

Correspondence



Smallpox, October 1945

To the Editor: Because of terrorism, we may be reviving smallpox vaccination. I had some experience with smallpox while stationed in Nagoya, Japan, in October 1945 with the 229th General Hospital. Joseph B. Kirsner, professor of medicine at the University of Chicago, was chief of gastroenterology at the hospital at that time and confirms the details of my recollections. Over a period of several weeks, we admitted 22 service personnel with smallpox. The initial case was diagnosed at autopsy, but subsequent cases were diagnosed quite early. The disease began with a high fever, with the temperature exceeding 40°C and then dropping, although never to normal, before it spiked again — in contrast to malaria, in which the temperature came down to normal before the next spike. Although some patients had pustular lesions, those who died had confluent subcutaneous hemorrhages that rapidly involved the entire body, with a similar enanthema involving the mucous membranes of the oral cavity, respiratory mucosa, and entire gastrointestinal tract. The pain was intense, and morphine relieved it only marginally. Every soldier with smallpox had been in the hospital because of other medical problems two weeks before the onset of smallpox. A messenger, who stopped in the laboratory only for a cup of coffee, returned two weeks later with smallpox. Clearly, the source was in the hospital itself. We heard nothing of smallpox at other Army hospitals and had no information about smallpox in the Japanese population. Eight of our infected service personnel died. The 14 who recovered had had patchy erythema, occasionally with a few bullae or pustules. All 14 had smallpox-vaccination scars on their

arms, whereas not 1 of the 8 patients who died had such a scar.

When we administered vaccinations, the reactions were graded as “primary” if a papule appeared after a few days and a vesicle developed and persisted for 2 or 3 weeks; as “accelerated” if the papule appeared on the 3rd or 4th day and the vesicle disappeared in 7 to 10 days; and as “immune” if the papule appeared within 48 hours and subsided without the development of a vesicle. Negative skin reactions or “no takes” were considered to be failures, due to poor vaccine or faulty technique, and revaccination was required. Since all soldiers had been vaccinated in childhood and again when they entered the Army, the absence of a scar in the eight patients who died probably indicated faulty vaccination technique and a “no take” that had been read incorrectly as an immune reaction.

All patients who came into the hospital were vaccinated. We staff members decided to vaccinate ourselves about every three weeks. We always had an immune reaction. Toward the end of the epidemic, a batch of vaccine came in that was reputed to be from the Philippines, and we all had substantial reactions to it — they looked like primary reactions and lasted for several days. The vaccine was cultured and grew pure staphylococcus.

Years later, as an internist, I vaccinated patients with near-religious fervor, using the prick method and counting 30 pricks (since these patients had been vaccinated previously). I was careful not to allow bleeding, which is said to neutralize the virus. I recall only one case in which there was a “no take” despite two or three repetitions, for which I never found an explanation.

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Naltrexone for Alcohol Dependence

To the Editor: Krystal et al. (Dec. 13 issue)¹ “found no evidence that naltrexone combined with psychosocial therapy

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was an effective treatment for alcohol dependence.” We are concerned that the characteristics of the study sample may have made it difficult to detect significant differences among the treatment groups. Only 19 percent of the veterans initially evaluated were enrolled. In this extremely selected study sample, the results with naltrexone were similar to those without naltrexone. We were surprised that no significant differences were found among the study groups in the median number of days to relapse (176 days in the group assigned to 12 months of naltrexone, 115 days in the group assigned to 3 months of naltrexone, and 104 days in the placebo group). We recently reported the results of a comparison of naltrexone and acamprosate for alcohol treatment in which, after a 12-month follow-up, the mean number of days to relapse was 63 with naltrexone and 42 with acamprosate.²

Krystal et al. report good results in all the groups, in contrast to others’ findings.³⁻⁵ The conclusion that naltrexone was ineffective is not justified.

