Correspondence

Immunotherapy for Asthma

To the Editor: The failure of the study by Adkinson et al. (Jan. 30 issue)[1] to demonstrate a significant benefit of immunotherapy with a few allergens to a particular group of children with asthma does not negate the positive benefit demonstrated in numerous other studies. The meta-analysis by Abramson et al.[2] suggests that 33 negative studies would be necessary to overturn the results that demonstrated significant odds of symptomatic improvement, decreased medication use, reduction in bronchial hyperreactivity, and improvement in forced expiratory volume in one second with immunotherapy.

Some of the patients may have been sensitive to allergens not included in treatment (or presumably in testing). These might include cockroach, other molds, and other tree and fall-weed pollens. Most allergist-immunologists are familiar with the wide variety of pollens at different seasons in their areas, and they test and treat with all the major pollens that have positive results on skin-prick testing. They would not expect improvement if they treated with only one type of allergen for the season. Adkinson et al. chose to limit the number of allergens in order to reach very high doses and perhaps threw out the baby with the bath water.

The authors themselves suggest caution in interpreting their results. The patients received maintenance treatment with free medications with close follow-up, and any participating children who did not comply were dropped from the study. I concur that allergy shots may be more useful in patients in the real world who tend to have lower levels of compliance with pharmacotherapy.

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1. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31.
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: In the study by Adkinson et al. the patients differed from people with asthma in the real world in two respects. All the patients, and their parents, volunteered for the study. Volunteers are generally far more interested in their disease and in adhering to lifestyle alterations likely to help it than are most patients with asthma. These volunteers were uncommonly likely to comply with prescribed management and also received unusually intense follow-up by the clinical research team. The compliance rate with medication was 93 percent.

The clinical improvement reported by Adkinson et al. in both the immunotherapy and placebo groups is similar to that achievable in less strongly motivated patients, followed less intensively, but with immunotherapy to supplement environmental controls and medications.[1]

Might it be most appropriate to conclude that for uncommonly motivated patients, coached and monitored by an allergy research team that checks closely for compliance with medications, adding immunotherapy probably will not make them much better?

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1. Coifman RE. Dynamic approach to asthma. J Asthma 1983;20:45-52.

To the Editor: The study by Adkinson et al. has important flaws. The placebo group received injections of histamine. Histamine is not an inert agent and is thus inappropriate for use in a placebo. Histamine has physiologic activity on the immune system, even at low doses,[1] and has been used for therapy for several conditions.[2] Therefore, failure to demonstrate a difference between the histamine group and the immunotherapy group could indicate that both treatments were active. In fact, this possibility is suggested by the observed decreases in medication-use scores and in methacholine sensitivity that occurred in both groups.

Each patient in the immunotherapy group was treated with only two to six inhalant allergens. The omission of many important perennial allergens from treatment, including animal danders, cockroach, penicillium, helminthosporium, and others, may have resulted in treatment with insufficient numbers of allergens to reduce the total allergy load significantly. Both the history and clinical testing frequently incriminate multiple allergic triggers of asthma in a single patient, and failure to treat enough of these triggers adequately is a very possible reason for the failure of any immunotherapy program.[3]

This study shows a large effort and commendable attention to detail, but unfortunately, the methods used do not exclude several large possible sources of error. Therefore, I believe that the authors' conclusion that immunotherapy was of no benefit in this study group may be invalid.

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1. Brune M, Hellstrand K. Remission maintenance therapy with histamine and interleukin-2 in acute myelogenous leukaemia. Br J Haematol 1996; 92:620-6.
2. Fischer AJ. Histamine in the treatment of vertigo. Acta Otolaryngol Suppl (Stockh) 1991;479:24-8.
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To the Editor: The study by Adkinson et al. found that treatment with multiple-allergen immunotherapy in polysensitized children with asthma is not efficient. These results are very interesting. However, the panel of allergens for which children were tested was not reported, nor the prevalence of some perennial allergens such as cockroach. Cockroach is an important perennial allergen in the pediatric population of North America. Because eviction of this allergen is difficult to obtain and no extract is available for immunotherapy, continuous exposure to it could maintain bronchial inflammation and explain the lack of efficacy of immunotherapy in these polysensitized patients. Moreover, one benefit of participation in this protocol was free asthma medications, and this could have led to a selection bias toward children of low socioeconomic status and thus more exposure to cockroach allergen. For all these reasons, more details would be appreciated on these aspects of the study and should be considered in interpreting the results.

