

Correspondence



Exercise Capacity and Mortality

To the Editor: Myers et al. (March 14 issue)¹ report that in their study, exercise capacity was a stronger predictor of mortality than other established risk factors, after adjustment for several clinical variables. In an earlier article in the *Journal*, Cole et al. stressed the importance of recovery of the heart rate after exercise; in an analysis adjusted for many confounding variables, a low value for heart-rate recovery, defined as a reduction of 12 beats per minute or less from the heart rate at peak exercise (symptom-limited), was predictive of death from all causes (adjusted relative risk, 2.0; $P < 0.001$).² The same authors stated that in an analysis adjusted for age and sex, the heart rate at rest, before exercise, was predictive of the risk of death (hazard ratio, 1.29; $P < 0.001$).³

In the group of normal subjects studied by Myers et al., the resting heart rate was much higher in the subjects who died than in those who survived ($P < 0.001$),¹ but neither the resting heart rate nor heart-rate recovery after exercise was included in the multivariate regression analysis of mortality. The heart rate, especially during recovery, is a good marker of physical fitness,⁴ as demonstrated in the study by Cole et al. Thus, it is possible that inclusion of the heart rate as a variable would exclude exercise capacity from the Cox proportional-hazards model in the study by Myers et al. To clarify the respective roles of exercise capacity and heart rate, measured either at rest or after exercise, Myers et al. should re-analyze their data, taking into account this easily measurable variable.

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1. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793-801.
2. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351-7.
3. Lauer MS, Cote CR. Recovery of heart rate after exercise. *N Engl J Med* 2000;342:662-3.
4. Palatini P, Julius S. Heart rate and the cardiovascular risk. *J Hypertens* 1997;15:3-17.

To the Editor: Myers et al. used Cox proportional-hazards models to determine whether there was an independent association between exercise capacity and mortality. The results of such analyses depend on how the models were developed and particularly on the variables that were considered. However, none of this information is provided.

The authors do not describe the techniques used to develop the predictive models (e.g., stepwise procedures) or the criteria for inclusion or exclusion of variables. They do not state whether variables that were not in the final model — for example, previously established predictors such as obesity¹ and heart-rate recovery² — were considered or excluded. Finally, only limited information is provided on the definitions and coding of coexisting conditions, which can be important sources of confounding. For example, no definition of “mild pulmonary disease” is provided, nor is there information about the specific questions used to determine its presence. Thus, the clinical relevance of the increased risk associated with this variable and how its inclusion in the model may have influenced other estimates are unclear.

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1. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999;282:1547-53.
2. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351-7.

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To the Editor: Balady's editorial¹ on the finding by Myers et al. that physical fitness is linked to longevity is thoughtful and informative. However, in the opening paragraph, he suggests the erroneous (albeit enticing) notion that Charles Darwin reached a similar conclusion nearly 150 years ago. The concept of fitness in evolutionary terms has nothing to do with being in shape. Instead, it refers to unintentional, genetically determined adaptation to the environment that leads to success in sexual reproduction. In fact, Darwin argued that modifications in lifestyle are irrelevant in determining the survival of the fittest (and are downright Lamarckian): "with animals, as with plants, any amount of modification in structure can be effected by the accumulation of numerous, slight, and as we must call them accidental, variations, which are in any manner profitable, without exercise or habit having come into play. For no amount of exercise, or habit, or volition, in the utterly sterile members of a community could possibly have affected the structure or instincts of the fertile members, which alone leave descendants."² Assuming that the reduction in mortality from all causes in association with exercise, reported by Myers et al., reflects a substantial reduction in cardiovascular events, most people, physically fit or unfit, will have had children before any effect of exercise on survival has been realized.

Dr. Balady's editorial appears in a journal based in the biological sciences. Therefore, it is of symbolic importance — not only of semantic interest — that his reference to Darwin's theory be clarified.

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1. Balady GJ. Survival of the fittest — more evidence. *N Engl J Med* 2002; 346:852-4.
2. Darwin C. On the origin of species: a facsimile of the first edition. Cambridge, Mass.: Harvard University Press, 1975:242.

