Correspondence

B-Type Natriuretic Peptide in Heart Failure

To the Editor: Maisel et al. (July 18 issue)[1] suggest the usefulness of measurement of B-type natriuretic peptide in the diagnosis of left ventricular dysfunction in patients with acute dyspnea, but their conclusions must be challenged. With a cutoff level of 50 pg per milliliter for B-type natriuretic peptide, the negative likelihood ratio was 0.04, allowing them to rule out the diagnosis. Conversely, the specificity (83 percent) and the positive likelihood ratio (5.1) obtained with a cutoff level of 150 pg per milliliter seem too low to confirm the diagnosis definitely, because the post-test probability of symptomatic left ventricular dysfunction increases from 49 percent to 83 percent, leaving 17 percent of cases still undiagnosed. A very similar positive likelihood ratio has been obtained in patients with a lower pretest probability of left ventricular dysfunction (32 percent),[2] thus supporting less optimistic conclusions concerning the diagnostic performance of the B-type natriuretic peptide value.

Furthermore, to overcome the imperfect sensitivity of echocardiography (the current gold standard), the authors based their diagnoses of left ventricular dysfunction on the clinical judgment of two cardiologists. However, it is unclear why a review of medical records should be more reliable than the probability assigned by the physician involved in the patient's care. In addition, the rate of agreement between these two diagnostic assessments, as well as the rate of agreement between the two cardiologists, should have been clearly evaluated and reported. Finally, the lack of longitudinal data makes it impossible to estimate the relation between B-type natriuretic peptide levels and the severity of left ventricular dysfunction or to evaluate the prognostic effectiveness of the measurement of B-type natriuretic peptide or its superiority over the easier and cheaper New York Heart Association classification.

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To the Editor: In their recent report, Maisel et al. have calculated their predictive values with a pretest probability of 47 percent. This is an extraordinarily high prevalence of disease and is reflective of the sick nature of the population studied for this report. It should be pointed out that with a different prevalence of disease, perhaps in a different clinical setting, the predictive values would be completely different. It is therefore important to clarify that these numbers would only be reproducible in clinical situations with a high prevalence of disease.

It should also be pointed out that the negative predictive value for a B-type natriuretic peptide level of 50 pg is associated with a false positive rate of nearly 40 percent. This makes it effective only as an initial screening test, with a more specific test required to confirm the diagnosis.

It is also obvious that the large standard deviations around the various means for different disease groups indicate the huge variance in B-type natriuretic peptide levels within the same disease group. This variation makes B-type natriuretic peptide less useful as a diagnostic tool, because the

range is not narrow enough to include a normal population within 2 SD of the mean. It does not, however, preclude the use of the test for prognostic purposes, with the use of the base-line measurement for an individual patient serving as a control value. Finally, it would have been much more informative to compare the odds ratio associated with B-type natriuretic peptide measurements with a cumulative odds ratio associated with history, physical findings, and radiographic abnormalities.

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To the Editor: Maisel et al. present data supporting previous observations that B-type natriuretic peptide levels are elevated in patients with left ventricular dysfunction. The question of the usefulness of this test in diagnosing heart failure in symptomatic patients is more complex.

As the authors note, the diagnosis of heart failure remains largely clinical, based on a pattern of signs, symptoms, and imaging studies. The important practical question is whether the measurement of B-type natriuretic peptide adds to the accuracy of the clinical diagnosis when it is in doubt. The authors do not report the diagnosis given to their study patients by emergency physicians; without this information, it is not possible to determine whether the measurement of B-type natriuretic peptide added diagnostic accuracy. If the emergency physician was already correct, no additional diagnostic information was provided by the B-type natriuretic peptide level.

Further reason for caution in interpreting B-type natriuretic peptide levels is that recent investigations have found elevated levels in patients with right ventricular dysfunction.[1,2] Thus, the attribution of elevated B-type natriuretic peptide levels in patients with dyspnea to left ventricular failure might lead to dangerous misdiagnosis in, for example, cases of pulmonary embolism.

Finally, the authors' analysis of odds ratios for clinical signs of heart failure appears to violate the maxim that studies of the accuracy of a test cannot examine tests that are diagnostic criteria for the disease in question.[3] For example, rales and cephalization of vessels are both included in the criteria for heart failure used in the Framingham Heart Study and the National Health and Nutrition Examination Surveys. Despite the promise of B-type natriuretic peptide as a marker of heart failure, it remains unclear at present which patients will benefit from its measurement and what the clinical implications of a single value — particularly if it is in the moderately elevated range — ought to be.

