

that coagulation activity is significantly increased in the left atrium of these patients, even with appropriate anticoagulation therapy. The results also suggest that platelet activity is not increased in the left atrium, and thus antiplatelet drugs may not be an appropriate choice for the prevention of thromboembolism in patients with mitral stenosis.

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BRONCHODILATOR THERAPY WITH OR WITHOUT INHALED CORTICOSTEROID THERAPY FOR OBSTRUCTIVE AIRWAYS DISEASE

To the Editor: I wish to comment on the dose of beclomethasone used by Kerstjens et al. (Nov. 12 issue)* in their study of bronchodilator therapy with and without inhaled corticosteroids for chronic obstructive pulmonary disease (COPD). Readers should be aware that preparations of beclomethasone that are currently available in this country yield 42 μg per puff. The dose used by Kerstjens et al. was 800 μg per day. Thus, a patient would require approximately 20 puffs a day to reach this dose. A 200-puff canister retails for approximately \$33. A patient using 20 puffs a day would need three canisters a month, at a cost of approximately \$100. It is difficult enough to get a patient to take the standard dose of two puffs four times a day, let alone five puffs four times a day. The problem of compliance with taking this dose of inhaled steroid reflects both the difficulty in inhaling 20 puffs a day and the cost. Readers should be aware, therefore, that they will probably not be able to match the results of the study of Kerstjens et al. A major gap in our drug therapy for asthma and COPD is the unavailability in this country of more potent inhaled steroids that might increase compliance by reducing the need for multiple administrations and that might also reduce costs.

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*Kerstjens HAM, Brand PLP, Hughes MD, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N Engl J Med* 1992;327:1413-9.

To the Editor: Therapy with inhaled corticosteroids is efficacious for the amelioration of the symptoms of asthma, but it is unknown whether antiinflammatory therapy will affect the accelerated decline in the forced expiratory volume in one second (FEV₁) noted in patients with this disorder.¹⁻³ The data of Kerstjens et al. suggest that inhaled corticosteroid therapy may not protect against the accelerated loss of

FEV₁ in patients with obstructive lung disease. In their study, inhaled bronchodilator therapy alone was compared with inhaled bronchodilator therapy plus inhaled corticosteroid therapy (one group received a beta-agonist alone, another group received a beta-agonist plus an anticholinergic drug, and a third group received a beta-agonist plus a corticosteroid) in adults with bronchial hyperresponsiveness and a decreased FEV₁ whose symptom-based diagnoses included asthma, chronic asthmatic bronchitis, and COPD. After three months of treatment, airways hyperresponsiveness was significantly reduced and the FEV₁ significantly increased in the group assigned to inhaled corticosteroid, as compared with the other two groups. On the other hand, the authors reported that from month 3 (when the inhaled corticosteroid had a maximal effect on the FEV₁) to month 21 (when the trial ended), the FEV₁ declined by an average of 64 ml per year in the group receiving a beta-agonist, 19 ml per year in the group receiving a beta-agonist plus an anticholinergic drug, and 33 ml per year in the group receiving a beta-agonist plus a corticosteroid (average for three groups, 39 ml per year). These negative slopes were reported to be not significantly different from one another. A 12-year longitudinal study of 3948 subjects from six U.S. cities found significantly greater losses in the FEV₁ in adults with respiratory symptoms as compared with those without symptoms³ (a negative slope of 41 ml per year among men with symptoms and 32 ml per year among women with symptoms, as compared with the average negative slope of 39 ml per year cited above).

Longer follow-up of larger groups of patients with obstructive airways disease will be required to determine whether inhaled corticosteroid therapy will affect the excess decline in the FEV₁ in patients with asthma as compared with subjects without respiratory symptoms. . . .

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The authors reply:

To the Editor: The U.S. Department of Health and Human Services recently issued an international consensus report¹ advocating 400 to 750 μg of inhaled corticosteroids as a starting dose for treating asthma, to be increased to 800 to 1000 μg for moderate asthma and even higher for severe asthma under a physician's supervision. We acknowledge the problems associated with administering 800 μg of beclomethasone a day from small-dosage canisters. In Europe, systems delivering 200, 250, and 400 μg of inhaled corticosteroids per puff are readily available, and this probably greatly enhances compliance with taking doses in the ranges mentioned above. . . .

