the study by Yağcıoğlu et al., this study does not suggest that the negative findings of the Honer study resulted from an inadequate dose of risperidone. I apologize for my mistake. I found no evidence of bias in terms of pharmaceutical-industry sponsorship on the efficacy data from the randomized, controlled trials comparing second-generation with first-generation antipsychotic agents. All these drugs are effective, but randomized, controlled trials establish clozapine as the most efficacious.[1,2] However, the initial European experience found clozapine associated with agranulocytosis in about 1 to 2 percent of the patients (one third of cases were fatal). I agree with Dr. Gerson's conclusions. Mandatory monitoring of white-cell counts does indeed greatly minimize the risk of this complication.

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Hypertonic Saline for Cystic Fibrosis

TO THE EDITOR: We question the selection by Elkins et al.[1] and Donaldson et al.[2] (Jan. 19 issue) of 7 percent hypertonic saline, which can result in bronchoconstriction, in these studies of therapy for cystic fibrosis. Elkins et al. report a fall of 94 ml in the forced expiratory volume in one second (FEV_1) after the first dose of medication, which is greater than the reported final improvement in FEV_1 of 68 ml. Conversely, Donaldson et al. do not specify any change in FEV_1 with the use of 7 percent hypertonic saline. Robinson et al.[3] have compared mucociliary clearance with the use of different concentrations of hypertonic saline and did not find any difference in efficacy between solutions of 3 percent and 7 percent hypertonic saline solutions. We have shown that the use of 3 percent hypertonic saline is effective and has the additional advantage of not causing a substantial change in FEV_1, oxygen saturation, or symptom score.[4] Hence, the choice of the strength of the hypertonic saline solution administered should be based on the potential effects of hypertonic saline on pulmonary function, oxygen saturation, palatability, and the patient's preference.

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TO THE EDITOR: Donaldson and colleagues report that hypertonic saline after pretreatment with amiloride did not result in a sustained increase in mucus clearance or improvement in lung function or respiratory symptoms because of inhibition of apical membrane water permeability. Animal airways have a moderate osmotic water permeability and express aquaporin water channels, one of which is aquaporin-3.[1-3] In Table 1 of their article, the authors report that 50 percent of the patients in each of the two study groups received inhaled steroids concomitantly. Corticosteroids have been found to induce the expression of aquaporin-3 in A549 cells, a human airway epithelial-cell line derived from lung adenocarcinoma, in vitro.[3] In addition, hypertonicity induces the expression of aquaporin-3 in Madin–Darby canine-kidney cells, a renal epithelial-cell line, in vitro.[4] Perhaps patients receiving concomitant treatment with inhaled steroids should have been studied separately, in order to identify the possible contribution of aquaporin-3 overexpression to hypertonic saline treatment.

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TO THE EDITOR: The importance of the volume of the airway surface liquid in the pathophysiology of cystic fibrosis lung disease is supported by the findings of Elkins et al. and Donaldson et al. As pointed out in the accompanying editorial by Ratjen,[1] the mechanism of the prolonged action of inhaled hypertonic saline remains to be elucidated. We suggest that one mechanism pertains not to the volume of the airway surface liquid but, rather, to the effect of sodium ions on the viscosity of the mucus gel. Studies of gastrointestinal mucins have shown that calcium is the main cation that binds to mucins; the interaction increases the viscosity of the mucus gel.[2] Calcium binding to mucin is displaced by hypertonic sodium chloride.[3] Whether these observations pertain to airway mucins in patients with cystic fibrosis requires further investigation. Since mucus hyperviscosity has been implicated in the intestinal, hepatobiliary, and pancreatic manifestations of cystic fibrosis, hypertonic saline might be useful for the prevention of complications in these organs as well.

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DRS. BYE AND ELKINS REPLY: Drs. Aziz and Kastelik question the selection of a concentration higher than 3 percent in our phase 3 trial of inhaled hypertonic saline for cystic fibrosis. On the basis of the single-intervention studies they cite, we agree that a single dose of 3 percent saline increases the weight of sputum expectorated and improves mucociliary clearance to a degree similar to 7 percent saline. However, the primary outcome of our trial was lung function, which was chosen because it correlates with mortality in patients with cystic fibrosis.[1] When designing the trial, we therefore also considered the data from phase 2 trials that examined the effect of the regular use of hypertonic saline on lung function. We were unable to find evidence of an improvement in lung function with 3 percent saline. At higher concentrations, however, there was evidence of a benefit in both mucociliary clearance and lung function.[2] Our observations that 7 percent saline did not result in excessive side effects in clinical practice and in previous trials were supported by others.[3] We therefore chose 7 percent saline as the intervention for our trial. Further studies comparing various concentrations, as well as dosages and delivery systems, would help to refine the treatment protocol.

Drs. Aziz and Kastelik also express concern that the 94-ml fall in FEV_1 after the first dose of hypertonic saline was greater than the final improvement in FEV_1, of 68 ml. As stated in the article, premedication with a bronchodilator resulted in a 60-ml improvement in FEV_1 that limited the effective fall from baseline. We also stated that the final improvement of 68 ml was relative to baseline. Thus, any initial fall in FEV_1 was recovered, and then an additional average improvement of 68 ml was achieved.

Drs. Kuver and Lee suggest that a possible mechanism of action of hypertonic saline in the lungs is the effect of sodium ions on the viscosity of the airway mucus gel. Other authors have examined this possibility, as mentioned in our article and as reviewed more comprehensively by King.[4] Our trial did not provide any data to indicate whether hypertonic saline would have an effect on mucins from other organs.