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To the Editor: The negative results with naltrexone reported by Krystal et al. are consistent with our findings^{1,2} but are not relevant to the question of whether naltrexone is effective. Naltrexone yields significant benefits but not in protocols such as theirs that support complete abstinence.¹⁻⁴

In Finland, we conducted a 32-week, double-blind, randomized trial,¹ in which we divided 121 alcohol-dependent outpatients into four groups. Two of the groups were instructed to abstain from alcohol, as in the study by Krystal et al. In these groups, naltrexone (50 mg) was no better than placebo. The other two groups had therapy aimed not at abstinence but at the prevention of binges; in these groups, naltrexone was significantly better than placebo and was significantly better than naltrexone given with instructions to abstain from alcohol. Similarly, we found that naltrexone was not effective in patients who were asked to abstain from alcohol but was effective in those who were not required to abstain.² The same pattern was found in a Swedish study³ and in other trials.⁴ The primary benefits have consistently

been seen in patients who drink alcohol while receiving naltrexone.⁴

The practical question is how to get this message across. Abstaining alcoholics cannot be advised to drink. The solution is to begin treatment with naltrexone before detoxification, when patients are still drinking. We found this approach to be both effective and safe.¹ It is also considerably less expensive and more acceptable to patients than procedures involving prior detoxification.

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1. Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2001;21:287-92.
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The authors reply:

To the Editor: Rubio and colleagues suggest that the time to a relapse of heavy drinking was longer in our study than in previous trials. They question whether the composition of the sample of patients might have contributed to this difference. Our criteria for enrollment were based on the advice of investigators who had conducted the principal U.S. studies of naltrexone with the objective of sampling a broadly representative group of alcohol-dependent patients treated at Department of Veterans Affairs institutions. Our results apply most directly to this population. The population we enrolled was similar to those in other studies, but the group that received placebo had better outcomes than placebo groups in other trials.

The recommendation to give naltrexone to patients who continue to drink is based on the hypothesis of Sinclair and colleagues that this method extinguishes the urge to drink alcohol by blocking the rewarding effects of alcohol. We attempted to determine whether our study provided indirect support for this hypothesis by conducting a post hoc analysis in which patients who sampled alcohol before a relapse were compared with those who did not sample alcohol before a relapse. Using our three end points of the time to relapse, the number of drinks per drinking day, and the percentage of drinking days, we found no significant differences between the patients who were taking naltrexone and those who were taking placebo. This result does not support the findings of Sinclair et al., but this comparison was not a di-

rect test of their hypothesis because it was not part of our protocol design.

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Patent Foramen Ovale, Atrial Septal Aneurysm, and Recurrent Stroke

To the Editor: Mas et al. (Dec. 13 issue)¹ describe multiple potential thromboembolic mechanisms that may account for the increased risk of recurrent stroke in young patients with both patent foramen ovale and atrial septal aneurysm.

The initial descriptions of paradoxical embolism with stroke provide clear evidence of a thrombotic source (e.g., deep-vein thrombosis), evidence of thrombus movement elsewhere (pulmonary embolus, ischemia in other organs, such as the kidney, or both), and a cardiac abnormality.^{2,3} Curiously, more recent articles have failed to identify an increased risk of deep-vein thrombosis, pulmonary embolism, or ischemia in other organs in patients with cardiac abnormalities such as patent foramen ovale and stroke. In Table 2 of their article, Mas et al. indicate that one patient had systemic embolism. Furthermore, it is unclear why the presence of both abnormalities would be necessary to account for the increased risk, rather than either one or none. Similarly, in this and numerous other studies, there has not been evidence of thrombus within the cardiac defects or an increased risk of cardiac arrhythmia among these patients.

Thus, it may be that in young patients who have had a stroke without an identifiable cause, these cardiac abnormalities are either epiphenomena of the stroke or markers of some other abnormality that confers a predisposition to stroke.

