To the Editor:

Verhaar and colleagues, in their recent article, report on improvement in forearm endothelial function after 4 weeks of oral treatment with folic acid at a dose of 5 mg daily in 20 subjects. They used a randomized crossover design without an intervening washout period.

Our research group conducted a similar randomized crossover study of folate supplementation in healthy subjects with hyperhomocysteinemia in which 18 subjects received oral folic acid 5 mg daily for a slightly longer period of 6 weeks. We included a washout period of 6 weeks between treatments, but despite this, there was a considerable carryover effect in those subjects who received folic acid before placebo. This was not surprising considering the high dose of folic acid used and the fact that folic acid is stored in red blood cells, which have a life span of ~120 days. Such carryover effects in trials involving the use of folic acid have important implications in the interpretation of results and in the design of such studies.

The authors do not mention any carryover effect in their article. Was any such effect observed in those subjects randomized to receive folic acid first? Examination of the red cell, folate levels of the baseline and placebo groups given in their article would suggest there was.

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Response

We thank Dr Bellamy et al for their interest in our article. They are concerned with a potential carryover effect of 4 weeks of oral folic acid therapy, followed by 4 weeks of placebo therapy. Kinetic data on oral folic acid therapy have revealed that the decline in serum folate can be described by a biexponential model that yielded a rapid-phase half-life of 0.11 days and a slow-phase half-life of 18.7 ± 2.3 days. In our study, lack of total washout was exemplified by the (not significantly) higher folate levels during placebo compared with baseline (18.3 versus 12.8 nmol/L), also demonstrable in red cell folate (636 versus 489 nmol/L). These levels are low compared with the folate-loaded subjects (folate 151 nmol/L; red cell folate 1175 nmol/L). Using an independent *t* test, we tested whether there was a carryover effect of folic acid after a 4-week placebo period. There were no significant differences in the sum of maximal serotonergic responses of subjects receiving placebo followed by folic acid compared with the sum of maximal serotonergic responses of subjects receiving folic acid followed by placebo. It is interesting to note that even if a carryover effect had occurred, which would attenuate a potential difference between placebo and folic acid treatment, we still observed a clear difference between placebo and folic acid therapy. This observation further underscores acute effects of folic acid on vascular reactivity that are independent of cholesterol and homocysteine levels.

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Folic Acid in Endothelial Function in Familial Hypercholesterolemia
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