The authors reply:

To the Editor: Dr. Palatini notes that both the resting heart rate and heart-rate recovery after exercise have been shown to be strong predictors of mortality.¹⁻⁴ In our study, we addressed the role of both the resting heart rate and heart-rate recovery in predicting mortality. Although the resting heart rate was significantly higher among the subjects who died, it was not independently and significantly associated with the time until death according to a survival analysis. Because of space limitations, we were not able to present all the variables in the model in Table 3 of our article. With regard to heart-rate recovery, in 2001, we reported a study conducted with our data base that focused on this factor.¹ Our results were similar to those of other studies in that abnormal heart-rate recovery (which we defined as a reduction of less than 22 beats per minute two minutes after peak exercise) was a strong predictor of death, with a hazard ratio of 2.6 for the comparison with normal recovery. This risk was similar to that associated with low exercise capacity. Subjects with a peak value of less than 5 metabolic equivalents and an abnormal value for heart-rate recovery were at highest risk. Ko and colleagues are correct in pointing out that any

multivariate analysis is highly dependent on model development and the specific variables considered. The manuscript we originally submitted, which included more details about the model, was roughly twice the length of the final manuscript. Most of these details were deleted in order to meet the *Journal's* maximal word count. We used the term "standardized clinical definitions" to denote generally accepted definitions of risk factors (e.g., for obesity, a body-mass index [the weight in kilograms divided by the square of the height in meters] of 30 or more; for hypercholesterolemia, a cholesterol level that exceeds 220 mg per deciliter; and for mild pulmonary disease, a history of such disease, a forced expiratory volume in one second that is less than 75 percent of the predicted value, or both). Variables were included in the model only if they had previously been established as risk factors for cardiovascular disease or death from all causes.

In terms of model development, the best-performing variables according to univariate analysis were entered into the multivariate model in a stepwise fashion, with pretest variables (historical and risk-factor data) followed by exercise-test data. To keep the model as simple and clinically applicable to an exercise-laboratory setting as possible, detailed electrocardiographic variables in the resting state will be addressed in a separate report. We hope that this information clarifies the questions raised about our analysis of the association between exercise capacity and mortality from all causes.

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1. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol* 2001;38:1980-7.
2. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351-7.
3. Palatini P, Julius S. Heart rate and the cardiovascular risk. *J Hypertens* 1997;15:3-17.
4. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and exercise treadmill score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000;284:1392-8.

The editorialist replies:

To the Editor: My allusion to Darwin was not meant to misrepresent evolutionary theory; rather, it was meant to extrapolate broadly the concept of survival of the fittest to the contemporary notion of cardiovascular endurance "when fitness is measured and study subjects are followed for years."¹ These words were carefully chosen to highlight the important new data reported by Myers et al., which, added to the growing body of contemporary studies, provide more evidence of a link between higher levels of measured cardiovascular fitness and lower rates of mortality. Dr. Perlo's clarification of the term "fitness," as viewed by Darwin, is appropriate in order to provide a balanced perspective on these issues.

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1. Balady GJ. Survival of the fittest — more evidence. *N Engl J Med* 2002; 346:852-4.

Impaired Glucose Tolerance in Obese Children and Adolescents

To the Editor: The report by Sinha et al. (March 14 issue)¹ provides important and timely information about the association between impaired glucose tolerance and obesity in children. However, it is important to note that the study sample was derived from a clinic population that may not be the most representative sample suitable for deriving prevalence estimates. Moreover, it is interesting to note that in 1968 Paulsen et al.² reported a very similar finding. Using the same criteria of the American Diabetes Association (ADA) used by Sinha et al. in 2002, Paulsen et al. reported that 17 percent of the 66 obese children they studied had impaired glucose tolerance, and 6 percent met the criteria for type 2 diabetes.

