

Correspondence



Ragweed Immunotherapy in Adult Asthma

To the Editor: Creticos et al. (Feb. 22 issue)¹ found that in adults with asthma exacerbated by seasonal exposure to ragweed, immunotherapy improved objective measures of asthma and allergy, but the clinical effects were limited, and many were not sustained over a period of two years. Their findings support the conclusions of our meta-analysis of randomized, controlled trials.² However, their failure to demonstrate a significant difference from base line in medication use and asthma symptoms in the second year requires critical analysis.

Screening of volunteers resulted in a drop in the number of suitable subjects from 1000 to 127. One of the inclusion criteria was worsening of asthma during the fall season, but what constituted worsening is not stated. This may have resulted in the selection of a group biased toward pronounced worsening. There was a difference in the attrition of subjects randomly assigned to placebo (16 of 40 patients) and that of subjects assigned to immunotherapy (8 of 37). This would have reduced the statistical power of the trial to identify significant differences in the second year.

The medication score lumped bronchodilator and anti-inflammatory drugs together, and therefore, it is not possible to identify patients who were dependent on corticosteroids. Various doses of medications were scored as 1 unit, including one puff of a nasal corticosteroid. Nasal corticosteroids can relieve upper-airway symptoms and assist indirectly in asthma control, but they should not be considered antiasthma drugs. For oral corticosteroids 0.5 mg of prednisone was scored as 1 unit. The inclusion of small numbers of patients with frequent or sustained use

of oral corticosteroids during the analysis period, perhaps because of viral infection, could have skewed the data. For example, during week 6 of the second year the higher amount of medication used by subjects randomly assigned to immunotherapy, as compared with those assigned to placebo, could be explained by the inclusion of as few as three patients who required 50 mg of prednisone daily. The identification of each class of medication would allow a proper comparison of the groups.

Finally, the peak ragweed-pollen count ranged from 600 to 1500 pollen grains per cubic meter, but there was no comparison of the pollen counts for each treatment year. A less intense pollen season (fewer days with a high pollen count) in the second year could have reduced the difference between the treatment and control groups.

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1. Creticos PS, Reed CE, Normal PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501-6.

2. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-74.

To the Editor: The study by Creticos et al. is an important addition to the medical literature. However, as officials of the American College of Allergy, Asthma and Immunology, we are disturbed by the interpretation of the data in the accompanying editorial by Barnes.¹

Barnes fails to acknowledge the principal finding that immunotherapy had a beneficial effect on peak expiratory flow rates and sensitivity to bronchial provocation by allergens despite decreased medication use in the active-treatment group. This conclusion is corroborated by the reduced seasonal increase in IgE and the reduced skin-test sensitivity to ragweed.

The difference in symptom scores between the active-

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treatment and placebo groups did not reach statistical significance; however, the patients in the placebo group were taking more medication than those in the active-treatment group. Instead of concluding that immunotherapy was not effective, can one not with equal likelihood conclude that the improvement in the placebo group was due to greater use of medications? Also, might the apparently reduced efficacy in the second year represent regression toward the mean, given the continued efficacy in the third year in some participants?

Patients with asthma who are sensitive only to ragweed are rare; it was necessary to include patients with sensitivities to other antigens. Exposure to these antigens may peak during the ragweed season in much of the United States; hence, it is remarkable that a significant difference was found for any of the measured variables.

Barnes's comments about the safety of immunotherapy should be balanced against the alarming increase in mortality rates for asthma. He concludes that the cost of immunotherapy is difficult to justify in view of the relatively small gain. However, Creticos et al. found that pulmonary function increased and medication use and asthma-symptom scores decreased after a year of immunotherapy. The difference in the cost of medication was \$2.50 more per week for immunotherapy. Patients whose quality of life improved might have a different view than Barnes of the balance of costs and benefits.

Barnes states that drug therapy and the avoidance of allergens are the recommended approach to the management of asthma but does not reveal whose recommendation this is. In the United Kingdom, immunotherapy is an infrequent procedure for reasons not necessarily scientific. The actual findings of the study by Creticos et al. and of the other numerous studies that have demonstrated the efficacy of immunotherapy in asthma by objective measures should be remembered.

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1. Barnes PJ. Is immunotherapy for asthma worthwhile? *N Engl J Med* 1996;334:531-2.

