Renovascular Hypertension, Endothelial Function, and Oxidative Stress

To the Editor: In their elegant study, Higashi et al. (June 20 issue)\(^1\) conclude that elevated angiotensin II levels in patients with renovascular hypertension constitute a principal cause of increased oxidative stress that results in impaired endothelium-dependent vasodilation. Down-regulation of the renin–angiotensin system after angioplasty in conjunction with reduced levels of markers of oxidative stress and improved forearm blood flow is cited as supporting evidence. However, there is an alternative explanation for these findings.

It is well established that total plasma levels of the putative atherothrombotic amino acid homocysteine are inversely related to the glomerular filtration rate.\(^2,3\) Thus, as the glomerular filtration rate increases, total homocysteine levels decline. The mechanism through which homocysteine exerts its pernicious effects has not been definitively established. However, recent studies support the premise that homocysteine impairs flow-mediated endothelium-dependent vasodilation. Down-regulation of the renin–angiotensin system after angioplasty in conjunction with reduced levels of markers of oxidative stress and improved forearm blood flow is cited as supporting evidence. However, there is an alternative explanation for these findings.

Angioplasty of renal arteries may improve renal perfusion and increase the total glomerular filtration rate, which, in turn, will lower the total plasma homocysteine level. It is plausible to suggest that the improvement in endothelial function and the reductions in markers of oxidative stress after angioplasty are a result of lower plasma total homocysteine levels rather than, or in conjunction with, lower angiotensin II levels. This hypothesis could easily be confirmed by measurement of the glomerular filtration rate and plasma homocysteine levels before and after angioplasty in the study subjects.

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be important in the development of new therapeutic approaches that block NAPDH oxidase in such patients.

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To the Editor: Higashi et al. report that repair of renal-artery stenosis increases the forearm vasodilator response to acetylcholine. Acetylcholine increases endothelial nitric oxide release. Shear stress across the vascular endothelium also increases nitric oxide release; this is the mechanism responsible for flow-mediated vasodilatation. The amount of nitric oxide released by the endothelium is directly related to systolic blood pressure. The subjects with hypertension in the study by Higashi et al. had a systolic blood pressure of 161 mm Hg, whereas the control group had a systolic blood pressure of 115 mm Hg.

Higashi et al. believe that the return of a normal endothelial response to acetylcholine after angioplasty is attributable to diminished oxidative stress. A much simpler explanation is that the systolic blood pressure was decreased from 161 to 124 mm Hg. This decrease in blood pressure should decrease flow-mediated nitric oxide release and permit a greater nitric oxide response to acetylcholine. As the authors note, endothelial function becomes progressively impaired as hypertension worsens. Patients with atherosclerosis, like those in this study, have damaged endothelium. They are unable to make sufficient nitric oxide in response to the combination of a high systolic blood pressure and acetylcholine. Lowering the systolic blood pressure provides some reserve nitric oxide—producing function and thus allows a greater response to infusion of acetylcholine.

Higashi et al. report higher urinary nitrate and nitrite levels after angioplasty. Much of the nitrate and nitrite in urine comes from a normal diet; four days of a restricted diet have been shown to substantially decrease nitrate and nitrite levels. Did the subjects in this study follow a special diet?

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To the Editor: As Sowers notes in his editorial, there is increasing evidence that oxidative stress may be the common pathway in endothelial damage, not only in renovascular hypertension, but also in hyperglycemia. This may explain why the beneficial effects of angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers in delaying progressive nephropathy in patients with diabetes exceed those that would be anticipated on the basis of their hypotensive effects alone. Current research indicates that the antioxidant ascorbate not only attenuates vasoconstriction induced by infusion of angiotensin II but also restores endothelium-dependent vasodilatation, which is impaired by hyperglycemia.

Hyperglycemia has been shown to activate protein kinase C-β (PKC-β), which, in turn, has been demonstrated to decrease endothelium-derived nitric oxide. In addition, an experimental inhibitor (LY333531) of PKC-β has been demonstrated to prevent impairment of endothelium-dependent vasodilatation caused by hyperglycemia in humans.