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The authors reply:

To the Editor: Four important points have been raised regarding our study and the use of B-type natriuretic peptide in the emergency diagnosis of congestive heart failure. In response to Hassan et al., we would note that sampling was an important issue, in that our population was broadly inclusive of adults who presented with acute dyspnea as a primary symptom. The prevalence of 47 percent for congestive heart failure exceeded our prediction of 30 percent and, hence, makes the important point that congestive heart failure was quite common as an underlying cause of dyspnea in one of the largest studies conducted in this area. The prevalence of the condition does drive the positive and negative predictive values, and given the frequency of congestive heart failure in our population, we believe our predictive-value statistics are quite stable.

Second, as Colli et al. and Hassan et al. point out, there are multiple issues raised by the forcing of a continuous measure such as B-type natriuretic peptide into binary "positive" and "negative" categories. As the B-type natriuretic peptide level decreases through its measurable range, the likelihood that heart failure is present in a given population also decreases. Conversely, as the B-type natriuretic peptide level increases, the likelihood that heart failure is present increases. Certainly, we embrace an integrative approach to the use of the B-type natriuretic peptide level along with clinical judgment in the diagnosis of congestive heart failure and do not support turning B-type natriuretic peptide into a binary variable for clinical use.[1]

Third, in response to Foote and Pearlman, the reference or gold standard for the diagnosis of congestive heart failure was agreement on that diagnosis by two cardiologists who independently reviewed the case, with all the clinical data assembled, 30 days after the encounter. These data included the response to treatment, additional diagnostic tests, and follow-up data that were not available to the emergency physician. Agreement between the two cardiologists was 90 percent, leaving 10 percent of cases to be adjudicated by a panel seeking consensus on the final diagnosis. The reference standard did not depend solely on standardized congestive heart failure scores; hence, the multivariate analysis for the outcome of congestive heart failure as determined by the reviewing cardiologists is valid.

Fourth, we have demonstrated in a subsequent publication how the B-type natriuretic peptide measurement would add to clinical judgment in the diagnosis of congestive heart failure.[1] The blood test will not replace the clinician but will enhance the speed and accuracy of the di-

agnosis in one of the most difficult settings — the emergency department.

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Toll-like Receptor 4 Polymorphisms and Atherogenesis

To the Editor: Kiechl and colleagues (July 18 issue)[1] provide interesting evidence that the toll-like receptor 4 (TLR4) 896G (299Gly) polymorphism may confer susceptibility to bacterial infection. As part of ongoing collaborative projects,[2-4] we have investigated the role of this polymorphism in a large United Kingdom study of invasive pneumococcal disease and a large West African study of pulmonary tuberculosis. There was no evidence of an association between the TLR4 896G allele and invasive pneumococcal disease or pulmonary tuberculosis (Table 1). These data add to the findings of Read et al.[5] that the TLR4 896G polymorphism was not associated with susceptibility to, or severity of, meningococcal disease. Together, they suggest that this polymorphism is likely to influence the course of infection only by specific organisms, not by a broad spectrum.

The study by Kiechl et al. included eight persons with putative bacterial infection who carried the TLR4 896G allele. It would be informative to know which infectious pathogens were identified in the study participants and how the authors' analysis might be affected by excluding those without confirmed bacterial infection. Exclusion of particular pathogens (for example, *Streptococcus pneumoniae, Mycobacterium tuberculosis,* and *Neisseria meningitidis*) might allow a clearer identification of significant biologic effects. The effects of the TLR4 polymorphism that have been identified to date have been small at best, and confirmation of an association with infectious disease will require large, well-designed studies with precise clinical and microbiologic phenotyping.

TABLE 1. ASSOCIATION BETWEEN THE TOLL-LIKE RECEPTOR 4 896G ALLELE AND INVASIVE PNEUMOCOCCAL DISEASE OR PULMONARY TUBERCULOSIS.