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1. Mas J-L, Arquiza C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;345:1740-6.
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To the Editor: Mas et al. used semiquantitative transesophageal echocardiography with contrast medium, a technique with pitfalls, to determine the size of a patent foramen ovale.¹⁻³ Transesophageal echocardiography with contrast material administered through a cubital vein has a low level of accuracy for determining the size of a patent foramen ovale.^{2,3} Our study of patients with cryptogenic stroke and patent foramen ovale showed a significant association between the degree of interatrial septal deviation

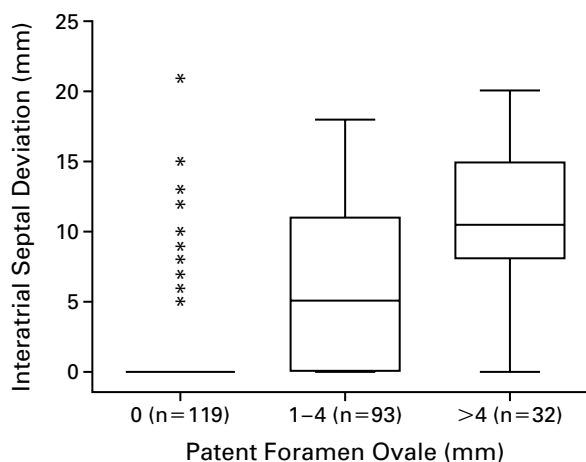


Figure 1. Correlation between the Size of a Patent Foramen Ovale and the Degree of Atrial Septal Deviation.

The horizontal lines in the boxes indicate the 25th, 50th, and 75th percentiles, and the lower and upper T bars indicate the minimal and maximal values, respectively. The asterisks represent values beyond the T bars (which are limited to 1.5 times the interquartile range).

and the size of the patent foramen ovale (correlation coefficient, 0.61; $P < 0.001$) (Fig. 1). This finding suggests that an atrial septal aneurysm is an indicator of a large patent foramen ovale, which is associated with a substantial risk of recurrent stroke.³ We hypothesize that in the study by Mas et al., the high rate of recurrent stroke in the patients with both patent foramen ovale and atrial septal aneurysm was due predominantly to the presence of a large patent foramen ovale.

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To the Editor: The article by Mas et al. has important implications for the management of cryptogenic stroke and patent foramen ovale. In particular, the low rate of recurrent stroke among the patients who had patent foramen ovale without an atrial septal aneurysm calls into question the use of oral anticoagulants and closure of the patent foramen ovale in patients who are not enrolled in controlled clinical trials. Paradoxical embolism is assumed to be a probable mechanism of stroke in many patients with patent foramen ovale. Hypercoagulable states may confer a predisposition to paradoxical embolism and cryptogenic stroke in patients with patent foramen ovale.^{1,2} Although the authors state that coagulation studies were performed in their patients, they do not report the results of these studies. Furthermore, two major hereditary hypercoagulable conditions, the factor V Leiden mutation and the G20210A factor II mutation, are not mentioned. It would be of great interest to know whether the patients with patent foramen ovale had a higher prevalence of coagulation abnormalities than those without patent foramen ovale; how many patients were tested for resistance to activated protein C, the factor V Leiden mutation, and the G20210A factor II mutation and whether the results differed between the groups; and in how many patients venous thrombosis was diagnosed (although venous thrombosis was probably not systematically investigated in this large cohort).

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1. Chaturvedi S. Coagulation abnormalities in adults with cryptogenic stroke and patent foramen ovale. *J Neurol Sci* 1998;160:158-60.
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The authors reply:

To the Editor: Statistical association does not necessarily imply causality, since it may result from selection or information bias, chance, or confounding factors.¹ Although bias and chance are unlikely to explain the findings of numerous studies linking patent foramen ovale and atrial septal aneurysm to stroke,² it is more difficult to exclude the presence of an as yet unknown confounding factor that is associated with these septal disorders and that affects the outcome (stroke). The criteria that support causality include a temporal sequence, a strong and consistent association, a dose-response relation, biologic plausibility, and experimental evidence.^{1,2} The association of stroke with the above-mentioned cardiac disorders meets the first three criteria.²

Large shunts have been reported to be more strongly associated with stroke than smaller ones, suggesting a dose-response relation. However, since atrial septal aneurysm has not usually been taken into account, stroke may be associated with the two lesions in combination, rather than with patent foramen ovale alone. Potential mechanisms of stroke include paradoxical embolism and in situ thrombosis, but we

agree that these mechanisms have rarely been documented. Causality will eventually be confirmed if randomized trials demonstrate that endovascular or surgical "removal" of these septal disorders substantially reduces the risk of subsequent stroke, in the same way that the clinical relevance of carotid stenosis has been confirmed by the finding that carotid endarterectomy substantially reduces the risk of subsequent ipsilateral stroke.