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To the Editor: In the study by Adkinson et al. the patients received mixtures of allergens, but mixing induces rapid degradation of allergens.[1] Although changes in skin-test results and levels of specific IgG were observed, such changes do not preclude an effect of the composition of the allergen extract. If some allergens essential to the patient's sensitivity are degraded, immunotherapy is less effective. This comment is substantiated by the study itself, since when patients were receiving more than five allergens, there was strictly no effect of immunotherapy. . . .

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1. Nelson HS, Ikle D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. J Allergy Clin Immunol 1996;98:382-8.

To the Editor: Figure 1 of the article by Adkinson et al. shows the medication scores for the immunotherapy group and the placebo group at randomization and at the last follow-up visit. The text states that Table 3 shows the mean change in scores between base line and the last follow-up visit. If base line is the time of randomization, there seems to be a discrepancy. Figure 1 shows the score for the immunotherapy group to be greater than that of the placebo group, and both appear to be greater than 5. Table 3 shows the base-line score for the placebo group to be 5, and the score for the immunotherapy group is only 4.9. Are the figure and table showing different data?

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To the Editor: The report by Adkinson et al. concludes that immunotherapy may be of limited value in the management of asthma in allergic children, a position many allergists can accept on the basis of experience. But it is very

important to point out that the study does not indicate that accurate diagnosis of the child's allergies is unimportant. Children can be much better protected from house dust, a moldy environment, or a cat when their reactivity is documented and the physician can focus the parents' attention on appropriate environmental-control measures. These avoidance techniques are very important in treating childhood asthma and were used in both the treated and the control groups in this study with excellent results. Specific diagnosis of allergy is an essential component of the successful treatment of children with asthma. Radioallergosorbent tests or skin tests can provide accurate assessment of allergy.

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The authors reply:

To the Editor: Dr. Wray suggests that the meta-analysis of 20 asthma-immunotherapy studies by Abramson et al. demonstrated efficacy that outweighs our negative results. Most of the trials Abramson et al. analyzed dealt with single allergens, seasonal disease models, or both.[1] We do not dispute the protective benefit of immunotherapy in selected cases, but our study demonstrates that it is not clinically indicated in children with well-managed moderate to severe perennial asthma.

Drs. Wray and Coifman express concern that the patients selected for our study were highly compliant and therefore not representative of typical immunotherapy patients. Although this may be true, we do not believe it explains our negative results, since there was still much symptomatic disease after stabilization at base line and multiple disease markers improved significantly in both groups during the study. If immunotherapy had been effective in these subjects, the study design was sufficient to have shown it.

Another concern expressed is that there were critical omissions of important aeroallergens, especially cockroach. In mid-study we performed cockroach skin testing and home-dust analysis for cockroach allergens for 87 of the 121 subjects.[2] Only 20 children had positive cockroach skin tests and bedroom *Bla g* I levels >1 unit per gram. If the omission of cockroach or any other locally important allergen is essential for a successful outcome of immunotherapy, then much of the immunotherapy currently administered for asthma in the United States must be considered suspect.

Dr. Gordon objects that histamine has biologic effects and should not have been used in our placebo solutions. Diluents containing 1 to 10 μg of histamine per milliliter have been used in numerous controlled studies of immunotherapy with positive outcomes.[3,4] It would be surprising if small doses of histamine injected intradermally weeks apart ameliorated asthma symptoms, and we would welcome any evidence that this is the case.

Dr. Bousquet and colleagues point to evidence that allergen mixtures may lead to autodegradation of important allergens, thereby rendering them impotent. In our study we observed pronounced IgG-antibody responses and altered skin-test reactivity, suggesting that, at least for most allergens, substantial biologic potency remained. The work of Litwin et al.[5] shows that enzyme degradation of ragweed may actually convey advantages for immunotherapy.

The apparent discrepancy in base-line medication scores between Table 3 and Figure 1 reflects the fact that median levels are shown in Figure 1, whereas the scores in Table 3 are means.