Thus, the association of obesity with impaired glucose tolerance and type 2 diabetes in children may not be a new phenomenon. However, the number of obese children is increasing rapidly, especially in some ethnic groups.³ Thus, the absolute number of children in the population who have impaired glucose tolerance and type 2 diabetes is increasing because of the increased numbers of obese children. Future research should focus on why an accumulation of excess body fat becomes detrimental to health. Public health efforts should focus on reducing the prevalence of obesity among children, since this factor alone is likely to have a major effect on the current and future risk of type 2 diabetes.

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1. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802-10. [Erratum, *N Engl J Med* 2002;346:1756.]

2. Paulsen EP, Richenderfer L, Ginsberg-Fellner F. Plasma glucose, free fatty acids, and immunoreactive insulin in sixty-six obese children: studies in reference to a family history of diabetes mellitus. *Diabetes* 1968;17: 261-9.

3. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986-1998. *JAMA* 2001;286:2845-8.

To the Editor: Sinha et al. report that the prevalence of impaired glucose tolerance was 25 percent in children (4 to 10 years old), which was similar to the prevalence in the group of adolescents studied, who should also have had insulin resistance of puberty,¹ making impaired glucose tolerance more likely. Although the purpose of this study was not only to determine the prevalence of impaired glucose tolerance, these prevalence data were given prominence in the abstract and discussion. We suggest that the unexpectedly high prevalence of impaired glucose tolerance in the group of children who were 4 to 10 years old may be due to referral bias in favor of extremely overweight children, who may have already had evidence of dysmetabolic syndrome X.

We evaluated glucose tolerance in substantially overweight black children and white children (6 to 11 years old) who

TABLE 1. RESULTS OF METABOLIC STUDIES IN OVERWEIGHT CHILDREN AND CHILDREN OF NORMAL WEIGHT WHO WERE RECRUITED FROM THE COMMUNITY.*

VARIABLE	OVERWEIGHT (N=121)	NOT OVERWEIGHT (N=104)
Race — no.		
Black	52	30
White	69	74
Sex — no.		
Male	54	42
Female	67	62
Impaired fasting glucose — no. (%)†	0	0
Impaired glucose tolerance — no. (%)†	5 (4.1)	0
Age — yr	8.4±1.5	8.6±1.3
BMI		
Mean	27.0±5.8	17.0±1.7‡
Range	17–46	13–23
Standard-deviation score for BMI	4.3±2.5	1.2±1.4‡
Insulin-resistance index§	3.4±2.7	1.5±0.8‡
Insulin sensitivity¶	0.33±0.03	0.38±0.04‡
Insulinogenic index	0.17±0.14	0.07±0.04‡

*Children were recruited from the community for metabolic studies at the National Institutes of Health. Children were classified as overweight if they had a body-mass index (BMI), calculated as the weight in kilograms divided by the square of the height in meters, at or above the 95th percentile for age, sex, and race; children were classified as not overweight if they had a BMI between the 5th and 95th percentiles.² Plus-minus values are means ±SD.

†Impaired fasting glucose and impaired glucose tolerance were defined according to the criteria of the American Diabetes Association, as described by Sinha et al.³

‡P<0.05 by the t-test.

§The insulin-resistance index was calculated with the use of homeostatic model assessment; values are on a scale from approximately 1 to 15, with higher values indicating greater insulin resistance.⁴

¶Insulin sensitivity was calculated with the use of the quantitative insulin-sensitivity check index (QUICKI); values are on a scale from approximately 0.25 to 0.40, with higher values indicating greater sensitivity to insulin.⁴

||The insulinogenic index indicates pancreatic beta-cell function.⁵

were recruited from the local community and whose parents were not seeking treatment for the weight problem. The prevalence of impaired glucose tolerance was much lower in this group of children (4.1 percent; 95 percent confidence interval, 2 to 9 percent), even though they had significantly greater insulin resistance and a significantly higher index of beta-cell function than did children who were not overweight (Table 1). An evaluation of children in our cohort who had a mean (±SD) body-mass index of 32±5 (calculated as the weight in kilograms divided by the square of the height in meters), which was similar to the mean value in the cohort described by Sinha et al., showed that only 3 of 48 children had impaired glucose tolerance (6.3 percent; 95 percent confidence interval, 1 to 17 percent).

