.1 ± 10.7	P<0.0001
Gender, N (%)			
F	13 (52.0)	13 (38.3)	
M	12 (48.0)	21 (61.8)	P=0.522
Residence, N (%)			
Urban	18 (72.0)	22 (64.9)	
Rural	7 (28.0)	12 (35.2)	P=0.559
Blood value			
Total serum cholesterol – mmol/l	5.56±0.97	5.82±1.02	P<0.001
Serum Triglycerides – mmol/l	1.58±1.11	1.91±1.20	P<0.001
LDL – mmol/l	3.35±0.87	3.60±0.52	P<0.001
HDL – mmol/l	1.37±0.38	1.21±0.33	P<0.001

Table 2. Levels of Inflammatory markers

	Control n=25	Study n=34	P-value
Interleukin 1 β (µg/ml)			
Mean ± SD	2.1 ± 2.2	11.0 ± 10.8	P<0.002
Range	0.2 - 7.6	3.1 - 49.4	
Interleukin 6 (pg/ml)			
Mean ± SD	1.9 ± 1.6	21.6 ± 48.8	P = 0.024
Range	0.4 – 4.6	0.41 – 162.7	
TNF - alpha (pg/ml)			
Mean ± SD	64.6 ± 72.3	98.8 ± 92.0	P = 0.09
Range	8.9 – 285	24.9 – 412.0	
Hs CRP (pµg/ml)			
Mean ± SD	2.5 ± 2.6	10.9 ± 5.5	P<0.0001
Range	0 – 3.1	0.64 – 14.9	

Discussion

- In the past decade, the important role of inflammatory processes in the development and progression of atherosclerosis has clearly established.
- Different inflammatory biomarkers indicating the instability of atherosclerotic plaques have been identified.
- These new markers do not only serve as diagnostic tools for the identification of patients with unstable angina or acute myocardial infarction but also help us to identify high-risk patients.

Enrico Ammirati, Francesco Moroni, Giuseppe Danilo Norata, Marco Magnoni, and Paolo G. Camici, "Markers of Inflammation Associated with Plaque Progression and Instability in Patients with Carotid Atherosclerosis," Mediators of Inflammation, vol. 2015, Article ID 718329, 15 pages, 2015.

- The results of our study demonstrated that patients with coronary heart disease had increased circulating levels of proinflammatory cytokines and hs-CRP compared with healthy group.
- CRP is the best studied of the inflammatory biomarker in CAD .
- CRP is not only a powerful inflammatory marker, but increasing evidence suggests that CRP may also directly participate in the inflammatory process of atherogenesis.

Nicola R. Sproston , Jason J. Ashworth. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front. Immunol., 13 April 2018 |

Conclusion

- Cytokines and inflammatory mediators are key factors for the development of Systemic disease.
- Cytokines are associated with diverse clinical manifestations (i.e., clinical subphenotypes), and some of them have been associated with activity and severity of disease.
- This suggests that cytokine profiles, if used as biomarkers, could aid in the monitoring and treatment of disease. However, it is necessary to recognize that these inflammatory mediators are associated with other biological variables that could reduce or increase their impact on different biological levels.
- Thus, additional studies to clarify those complex interactions are warranted.

Thank you !

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