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To the Editor:

We were interested by the possible association between the control serum K^+ levels and maximum decrease in serum K^+ after beta_2-adrenergic drug administration described by Raimondi et al. When we re-examined our data in this light there was no linear correlation found in the group that received IM albuterol (r = .10), a weak correlation in the IV albuterol group (r = .50) and a good linear correlation in the SC albuterol group (r = .79). Overall our data may suggest a linear correlation between control serum K^+ and the maximum decrease in serum K^+, but certainly not as strongly as the data shown by Raimondi et al (r = .87). Unfortunately, the authors do not mention whether or not their subjects had recently received any beta_2-adrenergic agents prior to the evaluation day.

Even if this correlation is borne out by future work in this area, it must be kept in mind that we observed significant EKG abnormalities in subjects with a relatively low control serum K^+, but not in subjects with the largest decrease in serum K^+.

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Erratum

To the Editor:

Our published abstract entitled "Impact of Diagnosis-related Groups' Prospective Payment on Utilization of Medical Intensive Care" contains an error due to a previously-overlooked miscalculation. (Chest 1986; 89:445s.)

The middle of the abstract states, "In the first six months of 1985, 1,13 Medicare patients treated in ICU showed an average loss per discharge of $9,807, which rose to $18,360 among those who expired (35 percent)." The corrected statement should read, "In the first six months of 1985, 1,13 Medicare patients treated in ICU showed an average loss per discharge of $11,875, which rose to $30,304 among those who expired (35 percent)."

This correction does not affect any way change the message or the conclusions of the abstract.

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Steroids in COPD

The Scripture According to Albert

To the Editor:

The controversy of corticosteroid use in stable chronic obstructive pulmonary disease rages on (Chest 1986; 89:494-90). However, the apparent efficacy of steroid treatment in acute exacerbations of COPD has been resoundingly established forever with a single well-designed trial by Albert. This study has been referenced in nearly every article on the topic of steroids in COPD since it was reported in 1980. Sahn, Hudson, Mendell and even Eliasson (a staunch opponent of steroids in COPD) proselytize a role for corticosteroid therapy in patients with chronic bronchitis and acute respiratory failure.

Because it is a "landmark" case and the sole study quoted to justify steroid use in acute exacerbations of COPD, I believe Albert's study deserves special scrutiny. When analyzed correctly, his trial does not support the use of steroids, but rather clearly demonstrates the lack of efficacy in this situation.

Albert et al designed an excellent study. They conducted a double-blind, randomized, placebo controlled trial of patients with acute exacerbations of COPD. Both groups received therapy with intravenous aminophylline, inhaled isoproterenol and ampicillin. The steroid group received 0.5mg/kg of methylprednisolone every 6 hrs intravenously. At the initiation of the study, the steroid and placebo groups were felt to be statistically similar with respect to a number of variables including age, arterial blood gases, FEV and FVC. The only flaw in this protocol was the failure to report and compare presenting theophylline levels or evidence of pulmonary infection such as sputum cultures or chest x-ray findings. Differences in these data between the two groups would influence an apparent response to treatment. If at presentation the patients in the methylprednisolone group had significantly lower theophylline levels, a clinical response (as compared to placebo) may have been falsely attributed to corticosteroid therapy when in fact instituting adequate theophylline levels made the difference.

Unfortunately, despite a good study design, Albert used unsound statistical methods to analyze the data. He consequently erroneously rejected the null hypothesis and claimed a statistically significant difference between the control and steroid groups. His major mistake was to compare the percent change in FEV, and FVC relative to the presenting values. Any two measurements over time from the same individual are not independent but correlated. Therefore, the difference or percent change in these measurements are not solely a function of the subjects' experience or treatment in the time interval. Albert should have simply used the Student's unpaired t-test to compare the absolute FEV, and FVC of the placebo and steroid groups at the end of the trial as he did at the beginning.

Albert states that the admitting FEV, levels for the placebo group (675 ± 267 ml) and the steroid group (602 ± 240 ml) were not statistically different (p<0.1). However, the degree of obstruction is important because of the effect of regression to the mean. The lower the initial pulmonary function (further from the mean), the greater the likelihood for a subsequent measurement to show improvement (movement towards the mean). Albert amplifies this tendency by using the initial FEV, as the denominator to calculate the percent change in subsequent FEV, measurements. Regardless of treatment, the methylprednisolone group has a greater probability of showing a significant improvement because of its greater initial obstruction.

Albert did not report his raw data, but I was able to estimate the prebronchodilator FEV, for the placebo and methylprednisolone groups from the graph of mean percent changes he presented. At the end of the trial, the mean placebo and steroid FEV, were approximately 796 ml and 801 ml respectively. I doubt they are statistically different.