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1. Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. *J Clin Endocrinol Metab* 1991;72:277-82.
2. Must A, Dallal GE, Dietz WH. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht²) and triceps skinfold thickness. *Am J Clin Nutr* 1991;53:839-46. [Erratum, *Am J Clin Nutr* 1991;54:773.]
3. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802-10. [Erratum, *N Engl J Med* 2002;346:1756.]
4. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;85:2402-10.
5. Kosaka K, Hagura R, Kuzuya T. Insulin responses in equivocal and definite diabetes, with special reference to subjects who had mild glucose tolerance but later developed definite diabetes. *Diabetes* 1977;26:944-52.

To the Editor: We have recently studied the prevalence of impaired glucose tolerance and the relation between cardiovascular risk factors and levels of glycemia in 710 grossly obese Italian children and adolescents (age range, 6 to 18 years; mean age, 14 years; standard-deviation score for body-mass index, 3.8 ± 0.7), all of whom were of European origin for at least two generations. The frequency of impaired glucose tolerance and of type 2 diabetes was 4.5 percent and 0.1 percent, respectively — figures that are consistently lower than those reported by Sinha et al. in their cohort of obese American children. The obese Italian children had considerably lower values for insulin resistance, calculated by homeostatic model assessment, than their American counterparts. In a multivariate analysis, glucose values measured two hours after an oral glucose dose (1.75 g per kilogram) were significantly and independently related to insulin resistance ($P < 0.001$) and to insulin secretion, measured as the insulinogenic index ($P < 0.001$), suggesting that both an impaired insulin response and reduced insulin sensitivity contributed to the hyperglycemia in the Italian children. We believe that differences in ethnic background and in lifestyle and dietary habits may account for the striking disparity in the prevalence of impaired glucose tolerance between these two cohorts of obese children.

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To the Editor: It would be helpful if Sinha and colleagues would comment on the usefulness of screening 22 million obese children worldwide with an oral glucose-tolerance test rather than a simpler and less expensive method. Table 2 of their report shows a significant difference in the fasting insulin level between obese children and adolescents with normal glucose tolerance and those with impaired glucose tolerance. If this difference is consistent and reproducible, why not use the insulin-resistance index as a screening tool?

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To the Editor: The findings reported by Sinha et al. provide strong evidence that, even in childhood, obesity with its associated conditions represents an epidemic with substantial effects on public health. In the accompanying editorial by Rocchini,¹ the final paragraph, on effective strategies to combat obesity-related diabetes, contains a statement that concerns me. Rocchini notes that the prevention of obesity is an obvious strategy but states that “despite all our best efforts, prevention of childhood obesity eludes our grasp.” Rocchini suggests that a more effective strategy would be to identify obese children who are at high risk for diabetes on the basis of oral glucose-tolerance testing and to target them for intensive weight-loss treatment.

In my opinion, the solution to the obesity epidemic must be based on much broader public health and clinical strategies. The time has come to develop comprehensive national obesity-prevention programs that include educational, behavioral, and environmental components analogous to those already in place for tobacco use. Examples of effective prevention programs that focus on children and adolescents are school-based interventions designed to increase physical activity and consumption of healthier foods and home-based interventions designed to reduce television viewing.^{2,3} Physicians and other health care professionals, elected officials, educators, and parents need to recognize the impact of this major health problem and have the will and energy to correct it through preventive approaches.

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1. Rocchini AP. Childhood obesity and a diabetes epidemic. *N Engl J Med* 2002;346:854-5.
2. Gortmaker SL, Peterson K, Wiecha J, et al. Reducing obesity via a school-based interdisciplinary intervention among youth: Planet Health. *Arch Pediatr Adolesc Med* 1999;153:409-18.
3. Robinson TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA* 1999;282:1561-7.

