

lowest inspiratory pressures or volumes needed to improve patients' comfort (by decreasing both the respiratory rate and respiratory-muscle unloading) and to improve gas exchange.

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Folate Therapy and In-Stent Restenosis

TO THE EDITOR: Lange et al. (June 24 issue)¹ report an increase in the relative risk of restenosis after bare-metal stenting in patients receiving B vitamins to lower homocysteine levels. This seems to be in contrast to a previous report of a dramatic reduction in restenosis with the use of homocysteine-lowering B-vitamin treatment after coronary angioplasty.² These two studies differ substantially (e.g., with respect to the vitamin dose, lesion length, and percutaneous coronary intervention procedures investigated). Mechanisms of restenosis in swine in response to arterial injury differ substantially between angioplasty and stenting.³ Homocysteine stimulates the proliferation of vascular smooth-muscle cells, presumably thereby contributing to neointimal thickening.⁴ Homocysteine metabolism in human vessels is limited to remethylation, because vitamin B₆-dependent cystathionine synthase activity is absent in adult cardiovascular cells.⁵ The high dose of vitamin B₆ used by Lange et al. thus cannot be effective as speculated. The two studies are not in conflict but instead may illustrate the procedure-specific mechanisms of damage and repair. They suggest that the lowering of homocysteine levels is beneficial both after angioplasty² and in women, patients with diabetes, and those with hyperhomocysteinemia who are undergoing bare-metal stenting.¹ Studies of the use of drug-eluting stents with specific patterns of action and vessel reaction are needed.

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THE AUTHORS REPLY: Stanger et al. suggest that the findings of our trial are complementary, rather than contradictory, to those of Schnyder et al.¹ With respect to our finding that in patients with hyperhomocysteinemia (i.e., those with plasma homocysteine levels above 15 μmol per liter), folate-containing B vitamins tended to have a beneficial effect on stent restenosis, we concur with Schnyder et al. Thus, our study supports rather than refutes the hypothesis that lowering the level of homocysteine is beneficial after stenting. What was not sufficiently appreciated before our study is the strong proliferative effect of folate on neointimal growth, which exceeds the positive effect of lowering homocysteine levels, particularly in men without markedly elevated levels. With regard to such patients, the two studies came up with entirely contradictory findings, which can be explained only partially by differences in the study populations, vitamin content, and angioplasty technique.² Notably, the study

by Schnyder et al. did not include subjects with homocysteine levels higher than 13.5 μmol per liter. Studies are needed that will test the efficacy of homocysteine-lowering vitamin regimens containing betaine instead of folate.

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EGFR Mutations and Sensitivity to Gefitinib

TO THE EDITOR: The important study by Dr. Lynch and colleagues (May 20 issue)¹ suggests that specific mutations in the epidermal growth factor receptor (EGFR) characterize a subgroup of non-small-cell lung cancers that may be highly responsive to gefitinib therapy. Do these mutations predict a greater sensitivity to chemotherapy as well? The overall objective response rate to first-line combination chemotherapy for metastatic non-small-cell lung cancer is about 20 percent.² Only tumors from a small cohort of patients who had a response to gefitinib were studied for the specific mutations, but all patients except one had also received prior chemotherapy. Although the authors describe Patient 6 as “representative” of the cohort, the percentage of other patients who previously had a response to chemotherapy is not reported. If the rate of response to first-line chemotherapy was high for the other patients in the cohort who had a response to gefitinib, the specific mutations may be predictive of either chemotherapy or gefitinib sensitivity, thus identifying a distinct subgroup of patients with non-small-cell lung cancer.

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TO THE EDITOR: Lynch et al. and Paez et al.¹ report that mutations in the EGFR kinase domain in lung cancers are associated with responsiveness to gefitinib. We performed a mutational analysis of the EGFR kinase region on tumor tissue from nine pa-

tients with an event-free survival of more than 24 weeks in our phase 2 trial of gefitinib in patients with glioblastoma.² No mutations affecting the amino acid sequence in the kinase region were detected. However, our experience with EGFR immunolocalization in brain and lung tumors indicates that the cytoplasmic and membranous localization of wild-type EGFR and the constitutively active mutant EGFRvIII in brain tumors as compared with only membranous localization in lung tumors supports additional differences in the biology of EGFR between these tumor systems (McLendon R: personal communication). In summary, EGFR in glioblastoma did not have mutations in the kinase region, and any activity of gefitinib in glioblastoma would occur through an alternative mechanism reflective of important pathophysiological differences between glioblastomas and lung carcinomas.

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TO THE EDITOR: Lynch et al. elegantly demonstrate the presence of gain-of-function mutations of EGFR in patients with non-small-cell lung cancer who had a response to gefitinib. However, the authors do not mention whether there were correlations between mutational findings and the results of immunohistochemical studies or fluorescence in situ hybridization (FISH), the most commonly used techniques for detecting EGFR. In fact, we observed that responsive cases had heterogeneous results of FISH