We heartily agree with Dr. Marinkovich's assertion that accurate diagnosis of allergy in children with allergic asthma is indispensable to proper environmental control and patient education. Irrespective of the issue of immunotherapy, we believe that every child with asthma deserves and will benefit from comprehensive allergy evaluation and management.

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1. 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.
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A Prediction Rule for Community-Acquired Pneumonia

To the Editor: Fine and colleagues (Jan. 23 issue)[1] present a detailed analysis of community-acquired pneumonia. An important complicating factor not specifically addressed in their prediction rule is pregnancy. Pneumonia is one of the most common and serious nonobstetrical infections during pregnancy. Before 1940, maternal mortality from pneumonia was as high as 30 percent. Substantial maternal and perinatal morbidity and mortality still result from antepartum pneumonia (Table 1).[2-6]

The risk-scoring system derived by Fine and colleagues favors outpatient therapy for young, otherwise healthy women. In the two maternal–fetal deaths in our series at Parkland Hospital,[4] both women would have been in risk class II and could have been assigned to outpatient management by the prediction rule.

We support the development of standardized treatment plans for the management of pneumonia in pregnant women. Until this scheme is evaluated prospectively, however, we continue our policy of promptly hospitalizing all pregnant women with radiographically confirmed pneu-

TABLE 1. MATERNAL AND PERINATAL OUTCOMES IN PREGNANCIES COMPLICATED BY PNEUMONIA.

STUDY	YEAR	NO. OF PREGNANCIES	ADVERSE MATERNAL OUTCOMES	ADVERSE PERINATAL OUTCOMES
Madinger et al.[2]	1989	25	5 intubations 1 death	9 preterm births 3 neonatal deaths
Berkowitz and LaSala[3]	1990	26	2 intubations 0 deaths	0 preterm births 0 perinatal deaths
Richey et al.[4]	1994	71	5 intubations 2 deaths	1 preterm birth 4 stillbirths
Briggs et al.[5]	1996	34	7 intubations 2 deaths	1 neonatal death 1 stillbirth
Munn et al.[6]	1997	53	5 intubations 1 death	Mean gestational age at delivery, 36 weeks
Total		209	11.5% intubated 2.9% mortality	4.3% perinatal mortality

monia in order to ensure that optimal respiratory support is provided and to determine the responsiveness of the infection to therapy.

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1. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336:243-50.
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5. Briggs RG, Mabie WC, Sibai BM. Community-acquired pneumonia in pregnancy. Am J Obstet Gynecol 1996;174:389. abstract.
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To the Editor: . . . The elderly nursing home residents whom we are called to admit with the diagnosis of pneumonia usually have underlying disorders such as congestive heart failure, stroke, and renal dysfunction. These patients easily meet the criteria for class IV and, according to the prediction rule of Fine et al., should be admitted. Many of these patients are clinically stable enough to be treated with intravenous antibiotics in the monitored environment of the long-term care facility. Would there be a way to prevent unnecessary admissions in this patient population?

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The authors reply:

To the Editor: On the basis of anecdotal clinical experience and five published articles on the maternal and fetal outcomes of pneumonia during pregnancy, Bloom and colleagues recommended hospitalization for all pregnant women with community-acquired pneumonia. However, the studies they cite differed from ours in that they focused exclusively on hospitalized pregnant women, potentially biasing the study populations toward more severely ill patients.

Among the 2287 patients enrolled in the Pneumonia Patient Outcomes Research Team (Pneumonia PORT) study, there were only five pregnant women. Three were classified as being in risk class I and two as being in risk class II. Two patients in risk class I and one in risk class II were treated as outpatients. None of the five patients died or were admitted to intensive care units because of respiratory failure or hemodynamic compromise. However, the low prevalence of pregnant women in our study precluded the assessment of pregnancy as a predictor of short-term mortality or of the implications of our proposed hospitalization strategy for this patient population. Given the potential risk to both mother and fetus, the threshold for hospitalization of pregnant women with pneumonia may need to be lowered. Future studies are required to assess maternal and fetal outcomes in the full spectrum of pregnant women with community-acquired pneumonia.

Our data support the point of Drs. Tsiodras and Malhotra that most nursing home patients with community-acquired pneumonia who are referred for hospitalization are elderly and have multiple coexisting illnesses. There were a total of 195 Pneumonia PORT study patients who resided in nursing homes (8.5 percent), of whom 86 percent were older than 70, 95 percent had one or more coexisting illnesses, and 91 percent were in risk class IV or V. Thirty-day mortality was 16 percent in class IV nursing home patients and 36 percent in class V.