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DR. DONALDSON AND COLLEAGUES REPLY: Mr. Zarogiannis et al. point out that corticosteroids and hypertonicity up-regulate aquaporin-3 and speculate that the use of inhaled corticosteroids could have influenced responses to amiloride, hypertonic saline, or both. Because the effect of amiloride on water transport was discovered only after the completion of our clinical trial, we neither excluded nor studied separately patients receiving inhaled corticosteroids. Reassuringly, inhaled corticosteroid use was balanced in the randomized groups, and all subjects were exposed to hypertonic saline, making it unlikely that an effect on aquaporin-3 greatly influenced the trial outcomes. Finally, recent in vitro experiments in our laboratory (unpublished data) suggest that water transport by means of aquaporin-3 is not attenuated by amiloride.

Drs. Aziz and Kastelik question the selection of 7 percent (as compared with 3 percent) saline. They refer to their own study, which reported safety with a single dose of 3 percent saline used for sputum induction. Because the mass of salt deposited on airway surfaces determines the magnitude of the increase in the volume of airway surface liquid, we sought to use the highest concentration of hypertonic saline that would be safe and well tolerated. Robinson et al.[1] provided good evidence for a dose–effect relationship between hypertonic saline and mucociliary clearance, despite the absence of a significant difference between the 3 percent and 7 percent groups. Twelve percent saline was poorly tolerated, however, because of oropharyngeal irritation. Therefore, 7 percent saline was selected on the basis of the study by Robinson et al. and other short-term studies of hypertonic saline in cystic fibrosis. In our study, we report FEV_1 values at two hours after administration of the first dose of hypertonic saline — values that, in fact, increased from baseline, further supporting the assertion that 7 percent saline is well tolerated in patients with cystic fibrosis.

Drs. Kuver and Lee propose an alternative mechanism linking the use of hypertonic saline and stimulated mucociliary clearance. Displacement by sodium of the calcium ions that bind mucins is postulated to explain the expulsion of mucins during exocytosis, and may influence the rheologic properties of mucus once secreted.[2] In fact, we did invoke the "electrostatic effects" of hypertonic saline to explain acutely stimulated mucociliary clearance after amiloride plus inhalation of hypertonic saline, because in vitro data suggested that little increase in airway surface liquid volume occurs in this situation because amiloride blocks water transport. During treatment with hypertonic saline without amiloride, however, isotonicity is restored rapidly (in approximately two minutes) in the airway lumen,[3] suggesting that both the acute and the sustained effects on mucociliary clearance of placebo or hypertonic saline were due to improved hydration of secretions, rather than to the persistence of a high salt environment.

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DR. RATJEN REPLIES: Drs. Kuver and Lee propose that the beneficial effect of inhaled hypertonic saline in cystic fibrosis may be due to the displacement by sodium of calcium ions bound to mucins, thereby reducing the viscosity of airway mucus. Hypertonic saline has indeed been shown to improve sputum rheology, and it is conceivable that changes in mucin ion composition contribute to this finding.[1] However, changes in the mechanical properties of mucus would not explain the prolonged effect of hypertonic saline on airway surface liquid height in vitro, since these experiments were performed in the absence of a mucus layer. In addition, agents that merely change the rheology of airway secretions do not affect mucociliary clearance in cystic fibrosis. This is highlighted by studies with recombinant human DNase, which reduces sputum viscosity but, unlike hypertonic saline, does not increase mucociliary clearance.[2,3] These observations would therefore support the concept that hypertonic saline, rather than acting primarily as a mucolytic agent, improves mucociliary clearance through an increase in airway surface liquid height.

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Illness in Returned Travelers

TO THE EDITOR: Freedman et al. (Jan. 12 issue)[1] has called attention to hazards for travelers. As the authors state, the study does not reflect the full epidemiology of travelers' diseases. There is a great danger that patients and practitioners who anticipate and strive to prevent the serious threats to health for travelers will mistakenly consider only infectious diseases. Physicians advising patients who are planning travel to tropical countries must warn them of the real burden of illness: premature death from injury.

In earlier studies of deaths of Americans overseas, some 10,000 deaths were analyzed according to cause, age, and place of occurrence.[2,3] There were 601 deaths from injuries and only 25 deaths caused by infectious diseases. Death rates from injuries in developing countries were considerably higher than those in the United States. Similar findings came from an earlier study involving Peace Corps volunteers.[4]

Travel clinics would be seriously remiss if they did not counsel travelers on the dangers of injuries. Advice to avoid motorcycles, small vehicles, unscheduled aircraft, and swimming in unfamiliar waters is essential to help protect travelers.[5]

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THE AUTHORS REPLY: We concur with the point made by Bishai and Baker. The literature indicates that about 25 percent of overseas deaths are from injury, with the remainder largely from natural causes.[1,2] MacPherson et al. estimated that about 36 percent of all overseas deaths are preventable.[1] As travel patterns have changed and adventure travel has increased, new studies are needed. An unanswered question is whether the risk of dying from causes other than natural ones while traveling overseas is different from that while staying home.

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Unprofessional Behavior among Medical Students

TO THE EDITOR: The real shocker in the report by Papadakis et al. (Dec. 22 issue)[1] regarding disciplinary action by medical boards is the enormous prevalence of unprofessional behavior among medical students in the control group (nearly 20 percent). If unprofessional students become unprofessional doctors, then we face a real crisis, with huge numbers of unprofessional physicians currently in practice.

Medical students are reflective of society at large. Lack of professionalism among medical students is hardly surprising when high schools