DISEASE	NONCARRIERS	CARRIERS	TOTAL
Invasive pneumococcal disease			
Cases — no. (%)	251 (83.7)	49 (16.3)	300
Controls — no. (%)	529 (84.0)	101 (16.0)	630
Total — no.	780	150	
Odds ratio		1.02	
P value		0.56	
Pulmonary tuberculosis			
Cases — no. (%)	773 (79.2)	203 (20.8)	976
Controls — no. (%)	709 (80.4)	173 (19.6)	882
Total — no.	1482	376	
Odds ratio		1.08	
P value		0.53	

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FOR THE TUBERCULOSIS, GENETICS, AND ENVIRONMENT (TBGENENV) AND THE OXFORD PNEUMOCOCCAL SURVEILLANCE STUDY GROUPS

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To the Editor: If "snake eyes" are thrown three times in a row ($P=0.000021$), can we conclude that the dice are loaded? Not if the dice have been rolled 3000 times, and triple snake eyes observed only once ($P=0.062$). The same principle makes us reluctant to accept the conclusion that the common white variant of TLR4 provides protection against atherosclerosis, as Kiechl and colleagues claim. They had many end points from which to choose — for example, femoral atherosclerosis was measured in the study population[1] but was not reported as a comparison in the article.

In a population studied previously,[2] 71 patients had undergone carotid endarterectomy. In contrast to the findings of Kiechl et al., the number of patients who had undergone endarterectomy and who were carrying the mutant TLR4 genotype was actually larger than the number of carriers in a set of matched controls (Table 1).

Even if statistically valid, a correlation may merely represent linkage with a nearby mutation that actually confers a risk, or it may be due to population structure; the prevalence of the compound TLR4 variant differs greatly between populations.[3] Small differences in the frequency of the TLR4 allele in phenotypically distinguishable groups may merely reflect residual inhomogeneity of the population that is being studied.

TLR4 evolved to detect lipopolysaccharide, a function that led to positional cloning of the gene in 1998.[4] Strong

TABLE 1. TLR4 PROMOTER GENOTYPES OF 70 PATIENTS WHO UNDERWENT CAROTID ENDARTERECTOMY AND 68 MATCHED CONTROLS.*

GENOTYPE	PATIENTS	CONTROLS	TOTAL
		number	
12874 A/A, 13174 C/C	62	62	124
12874 A/G, 13174 C/T	8	5	13
12874 A/A, 13174 C/T	0	1	1
Total	70	68	138

*Stored DNA from 71 patients who underwent endarterectomy was compared with DNA from 71 controls matched for age, sex, and ethnic background. Four samples could not be amplified on polymerase chain reaction.

circumspection is warranted with regard to other functions. Genotyping is easily achieved in large populations and may disclose risk factors for disease, but exceptional caution must be exercised when interpreting the data.

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The authors reply:

To the Editor: Cooke et al. report that the Asp299Gly TLR4 polymorphism is not associated with an increased risk of invasive pneumococcal infection, pulmonary tuberculosis, or meningococcal disease. The latter two types of infection are comparatively rare in Western countries and contribute little to the overall burden of severe acute infections. Although it is beyond doubt that TLR4 is not directly involved in the immune response to all pathogens, its relevancy to a broad spectrum of widespread and clinically relevant microorganisms (chlamydia, helicobacter, haemophilus, *Escherichia coli,* klebsiella, salmonella, porphyromonas, anaerobic pathogens, respiratory syncytial virus, candida, and many more) has been proposed. In our study, microbiologic phenotyping was not feasible for all infections for reasons such as pretreatment with antibiotics or a lack of cultures. This, however, does not diminish our finding of a significant association between the TLR4 polymorphism and the overall burden of severe acute infections in the general community.

Beutler and Beutler believe that we have selectively presented end points related to the TLR4 polymorphism and have omitted those without a significant association. We are surprised by such a statement, because our analyses followed a uniform protocol, and all main longitudinal end points were carefully considered. In fact, we observed a similar protective effect of the Asp299Gly TLR4 polymorphism in the development of femoral-artery atherosclerosis (Table 1).

TABLE 1. ASSOCIATION BETWEEN THE ASP299GLY TOLL-LIKE RECEPTOR 4 (TLR4) POLYMORPHISM AND INCIDENT FEMORAL-ARTERY ATHEROSCLEROSIS (1995–2000) IN THE BRUNECK STUDY.*

GENOTYPE†	SUBJECTS WITH INCIDENT FEMORAL-ARTERY ATHEROSCLEROSIS	ODDS RATIO (95% CI)‡	
		ADJUSTED FOR AGE, SEX, AND BASE-LINE ATHEROSCLEROSIS	MULTIVARIATE ADJUSTMENT§
	no./total no. at risk (%)		
TLR4 Asp299Gly$^-$	169/625 (27.0)	1.00	1.00
TLR4 Asp299Gly$^+$	5/46 (10.9)	0.32 (0.12–0.82)	0.30 (0.12–0.80)
P value		0.019	0.016

*Incident femoral-artery atherosclerosis was defined by the occurrence of new plaques in previously normal vessel segments. Data were available for 671 subjects.