To the Editor: In the study by Creticos et al., the reported effects of treatment were not limited as compared with those of most other treatments for asthma subjected to one-year controlled trials. In his editorial, Barnes concludes that the "small" effects of immunotherapy are not worthwhile when compared with those of other treatments that are "highly effective." He states that "inhaled glucocorticoids are of particular value." This view appears to ignore the fact that hospital admissions for asthma in the United Kingdom and elsewhere have continued to rise despite widespread use of inhaled glucocorticoids. The editorial supports the case for inhaled-corticosteroid treatment by citing a Canadian study on rhinitis that compared topical budesonide with immunotherapy using modified ragweed tyrosine adsorbate (Pollinex-R).¹ This is a surprising choice, since this preparation of allergen, which is first treated with glutaraldehyde and then adsorbed to tyrosine,

has not been shown to be clinically effective and does not produce an IgG antibody response.

In the United Kingdom, physicians and patients are generally not aware of the high costs of inhaled corticosteroids and there are very few specialists in the management of allergic disease. Barnes refers to the use of immunotherapy in "general practice." It was precisely physicians in general practice in the United Kingdom who encountered severe side effects when administering immunotherapy. In the United States immunotherapy is carried out by specialists and is reserved for patients who have not responded adequately to treatment with inhaled medicines and avoidance of specific allergens.

It is clear from a recent meta-analysis² and the report by Creticos et al. that immunotherapy can be an effective treatment for asthma and should be considered in cases of mild-to-moderate asthma in which other treatments do not produce adequate control.

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1. Juniper EF, Kline PA, Ramsdale EH, Hargreave FE. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1990;85:606-11.

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To the Editor: Barnes notes that few people with asthma have symptoms confined to ragweed season. This phenomenon may reflect the fact that the ragweed-pollen grain is approximately 20 μm in diameter.¹ Consequently, ragweed-pollen grains are less likely to penetrate past the glottis. Alternatively, the perennial allergens house-dust mites and cat dander may be airborne in particles less than 20 μm in diameter² and are more likely to enter the bronchial tree.

Although Barnes writes that immunotherapy with dust-mite allergen appears to be less effective than immunotherapy with seasonal allergens, the clinical benefit of immunotherapy with a standardized dust-mite extract has been demonstrated.³ As implied by Creticos et al., a double-blind, placebo-controlled multicenter trial using standardized extracts of perennial allergens, and possibly of allergens encountered during multiple pollen seasons, would address the situations of most patients who have allergic asthma and of many of the patients screened for the study who did not meet the entry criteria.

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3. Bousquet J, Hejjaoui A, Clauzel AM, et al. Specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. II. Prediction of efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;82:971-7.

To the Editor: Creticos et al. emphasized the importance of twice-daily peak flow readings as “objective day-to-day assessments of the seriousness of asthma.” Our research casts serious doubt on the usefulness of unmonitored peak flow readings and the accuracy of diaries.¹ During a relatively short five-week study of 20 patients with asthma, we compared the electronic memory of the peak flowmeter with the written diary of each participant. Allowing a 10 percent deviation in recording due to random error, we found that over 20 percent of the final week’s recordings in the diaries were in error. A tendency to inflate the peak expiratory flow rate occurred. There were a substantial number of phantom readings in which peak flow was recorded in the diary as having been measured but was never actually measured. During a multiyear study, phantom readings may lead to a regression toward the mean similar to the profile of data obtained during the second year of the study by Creticos et al.

The diaries’ records of the use of antiinflammatory inhaler sprays showed a similar pattern of inaccuracy, with 47.1 percent of all base-line recordings off by more than 10 percent, and 57.9 percent of all final-week recordings showing errors. There was a tendency to record more medication use than actually occurred. Others have also found marked inaccuracies in the reporting of inhaler use.²⁻⁴

Considering the long time frame for the ragweed-immunotherapy study and the limited sample size, it is likely that there was some inaccuracy in the diary recordings that seriously undermined the results. Whatever motivates a patient to report erroneous or phantom recordings, inaccuracies are a serious methodologic threat to studies that rely on the use of diaries.

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The authors reply:

To the Editor: Many people with asthma receive immunotherapy in an attempt to desensitize them to their allergies. The introduction of characterized and standardized allergen extracts has allowed a precisely defined therapeutic dose to be calculated and administered.^{1,2}

We agree with Weiner et al. that the findings in the first year of our study are more likely to represent the true effects of immunotherapy. That these favorable changes were less pronounced in the second year of treatment is consistent with a regression toward the mean. The attrition in the placebo group — secondary to a poor response — certainly reduced the statistical power of our findings

in the second treatment year. However, the group of 17 patients immunized for a third year continued to show a similar magnitude of improvement in symptoms, peak flow, and medication use, providing evidence that the improvement is not short-lived but is persistent.