The accelerated decline in lung function in many patients with respiratory symptoms, pointed out by Dr. Hahn, was one of the main targets of our study. This decline leads to early disability and death.² The improvement in the FEV₁

that we found after three months of treatment with inhaled corticosteroids leads, by extrapolation, to the postponement of disability due to a loss of lung function.

The slopes for the FEV₁ from three months onward, as cited by Hahn, were not significantly different, but there was nevertheless a trend toward a more favorable slope with the use of inhaled corticosteroids than with placebo. We therefore fully agree that longer follow-up (and perhaps a larger number) of patients receiving inhaled corticosteroids will be needed to determine accurately whether there is a protective effect against excess decline. With our current knowledge, however, an ethical problem would arise if a large control group of patients with moderately severe respiratory symptoms were not given inhaled corticosteroids for a prolonged period.

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MOPP, ABVD, OR BOTH TO TREAT HODGKIN'S DISEASE

To the Editor: The article by Canellos et al. (Nov. 19 issue)¹ makes an important contribution to the longstanding controversy^{2,3} about the optimal drug regimen for advanced Hodgkin's disease. On the basis of their investigation, the authors conclude that treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is superior to treatment with the older combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), a conclusion that has been in the wind for some time. Because a definitive study is likely to define standard practice, the new investigation deserves close scrutiny.

The most worrisome complication of ABVD therapy is the pulmonary toxicity, frequently fatal, that is attributable to bleomycin. In Table 4 of their paper, Canellos et al. list three deaths due to pulmonary toxicity in the ABVD group and one among those receiving MOPP and ABVD. In addition, a death from cardiac causes, possibly related to doxorubicin, is mentioned. However, it is impossible fully to assess treatment-related mortality as a function of the drug regimen from the data presented in the text and tables. A complete accounting of treatment-related mortality is essential. With salvage from the crossover regimen mitigating the mortality due to relapse, the ultimate arbiter of survival could be treatment-related mortality — i.e., bleomycin-induced pulmonary mortality as compared with alkylating-agent-induced acute nonlymphocytic leukemia.

The authors point out various plausible explanations for the absence of statistically significant improved overall survival in the groups treated with doxorubicin as compared with the patients treated with MOPP alone: the long natural history of Hodgkin's disease, a salutary effect of salvage, and a difference too small to be statistically significant in the available follow-up period. Calculation of disease-free survival after salvage⁴ can provide an earlier indication of the

final disposition of patients with a disorder such as Hodgkin's disease, which can be cured after one or more relapses. The superiority of failure-free survival after crossover from ABVD to MOPP as compared with that of the opposite crossover (in Fig. 4 of their article) suggests that the ABVD group will enjoy a statistically significant advantage in disease-free survival after salvage.

Although I agree with the authors that with the passage of time, ABVD looks increasingly good when compared with MOPP, the issue should not be closed prematurely.

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To the Editor: Canellos et al. state, "The Milan group noted that ABVD [as primary therapy for advanced Hodgkin's disease] was not associated with either permanent male sterility or treatment-induced myelodysplasia or leukemia." Since treatment-induced sterility, especially in men, is a frequent and permanent side effect of MOPP and MOPP-like regimens¹ and is less frequently encountered with the ABVD regimen used by the Milan group,² we were surprised to find that Canellos et al. did not mention this complication in the three treatment groups included in the study.

We have observed that many oncologists and hematologists frequently overlook sterility as a "minor" secondary effect of chemotherapy, when in fact many patients consider it a serious handicap.

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Dr. Canellos replies:

To the Editor: Dr. Aisenberg raises an important point about the potential for fatal bleomycin-related toxicity during treatment with ABVD. It continues to be a rare but real complication of ABVD and may be accentuated by previous exposure to radiation therapy. Although there will be continued follow-up of our series, the short-term toxic effects that we reported included the deaths due to pulmonary toxicity, whereas the occurrence of leukemias and other cancers was listed separately from the analysis of short- and long-term toxicity. It is clear that there may be a trade-off in terms of toxic effects when MOPP or a MOPP-like regimen is compared with ABVD. This should provide an impetus for the development of a nonalkylating regimen that