†Subjects with Asp299Gly$^+$ Thr399Ile$^+$ (n=40) and Asp299Gly$^+$ Thr399Ile$^-$ (n=6) were grouped together because of the low number of subjects in the latter category.

‡The odds ratio and 95 percent confidence interval (CI) were derived from logistic-regression analysis, as described in our article.

§The analysis was adjusted for age, sex, levels of low-density and high-density lipoprotein cholesterol, lipoprotein(a), presence or absence of hypertension, smoking status, level of alcohol consumption, ferritin level, presence or absence of diabetes, presence or absence of microalbuminuria, and base-line femoral-artery atherosclerosis.

Beutler and Beutler further state that correlations may merely reflect a linkage with nearby mutations. This possibility cannot be ruled out, as we discussed in our article, but it seems unlikely, because the functional significance of the TLR4 polymorphism is well documented in vivo and in cellular transfection studies,[1] and the experimental and epidemiologic findings are highly consistent.

Finally, Beutler and Beutler present data from a small case–control study comparing patients who underwent carotid endarterectomy with controls. Even if we assume that this study is free from bias, that it is adequately powered, and that our Asp299Gly and their TLR4 promoter polymorphisms are functionally equivalent, the findings are not in conflict with ours, because they tested the wrong hypothesis: pathogenic mechanisms underlying vessel stenosis are substantially different from those involved in atherogenesis. We have previously shown that the development of carotid stenosis relies primarily on atherothrombosis and on procoagulant risk factors[2,3] and that this advanced stage in vessel disease is not significantly related to inflammation and infectious illness.[4]

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Bronchiolitis in Popcorn-Factory Workers

To the Editor: Kreiss et al. (Aug. 1 issue)[1] report a high incidence of bronchiolitis obliterans at a microwave-popcorn factory. The chemical diacetyl (2,3-butanedione) was singled out as a possible causal agent of this deadly condition and other medical problems found in workers in this plant. As a chemist, biochemist, and toxicologist, I would like to point out that 2,3-butanedione is in chemical equilibrium with 1,3-butane-diene-2,3-diol (Fig. 1, facing page). This phenomenon, which is well known in organic chemistry, is called keto-enol tautomerism. This isomer is expected to be very reactive with oxygen both at room temperature and on heating. Thus, 1,3-butane-diepoxide-2,3-diol would be expected as a product. Although the parent compound is known to be reactive with arginine, the diepoxide is of particular interest, since butadiene diepoxide is a known human carcinogen. The appropriate government agencies must investigate and evaluate whether diacetyl should be banned from food products.

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To the Editor: Kreiss and colleagues report frequent cases of bronchiolitis obliterans among workers in a popcorn plant that were attributed to the inhalation of the volatile ingredient diacetyl in the butter flavoring. Although this conclusion is in keeping with the toxic effects of diacetyl on the respiratory epithelium in animals, and although a dose–response relation (a decreasing forced expiratory volume in one second associated with increasing exposure to diacetyl) was established, it may not be the only causative agent. The workers who were affected the most were also exposed to the highest concentrations of other volatile compounds and respirable dust. Maize bran, glumes, and stigmas contain considerable amounts of tannins,[1] which are necessarily constituents of airborne particles. Inhaled tannins are considered to be an important causal factor in obstructive pulmonary diseases among workers exposed to dust of plant origin, such as those who work in cotton mills or grain elevators and those who work with herbal tea.[2] Therefore, tannins may be one of the substances implicated in the development of "popcorn worker's lung." This hypothesis is supported by the finding that clinical symptoms that follow the occupational inhalation of tannins are similar to those reported among popcorn workers. In addition, the lack of improvement in the symptoms with β_2-agonist bronchodilators is consistent with the inhibitory effect of tannin on adenylate cyclase in airway epithelial cells.[3]

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To the Editor: In his editorial (Aug. 1 issue),[1] Schachter comments on occupational airway diseases but leaves out what I think is an important finding described in the accompanying article by Kreiss et al. As the occupational physician involved in this case, I noted that not only was an epidemic of bronchiolitis obliterans present, but the number of tobacco smokers involved was unusually small.[2]