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The authors reply:

To the Editor: Dr. Friedman’s hypothesis that the improvement of endothelial function and reduction in oxidative stress after angioplasty are due to reduced plasma total homocysteine levels caused by an increased glomerular filtration rate is interesting and well conceived. However, we found no significant difference between the mean (±SD) total glomerular filtration rate as measured by inulin clearance before and after angioplasty (68.5±12.3 vs. 71.2±11.4 ml per minute per 1.48 m² of body-surface area, P=0.26) in 7 of the 15 patients with renovascular hypertension, although we did not measure the plasma total homocysteine levels. There have been conflicting findings concerning the effects of angio-
plasty on the glomerular filtration rate in patients with renovascular hypertension.\textsuperscript{1,2}

We agree with the comment of Dr. Ritter et al. that other stimuli besides increased angiotensin II levels activate NADPH oxidase. In addition, xanthine oxidase, endothelial nitric oxide synthase uncoupled by the depletion of tetrahydrobiopterin, and cyclooxygenase may contribute to the production of the reactive oxygen species in patients with hypertension. The development of new antioxidant therapies that avoid the pleiotropic effects of agents such as statins and angiotensin-converting–enzyme inhibitors is awaited with great interest.

Indeed, as Drs. Ziegler and Bao suggest, the amount of nitric oxide released from vascular endothelial cells is directly related to systolic blood pressure, although the precise mechanisms by which shear stress stimulates nitric oxide release from the endothelium are not known. On the other hand, shear stress activates NADPH and NADH oxidases, leading to an increase in reactive oxygen species. The endothelium is sensitive to shear stress and can respond to changes in shear stress associated with several factors, including fluid viscosity.\textsuperscript{3} High blood pressure (high shear stress) does not always increase the bioavailability of nitric oxide. We believe that an imbalance between nitric oxide production and increased reactive oxygen species in patients with hypertension decreases the bioavailability of nitric oxide, resulting in endothelial dysfunction. Further studies are needed to determine whether the reduction in blood pressure itself is directly related to the improvement in endothelial function.

In our study, the subjects followed a regular diet that contained 170 mmol of sodium chloride per day, 100 mmol of potassium per day, 40 mmol of calcium per day, and a total intake of 40 calories per kilogram of body weight per day throughout the study. In a previous study, we confirmed that the day-to-day variation in the intake of nitrate and nitrite by a given subject was small (coefficient of variation, 7.2 percent).\textsuperscript{4}

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Thrombophilia Polymorphisms and Intrauterine Growth Restriction

To the Editor: Infante-Rivard et al. (July 4 issue)\textsuperscript{1} found no association between thrombophilic mutations and intrauterine growth restriction defined by a birth weight below the 10th percentile, as we\textsuperscript{2} and others\textsuperscript{3,4} have demonstrated, and they found an unexpectedly low rate of placental infarcts. Although the authors note that we used the 5th percentile for defining fetal growth restriction,\textsuperscript{2} they did not address other important differences between our study and their own.

The authors report that the mean (±SD) birth weight was 2393.5±606.2 g and that 83 percent of the mothers delivered between 36 and 40 weeks of gestation. Among our 44 newborns with growth restriction, the mean birth weight was 1387 g, and 64 percent of the mothers delivered at less than 36 weeks of gestation. The use of the 10th percentile in the definition for the primary analysis results in the inclusion of many constitutionally small fetuses with none of the clinically significant risks associated with growth restriction.\textsuperscript{5} Conversely, the combination of prematurity and growth restriction carries a high risk of serious long-term sequelae.\textsuperscript{6} Different study criteria may explain the fact that Infante-Rivard et al. did not find an association with thrombophilic mutations.

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To the Editor: Infante-Rivard and colleagues did not specify whether women with known causes of intrauterine growth restriction (such as diabetes, hypertension, other diseases, or prolonged and multiple pregnancies) were included in their study. Moreover, no information was given about the types of malformations included, the fetal karyotype, or transplacental infections, which may influence birth weight. Up to 19.5 percent of fetuses with intrauterine growth restriction may have chromosomal abnormalities, 11.5 percent may have structural malformations, and 6.2 percent may have proven congenital infections.\textsuperscript{1}

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The authors reply:

To the Editor: Kupferminc et al. underscore the fact that the 44 newborns with intrauterine growth restriction in their study were different in terms of birth weight, gestational age, and percentile of birth weight from the newborns we studied — which could explain the discrepancies between their results and ours. As we reported, our results in analyses using the 5th percentile as the cutoff for growth restriction were not different from those obtained in analyses using the 10th percentile as the cutoff. Our study included 60 newborns with a birth weight below 1500 g; their mean gestational age was 31.3 weeks. There were also 19 controls who weighed less than 1500 g at birth. The prevalence of the maternal MTHFR C677T polymorphism (one or two copies) was lower among these newborns than among the controls; one mother of a newborn with growth restriction had the factor V Leiden mutation (one copy), as compared with no mothers of controls; and two mothers of newborns with growth restriction had the prothrombin G20210A polymorphism (one copy), as compared with no mothers of controls. These results are compatible with our overall results. That we had an “unexpectedly low rate of placental infarcts” is a surprising comment, given that most of the few available studies of placental lesions and intrauterine growth restriction have found no difference in the prevalence of lesions between women with and without thrombophilia.1,4

Grandoni and Margaglione ask about known causes of intrauterine growth restriction (such as diabetes and hypertension). We included all newborns with intrauterine growth restriction born at our hospital during a defined period; however, adjustment for maternal diseases associated with intrauterine growth restriction in the analysis comparing newborns with growth restrictions and controls did not change our results. We should have noted that all newborns with clinically detectable and important malformations at birth were excluded.

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The authors reply:

To the Editor: Results of serologic testing for hepatitis C were available for 1274 of the 1505 patients in our study (84.7 percent); of these patients, 40 (3.1 percent) tested positive. Antibodies to hepatitis C were present in 13 of 453 patients with IgA nephropathy, 8 of 190 patients with focal segmental glomerulosclerosis, 2 of 75 patients with mesangiocapillary glomerulonephritis type I, 1 of 85 patients with pauci-immune crescentic glomerulonephritis, and 16 of 403 patients with other types of glomerulonephritis, but not in patients with membranous glomerulonephritis.

Allograft loss due to recurrent glomerulonephritis occurred in 49 of the 1274 patients with known hepatitis C status. Only one patient was seropositive for hepatitis C, and the recurrence was due to IgA nephropathy. Overall, there was no significant difference in the risk of allograft loss from recurrent glomerulonephritis between patients with antibodies to hepatitis C and those without such antibodies (P=0.57 by the log-rank test).

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The authors reply:

To the Editor: The article by Briganti et al. (July 11 issue)1 reminds us that the original renal disease may recur in renal transplants and identifies recurrence of glomerulonephritis as an important cause of late allograft loss. The authors report that mesangiocapillary (or membranoproliferative) glomerulonephritis type I and membranous glomerulonephritis have a high rate of recurrence (14.4 percent and 12.5 percent, respectively). It is well known that these glomerular lesions, particularly membranoproliferative glomerulonephritis type I, are associated with certain chronic viral infections, such as hepatitis C infection. Moreover, chronic infection with hepatitis C virus may also induce such immune-complex-mediated glomerular lesions in the transplant2 and is associated with accelerated allograft loss.3

Surprisingly, Briganti et al. do not mention hepatitis C and its influence on glomerular lesions in the allograft. Furthermore, the analyses of characteristics of the patients according to the type of glomerulonephritis (in Table 1 of the article) and of the risk of allograft loss secondary to recurrent glomerulonephritis (in Table 3) do not take into account the presence or absence of hepatitis C infection. I believe that such infection is an essential variable that should be included in the analysis if one is to conclude that “no risk factors for recurrence were identified that warrant altering the approach to transplantation.”

Allograft loss occurred in nine patients with mesangiocapillary glomerulonephritis type I; eight of them were seronegative for hepatitis C, and the hepatitis C status of the other one was unknown. Allograft loss occurred in five patients with membranous nephropathy, all of whom were seronegative for hepatitis C. Allograft loss from recurrent glomerulonephritis occurred in 3 of 231 patients whose hepatitis C status was unknown — 1 of the 15 patients with loss due to mesangiocapillary glomerulonephritis type I and 2 of the 79 patients with loss due to IgA nephropathy.

These population-based results for 1505 patients with biopsy-proved glomerulonephritis, including 1273 patients with known hepatitis C antibody status who received transplants between 1988 and 1997 in Australia, do not confirm the role of hepatitis C infection in allograft loss either due to recurrence of glomerulonephritis in general or attributable specifically to mesangiocapillary glomerulonephritis type I or membranous glomerulonephritis.