Although our findings demonstrate that nursing home residents with community-acquired pneumonia who are referred for hospital admission have a high risk of short-

term mortality, our proposed threshold for hospitalization based on the prediction rule may require modification. The nursing home environment permits both clinical observation and many of the treatments (e.g., oxygen therapy and intravenous antimicrobial therapy) that often dictate the need for hospitalization among noninstitutionalized patients.[1] Furthermore, for some nursing home residents with terminal illnesses, palliative care is desired by both the patients and their families.[2]

Our study did not address the prognosis or outcomes of patients with pneumonia diagnosed and treated at nursing homes without subsequent hospital referral, so the validity of our prediction rule in this patient population still needs to be assessed.

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1. Fine MJ, Hough LJ, Medsger AR, et al. The hospital admission decision for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 1997;157:36-44.
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The Epidemic of Cardiovascular Disease in Eastern Europe

To the Editor: Mortality from cardiovascular disease in Eastern Europe was low at the beginning of the 1960s, but a serious increase has occurred and in 1990 mortality was substantially higher than in Western Europe and the United States.[1] The political changes in Eastern Europe after 1990 caused serious economic problems and simultaneously led to a further increase in mortality from cardiovascular disease (Fig. 1). Premature mortality from cardiovascular disease among men in the Russian Federation is now almost four times as high as in the United States.

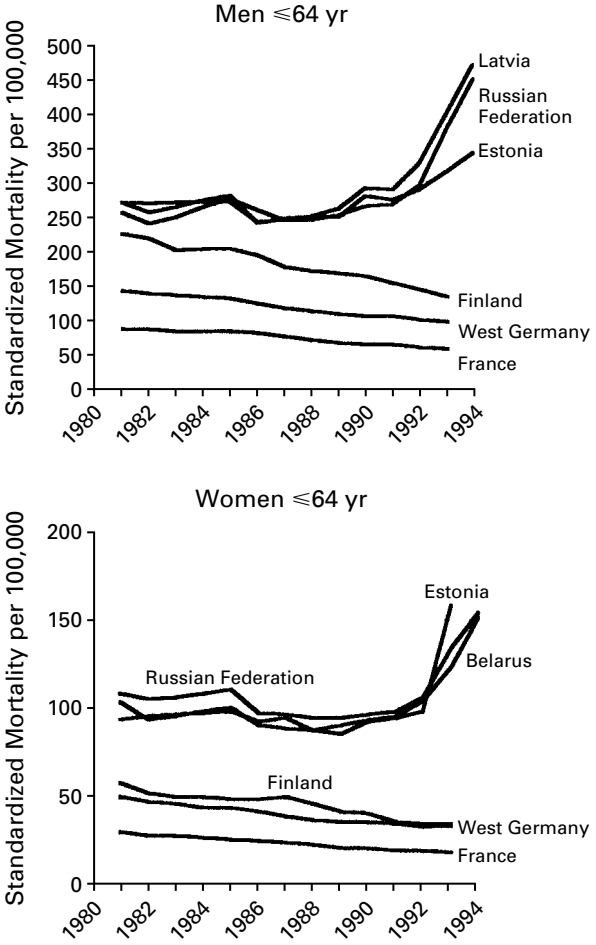

Figure 1. Trends in Premature Cardiovascular Mortality (Standardized Mortality Rates for Men and Women 64 Years of Age or Younger) in Europe. (Data are from the World Health Organization.[1])