As do Chmelik and Doughty, we recognize the pitfalls inherent in the use of daily monitoring of peak flow and diaries of medication use. Even with carefully trained patients, uncontrolled variables such as these require blinded observations in untreated control patients. Were we to initiate another study with similar aims, we would use microprocessor-based electronics for the peak flowmeters and inhalation devices. These were not available at the time of our study.

After treatment, there was a significant improvement in the response to bronchial challenge to ragweed in the immunotherapy group. This finding helps corroborate the measurable improvements in peak flow in the immunotherapy group as compared with the placebo group.

Klein questions the relevance of ragweed-induced asthma. Agarwal et al. demonstrated that a considerable fraction of airborne ragweed allergen exists as particles that are less than 10 μm in diameter.³ These aerosolized microparticles can easily reach the lower airways and provoke symptoms of asthma.

Patients with allergies are commonly sensitive to multiple aeroallergens. Our mandate was to study in detail the effects of immunotherapy on a dominant seasonal allergen. Ragweed was chosen because of the extensive work done to characterize and standardize it. We are currently extending our initial observations in ragweed asthma and studying the effectiveness of immunotherapy in adults with asthma and multiple allergies.

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1. Malling H-J, Weeke B, eds. Position paper: immunotherapy. *Allergy* 1993;48:Suppl 14:9-35.
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To the Editor: Portnoy and Finegold, representing the American College of Allergy, Asthma and Immunology, suggest that I did not acknowledge the beneficial effects of allergen immunotherapy reported by Creticos et al. I clearly stated that there was an objective beneficial effect during the first year of treatment, but I pointed out that this effect was small and was not sustained in the second year — a conclusion that the authors also made. Portnoy and Finegold also suggest that the small effect may be due to an improvement in the placebo group. This is precisely the reason for conducting placebo-controlled, double-

blind trials in diseases such as asthma, when large placebo effects may be observed.

The relatively small effect of specific immunotherapy must be compared with the high efficacy of inhaled glucocorticoids, which are effective in all patients and have few or no serious side effects at the doses required by most patients.¹ My statement that the avoidance of allergens and drug therapy are the preferred approach is based on the numerous national and international guidelines for asthma therapy, including those of the most recent National Heart, Lung, and Blood Institute–World Health Organization Global Initiative in Asthma Management.²

Platts-Mills suggests that the continuing high rate of hospital admissions in several countries implies that inhaled corticosteroids are not effective. This is a curious interpretation of the evidence. A striking finding in all long-term controlled studies of inhaled corticosteroids is a marked reduction in acute exacerbations and hospital admissions for asthma.¹ This has not been demonstrated for specific immunotherapy. As I stated, there is an urgent need for comparative studies of immunotherapy and inhaled corticosteroids. I cited the only study that I am aware of that compared topical corticosteroid therapy with immunotherapy. Although Platts-Mills implies that the allergen preparation used in that study is ineffective, it was in widespread use for the treatment of hay fever. He also refers to the high costs of inhaled corticosteroids. Several detailed pharmacoeconomic analyses, however, indicate that this treatment is the cheapest means of managing asthma, since it markedly reduces hospital admissions and the time lost from work.^{3,4} Such data have not been provided for immunotherapy.

I agree with Klein that ragweed immunotherapy may not be indicated in many patients. The study by Creticos et al. illustrated how difficult it is to find patients in whom it may be indicated. Most patients with asthma have multiple skin-test responses, and perennial allergens, such as house-dust mites and cat dander, are much more important than seasonal allergens. However, studies of specific immunotherapy with these allergens have generally been disappointing. Indeed, a recent large, placebo-controlled trial of multiple-allergen immunotherapy in children with asthma found that immunotherapy was completely ineffective.⁵⁻⁷

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2. Global strategy for asthma management and prevention. NHLBI/WHO workshop report no. 95-3659. Geneva: World Health Organization, 1995:1-176.

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High-Altitude Pulmonary Edema

To the Editor: We wish to highlight morphologic and hemodynamic characteristics of the pulmonary microcirculation that strongly support the concept of stress-induced failure of pulmonary capillaries in high-altitude pulmonary edema rather than pulmonary arterioles, as suggested by Jerome and Severinghaus (March 7 issue).¹

It is highly unlikely that small arterioles are the locus minoris resistentiae, since in animals susceptible to high-altitude pulmonary edema, pulmonary arterioles down to 20 μm in diameter have smooth-muscle cells. Moreover, animals subjected to chronic hypoxia have small arterioles with hyperplasia of immature smooth-muscle cells that form a distinct medium between the external and internal elastic membranes. The existence of these morphologic characteristics has also been confirmed in human highlanders, who are unusually prone to high-altitude pulmonary edema.²

The events leading to high-altitude pulmonary edema may be summarized as follows. Hypoxic pulmonary vasoconstriction of the well-muscularized terminal arteries and arterioles results in excessive pulmonary hypertension in persons prone to high-altitude pulmonary edema. The dramatic rise in pulmonary-artery pressure is further augmented by the enormous increase in cardiac output during strenuous exercise at high altitude. Thus, compliance of the arterial capacitance vessels is exceeded.

