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Moderate hyperhomocysteinemia and oxidative stress

To the Editor: In uremic patients, hyperhomocysteinemia was found to be unrelated to measurements of oxidative stress [1]. The data imply that hyperhomocysteinemia is no primary risk factor for vascular lesions and thrombotic events in chronic renal failure.

Moderate hyperhomocysteinemia is considered to develop when dietary supplementation of folate is insufficient. Accordingly, folate supplementation can easily correct hyperhomocysteinemia, and an inverse relationship between homocysteine and folate concentrations usually exists, which was also observed in the study by Mezzano *et al* [1]. Hyperhomocysteinemia often coincides with elevated neopterin levels, which indicate immune activation and oxidative stress emerging from activated macrophages [2], and, in patients with uremia, increased neopterin concentrations are associated with protein oxidation products [3]. Also in the study of Mezzano *et al*, oxida-

tion products correlated with markers of immune activation [1]. 5,6,7,8-Tetrahydrofolic acid, the biologically active cofactor, is very susceptible to oxidation, which may become relevant under oxidative stress conditions. Immune system-derived oxidative stress seems to be crucial for folate depletion, resulting in hyperhomocysteinemia even when dietary folate is within the recommended range [2]. In coronary artery disease, folate supplementation was found to improve endothelial function earlier than changes of homocysteine concentrations became apparent [4], and also the data of Mezzano *et al* support the view that hyperhomocysteinemia is an indirect consequence of hyperconsumption of antioxidant vitamins during prolonged states of immune activation. Then, hyperhomocysteinemia is not primary in the pathogenesis of vascular lesions and thrombotic events. Nevertheless, hyperhomocysteinemia still could contribute to accelerate the underlying pathogenic process.

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