We agree that future studies should include direct evaluation of the size of the foramen.³ However, whether the measurement of a morphologic characteristic (the size of the foramen) rather than a functional characteristic (the degree of shunting) results in a more accurate assessment of the risk of recurrent stroke remains to be determined. With regard to atrial septal aneurysm, we also found that its prevalence increased with the degree of shunting, but the degree of shunting was not a significant predictor of recurrent stroke in an analysis adjusted for atrial septal aneurysm.⁴

Our study was not designed to assess the role of a hypercoagulable state. Patients with a definite cause of stroke, including those with a coagulation disorder, were excluded from the study. (Among the patients who were excluded because of a definite cause of stroke, less than 5 percent had a coagulation disorder as the definite cause.) Tests for factor V Leiden and the G20210A factor II mutation were not available at the time the study was designed. About 50 percent of the patients with patent foramen ovale were evaluated for latent venous thrombosis within four weeks of the onset of stroke, mainly with the use of Doppler ultrasonography. Latent venous thrombosis was found in only 4 percent of these patients, a rate consistent with that in our previous study with the use of phlebography.⁵

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The Hemolytic-Uremic Syndrome

To the Editor: The data reported by Chandler et al. (Jan. 3 issue)¹ support the possibility of a severe prothrombotic dis-

turbance in the hemolytic-uremic syndrome, suggesting that the generation of thrombin and inhibition of fibrinolysis precede renal injury and may be the cause of such injury. These data could help to distinguish diarrhea-associated hemolytic-uremic syndrome from thrombotic thrombocytopenic purpura and to identify relapsing hemolytic-uremic syndrome in which there is a deficiency of a specific von Willebrand factor-cleaving protease, resulting in large multimers that promote platelet aggregation.² These coagulation abnormalities may also help to explain why plasma exchange, which is an effective treatment for thrombotic thrombocytopenic purpura, does not affect the long-term outcome or the duration of thrombocytopenia or anuria in the hemolytic-uremic syndrome. In the accompanying editorial, Grabowski suggests that studies such as this one "may ultimately provide us with therapeutic strategies (e.g., use of an antithrombotic agent directed against the targeted cell or coagulation protein) to use when exposure to toxin cannot be prevented."²

Three studies have found that antithrombotic agents are not effective in the hemolytic-uremic syndrome. In a controlled therapeutic trial, 15 children were given urokinase and heparin, and 18 children received supportive care; the long-term evolution of renal function and arterial pressure and the duration of thrombocytopenia and anuria were similar in the two groups.³ In a prospective study, 10 children with severe hemolytic-uremic syndrome were selected at random to receive heparin; the remaining 20 constituted the control group.⁴ Heparin treatment was associated with a higher mortality rate (60 percent vs. 30 percent) and was the cause of death in one patient (from intracranial hemorrhage). In another study, 58 infants and children with the hemolytic-uremic syndrome were randomly assigned to receive treatment either with heparin and dipyridamole or with supportive therapy only. There were no significant differences between the groups except for a higher incidence of anuria and a faster recovery from hypertension in the treated group.⁵ These studies indicate that treatment with heparin, dipyridamole, or urokinase has no benefit over symptomatic therapy alone in the typical form of childhood hemolytic-uremic syndrome and that such treatment may increase the risk of hemorrhagic complications.

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The authors reply:

To the Editor: Debourdeau et al. correctly caution against the use of agents that increase the risk of hemorrhagic complications in patients with the hemolytic-uremic syndrome, a disorder that is accompanied by hypertension, thrombocytopenia, and uremia. The adverse or neutral outcomes they refer to were in children with established microangiopathy.