Dr. Caprio replies:

To the Editor: I agree with Dr. Goran that prevalence rates are best derived from non-clinic-based samples. Of note is the recent school-based study by Grey et al.,¹ involving 42 obese adolescents whose parents were not seeking treatment. In this group, the prevalence of impaired glucose tolerance was 21.4 percent, and the prevalence of type 2 diabetes was 4.6 percent — findings that are very similar to ours. I disagree with Dr. Goran's statement that our findings were very similar to those reported by Paulsen et al. in 1968; they did not use the same ADA definitions that we used. When we recalculated the prevalence of impaired glucose tolerance in their study using the ADA criteria that we had used in our study, impaired glucose tolerance was present in 11 percent of the children, and 6 percent had type 2 diabetes mellitus.

The low prevalence of impaired glucose tolerance (6.3 percent) reported by Uwaifo et al. in obese children recruited from the community is probably due to a low insulin-resistance index. In fact, the mean insulin-resistance index in their obese children was 3.4 ± 2.7 , whereas in our children

it was 5 ± 0.6 in children with normal glucose tolerance and 7.2 ± 1 in those with impaired glucose tolerance.

Interestingly, Invitti et al. report that the cohort of children they studied, although grossly obese, had a considerably lower insulin-resistance index than our obese American cohort. As in our study, insulin resistance was found to be strongly and independently related to the glucose level at two hours. However, in contrast to our findings, the insulinogenic index was related to the glucose level at two hours. It is conceivable that our cohort was not large enough for us to detect differences in beta-cell function in patients with impaired glucose tolerance. We concur that differences in insulin resistance related to ethnic background and lifestyle may explain the striking disparity in the prevalence of impaired glucose tolerance between the two cohorts.

In response to Dr. Speiser's two important questions: we suggest that children with marked obesity undergo screening for fasting hyperinsulinemia and other features of the metabolic syndrome. The reproducibility of the insulin-resistance index (determined by homeostatic model assessment) is not known and varies greatly according to the method used to measure insulin and glucose levels. Furthermore, its predictive value in children needs to be determined.

We would also like to note that in our report, the values for proinsulin and for the ratio of proinsulin to insulin on page 806 and in Figure 2 are incorrect. All reported values for proinsulin and for the ratio of proinsulin to insulin should be divided by a factor of 10. In addition, the second part of the last sentence of the legend to Figure 2 should read, "to convert values for proinsulin to picomoles per liter, divide by 0.00939."

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The editorialist replies:

To the Editor: There are two commonly used strategies to combat a major public health problem such as adolescent obesity. One is a population-based strategy, as suggested by Dr. Gaenger. The other strategy is to identify persons at high medical risk (e.g., obese adolescents with impaired glucose tolerance) and target them for disease-specific therapy. The population-based strategy works well when the program is both effective in preventing or curing the problem and low in cost. An excellent example of an outstanding population-based strategy is the use of vaccinations to prevent childhood diseases. However, there is no effective low-cost treatment for childhood obesity. I agree with Dr. Gaenger that the time has come to develop comprehensive national obesity-prevention programs similar to programs aimed at tobacco use. However, until we have a prevention program that has been proved to reduce the incidence of childhood obesity significantly, I stand by my recommendation to identify obese

children who are at high risk for diabetes and target them for intensive weight-loss treatment.

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Bosentan for Pulmonary Hypertension

To the Editor: We would like to express our concern about the conclusions reported by Rubin et al. (March 21 issue)¹ in their article on bosentan therapy for pulmonary arterial hypertension. To prove the efficacy of bosentan for the treatment of pulmonary arterial hypertension, it would be logical to demonstrate a decrease in mean pulmonary-artery pressure. Such data have unfortunately not been presented. The authors have previously reported that bosentan significantly reduced mean pulmonary-artery pressure in patients with pulmonary arterial hypertension, but on close scrutiny of these data, the actual decrease in the pulmonary-artery pressure — from 54.0 to 52.4 mm Hg — seems clinically insignificant, although it was statistically significant.² Second, the authors demonstrated that the distance walked in six minutes increased by 36 m in the overall group of patients who received bosentan, as compared with a decrease of 8 m in the placebo group (an actual difference of only 30 m). It is difficult to consider this decrease clinically significant because the standard deviation of more than 73 m in all groups suggests a wide variability in their base-line exercise capacity.