The higher intraluminal pressure in the pulmonary arteries is transmitted to the pulmonary capillaries, as previously demonstrated by direct micropuncture of pulmonary microvessels during alveolar hypoxia.³ In addition, direct measurements of microvascular diameter⁴ or micropressure³ reveal hypoxic constriction of pulmonary venules, which further contributes to the increase in transmural pressure in alveolar capillaries without affecting pulmonary-capillary wedge pressure. Because of the distribution of intravascular pressure, the capillaries in the perihilar regions are primarily affected.

As to the initial radiographic appearance of slough infiltrates in the perihilar tissue, the greatest attention must be paid to the peculiar morphology of the pulmonary-arteriolar-vessel tree. Pulmonary capillaries do not originate solely from small precapillaries but may branch directly off the vascular wall of large arterioles of at least 100 μm in diameter.⁵ Thus, predominantly proximal alveolar capillaries originating directly from the large arterioles are less protected or are unprotected by hypoxic pulmonary vasoconstriction and are in particular exposed to excessive pulmonary hypertension and transmural pressure. These capillaries undergo stress-induced failure first, whereas terminal pulmonary arterioles are protected by smooth muscle as well as by the intima of their internal and external elastic membranes. The therapeutic efficacy of oxygen, nifedipine, or nitric oxide in high-altitude pulmonary edema can be attributed to the abolition of hypoxic pulmonary vasoconstriction.

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To the Editor: Jerome and Severinghaus did not seem to consider the model of high-altitude pulmonary edema proposed by Cosby et al.¹ Noncardiogenic high-altitude pulmonary edema is induced in part by the action of atrial natriuretic factor and the ischemia-induced release of vasopressin. Pulmonary hypertension increases right atrial pressure, and this induces the release of atrial natriuretic peptide, a counterregulatory hormone that acts on pulmonary and renal vascular receptors. Atrial natriuretic peptide causes vasodilatation of the preterminal pulmonary arterioles and an increase in pulmonary- (and cerebral-) capillary permeability. This is the direct cause of the vasogenic pulmonary edema on the one hand and of the intrapulmonary shunting on the other and explains the high protein and cellular content of edematous fluid as well as the ventilation-perfusion mismatch, the resulting cyanosis, and the cerebral component of the syndrome. At the same time atrial natriuretic peptide induces natriuresis and inhibits activation of the renin-angiotensin-aldosterone system. Indeed, Cosby et al. found substantial hyponatremia and normal or decreased plasma renin activity and aldosterone concentrations in patients with high-altitude pulmonary edema.

The second main mechanism of high-altitude pulmonary edema is hypoxemia-induced release of vasopressin, which produces water retention and contributes to the hyponatremia induced by atrial natriuretic peptide. Cosby et al. also found inappropriately elevated arginine vasopressin levels (mean, 1.8 ± 0.4 pmol per liter in patients with high-altitude pulmonary edema, as compared with 0.9 ± 0.3 pmol per liter in controls), which decreased (to 1.23 ± 0.34 pmol per liter) during recovery, whereas the lowered plasma sodium concentration had not normalized within 24 hours after recovery. The humoral counterregulatory model of Cosby et al. explains some obscure points in the hemodynamic model proposed by Jerome and Severinghaus, although there are still many unexplained issues.

A last question of practical importance is whether alcohol, a known vasodilator, vasopressin antagonist, diuretic, and antifrothing agent (when inhaled in pulmonary edema), should be replaced by compressed nitrous oxide in the barrels attached to the collars of Saint Bernard mountain-rescue dogs in Switzerland.