The causes of the epidemic of cardiovascular disease in Eastern Europe are not known. The affected area has 400 million inhabitants and is almost 2.5 times as large as the United States. Mortality from cardiovascular disease in Eastern Europe has substantially overtaken the previous maximum rate, reached in the 1960s in the United States and Finland. Currently, nearly 500 in 100,000 men in the Russian Federation die prematurely from cardiovascular disease. Such a level has never before been observed anywhere in the world and is twice as high as the maximum reached in the United States in the 1960s. The epidemic is concentrated in the countries that were governed by Communist regimes; if one passes through the former Iron Curtain from west to east, mortality from cardiovascular disease increases by two to six times. The epidemic affected not only the post-Communist countries of Central Europe that had a lifestyle similar to that of Western Europe, but also the former Soviet republics of Central Asia that have cultures influenced by Islam. The World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project[2] found a higher prevalence of smoking and hypertension in men living in Eastern Europe than in Western Europe, but the prevalence of hypercholesterolemia was lower. In women, the prevalence of hypertension was higher than in Western Europe, but the number of female smokers and the level of cholesterol were lower,[2] because economic problems in this area limited consumption of meat and dairy products. In the United States, epidemiologic studies have quantified the effects of smoking, hypertension, and hypercholesterolemia on coronary mortality.[3] Similar studies are not possible in Eastern European countries for economic reasons, so the help of the international scientific community is necessary. Such help would not only be humanitarian, but research on the epidemic of cardiovascular disease in Eastern Europe could

also broaden our knowledge of nontraditional cardiovascular risk factors.

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1. Health for All. Statistical database 1996. Copenhagen, Denmark: World Health Organization Regional Office for Europe, 1996.
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Risk of Stroke after Myocardial Infarction

To the Editor: The report by Loh et al. (Jan. 23 issue),[1] evaluating the association between left ventricular dysfunction and the risk of stroke in patients enrolled in the Survival and Ventricular Enlargement (SAVE) trial, raises important questions regarding the care of patients who have had myocardial infarctions. Two of the most important predictors of stroke are a history of stroke and transient ischemic attacks.[2,3] Although the authors document the effect of a history of smoking, diabetes, and hypertension and of previous myocardial infarction, they do not comment on those two well-documented risk factors. I am curious whether their conclusions regarding the association of ventricular dysfunction and stroke would still hold if their analysis had controlled for a history of stroke and transient ischemic attacks.

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1. Loh E, St John Sutton M, Wun C-CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 1997;336:251-7.
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To the Editor: Loh et al. report that a decreased ejection fraction and older age are both independent predictors of an increased long-term risk of stroke after myocardial infarction. Besides the role of chronic atrial fibrillation as a known risk factor, which the authors address, a potential role of blood pressure should also be considered. Although the authors report that the proportion of patients with a history of hypertension did not differ significantly between the two groups, blood-pressure measurements would have been helpful in clarifying the role of this factor.

In a review of 45 prospective observational studies, the risk of stroke was strongly related to diastolic blood pressure.[1] The relation did not tend to flatten out at levels below 80 mm Hg, and there was no threshold below which diastolic blood pressure was not positively associated with the risk of stroke. Most important, this positive relation was observed both in patients with and in those without preexisting coronary heart disease at base line.[1]

Pharmacologic treatment of hypertension plays a crucial part in the risk of long-term morbidity and mortality due to cerebrovascular accidents.[2] In agreement with a recent study in a similar setting,[3] the authors report that at the time of randomization approximately 40 percent of patients were receiving calcium-channel blockers and 35 percent were receiving beta-blockers. Both agents modulate blood pressure, but they have different prognostic value. Whereas a reduced risk of stroke in hypertensive patients treated with beta-blockers has been documented,[2] calcium-channel blockers seem to increase overall mortality.[3,4] Interestingly, calcium-channel blockers exert an antiplatelet effect, which might have been protective against embolic strokes. We believe that cardiovascular medications taken by the patients at randomization should have been included in the analysis.

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1. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. Lancet 1995;346:1647-53.
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The authors reply:

To the Editor: We agree with Dr. Michaels that a history of stroke or transient ischemic attacks is a risk factor for subsequent stroke after myocardial infarction. Unfortunately, in the SAVE trial, prerandomization data-base forms did not include this information. Accordingly, these variables could not be considered in the multivariate analysis.

We also agree with the comments of Gambassi et al., which emphasize the important role of antihypertensive agents such as beta-blockers in reducing the risk of stroke in patients with hypertension, regardless of the presence or absence of coronary heart disease. In our population of patients with left ventricular dysfunction after myocardial infarction and a mean prerandomization blood pressure of 113/70 mm Hg, we were not able to demonstrate that the nonrandomized use of beta-blockers, nitrates, or calcium-channel blockers affected the risk of subsequent stroke. Furthermore, in this blood-pressure range, even the randomly assigned use of the angiotensin-converting–enzyme inhibitor captopril did not reduce the risk of stroke. However, the nonrandomized use of beta-blockers was associated with an improvement in clinical outcomes (decreased risk of death from cardiovascular causes and of

heart failure), to which the effect of angiotensin-converting–enzyme inhibitors was additive.[1]

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1. Vantrimpont P, Rouleau JL, Wun CC, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. J Am Coll Cardiol 1997; 29:229-36.