With appropriate supportive care and surveillance for surgical complications, the immediate prognosis is good for most children with the hemolytic-uremic syndrome who are treated in pediatric nephrology centers. Nonetheless, our finding that prothrombotic coagulation abnormalities develop before the hemolytic-uremic syndrome, at a point when hypertension, thrombocytopenia, and uremia have not yet occurred, raises the possibility that short-acting antithrombotic or profibrinolytic interventions may prevent or reduce subsequent injury. Determining which type of therapy should be evaluated, however, requires careful thought. For example, in view of the elevated levels of plasminogen-activator inhibitor type 1, infused tissue plasminogen activator is unlikely to be effective. Moreover, it will be important to assess both the risks and benefits of such agents in children with *Escherichia coli* O157:H7 infections, since the hemolytic-uremic syndrome will develop in only approximately 15 percent of such children and will be fatal in only a minority.

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The editorialist replies:

To the Editor: Debourdeau et al. call attention to perhaps the most controversial aspect of the hemolytic-uremic syndrome: its treatment. Although I agree that no study has yet demonstrated a clear benefit of antithrombotic therapy in the hemolytic-uremic syndrome, it would be unwise to suggest that no such therapy could ever be effective. In fact, in my editorial I suggested that antithrombotic therapy directed against a targeted cell or coagulation protein implicated in the as yet unknown pathophysiology of the disorder might prove beneficial. Such focused therapy, moreover, might prove especially useful in patients at high risk for the hemolytic-uremic syndrome if it is directed against the coagulopathy that Chandler et al. demonstrate precedes the syndrome. The situation is, in some respects, analogous to the situation that once pertained to the use of aspirin for the prevention or treatment of acute coronary syndromes. The important role of platelet thrombi in the pathophysiology of acute coronary syndromes only began to be widely recognized after such angiographic studies as that of DeWood et al.¹ Before 1980, the role of platelets and, consequently,

the strategy of using antiplatelet therapies might have been rejected as unproved if not also unsafe.

The report by Van Damme-Lombaerts et al.,² to which the correspondents refer, actually supports the use of a more innovative approach to anticoagulant therapy in the hemolytic-uremic syndrome. Van Damme-Lombaerts et al. state, "antithrombotic therapy might be beneficial in some selected cases. Indeed, the three major long-term problems arose only in patients from the control [non-heparin] group." With respect to the adverse results attributed to heparin,³ a review of the data of Vitacco et al. shows 4, not 6, deaths among 10 children treated at presentation with heparin, as compared with 6 among 20 controls.³ Two additional deaths did occur among three patients given heparin, but these three patients constituted a group given heparin only late in the course of their disease owing to clinical deterioration related to the hemolytic-uremic syndrome. There was no corresponding control group.

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Post-Traumatic Stress Disorder and Sleep

To the Editor: Lavie (Dec. 20 issue)¹ has shown that objective, sleep-laboratory measures do not consistently support the subjective reports of insomnia given by Western survivors of traumatic events. However, Lavie does not provide an explanation for this inconsistency.

We believe that beliefs about illness, which vary among cultures,² may play a part. Elevated rates of subjective reporting of insomnia after trauma are not necessarily found outside of the Western or industrialized world. In a population-based study comparing 526 Bhutanese refugees in Nepal who had been tortured with 526 who had not been tortured, those who had been tortured were more likely to report 16 of the 17 symptoms of post-traumatic stress disorder (PTSD) ($P < 0.05$); the exception was insomnia (chi-square statistic = 1.3, $P = 0.25$).³ The frequency of reports of nightmares, however, was elevated among the refugees who had been tortured. This observation is consistent with Lavie's review, which does not provide any strong or objective evidence that nightmares are overreported by survivors of traumatic events.

We expect that future investigations will confirm that insomnia is not specific to PTSD but that trauma-related nightmares are a core symptom of the disorder. In contrast to Lavie's recommendation regarding sleep disturbances, trauma-related nightmares should therefore be treated as a symptom of PTSD rather than as an independent clinical

entity. Effective therapies for PTSD are available.^{4,5} Moreover, evidence-based explanations of the reasons behind the overestimation of insomnia by Western survivors of trauma will improve understanding of their overall experience of trauma.