To the Editor: Kent and Poterucha (May 23 issue) present excellent angiographic images of an aberrant right subclavian artery, which was causing intermittent dysphagia. However, it is our opinion that angiography of the subclavian artery (at left) is necessary, magnetic resonance imaging will reveal the vessels, their origins and course, and their effect, if any, on the esophagus and trachea.

We disagree strongly with the authors’ choice of imaging techniques. It is not acceptable to subject patients, especially if their symptoms are “mild and intermittent,” to radiation and to the risks associated with invasive procedures when there is a suitable alternative. The radiation exposure associated with thoracic CT and arch angiography as performed in this patient is equivalent to more than six times the annual background dose of radiation.

The principle of “Primum non nocere” still exists.

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References

Hypocapnia

To the Editor: The otherwise excellent review of hypocapnia by Laffey and Kavanagh (July 4 issue) was somewhat diminished by an oversimplified discussion of the effects of hypocapnia on the cerebral circulation. We would like to add two points. First, hypocapnia reduces cerebral blood flow but expands the plateau region of the cerebral autoregulatory curve, thereby improving cerebral autoregulation, the inherent ability of the cerebrovasculature to keep cerebral blood flow constant for a wide range of perfusion pressures. As the authors rightly point out, increasing cerebral blood flow by whatever means may not always be in a patient’s best interest, because of the risks of raised intracranial pressure and reperfusion injury. In certain disease states, methods that aim to improve cerebral autoregulatory capacity, including the induction of mild-to-moderate hypocapnia, may ultimately be shown to be more clinically beneficial than methods that alter the actual magnitude of cerebral blood flow.

Second, hypocapnia increases the critical closing pressure of the cerebral circulation. Critical closing pressure is the pressure below which blood flow in a vessel ceases (usually some value above 0 mm Hg) and is thought by some to be the most important determinant of cerebral blood flow. Although it improves autoregulatory capacity, hypocapnia may ultimately impair cerebral blood flow if the critical closing pressure approaches the cerebral perfusion pressure. Indeed, it has been suggested that this is the pathophysiological mechanism that explains cerebral hypoperfusion before vasovagal syncope.

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Acute Exacerbations of Chronic Obstructive Pulmonary Disease

To the Editor: In their review of hypocapnia, Laffey and Kavanagh omit hyperammonemia in the absence of hepatic failure from the list of causes of hypocapnia in Table 1 of their article. For example, hyperammonemia may occur in patients with urea synthesis in stagnant urine or urea-cycle disorders and in those receiving valproate therapy or cytochrome P450 3A4 inhibitors and immunosuppressive therapy. Because hypocapnia and respiratory alkalosis may be discovered before plasma ammonia levels are measured, respiratory alkalosis in these clinical settings should raise the suspicion of impending hyperammonemic encephalopathy.

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The authors reply:

To the Editor: The literature detailing the multiple mechanisms by which hypocapnia may alter cerebral blood flow is extensive. The mechanisms alluded to by Carey, though of interest, are not currently well supported in the literature, nor are they of obvious clinical importance, so we did not give them priority in our review. Of particular concern is the suggestion that there may be a role for the use of hypocapnia as a cerebral protectant. We believe that there are no clinical data to support such a practice and point out that data from prospective, randomized studies indicate that it is dangerous. Any inference that hypocapnia might exert clinically beneficial neurologic effects, except for very specific indications, is not warranted.

We agree with Brusilow that hyperammonemia in the absence of hepatic failure is associated with hyperventilation. However, we know of no studies showing that the relation is causative.

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Acute Exacerbations of Chronic Obstructive Pulmonary Disease

To the Editor: In his Clinical Practice article (March 28 issue), Stoller states that the use of methylxanthines in patients with exacerbations of chronic obstructive pulmonary disease (COPD) remains “unclear.” My colleagues and I disagree. In a meta-analysis of randomized trials of methylxanthines, my team found no consistent benefit of methylxanthines for exacerbations of COPD and a clear increase in the risk of adverse effects. These findings concur with results of a systematic review of methylxanthines for exacerbations of asthma in adults.

Stoller cites a large reduction in the rate of hospitalization among patients treated with aminophylline in one study of patients presenting to the emergency department with acute exacerbations of asthma or COPD. However, this reduction was not statistically significant among the patients with COPD and may have been offset by the trend toward increased rates of relapse among patients treated with methylxanthines and then sent home.