Restrictive Cardiomyopathy

To the Editor: We wish to raise some points of disagreement with the description of cardiac amyloidosis by Kushwaha et al. (Jan. 23 issue)[1] in their article on restrictive cardiomyopathy. The internationally accepted classification of the amyloidosis is based on the chemical nature of the deposited protein fibrils.[2] Secondary amyloidosis refers exclusively to the reactive form characterized by deposition of a nonimmunoglobulin, amyloid A (AA), in association with chronic infection and inflammation (e.g., rheumatoid arthritis, inflammatory bowel disease, osteomyelitis, tuberculosis, or leprosy). The familial and senile amyloidoses are distinct entities that have never been classified as secondary and that have unique biochemical and clinical features. The majority of patients with primary (now known as AL) amyloidosis do not have multiple myeloma.[3] This is important, because the clinician must consider AL amyloidosis if features of a restrictive cardiomyopathy are present, despite the absence of signs of myeloma.

We disagree with several of the authors' clinical statements about cardiac amyloidosis. They state that the ventricular cavities are often moderately dilated, that cardiomegaly is uncommon, and that atrial dilatation is a function of atrioventricular valvular regurgitation. In our own data base of more than 200 patients with cardiac amyloidosis (unpublished data), echocardiographic left ventricular dilatation was seen in only 3 percent of the patients and when present was frequently associated with coexisting coronary artery disease or substantial mitral regurgitation. Although atrial enlargement was common, it was generally unrelated to atrioventricular valvular regurgitation — rather, it was a function of high atrial-filling pressures. In our experience, mild-to-moderate cardiomegaly is frequently apparent on chest films once heart failure occurs. This may reflect either atrial enlargement and ventricular thickening or right ventricular dilatation, since the left ventricular cavity size remains normal.

While left-ventricular-wall thickness is a prognostic determinant in amyloidosis, the paper cited[4] does not deal exclusively with cardiac amyloidosis. Indeed, most patients with normal wall thickness (median survival, 2.4 years) had no evidence of cardiomyopathy. Once severe heart failure due to amyloid cardiomyopathy supervenes, the prognosis is very poor regardless of the degree of left ventricular thickening.

Finally, it should be mentioned that dose-intensive melphalan with autologous-blood stem-cell support for the treatment of AL amyloidosis is currently undergoing intensive evaluation.[5] Initial data suggest a good response of the plasma-cell dyscrasia, but the tolerability and effectiveness of this treatment in patients with cardiac amyloidosis are still undetermined.

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1. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. N Engl J Med 1997;336:267-76.
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To the Editor: The excellent review of restrictive cardiomyopathy by Kushwaha et al. requires some clarification of the often difficult problem of differentiating restrictive cardiomyopathy from constrictive pericarditis. Apart from the fact that constrictive pericarditis can be associated with an S_4 gallop, the contrast of S_3 in restrictive cardiomyopathy and pericardial knock in constrictive pericarditis is erroneous. The abnormal third heart sound of constrictive pericarditis has the same dynamics as any abnormal third heart sound (perhaps with an added element of diastolic suction). A truly "knocking" third heart sound is extremely uncommon today and characterizes a bygone era when diagnosis was delayed and the chronic constrictive pericarditis developed in the fortunate survivor. Acute and subacute constriction are more common today, mainly because of rapid recognition. Conceptually, the phenomenon is a third heart sound that both in constrictive pericarditis and restrictive cardiomyopathy tends to be earlier than other abnormal third heart sounds. Also, the pericardium itself does not generate the abnormal third heart sound, except to the extent that the constricting pericardium contributes to the degree of myocardial restriction.