When the data from Albert's study is analyzed as it should be (using absolute volumes rather than percent changes) there appears to be no significant differences between the control and methylprednisolone groups. The calculated probability of a type 2 error is less than 0.2 in this study. The null hypothesis must therefore be accepted and I conclude that steroid therapy does not play a
significant role in the treatment of acute exacerbations of COPD if aminophylline, isoproterenol and ampicillin treatments are used concomitantly.

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To the Editor:

Dr. Glenny's letter refers almost entirely to a paper by Albert and co-authors,1 so we are not quite qualified to respond without access to the raw data of that study. However, after reviewing the paper by Albert and his colleagues on the effect of corticosteroid therapy in acute exacerbations of COPD, we believe that Dr. Glenny has a point and that there is probably no statistically significant difference in FEV₁ between the placebo and steroid groups at the end of the trial.

The significant difference reported by Albert and his colleagues may well be an artifact, as pointed out by Dr. Glenny, due to the lower initial FEV₁ in the steroid group in spite of randomization, and the inappropriate method of calculating response as percent of the initial value which exaggerates the response in those with the lowest initial FEV₁.2 Theophylline levels, sputum cultures and radiographic findings probably do not affect the results, as these variables ought to be equal in both groups due to randomization.

This said, we take exception to being called staunch opponents of the use of corticosteroid therapy in COPD. Taking the attitude of therapeutic nihilism may prove more dangerous than overzealous use of corticosteroids in this disease. While Dr. Glenny has pointed out that the study by Albert and his colleagues probably does not have the statistical power to establish that corticosteroid therapy is beneficial in acute exacerbations of COPD, this should not be equated with lack of effect. Most of the studies on corticosteroid treatment of stable COPD have shown a small effect, although not always a statistically significant one as in our own study.3-5 We showed clearly that the probability of steroid response is inversely related to baseline FEV₁; thus, a patient with a FEV₁ of 700 ml has approximately 30 per cent chance of being a responder to high-dose steroid therapy, if the FEV₁ is 1,200 ml, the probability of response decreases to 5 per cent. How response is defined is obviously of major importance, and while the inverse relationship between response and pulmonary function is a good example of regression to the mean, one cannot write off the positive response as only a statistical artifact. In fact, when viewed together the results of studies of corticosteroid therapy in COPD have been highly consistent. The differences in opinion have resulted because each study has only dealt with a part of the whole, thus reminding us of the five blind men examining an elephant. All in all, our investigation revealed this consistency but at the same time showed that corticosteroid therapy has less of a role in stable COPD than previously thought. We never said that there was no role at all. That would be premature at this date.

As we pointed out in our paper, spirometric measurements in small patient groups may be an inadequate assessment of the therapeutic effect of a drug on the airways. Using events such as morbidity and mortality as outcome measures, and using life-table analysis may be more appropriate but would obviously require a large population to determine a potential treatment effect. This approach would result in clinically significant information, ie, whether corticosteroid therapy could prevent acute exacerbations of COPD, reduce need for emergency room visits and hospitalization, reduce mortality and morbidity related to acute respiratory failure, etc. Increased rate of recovery resulting in shortening of hospital stay might also be a potential benefit that would be highly cost-effective. Life-table analysis and the study of events as an outcome has been used in cardiovascular disease (ie, the use of beta-blocker therapy to reduce mortality after myocardial infarction), but its application to pulmonary disease has been limited. It is perhaps time to look past the spirometer and its inherent problems related to repeated measures which are difficult to deal with statistically and begin measuring the outcome of our therapeutic interventions in events of clinical significance. Corticosteroids may well be a prime candidate for such an evaluation.

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Diagnosing Pneumocystis carinii

To the Editor:

We feel that the recent communication by Mones et al4 quantitating the total number of biopsy fragments required to diagnose or confidently exclude Pneumocystis carinii pneumonia in AIDS patients by fiberoptic bronchoscopy is a helpful contribution to those performing this procedure. We do not agree with their conclusions regarding the poor diagnostic efficacy of transbronchial brushings and lavage, which we4 and others5 have found to correlate well with biopsy results. We wish to re-state the importance of adequate sampling for these procedures as well.

We feel our excellent correlation of bronchial brushing with biopsy (84 percent overall, 89 percent on initial biopsy) was due to use of a large sampling brush (7 mm) and preparation of at least four slides per brushing. Similarly, we feel our excellent (86 percent) correlation of bronchoalveolar lavage with biopsy occurred because the lavages were performed using two or three irrigations of 30 ml of saline solution through the bronchoscope wedged in a segmental...