erwise, the significance of the increase in bronchoalveolar lavage lymphocytes after irradiation and their role in radiation pneumonitis are less clear.

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To the Editors: I read with great interest the recent article by Roberts and colleagues (1). Of concern was the marked lymphocytosis present in lavage fluid before irradiation, as well as the slightly elevated cell count. The patients had an increased total cell count (22.4×10^6 cells with 61% macrophages, 34.5% lymphocytes, and 4% neutrophils). Such an increase in cellularity and prominent lymphocytosis represents a markedly abnormal baseline. In studies reviewed by the Bronchoalveolar Lavage Cooperative Group Steering Committee, total cell counts were generally less than 16×10^6 cells in nonsmoking patients when the lavage volume was less than or equal to 150 mL. The percentage of lymphocytes in bronchoalveolar lavage fluid in normal persons is universally less than 20% (10% on average). In normal smokers, the total cell count is generally increased on the order of 30 to 50×10^6 cells, with lymphocytes not expected to exceed 8% (2).

This finding suggests a baseline lymphocytic alveolitis before any radiotherapy that was apparently exacerbated by a course of unilateral thoracic irradiation.

Determining the cause of this baseline abnormality in these patients is essential before concluding anything about the true effect of unilateral thoracic radiation. These findings could be associated with methotrexate pneumonitis (3) or toxicity from another chemotherapeutic agent, or they could be secondary to extrinsic allergic alveolitis (4) related to a humidifier system or related to another antigen in the local environment. Studying bronchoalveolar lavage fluid obtained before chemotherapy, as well as screening the patients for hypersensitivity pneumonitis, would be helpful to clarify the underlying disorder.

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In response: Both letters comment on the apparently high percentage of lymphocytes in the preradiotherapy group (1). These lymphocyte percentages are due to important methodologic variables and not to another underlying abnormality. In our study, the pre-radiotherapy total cell number (22.4 ± 18.9 million) and proportion of lymphocytes (34.5% ± 13.4%) before radiotherapy did not differ significantly from the values for normal persons (34.7 ± 19 million and 29.1% ± 12.9%, respectively) (2), which we have determined in other studies (2, 3).

These letters do highlight an important common misconception about lymphocyte counts in bronchoalveolar lavage samples that is based on data from the inaccurate method for cell quantification, cytocentrifuge preparation, which is widely used because of its simplicity, because of the large body of data gathered using this method, and because of the absence of a need to justify the use of alternate nonstandard methods. Although the cytocentrifuge method appears to be relatively accurate for the enumeration of neutrophils, Saltini and colleagues (4) have shown that it *markedly* underestimates lymphocyte numbers. Even worse, the error is not predictable, obviating the use of any correction factor (4). These factors have led to the commonly held but inaccurate view that normal bronchoalveolar lavage fluid contains very low lymphocyte numbers.

Our experience (1–3) is consistent with that of Saltini and coworkers (4), and we use their suggested millipore filter method. Further, findings from flow cytometric evaluation, which is unlikely to distort relative cell numbers, are consistent with the percentage of lymphocytes present using the millipore filter (unpublished data). A recent article (5) concerning the distribution of cytocentrifuge-determined lavage cellularity data in large numbers of normal volunteers reinforces this point. Merchant and colleagues (5) found that the proportion of neutrophils and eosinophils, cells that are not subjected to the same errors during the cytocentrifugation procedure, follow a Poisson distribution. Lymphocyte and the inversely related macrophage proportions, however, failed to show either a normal or Poisson distribution. A random error of large magnitude generated by the cytocentrifuge counting method would certainly account for this otherwise unexpected and unexplained failure.

We strongly suggest that alternate methods to the cytocentrifuge should be used for determining the proportion of lymphocytes and macrophages in bronchoalveolar lavage fluid.

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Effect of Inhaled Steroids on the Course of Asthma

To the Editors: Kerstjens and associates (1) found no effect after 18 months of inhaled steroids on the decrease in forced expiratory volume in 1 second (FEV_1) in a randomized controlled trial that included a similar number of patients treated with inhaled steroids. However, Dompeling and coworkers (2) reported a significantly slower rate of decline in prebronchodilator FEV_1 during 18 months of inhaled corticosteroid treatment in 56 patients with asthma ($n = 28$) or chronic obstructive pulmonary disease (COPD) ($n = 28$), compared with the same group before initiation of inhaled steroid treatment. They interpreted this result as evidence that inhaled corticosteroids "slowed the unfavorable course of asthma or COPD seen with bronchodilator therapy alone."