Multiple international guidelines currently recommend methylxanthines for severe exacerbations. However, we agree with the American College of Physicians–American Soci-
ity of Internal Medicine and the American College of Chest Physicians that current evidence does not support the use of methylxanthines for acute COPD. It strikes us that findings from systematic reviews should be applied in the development of guidelines, at the bedside, and in the case of COPD, in the search for new therapeutic agents. If methylxanthines are to play any part in the treatment of exacerbations of COPD, then new, more selective methylxanthines with fewer adverse effects will be required. As with other agents, randomized clinical trials will be necessary to evaluate any (probably small) clinical benefit in patients with exacerbations of COPD.

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Dr. Stoller replies:

To the Editor: Barr favors a stronger recommendation against the use of methylxanthines in patients with acute exacerbations of COPD. I completely agree that randomized, controlled trials and systematic reviews are the preferred basis for making clinical recommendations and would not want my statement that the “benefits of using a methylxanthine drug . . . remain unclear” to be misconstrued as a strong endorsement for using methylxanthines in this setting. Rather, my goal in citing the morsel of evidence from randomized trials supporting the use of a methylxanthine in managing acute exacerbations of COPD was to help explain why four of the five available guidelines (including that of the Global Initiative for Chronic Obstructive Lung Disease) indicate that methylxanthines may be considered a “salvage” therapy in this setting.

I hope that in noting that I did not recommend methylxanthines for the patient described in the vignette in my article, Barr recognizes that my statement and his may differ more in tone and flavor than in substance.

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Peanut Allergy

To the Editor: Regarding the article on peanut allergy by Sampson (April 25 issue),1 one should note that although anaphylaxis is the hallmark of peanut allergy, this allergy can also manifest in the form of such chronic, non–life-threatening entities as atopic dermatitis. In addition, there may be a link between the growing availability of infant formulas containing isolated soy protein during the past 40 years and the increasing prevalence of peanut allergy. During the 30 years of my practice in the field of allergy, especially pediatric allergy, 62 percent of 82 patients with confirmed cases of peanut allergy had a history of feeding difficulties resulting in attempts to substitute one or more brands of soy formula for cow’s-milk formula. It seems possible that cross-sensitization between soy-protein antigens and peanut-protein antigens results in sensitivity to peanuts, because both belong to the legume family. Most of the infants in need of soy formula either had atopy or were predisposed to atopic diathesis in the first place.

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Dr. Sampson replies:

To the Editor: I agree with Dr. Kuwayama that peanut allergy can manifest as a chronic condition such as atopic dermatitis in young infants, but I have not seen this presentation in older children. It is certainly possible that the increasing use of soy protein might be partially responsible for the increase in the prevalence of peanut allergy. However, a number of factors should be kept in mind. First, children are typically given soy formula because of a suspected allergy to milk, and about 95 percent of children who are allergic to milk will later have another food allergy. Second, the allergenic epitopes on soy and peanut proteins are unique, and only about 10 percent of persons who are allergic to peanuts have an allergic reaction to soy protein. Finally, the substantial increase in the prevalence of peanut allergy appears to have occurred during the past 10 years, whereas the use of soy formula does not appear to have increased substantially over this period. What is responsible for the apparent increase in peanut allergy in Westernized countries remains a critical question.

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To the Editor:

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Dr. Sampson replies:

To the Editor: I agree with Dr. Kuwayama that peanut allergy can manifest as a chronic condition such as atopic dermatitis in young infants, but I have not seen this presentation in older children. It is certainly possible that the increasing use of soy protein might be partially responsible for the increase in the prevalence of peanut allergy. However, a number of factors should be kept in mind. First, children are typically given soy formula because of a suspected allergy to milk, and about 95 percent of children who are allergic to milk will later have another food allergy. Second, the allergenic epitopes on soy and peanut proteins are unique, and only about 10 percent of persons who are allergic to peanuts have an allergic reaction to soy protein. Finally, the substantial increase in the prevalence of peanut allergy appears to have occurred during the past 10 years, whereas the use of soy formula does not appear to have increased substantially over this period. What is responsible for the apparent increase in peanut allergy in Westernized countries remains a critical question.