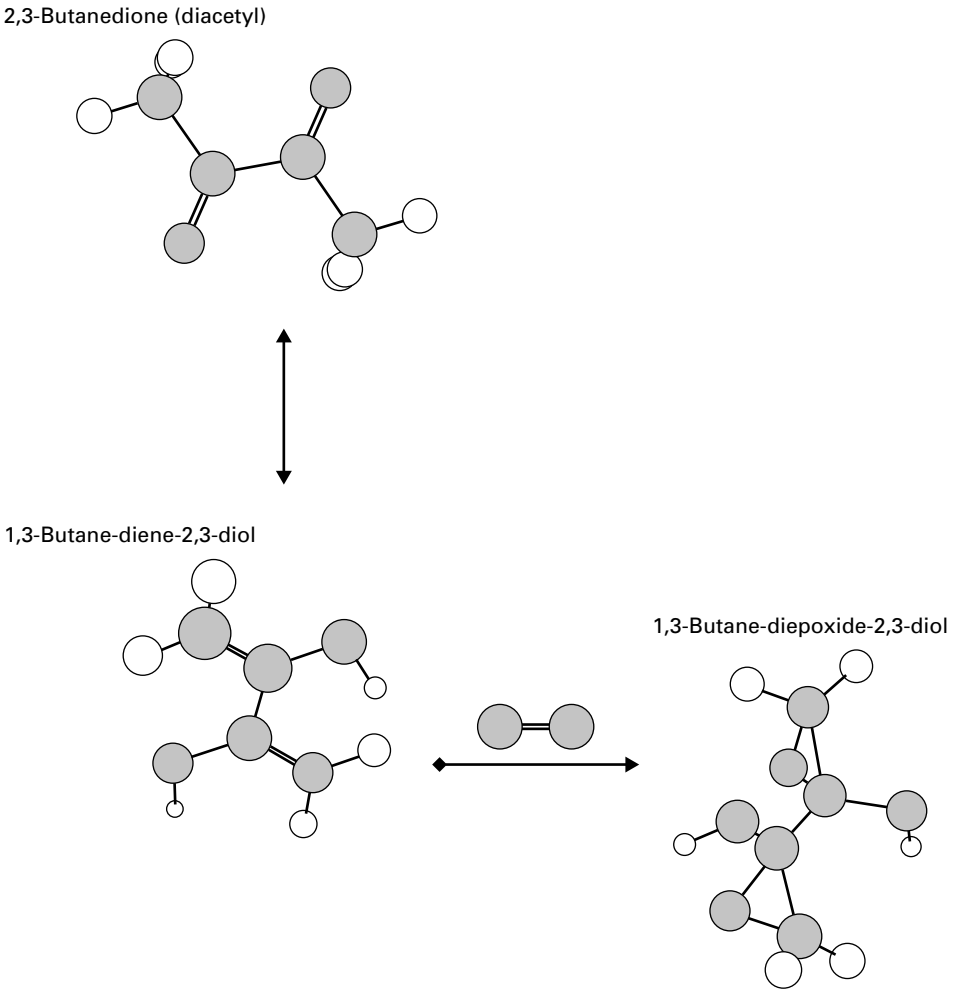

Figure 1. Chemicals 2,3-Butanedione and 1,3-Butane-Diene-2,3-Diol, and Their Expected Product, 1,3-Butane-Diepoxide-2,3-Diol.

Only one of the initial eight patients was a smoker. Nonsmokers were overrepresented among patients as compared with the exposed population. In the study population described by Kreiss et al., the workers who never smoked had a rate of airway obstruction that was three times as high as that among the smokers, although all workers were affected. An understanding of the mechanism of this protection could lead to preventive interventions.

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The authors and a colleague reply:

To the Editor: We used diacetyl as an index of exposure to volatile organic chemicals in the popcorn plant because it was the predominant one found in plant air. However, identification of the causal agent or agents in the flavoring will rely on studies in animals in which individual constituents are tested; such studies are now under way. Diacetyl is a leading candidate for investigation of potential respiratory toxicity because alpha-dicarbonyl compounds react with functionally reactive arginine residues in proteins and with guanine and inhibit superoxide dismutase and glutathione reductase, which are involved in protection from oxidative stress. In addition to Dr. Ezrailson's concern about the properties of a derivative diepoxide, diacetyl itself has been nominated for studies by the National Toxicology Program (NTP) because of widespread human exposure, limited evidence of mutagenicity, and relations to

carcinogens and mutagens in terms of structure and activity, as well as because diacetyl is representative of aliphatic alpha-diketones. (See the NTP Web site at http://ntp-server.niehs.nih.gov.)