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To the Editor: A press release from the American Society for Technion-Israel Institute of Technology¹ expanding on the article by Dr. Lavie states that he "questions the traditional treatment for traumatized patients, which is based on reliving the trauma." According to the press release, "Dr. Lavie's studies with Holocaust survivors suggest that learning to leave traumatic memories behind may be more effective for a good night's sleep." We adamantly disagree with Dr. Lavie's conclusions regarding the treatment of traumatized persons with chronic psychiatric disturbances such as PTSD.

PTSD is characterized by symptoms of reexperiencing the trauma, avoidance of reminders of the trauma, and increased arousal, including sleep disturbances. The treatment that has been found to be extremely effective in ameliorating PTSD in numerous studies is "prolonged exposure."² This approach involves having the patient repeatedly recount the traumatic memory in a therapeutic manner³ until the memory ceases to evoke strong anxiety. The goal of prolonged exposure is to help the survivor process the traumatic memory in such a way that he or she will be able to remember it without disruptive distress.

Dr. Lavie's assertions that survivors of trauma should "learn to leave traumatic memories behind" can be interpreted as encouraging survivors to avoid this type of processing of the traumatic event. Dissemination of Dr. Lavie's assertions is damaging and harmful, because such avoidance is known to prolong and exacerbate the symptoms of PTSD rather than ameliorate them. Research has demonstrated that survivors of trauma must emotionally process their traumatic experiences to be able to return to normal functioning and that systematic avoidance of the painful memories actually perpetuates PTSD.⁴ Survivors must face the memories to get past them. Advising them to "leave traumatic memories be-

hind” is counterproductive, and physicians should not recommend such avoidance to their patients.

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Dr. Lavie replies:

To the Editor: Rothbaum and Foa’s warning against advising patients to leave traumatic memories behind them is a surprise. The conviction and vehemence with which they attack this idea stand in sharp contrast to the scientific rigor that has been used in the evaluation of treatments for PTSD. As Foa and coworkers concluded in their guidelines for treatment of PTSD,¹ “the study of treatment efficacy for PTSD is still in its initial stage relative to other mental disorders.” They were right. None of the references that Rothbaum and Foa cite in their letter provide a shred of evidence that prolonged exposure is effective in severely traumatized patients such as Holocaust survivors or survivors of catastrophic traumatic experiences.

Moreover, in the same journal issue in which the guidelines of Foa et al. appear, Krakow et al.² present evidence that the use of the imagery rehearsal technique alleviates the symptoms of PTSD in rape victims; they explain that this “treatment discourages discussion of traumatic experiences and traumatic content of nightmares, and instructs patients to avoid rehearsing old nightmares.” Krakow et al. go on to note that “many of [their] participants reported that they were previously offered (or they had previously attempted) desensitization procedures to help them with their PTSD-related symptoms. Of those who attempted such therapy, essentially all reported no improvement or worsening.”

Finally, a review of the effectiveness of brief psychological debriefing in patients with PTSD,³ a method that is conceptually similar to prolonged exposure (albeit of shorter duration), concluded that “there is no current evidence that psychological debriefing is a useful treatment for the prevention of PTSD after traumatic incidents. Compulsory debriefing of victims should cease.”

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Mild Asthma

To the Editor: Naureckas and Solway (Oct. 25 issue)¹ discuss the treatment of mild intermittent and mild persistent asthma but do not discuss the importance of indoor allergens. Allergens not only are triggers of symptoms, but some are also regarded as causal factors in the development of the disease.^{2,3} Because they continuously induce allergic inflammation of the airways, allergens may be more important as a cumulative cause of bronchial hyperreactivity than as triggers of acute attacks.⁴ Furthermore, longitudinal studies have shown an accelerated decline in the forced expiratory volume in one second in older adults who are exposed to certain allergens.⁵ In other diseases that are caused by exposure to foreign substances, such as hypersensitivity pneumonitis, avoidance of exposure to relevant antigens is the first line of treatment. In asthma, environmental control measures to reduce exposure to indoor allergens should be considered a primary antiinflammatory treatment.² Such measures should help to prevent the development of chronic airflow limitation and, therefore, reduce the need for further pharmacologic treatment.