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1. Host A. Cow’s milk protein allergy and intolerance in infancy: some

**Recurrent Peanut Allergy**

To the Editor: Allergy to peanuts is potentially fatal, affects 1 in 150 persons in the United States, and until recently was considered to be permanent. However, recent reports document a 20 percent rate of resolution by school age. We offer an institutionally approved research protocol for double-blind, placebo-controlled oral food challenges for use in children older than 3.5 years of age who have been allergic to peanuts and who have a clinical profile consistent with potential resolution of peanut allergy, as defined by the absence of recent reactions and a serum peanut-specific IgE antibody concentration of less than 10 kU per liter.

We describe three of our patients who tolerated peanuts during such a challenge involving 8 g of peanut flour followed by a 32-g serving of peanut butter but who went on to have recurrence of peanut allergy. The three boys initially had convincing clinical reactions and laboratory evidence of peanut sensitization that diminished over time before the oral challenges (Table 1). In the year after having no allergic reaction on oral challenge, the boys ate peanuts infrequently and in small quantities. The recurrence of peanut allergy was documented in Patient 1 by a repeated challenge that elicited a generalized reaction, in Patient 2 by repeated mild reactions and a concentration of peanut-specific IgE antibody (15 kU per liter) that was highly (>95 percent) predictive of clinical reactions, and in Patient 3 by a severe reaction and recurrence of sensitization.

We can only speculate as to why these children became re-sensitized. Although they were not reactive, they were ingesting only small amounts of peanut intermittently — a regimen that is typically considered to be desensitizing. This regimen contrasts with typical regimens designed to build tolerance (which entail the continuous administration of small doses or the intermittent administration of large doses). These 3 patients were evaluated after 44 children entered our ongoing study of the resolution of peanut allergy. At that time, 26 children had no allergic reaction on oral challenge, and follow-up (mean duration, 15 months) in 21 children revealed that only 10 routinely ate peanuts. This observation is worrisome if the aforementioned hypothesis is correct.

The clinical ramifications of our observations are profound and may apply to other foods as well as to peanuts. Recurrence of peanut allergy is possible even when it has been shown to have resolved. It seems prudent to maintain access to emergency medications, such as self-injectable epinephrine, for patients with resolved peanut allergy until

| TABLE 1. IMMUNOLOGIC FINDINGS AND CLINICAL COURSE IN THREE BOYS WITH RECURRENCE OF PEANUT ALLERGY.* |
|---------------------------------|---------------|----------------|----------------|---------------------------------|
| PATIENT No. | AGES AT THE TIMES OF REACTIONS | SENSITIZATION HISTORY | AGE AT THE TIME OF NO REACTION ON ORAL CHALLENGE | EVIDENCE OF SENSITIZATION AFTER RECURRENTION |
| 1 | 1.5 | Positive skin-prick test at 1.5 yr (wheat, 7 mm; erythema, 10 mm); positive skin-prick test at 2.5 yr (wheat, 12 mm; erythema, 19 mm); peanut-specific IgE concentration at 5 yr, 3 kU/liter; positive skin-prick test at 9 yr (wheat, 5 mm; erythema, 23 mm) | 9 | Oral pruritus from peanut-containing foods; repeated oral challenge with 1.8 g led to oral pruritus, abdominal pain, and urticaria | Positive skin-prick test (wheat, 12 mm; erythema, 35 mm); peanut-specific IgE concentration, 1.2 kU/liter |
| 2 | 1.5, 1.7 | Positive skin-prick test at 1.7 yr (not measured); negative skin-prick test at 5 yr (wheat, 0 mm; erythema, 0 mm) | 5 | Oral symptoms from peanut-containing foods; repeated oral challenge deferred because of diagnostic high peanut-specific IgE concentration | Positive skin-prick test (wheat, 7 mm; erythema, 29 mm); peanut-specific IgE concentration, 16.6 kU/liter |
| 3 | 1, 4, 4.5 | Positive skin-prick test at 4 yr; negative skin-prick test at 8.5 yr (wheat, 0 mm; erythema, 0 mm) | 8.5 | Oral pruritus, facial erythema, chest pressure treated in emergency room | Positive skin-prick test (wheat, 4 mm; erythema, 19 mm); peanut-specific IgE concentration, 0.41 kU/liter |

*Results on skin-prick testing represent the mean diameter of wheals and the mean diameter of erythema. Peanut-specific IgE antibody concentrations were measured with the use of a fluorescence immunoassay (Pharmacia CAP System, Pharmacia Diagnostics), for which the lower limit of detection is 0.35 kU per liter.
peanuts are routinely tolerated in relevant quantities for at least one to two years.

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