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The authors reply:

To the Editor: Dr. Reisinger and colleagues correctly point out that the classification of amyloidosis is based on the chemical nature of the amyloid fibrils, and we agree that the majority of patients with primary amyloidosis do not have multiple myeloma. In fact, we stated in the article

that primary amyloidosis is *often* due to multiple myeloma, which does not necessarily suggest that multiple myeloma occurs in the majority of patients who present with primary amyloidosis. The intention of the paper was not to discuss the classification of amyloidosis but to review its relevance to restrictive cardiomyopathy. We acknowledge that familial and senile amyloidoses have unique biochemical and clinical features, which are discussed in the article, and that those diseases are best not classified as secondary forms of amyloidosis.

The unpublished observations of Reisinger and colleagues are interesting, and we agree that gross cardiomegaly is uncommon. In fact, as the review states, the ventricular cavities are often normal in this condition. Atrial enlargement may indeed be secondary to high atrial-filling pressures, but it is our observation that it tends to be more common in the presence of atrioventricular valvular regurgitation, which is also correlated with the development of heart failure. We agree that once cardiac failure due to cardiomyopathy supervenes, the prognosis is poor; however, this tends to be correlated with increased wall thickness — although this may not always be the case.

We thank Reisinger and colleagues for bringing to our attention the therapy with dose-intensive melphalan and autologous-blood stem-cell support, and it will be interesting to see what effect this therapy may have on the treatment of cardiac amyloidosis.

We recognize the expertise of Dr. Spodick on the pericardium and its physiology and would like to thank him for his insightful remarks and clarification regarding the third heart sound and the pericardial knock. We agree that this sound may be uncommon but contend that when it does occur, it is diagnostic. And we acknowledge that an S_4 gallop can also occur in constrictive pericarditis.

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Olfactory Dysfunction in Multiple Sclerosis

To the Editor: Multiple sclerosis, the most common neurologic disease in young adults, is accompanied by focal demyelinating plaques within the central nervous system, which can be quantified in vivo by using high-resolution magnetic resonance imaging (MRI). Thus, multiple sclerosis may be an excellent model for the study of the influences of focal lesions on some forms of sensory function. Since multiple-sclerosis–related plaques vary in number over time, differ considerably from patient to patient, and often occur in regions of the brain associated with the ability to smell,[1] we determined whether the number of multiple-sclerosis–related plaques in olfactory regions correlates with scores on the University of Pennsylvania Smell Identification Test (UPSIT), a standardized 40-odorant quantitative test of olfactory function.[2]

Nine men and 17 women (mean [±SD] age, 42.2±7.2 years) with confirmed multiple sclerosis were tested. Thin-section MRIs of the brain with gadolinium enhancement were performed on the same day as olfactory testing by using a 1.5-T Signa scanner (General Electric, Milwaukee) employing a standard head coil. Plaques were counted without knowledge of the patients' UPSIT scores.