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Positron-Emission Tomography and Alzheimer's Disease

To the Editor: Reiman et al. (March 21 issue)¹ conclude that abnormalities in glucose metabolism, evaluated by positron-emission tomography (PET) in asymptomatic subjects homozygous for the $\epsilon 4$ allele for apolipoprotein E, provide preclinical evidence of Alzheimer's disease. The $\epsilon 4$ allele is highly prevalent not only in patients with Alzheimer's disease but also in those with atherosclerotic vascular disease, including ischemic cerebrovascular disease and vascular dementia.²⁻⁴ The PET abnormalities cannot be used to distinguish vascular dementia (formerly called multi-infarct dementia) from Alzheimer's disease.^{5,6} Thus, apolipoprotein E genotyping, PET, or the two combined may not be reliable tools for confidently diagnosing presymptomatic Alzheimer's disease. In fact, healthy persons carrying two copies of the $\epsilon 4$ allele and thought to have Alzheimer's disease on the basis of brain abnormalities detected by PET may actually have unrecognized atherosclerotic cerebrovascular disease.

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1. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the $\epsilon 4$ allele for apolipoprotein E. *N Engl J Med* 1996;334:752-8.
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The authors reply:

To the Editor: Alzheimer's dementia is typically characterized by bilateral reductions in glucose metabolism in posterior cingulate, parietal, temporal, and prefrontal regions.¹ In contrast, vascular dementia is characterized by a variable pattern of reductions in glucose metabolism. These reductions are often focal, scattered, and asymmetric; they appear to be related to the location of infarcts.² Algorithms developed at the University of Michigan and used in our study to generate spatially standardized, three-dimensional surface-projection brain images improve the ability to detect the pattern of hypometabolism typically

associated with Alzheimer's disease and distinguish it from those associated with vascular dementia and other forms of cerebrovascular disease.³

Persons homozygous for the $\epsilon 4$ allele for apolipoprotein E appear to have an especially high risk of Alzheimer's dementia. In the original case-control study, 91 percent of $\epsilon 4$ homozygotes had Alzheimer's dementia by the age of 80.⁴ In our study, a cognitively normal group of $\epsilon 4$ homozygotes in their 50s and early 60s had bilateral reductions in glucose metabolism in the same posterior cingulate, parietal, temporal, and prefrontal regions as an older group of patients with Alzheimer's dementia. This group had few risk factors for ischemic cerebrovascular disease other than the $\epsilon 4$ allele and no indication of cerebrovascular disease on the basis of history, neurologic examination, or T₁-weighted magnetic resonance images.

Although the $\epsilon 4$ allele is a risk factor for both cardiovascular disease and Alzheimer's dementia, it remains to be determined whether this allele increases the risk of these disorders by the same or different mechanisms. The $\epsilon 4$ allele may be a risk factor for vascular dementia and other forms of ischemic cerebrovascular disease, but postmortem studies are needed to address the potentially confounding effect of coexisting Alzheimer's disease.

Clinically, apolipoprotein E genotyping and PET are not indicated to determine a healthy person's risk of Alzheimer's dementia. At this time, they cannot predict with sufficient certainty a person's risk of this disorder, they cannot predict with sufficient accuracy when symptoms might develop in a person at risk, and they do not indicate what measures might be taken to address the potential problem. Together, these tests promise to help researchers characterize the brain changes that herald the onset of Alzheimer's dementia; they may offer a relatively rapid way to assess future treatments to prevent this devastating disorder.

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Campylobacter jejuni Infection and Treatment for Guillain-Barré Syndrome

To the Editor: Rees et al. (Nov. 23 issue)¹ reported that patients with the Guillain-Barré syndrome and recent infection with *Campylobacter jejuni* have a more severe re-

TABLE 1. PATIENTS WITH GUILLAIN-BARRÉ SYNDROME WHO COULD WALK INDEPENDENTLY SIX MONTHS AFTER THE START OF TREATMENT.

INFECTION STATUS	PLASMA EXCHANGE (N = 67)	INTRAVENOUS IMMUNE GLOBULIN (N = 66)
	no. able to walk/no. in group (%)	
GM1-positive		
With <i>C. jejuni</i>	0/7	9/11 (82)
Without <i>C. jejuni</i>	3/3 (100)	2/2 (100)
GM1-negative		
With <i>C. jejuni</i>	10/17 (59)	7/11 (64)
Without <i>C. jejuni</i>	35/40 (88)	36/42 (86)

sidual disability after one year than patients without *C. jejuni* infection. In later studies they showed that patients with the combination of *C. jejuni* infection and antibodies against GM1 ganglioside have the worst prognosis.² The effect of treatment was not included in their analyses, however.

We studied the outcome in 147 patients with Guillain-Barré syndrome six months after their enrollment in a trial comparing plasma exchange with intravenous immune globulin.³ None of the patients could walk independently at the time of randomization. Pretreatment serum samples from 133 patients were tested serologically for *C. jejuni* and anti-GM1 antibodies.⁴ The patients were classified according to whether *C. jejuni* infection and anti-GM1 antibodies were present. Table 1 summarizes our findings.

