We were most interested in the case report by Claudy et al. [1]. Recently, we used 14C-chloroethyl-labelled fotemustine and established that it is a potent inhibitor of thioredoxin reductase in the human epidermis and in human metastatic melanoma [2, 3]. The drug inactivates thioredoxin reductase by alkylation of its thiolate-active site with a 'C-chloroethyl group. Thioredoxin reductase has been shown to be very important in the regulation of melanin biosynthesis by reduction of its natural, substrate thioredoxin. Reduced thioredoxin is an allosteric inhibitor of human tyrosinase, the key enzyme in melanin biosynthesis, and down-regulates enzyme activity to 30% of normal levels [4-6]. Tyrosinase expression is the same in the human epidermis regardless of skin type; with this enzyme being subject to down-regulation in fair-skinned individuals [7].

We treated 53 patients with metastatic melanoma intravenously with fotemustine monotherapy and 7 patients with 36 subcutaneous and cutaneous melanoma metastases by local injections of high concentrations (55 × 10^3 M) of the drug, subcutaneously and intratumorally, in a sequence of 20 min over 2 h [8-10]. So far, we have not observed the described supravenous hyperpigmentation in any of our cases.

We would like to suggest the following hypothesis for the observed hyperpigmentation in these 2 patients. Fotemustine diffuses rapidly through membranes, and therefore during a longer infusion time, a higher concentration of the drug would be delivered at the point of entry (i.e. the arm). If the venous blood of these 2 patients was more deoxygenated, e.g. due to chronic obstructive pulmonary disease or heavy smoking, then a more reduced local environment would cause a rapid reaction of fotemustine with target thioproteins such as thioredoxin reductase [3]. As a consequence, depletion of the reduced thioredoxin pool would activate tyrosinase resulting in the observed hyperpigmentation [5, 6].

References
Claudy AL, Lévigne V. Boucheron S: Serpentine supravenous hyperpigmentation induced by the nitrosourea fotemustine. Dermatology 1992;185:70-72.