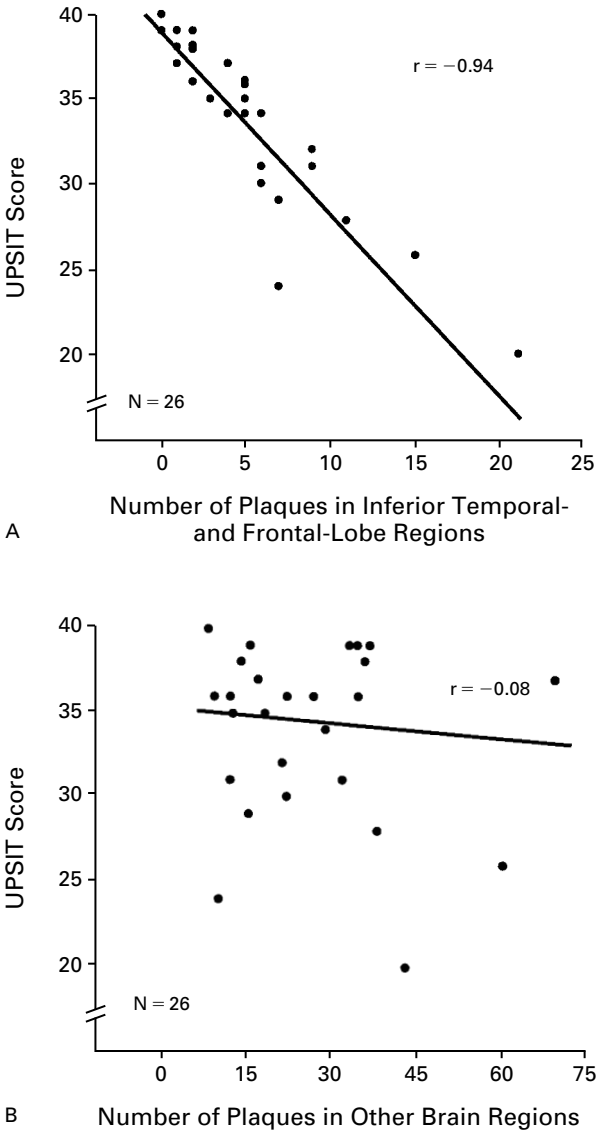

Figure 1. Relation between UPSIT Scores and the Numbers of Multiple-Sclerosis–Related Plaques in Olfactory (Panel A) and Nonolfactory (Panel B) Brain Regions.

The olfactory brain region is defined as the inferior frontal lobes (inferior and anterior to the body and genu of the corpus callosum, respectively) and the inferior temporal lobes (bounded by the plane of the sylvian fissure superiorly). These areas contain the major zones of known central-olfactory connections. UPSIT denotes University of Pennsylvania Smell Identification Test.

We found a strong negative relation (Spearman $r = -0.94$, $P<0.001$) between the UPSIT scores and the number of demyelinating plaques within the inferior frontal- and temporal-lobe regions, which are involved in olfaction (Fig. 1A). No such relation was found between the scores

and the numbers of plaques in brain regions not related to olfaction ($r = -0.08$, P not significant) (Fig. 1B), implying that the relation was restricted to brain structures directly involved in olfactory processing.

Relative to normative data based on nearly 4000 subjects,[3] 38.5 percent of the patients had demonstrable olfactory loss; 7.7 percent had severe bilateral microsmia, 19.2 percent moderate bilateral microsmia, and 11.5 percent mild bilateral microsmia. None had anosmia. No sex differences or meaningful left–right asymmetries in UPSIT scores or numbers of plaques were found.

These findings clarify the ongoing controversy over the presence of olfactory dysfunction in multiple sclerosis and invalidate claims of normal olfactory function in patients with the disease.[4] Notably, they support the concept that multiple sclerosis, with its relatively discrete focal regions of inflammation, demyelination, and gliosis, can serve as a useful model for the study of the influences of lesions of the central nervous system on sensory perception. Although numerous studies have reported olfactory dysfunction in several neurodegenerative disorders, including Alzheimer's disease and idiopathic Parkinson's disease,[5] our findings provide a clear physiologic explanation for decreased olfactory function in patients with any major neurologic disease. Given that olfaction influences the quality of life and provides a basic means for detecting smoke, leaking natural gas, and other environmental hazards, persons involved in the care of patients with multiple sclerosis should be aware of the potential for olfactory losses and counsel their patients accordingly.

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Insomnia

To the Editor: In the excellent review of the management of insomnia by Kupfer and Reynolds (Jan. 30 issue),[1] we read that "zolpidem may be less likely than benzodiazepines . . . to cause cognitive and psychomotor side effects (and may have fewer withdrawal effects)." It is clear that many clinicians believe this to be true, since zolpidem is the most commonly prescribed hypnotic agent in the United States.[2] However, the authors cite only three studies in support of this idea, two of which did not even compare zolpidem with a benzodiazepine.

The study that did compare these drugs with respect to rebound insomnia and withdrawal used a dose of triazolam that is now considered excessive, with twice the hypnotic potency of the zolpidem dose (0.5 mg of triazolam vs. 10 mg of zolpidem).[3] Nonetheless, little or no clinically significant difference was observed between the drugs in this study, and rebound insomnia occurred only after the first night of triazolam withdrawal.

Several well-designed studies have directly compared zolpidem and triazolam and have failed to show a difference in cognitive and psychomotor effects between the two drugs. The authors generally conclude that the cognitive and performance-impairing effects are remarkably similar, that they are linked directly to hypnotic potency, and that no clinically significant difference exists at the usually recommended, equipotent doses of these agents. Our conclusion from the available data is that zolpidem has no clinically important advantage over benzodiazepines (specifically, triazolam) with respect to the potential to cause cognitive, psychomotor, or withdrawal effects.

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