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To the Editor: Naureckas and Solway do not address the role of testing for allergens or precipitants. Effective management of mild asthma involves avoidance of allergens, and this often requires radioallergosorbent testing or careful skin testing.

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To the Editor: Naureckas and Solway provide definitions of mild intermittent and mild persistent asthma that are

based on the frequency of clinical symptoms and objective measures of lung function. These definitions are derived from international guidelines.¹⁻³ However, it is important to recognize that these definitions apply to untreated patients. After treatment has been established, and particularly after control medications are being taken regularly by the patient, the severity of the disease is defined not only by symptoms and lung-function values, but also by the amount of medication required to keep asthma under control — for example, low-dose inhaled corticosteroids for mild persistent asthma and short-acting inhaled β_2 -agonists as needed or before exercise for mild intermittent asthma.¹⁻³ This simple concept is included in the guidelines, but it is often overlooked.

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1. Expert Panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1997. (NIH publication no. 97-4051.)
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The authors reply:

To the Editor: We agree with Drs. Bonnin and Marinkovich that the avoidance of environmental triggers is beneficial in patients with asthma of any severity. Indeed, the guidelines of the National Asthma Education and Prevention Program (NAEPP)¹ recommend testing for individually relevant perennial allergens, but they also point out that the patient's history alone may be sufficient to suggest sensitivity to seasonal allergens. We note that the reduction of exposure to other exacerbating factors, such as inhaled irritants, is also worthwhile.

Drs. Romagnoli and Fabbri properly emphasize that the classification system outlined in the NAEPP guidelines¹ is intended for the initial evaluation of asthma — implicitly, before the initiation of therapy. Successful treatment results in the diminution of symptoms and improvement in other objective measures and does not change the classification of the severity of asthma in an individual patient.

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Potential Hazard of Wound Licking

To the Editor: A 42-year-old man with type I diabetes mellitus was treated for dislocation and a minor laceration

of the right thumb after a bicycle accident. After repositioning of the thumb, he was released without antibiotic treatment. Three days later, he was seen in an outpatient clinic with fever and swelling and pain in the right hand. A swab of the wound was obtained, and he was admitted to the hospital.

The patient was severely ill, with fever (temperature, 39.3°C), leukocytosis (white-cell count, 13,600 per cubic millimeter), an elevated blood glucose level (220 mg per deciliter), and a painfully swollen right hand, and he was taken directly to surgery. After an incision was made in the thumb and the palm, necrotizing fasciitis was diagnosed and surgically treated. Intravenous antibiotic treatment with piperacillin, sulbactam, clindamycin, and metronidazole was started. The patient recovered from the systemic infection within three days, but the distal phalanx of the right thumb had to be amputated after four weeks despite attempts of plastic surgeons to save it.

The aerobic bacterial culture of the first swab yielded *Eikenella corrodens*, *Streptococcus anginosus*, and *Haemophilus parainfluenzae*. The anaerobic culture was negative. A second swab taken from the area of the necrotizing fasciitis also yielded *E. corrodens* and *S. anginosus*. The patient recalled that he had licked the bleeding wound after the accident. All isolated microorganisms are part of the normal flora of the oropharynx. Although *E. corrodens* is a potential pathogen in bite wounds and injuries caused by the contact of a clenched fist with the mouth,^{1,2} in this case, only wound licking by the patient was involved. It is commonly found together with streptococci after contact of a laceration with saliva and can spread hematogenously or locally, causing septic arthritis, endocarditis, and abscesses in different organs.³

Wound licking after minor trauma of the hand is done instinctively, and there are some hints that saliva acts antimicrobially through the presence of nitric oxide.⁴ Our case report indicates that contact of a wound with saliva carries a risk of severe infection.

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