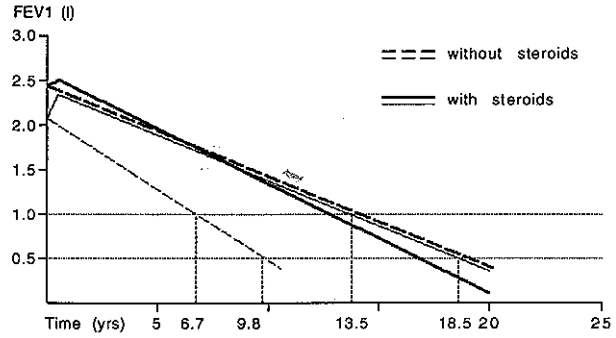

Figure 1. Theoretical comparison between the effects of beclomethasone therapy and bronchodilator therapy on the time to development of chronic airflow limitation. *Thin lines* = prebronchodilator results from Dompeling and colleagues' (1) Figure 3. *Thick lines* = postbronchodilator results, using the same data and assumptions of Dompeling and colleagues.

I question the validity of their interpretation that a decreased rate of decline of *prebronchodilator* FEV_1 indicates improvement in the unfavorable course of obstructive airway disease seen with bronchodilators alone. Spirometric evidence for irreversible airway obstruction, which develops at an accelerated rate in asthmatic patients, is best determined *after* maximal bronchodilator therapy (3). Therefore, analysis of *postbronchodilator* FEV_1 rate of decline should be a more realistic reflection of the rate of change of maximal airway function than measurement of prebronchodilator FEV_1.

To illustrate this point, I have added postbronchodilator FEV_1 slopes to Figure 3 of the article by Dompeling and colleagues (2). They interpreted their figure as indicating that inhaled steroids may double the time before low levels of lung function are reached (Figure 1). As can be seen from the redrawn figure, their theoretical comparison requires that prebronchodilator FEV_1 be greater than postbronchodilator FEV_1 after year 8 or 9. This result occurs because the rate of decline in postbronchodilator FEV_1 was actually greater after initiation of inhaled steroids (−120 mL/year) than before treatment with inhaled steroids (−98 mL/year). This paradox casts doubt on the validity of their extrapolation.

It is well established that therapy with inhaled corticosteroids improves asthma symptoms. The study of Dompeling and colleagues (2) showed decreased bronchial hyper-responsiveness in asthmatics and alleviation of symptoms and a decrease in the number of exacerbations in both asthmatics and patients with COPD, thus supporting this role for inhaled steroids. I suggest that the improvements in prebronchodilator FEV_1 found in their study probably relate to these changes in bronchial hyper-reactivity, symptoms and exacerbations of asthma and COPD, rather than to the irreversible inflammatory damage that presumably underlies accelerated declines in maximal FEV_1 noted among asthmatic patients.

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In response: To determine whether inhaled corticosteroid treatment prevents the accelerated decline in FEV_1 observed during bronchodilator therapy alone, patients must be observed during a prolonged bronchodilator treatment period with and without inhaled steroids. This was not done in the study by Kerstjens and colleagues (1), a randomized controlled trial of bronchodilator therapy with or without inhaled corticosteroids. Kerstjens and associates reported that patients who used only the β_2-agonist had an FEV_1 decline of 64 mL per year and that the patients who used the combination of the β_2-agonist and the inhaled steroid had an FEV_1 decline of 33 mL per year. It would have been interesting to follow the patients who received the β_2-agonist alone after the addition of an inhaled steroid.

As to the difference between prebronchodilator and postbronchodilator FEV_1 slope, the redrawn figure in which the postbronchodilator FEV_1 values are included is interesting. We agree that no difference was seen between the postbronchodilator value before and during corticosteroid therapy, and even a nonsignificant opposite trend (−98 mL/year compared with −120 mL/year) resulted in the paradoxical extrapolation. We observed a significant improvement, however, in postbronchodilator FEV_1 during the first 6 months of treatment (+105 mL/year), which seemed to occur only in patients with asthma (+201 mL/year) and not in patients with COPD (−5 mL/year).

We agree completely that the effects of steroid treatment were much more pronounced during prebronchodilator treatment than during postbronchodilator treatment. Indeed, this study proved that the prebronchodilator slope did not indicate an irreversible change in lung function: The steep average prebronchodilator decline of 320 mL during the 2-year bronchodilator treatment period was followed by an increase of 229 mL during the first 6 months of steroid treatment, indicating that at least 72% of this loss seems to be reversible. However, to some extent, this was true for the postbronchodilator change: The average postbronchodilator decline of 196 mL during the 2-year bronchodilator treatment period was followed by an increase of 53 mL during the first 6 months of steroid treatment, indicating that at least 27% of this loss seems to be reversible.

Apart from theoretical considerations, thus far, only the prebronchodilator FEV_1 slope has been shown to be a predictor of asthma mortality (2). We are not aware of any studies that investigated the postbronchodilator FEV_1 slope as an indicator of disease severity.

Finally, we should emphasize that extrapolations of observations made during only 2 to 4 years should be interpreted with extreme caution. As we mentioned (3), these extrapolations are a simplification. It can be questioned whether a linear model (as used in the extrapolations of ourselves and in this drawn figure) is adequate to predict the course of lung function over 10 to 20 years.

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