Our study confirmed the unfavorable prognosis in the patients with both *C. jejuni* infection and anti-GM1 antibodies. However, the more severe residual disability was found only after treatment with plasma exchange, not after treatment with intravenous immune globulin. Five of the patients treated with plasma exchange were studied again at least one year after randomization, and none could walk independently. In contrast, 8 of 10 patients with *C. jejuni* infection and anti-GM1 antibodies treated with intravenous immune globulin recovered. In a logistic-regression model, the percentage of recovery among the patients with *C. jejuni* infection and anti-GM1 antibodies was also lower after plasma exchange (18 percent) than after treatment with intravenous immune globulin (82 percent). The difference in outcome between the patients treated with plasma exchange and those treated with intravenous immune globulin could not be explained by other prognostic factors, such as age and severity of disease at onset. Our data indicate that the combination of *C. jejuni* infection and anti-GM1 antibodies is associated with a poor prognosis in patients with Guillain-Barré syndrome who are treated with plasma exchange. Prospective studies are needed to investigate whether such patients should be treated preferentially with intravenous immune globulin.

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4. Jacobs BC, van Doorn PA, Schmitz PIM, et al. *Campylobacter jejuni* infections and anti-GM1 antibodies in Guillain-Barré syndrome. *Ann Neurol* (in press).

Dr. Rees replies:

To the Editor: We are grateful to Jacobs et al. for their comments about the improved outcome at six months in patients with both *C. jejuni* infection and anti-GM1 antibodies who were treated with intravenous immune globulin rather than plasma exchange. We could not make a similar comparison in our group of 13 patients with *C. jejuni* infection and anti-GM1 antibodies, because none of our patients were treated with plasma exchange. Ten received intravenous immune globulin, and three were not treated at all. Follow-up data were available on 9 of the 10 patients treated with intravenous immune globulin. After one year, seven were walking, one could walk only with canes, and one had died. Therefore, we can neither confirm nor refute the observations of Jacobs et al., and we agree that further prospective studies are needed to answer this important question of management.

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Herpes Simplex Encephalitis

To the Editor: Drs. Watemberg and Morton (March 7 issue) describe a case of herpes simplex encephalitis in a 13-year-old boy and present the classic electroencephalographic finding of periodic lateralized epileptiform discharges.¹ Whereas it is gratifying to learn that the boy recovered fully after treatment with 15 mg of acyclovir per kilogram of body weight per day for 14 days, the only studies that have prospectively evaluated intravenous acyclovir for the treatment of herpes simplex encephalitis have used a dosage of 30 mg per kilogram per day (10 mg per kilogram every 8 hours) for 10 days.^{2,3} This standard dose of acyclovir should be used for the treatment of herpes simplex encephalitis unless there is evidence from clinical trials that demonstrates the superiority of another dosing regimen.

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1. Watemberg N, Morton LD. Periodic lateralized epileptiform discharges. *N Engl J Med* 1996;334:634.
2. Sköldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis: randomised multicentre study in consecutive Swedish patients. *Lancet* 1984;2:707-11.
3. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med* 1986;314:144-9.

To the Editor: The legend to the Image in Clinical Medicine on periodic lateralized epileptiform discharges refers several times to the wave forms shown in the image as having an activity of a certain number of "Hz per second." In the physical sciences, the unit of frequency is the hertz, abbreviated Hz. In primitive units, 1 Hz is equivalent to one cycle per second. The authors were pointing out the dominant frequencies of the wave forms, and the correct usage should have been either "Hz" or "cycles per second" but not "Hz per second."

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Costs of Visits to Emergency Departments

To the Editor: Although Williams's study of the costs of visits to emergency departments (March 7 issue)¹ appears to be generally well designed, I believe its whole premise is penny-wise and pound-foolish. When performed in many millions of patients, even relatively low-cost procedures result in large overall expenditures. Limiting any care that may be less than completely necessary, however inexpensive, is a worthy goal in this era of expanding costs and shrinking resources.

The lack of access in certain areas to any care other than that provided by the emergency department is an argument for improving access, not for providing nonurgent care in emergency departments, whatever the cost. Discouraging the use of hospital emergency departments for nonurgent care and making alternatives available might promote the use of regular physicians' services, which in turn might prevent not only nonurgent visits to the emergency department but also some urgent visits. A payment system that is fair to all might go a long way toward making this approach a reality. It would be worth the time and effort to identify incentives that will bring doctors to the inner cities and to persuade patients to obtain care in settings other than the emergency department.