We did not detect 1,3-butadiene-2,3-diol or 1,2;3,4-diepoxybutane-2,3-diol in any samples collected by thermal desorption tubes and analyzed with gas chromatography–mass spectrometry. However, we agree with Dr. Ezrailson that diacetyl would be present in equilibrium with its tautomers, as governed by the equilibrium constants for the conversions. Since diacetyl occurs naturally in butter and during the manufacture of alcoholic beverages, any proposed ban of diacetyl in food products raises issues of practicality.

As noted by Taubert and colleagues, other agents within the workplace may contribute to the clinical bronchiolitis obliterans seen in this workforce. Indeed, necrosis of the respiratory epithelium in the mainstem bronchus was more severe in rats exposed to butter-flavoring vapors than in rats exposed to diacetyl alone at a similar diacetyl concentration (unpublished data). We did not measure tannins. Workers managing the grain bins, presumably with greater exposure to organic dust, were in the low-risk group; mixers, who had almost no active contact with corn or its dusts, had the highest historical risk of fixed airway obstruction. The role of respirable salt dust in the airway damage found in microwave-popcorn production workers remains unclear. However, our observation that the same syndrome occurs in flavoring-production workers without exposure to grains or salt makes these agents less likely to be causal contributors.

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The editorialist replies:

To the Editor: Dr. Parmet points out an interesting but unexplained observation of his study and that by Kreiss et al. In his original study, nonsmoking workers accounted for the majority of index cases of bronchiolitis; among the workers studied by Kreiss et al., those who had never smoked had unusually high rates of airway obstruction. This latter finding is not particularly unusual, since a high prevalence of disease among nonsmokers is frequently used to confirm the presence of a true occupational or environmental effect.[1] What Parmet focuses on is the fact that although the frequency of airway obstruction in smoking workers in this cohort is increased (prevalence ratio, 1.6), it is not increased to the same extent as that among nonsmoking workers (prevalence ratio, 10.8). In occupational airway disease, the effect of the pollutant tends to be more pronounced among smokers, because the injury is frequently additive. Possible explanations for the lack of such an additive effect in this setting include a healthy-worker effect, by which sicker smoking workers would leave the industry at an early date, before the onset of bronchiolitis, and the possibility that cigarette smoking alters the deposition of inhaled particles[2] in such a way as to decrease the amount of other pollutants arriving in smaller airways. Further speculation is possible, but the primary public health message raised by these studies remains clear: injury to the airway in industries dealing with organic pollutants such as those associated with the manufacturing of microwave popcorn may be frequent, disabling, and occasionally life-threatening.

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Inflammatory Bowel Disease

To the Editor: In his review of inflammatory bowel disease (Aug. 8 issue),[1] Podolsky refers to interleukin-10 as a down-regulatory cytokine, citing findings in murine models. However, recent data do not support an antiinflammatory role for interleukin-10 in patients with inflammatory bowel disease. In this regard, Tilg et al. reported that recombinant interleukin-10 administered to patients with Crohn's disease increased the production of interferon-γ.[2] The inflammatory role of interleukin-10 found in their study paralleled the absence of significant benefits in clinical trials assessing the efficacy of high doses of recombinant human interleukin-10.[3,4] Such data reveal the complexity of the cytokine network in human inflammatory bowel disease, as well as the need for applying the findings of basic research to clinical practice cautiously.

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To the Editor: Podolsky states that probiotics may have a role in the treatment of inflammatory bowel disease. However, probiotics include many different preparations that are not equivalent in terms of efficacy. For example, available probiotics may contain bacteria at low, intermediate, or high concentrations (106 to 108, 109 to 1010, or 1011 or more colony-forming units per gram, respectively). Some preparations are made with only one bacterial strain; others, with two or more strains. Clinical studies of the use of probiotics with lactobacillus have shown variable results.[1-4] Thus, medical articles that refer to probiotics in a nonspecific manner may be misleading.

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Editor's note: Dr. De Simone reports that he is chief executive officer of VSL Pharmaceutical (Fort Lauderdale, Fla.). Dr. Famularo reports that he received an honorarium from VSL Pharmaceutical.

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To the Editor: In presenting various therapeutic options for the management of Crohn's disease, Podolsky briefly considers elemental nutrition, stressing the limited compliance with this approach. However, as discussed in a review by Ruemmele et al.,[1] such a nutritional approach can induce clinical remission and improve the growth failure associated with childhood Crohn's disease.[1,2] Moreover, a majority of young patients with growth failure are strongly motivated to accept tube feeding. The acceptance of this approach has increased with new oral formulas.[1]

Administration of thalidomide to patients with refractory Crohn's disease represents another important therapeutic option that is not emphasized in Podolsky's review. In our experience,[3] a low dose of thalidomide (0.5 to 2 mg per kilogram of body weight per day) was effective in inducing a sustained remission (two to five years) in patients with severe, refractory, corticosteroid-dependent Crohn's disease.

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To the Editor: In his extensive review of inflammatory bowel disease, Podolsky states that "surgery can have an important role in management, though a full consideration is beyond the scope of this review." This statement strikes me as inadequate and uninformative. It gives the reader the impression that surgical management is completely separate from medical management, which should not be so. Joint management based on both disciplines is the key to success in the care of patients with complicated disease.

Podolsky's discussion of the use of antibiotics is also incomplete. Metronidazole is an agent that should be considered for the prevention of postoperative relapse. In a randomized, controlled trial, metronidazole at a dose of 20 mg per kilogram of body weight given daily for three months after ileal resection significantly reduced the rate of endoscopic recurrence, to 52 percent as compared with 75 percent in the placebo group.[1] Further studies are required to confirm the benefit of longer-term treatment. Another trial[2] showed the efficacy of ornidazole at a dose of 1 g per day. This nitroimidazol antibiotic decreased the rate of endoscopic recurrence and also significantly diminished the rate of clinical recurrence.

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Dr. Podolsky replies:

To the Editor: In my review, I endeavored to highlight current concepts of the pathogenesis and approaches to treatment of inflammatory bowel diseases within the limited space available, with the intention that the article serve the needs of the general readership of the *Journal*. Therefore, in reply to Mohammed: space limitations did not permit a discussion of surgery, although the coordinated use of medical and surgical approaches is axiomatic for many clinical problems and not unique to inflammatory bowel disease. Although the data on the effect of metronidazole given for postoperative prophylaxis are interesting, the trial periods fall well short of the length needed to judge its value in routine care, and few would accept that its efficacy in this setting is proven.

Marchetti and colleagues are correct in noting that nutritional therapy may be more acceptable to children than

to adults and accordingly that such therapy may have a more important role in younger age groups. I disagree that thalidomide represents an important option. Although, as noted in the article, two pilot studies have suggested efficacy, the effects are modest. Larger, well-controlled trials of thalidomide in selected groups of patients over longer periods would be welcome. Famularo and colleagues are probably correct in suggesting that the efficacy of probiotics may depend on the composition of the agent being administered as well as other variables, including the type and location of disease, although the available data remain limited.

Finally, García de Tena et al. are correct in noting that the efficacy of interleukin-10 observed in clinical trials to date has been limited, if present at all. It is possible that better results may be obtained with the use of creative approaches currently being developed, in which greater local concentrations of this down-regulatory cytokine can be delivered. These approaches include both the use of engineered probiotic bacteria that can express interleukin-10 in the lumen of the gut and gene therapy.

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Illness after International Travel

To the Editor: The review by Ryan and colleagues (Aug. 15 issue)[1] about illness after international travel focuses mainly on tropical diseases, but common bacterial infections are a leading cause of illness in travelers.

Of 779 American travelers in one study, 202 (26 percent) reported 235 illnesses.[2] Diarrhea was the leading health problem (affecting 13 percent), followed by respiratory tract symptoms (in 10 percent) and skin problems (in 3 percent). The incidence of malaria was low (3.8 cases per 1000 travelers). In a retrospective Australian study of 232 consecutive patients, malaria was the most common diagnosis (incidence, 27 percent), followed by respiratory tract infection (24 percent), gastroenteritis (14 percent), dengue fever (8 percent), and pneumonia (6 percent).[3] In our series of 187 travelers, the most frequent diagnoses were malaria (44 percent), urinary tract infection (6 percent), gastrointestinal tract infection (5 percent), and respiratory tract infection (3 percent).[4] Bacterial skin infections are particularly important and ranked second in a prospective study of dermatologic conditions.[5]

Common bacterial infections are a growing cause of illness after travel.