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1. Williams RM. The costs of visits to emergency departments. *N Engl J Med* 1996;334:642-6.

To the Editor: Marginal costs alone underestimate the true cost of emergency care, as compared with the potential savings associated with the use of primary care. Misinterpretation of Williams's findings may lead to the false claim that expanded access to community-oriented primary care is unnecessary since emergency visits appear to be so inexpensive. A complete and accurate cost analysis has to include the costs of failure to prevent, when possible, the development of disease, acute exacerbations of disease, and sequelae, as well as the costs of unscheduled outpatient visits, hospitalizations, all encounters, and days lost from work or school.

For example, patients with asthma often report a history

of frequent visits to the emergency department. Establishing an ongoing relationship with a primary care provider allows for evaluation of the patient, education, and long-term management. In this example, primary care includes teaching the patient to avoid or control the triggers of asthma attacks; preventive care, including influenza and pneumococcal immunizations; long-term management with antiinflammatory agents; peak-flow monitoring at home; self-adjusted stepped treatment; and management by telephone. Such an approach reduces the total cost of care.¹⁻⁴

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1. O'Brien KP. Managed care and the treatment of asthma. *J Asthma* 1995;32:325-34.
2. Taitel MS, Kotses H, Bernstein IL, Bernstein DI, Creer TL. A self-management program for adult asthma. II. Cost-benefit analysis. *J Allergy Clin Immunol* 1995;95:672-6.
3. Trautner C, Richter B, Berger M. Cost-effectiveness of a structured treatment and teaching programme on asthma. *Eur Respir J* 1993;6:1485-91.
4. Sullivan SD, Weiss KB. Assessing cost-effectiveness in asthma care: building an economic model to study the impact of alternative intervention strategies. *Allergy* 1993;48:Suppl:146-52.

To the Editor: Williams reports a marginal cost of \$24.40 for nonurgent visits and concludes that visits to hospital emergency departments are much less costly than previously believed. By counting only marginal costs and assuming they contribute nothing to fixed costs (operationally defined by the author as those that do not vary from month to month), one could similarly conclude the emergency departments are efficient providers of services to any subgroup — say, for example, left-handed patients. Williams would have us believe that a 15 percent reduction in the total volume of emergency department visits, achieved by decreasing the number of nonurgent visits, as described by Selby et al. in the same issue,¹ would have no effect on fixed costs, such as the space assigned to emergency departments, routine staffing levels, or the number of emergency departments needed in a community.

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1. Selby JV, Fireman BH, Swain BE. Effect of a copayment on use of the emergency department in a health maintenance organization. *N Engl J Med* 1996;334:635-41.

To the Editor: I believe readers of the *Journal* should have been made aware that Williams received financial support from three emergency-physician staffing companies — Emergency Consultants, EMSA Limited Partnership, and Coastal Emergency Services — as he acknowledged in his University of Michigan doctoral dissertation on the costs of emergency department services. In addition, he

acknowledged the contribution of Physicians Billing for “invaluable assistance in the collection of data for this project.”¹ Williams’s sophisticated analysis included many assumptions and complicated manipulations of data, and biases may have influenced the results. I believe the financial grants are pertinent, as is Williams’s former position as president of the American College of Emergency Physicians and that organization’s use of the study published in the *Journal* as part of its current lobbying activities.

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1. Williams RM. The costs of emergency department services. (Doctoral dissertation. No. 9512232. Ann Arbor: University of Michigan, University Microfilms International Dissertation Services, 1995.)

Dr. Williams replies:

To the Editor: Hearst is incorrect in assuming that my conclusions about the relatively low costs of nonurgent emergency department care were based solely on the \$24 marginal cost of a nonurgent visit. I reported an average cost of \$62 for a nonurgent visit, which is roughly similar to the cost of a visit to a private physician’s office.

I agree with Auerbach and Becker that care in the emergency department is not an ideal substitute for ongoing care by a primary care physician. As shown in a recent study, however, Americans who rely on the emergency department for virtually all their medical care may not have access to primary care.¹ It could be argued that for patients who lack access to a primary care provider, visits to the emergency department during the early stages of a disease may be cost effective if they prevent the progression of the illness and subsequent hospitalization.

Baier raises an important policy issue. Clearly, there are inequities in the financing of emergency services. Hospitals are required by law to evaluate every patient seeking care.² The costs of uncompensated care are passed along, through higher charges, to patients who have the means to pay for their care, making it more difficult for hospitals to compete in the medical marketplace on the basis of price. Excess charges may amount to \$7 billion per year, prompting managed-care plans and state Medicaid programs to implement strategies to discourage the use of the emergency department.^{3,4}

It is unfair for patients to pay twice the actual costs of the services received, and it seems prudent and reasonable to prevent these high costs by discouraging the use of the emergency department — for example, through copayments and deductibles. Yet, from the vantage point of the health care delivery system, the diversion of insured patients away from emergency departments compounds the financing problem by reducing the pool of patients who can pay for their care and may lead to the closure of many emergency departments. Without an adequate and equitable financing mechanism, many Americans could be left without access to emergency services.

In response to Lucey, as I acknowledged in my doctoral dissertation but not in my report in the *Journal*, three organizations provided grants that supported the research. The funds were donated directly to the University of

Michigan and were used for computer equipment, software, and supplies. I received no compensation from these grants. None of the organizations that provided grants participated in the study design or analysis of the data. As I state in my report, the hospital-selection process is described in NAPS document 05283 (available from Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163).

Physicians Billing, which I did not identify by name in the article, provided assistance only in the collection of data on physicians' billing and made no financial contribution to the research. The fact that all six hospitals used the same billing company was acknowledged in the article as a limitation of the study.

My term of office as president of the American College of Emergency Physicians ended before the initiation of this research.

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1. The Medicaid Access Study Group. Access of Medicaid recipients to outpatient care. *N Engl J Med* 1994;330:1426-30.
2. Emergency Medical Treatment and Active Labor Act, P.L. 99-272, 42 U.S.C. sec 1395 DD (1985) (renamed in 1989).
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4. Winslow R. Emergency-room visits fall as HMOs target overuse. *Wall Street Journal*. March 7, 1996:B2.

College Women and Condom Use, 1975-1995

To the Editor: We surveyed the frequency of condom use in 1995 by 147 women at a private university in New England and compared it with that reported previously in the *Journal* for 486 women surveyed in 1975, 161 women surveyed in 1986, and 132 women surveyed in 1989 at the same university health service.¹ Each participant completed the same anonymous questionnaire. The key question was "When you have intercourse, how often does your partner use a condom?"

The women studied in 1995 did not differ significantly from the earlier groups with respect to age (mean age of the 1995 sample, 21.5 years), age at menarche, level of education, or gravidity. More Asians responded to the survey in the more recent years, a trend that reflected the composition of the student body. In 1995, 87 of 118 sexually active women (74 percent) stated that their partners "always or almost always" used condoms during sexual intercourse, as compared with 49 of 427 women in 1975 (11 percent), 30 of 140 women in 1986 (21 percent), and 46 of 113 women in 1989 (41 percent) ($P < 0.001$ by the chi-square test for linear trend) (Table 1). This trend could not be explained by changes in racial distribution or differences in the reasons for visiting the clinic.

From these data it appears that the use of condoms in this college population has increased over the years surveyed. Choi and Catania recently analyzed the results of two surveys using random-digit dialing and probability sampling in the contiguous United States and found that consistent (i.e., 100 percent of the time) condom use by 18-to-49-year-old heterosexuals with risk factors for human immunodeficiency virus (HIV) infection increased

TABLE 1. FREQUENCY OF CONDOM USE DURING SEXUAL INTERCOURSE AS REPORTED BY COLLEGE WOMEN VISITING A STUDENT HEALTH CLINIC.*

FREQUENCY OF USE	YEAR			
	1975 (N=427)	1986 (N=140)	1989 (N=113)	1995 (N=118)
	no. of women (%)			
Always or almost always	49 (11)	30 (21)	46 (41)	87 (74)
Seldom or never	370 (87)	99 (71)	66 (58)	28 (24)
Uncertain	8 (2)	11 (8)	11 (1)	2 (1)
No answer	0	0	0	1 (1)

*Numbers shown include only sexually active women.

from 11 percent to 21 percent. The increase was not found in all groups, however; women, whites, the college-educated, and people in their 20s and 40s made few changes in their condom use.² In contrast, our survey documents a consistent and significant increase in the proportion of young university women seeking care at a student health clinic who reported the use of condoms "always or almost always." The change may be due to the condom-promotion efforts in the university community and to an increased focus on condoms for the primary prevention of sexually transmitted diseases and HIV.

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2. Choi K-H, Catania JA. Changes in multiple sexual partnerships, HIV testing, and condom use among US heterosexuals 18 to 49 years of age, 1990 and 1992. *Am J Public Health* 1996;86:554-6.

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