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To the Editor: In their review of illness after international travel, Ryan et al. might have given more attention to the importance of psychological problems. From disabling anxiety attacks to frank psychosis, these problems often force termination of a trip to distant lands. The relative poverty, amazing cultural differences, and sometimes unusual environments (e.g., high altitude) can precipitate acute psychological problems that must be recognized and dealt with. Travel can be stressful.[1]

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The authors reply:

To the Editor: As Caumes and Bricaire point out, bacterial infections are frequent causes of illness after travel. In our review, we tried to emphasize the need for a standard history taking and physical examination and, where appropriate, evaluation of the urine, chest radiography, and evaluation of the stool for evidence of any infection. We also agree with Basnyat. Psychological stress related to travel can result in disabling psychological conditions.

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Abortion and Maternal Mortality in Africa

To the Editor: The World Health Organization (WHO) estimates that 5 million unsafe abortions are performed annually in Africa, resulting in the deaths of an estimated 34,000 women.[1] In Africa, abortion is illegal or very restricted, making it difficult to estimate the number of procedures performed or the frequency of associated complications including death.[2,3] In a large African multicenter study, we assessed the contribution of complications of abortion to maternal mortality.

TABLE 1. DISTRIBUTION OF OBSTETRICAL COMPLICATIONS AND MATERNAL DEATHS IN THREE AFRICAN COUNTRIES.

TYPE OF COMPLICATION	BENIN	IVORY COAST	SENEGAL	TOTAL	PREGNANCY-RELATED DEATHS	FATALITY RATE (95% CI)*
	no. (%)				no.	
First trimester						
Complications of induced abortion	117 (36.2)	824 (40.2)	584 (33.5)	1525 (37.1)	37	2.43 (1.68–3.24)
Complications of spontaneous abortion	119 (36.8)	680 (33.1)	1035 (59.4)	1834 (44.6)	1	0.05 (0.01–0.15)
Ectopic pregnancy	80 (24.8)	489 (23.8)	82 (4.7)	651 (15.8)	3	0.46 (0.06–1.00)
Molar pregnancy	7 (2.2)	59 (2.9)	40 (2.3)	106 (2.6)	1	0.94 (0.91–2.85)
Third trimester						
Major complications during delivery	605 (22.3)	1186 (43.8)	917 (33.9)	2708 (100.0)	79	2.92 (2.36–3.66)

*CI denotes confidence interval.

From May to October 1999, we prospectively enrolled all women admitted within 15 weeks after their last menstrual period for conditions including ectopic pregnancy, complications of spontaneous abortion, complications of induced abortion, and molar pregnancy in 12 main obstetrical hospitals in three African countries (Benin, the Ivory Coast, and Senegal). The study protocol was approved at all sites, and oral informed consent was obtained from all women. We also collected data on the number of deliveries, complications of delivery, and maternal deaths at these hospitals.

Information was obtained from medical records and through a confidential face-to-face interview. Many women are reluctant to acknowledge having had an induced abortion, especially in countries where abortion is illegal and punishable. To minimize misclassification of induced abortion as spontaneous abortion, all the interviewers were women who were trained to elicit information in a nonjudgmental and empathetic manner. This approach has been shown to improve the quality of information women provide concerning their reproductive histories.[4]

There were 4116 women admitted for obstetrical complications during the first trimester of pregnancy (Table 1). Of these, 1525 (37 percent) were admitted for complications of induced abortion, 1834 (45 percent) for complications of spontaneous abortion, 651 (16 percent) for ectopic pregnancies, and 106 (3 percent) for molar pregnancies. A total of 42 of these 4116 women died (Table 1); 37 (88 percent) of these deaths resulted from complications of induced abortion, confirming that complications of induced abortion are the leading cause of maternal death during the first three months of the pregnancy.

During the study period, 10,744 women were admitted for delivery, of whom 2708 (25 percent) had major complications (hemorrhage, sepsis, obstructed labor, uterine rupture, or high blood pressure). Of these 2708 women, 79 died. This fatality rate (3 percent) was similar to the fatality rate of 2.4 percent (37 of 1525) observed among women admitted for complications of induced abortion.

Our study included women who had major complications related to an abortion that necessitated hospitalization. Many women who have abortions have no or only minor complications that do not necessitate hospitalization. Some of the women who had major complications after an abortion may have been admitted to health facilities that were not included in our study. Nevertheless, members of the obstetrical staffs of private maternity hospitals or clinics in these regions regularly transfer women to the emergency obstetrical units that were included in our study. Thus, it is likely that we registered a large proportion of complications and deaths related to abortions in the regions we studied.[5]

Our results suggest that complications of induced abortion may be responsible for nearly a third of all maternal deaths in West African countries. These data suggest that previous WHO estimates that complications of abortion may account for about 15 percent of all maternal mortality should be revised upward.

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