Third, the authors suggest that bosentan therapy reduced the Borg dyspnea index from 3.3 to 3.2, which, on a scale of 0 to 10, appears to be clinically irrelevant. Finally, the authors suggested that bosentan improved functional status. In fact, although 42 percent of the bosentan-treated patients had an improvement in functional class, so did 30 percent of the patients in the placebo group. This, along with the lack of a dose-response effect in the bosentan-treated patients, suggests that this is unlikely to be a bosentan-related effect. In conclusion, more studies of bosentan as a treatment for pulmonary hypertension must be conducted before claims about its efficacy can be made.

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1. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903. [Erratum, *N Engl J Med* 2002;346:1258.]

2. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.

To the Editor: Rubin et al. report a high incidence of hepatic side effects during treatment with bosentan. However, the nature and extent of hepatotoxicity remain poorly de-

defined as "abnormal hepatic function." How many patients treated with bosentan had increases in aminotransferase to levels that were more than two times the upper limit of the normal range? Did the authors examine such factors as cholestasis or liver function in addition to aminotransferase levels? According to a recent report, at the molecular level, bosentan-induced hepatotoxic effects are due, at least in part, to inhibition of the major canalicular bile-salt-export pump.¹ Thus, serum bile-salt levels (and alkaline phosphatase levels) are most sensitive, whereas γ -glutamyltransferase levels are typically not elevated in patients with inherited or acquired dysfunction of the canalicular bile-salt-export pump.²

The authors state, "Treatment with 125 mg of bosentan twice daily was not associated with a significant increase in adverse events or with a change in their nature." However, in two patients, aminotransferase levels increased to more than eight times the upper limit of the normal range, which can be a sign of severe toxic hepatitis. We think that the risk of hepatotoxic effects should not be underestimated, especially since bosentan was administered for only 16 to 28 weeks in this study. Patients with pulmonary hypertension often present late in the course of disease, with right ventricular failure aggravating hepatic damage. The incidence and extent of liver injury may be higher in these patients and other subgroups of patients, indicating the need for comprehensive documentation of hepatic side effects.

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1. Fattinger K, Funk C, Pantze M, et al. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* 2001;69:223-31.

2. Jansen PL, Strautnieks SS, Jacquemin E, et al. Hepatocanalicular bile salt export pump deficiency in patients with progressive familial intrahepatic cholestasis. *Gastroenterology* 1999;117:1370-9.

The authors reply:

To the Editor: We disagree with Pereira and Salvi that the efficacy of treatment for pulmonary hypertension is dependent solely on the demonstration of a reduction in pulmonary-artery pressure. In pulmonary hypertension, both survival¹ and clinical improvement are related less to the degree of elevation in pulmonary-artery pressure than to right-heart function. Despite only small reductions in mean pulmonary-artery pressure (mean change, 6.7 mm Hg), continuous intravenous epoprostenol therapy significantly improves exercise capacity and measures of right-heart function and prolongs survival among patients with primary pulmonary hypertension.² Similar clinical and hemodynamic effects have been reported with bosentan by us and others.³

Although in our study the Borg dyspnea index decreased only slightly from the base-line value in the patients treated with bosentan, this finding should be viewed in the context of the clinically and statistically significant difference between the bosentan and placebo groups in the change from base line with regard to the distance walked in six minutes (a difference of 44 m between the two groups), suggesting that

the patients treated with bosentan were capable of walking farther with less dyspnea. Additional data supporting the efficacy of bosentan include the demonstration of sustained responses with long-term treatment⁴ and improvement in echocardiographic findings with regard to right ventricular function.⁵ The absence of a dose-response effect is not surprising in the light of the efficacy of endothelin-receptor blockade by bosentan in low doses. Thus, the efficacy of bosentan therapy for pulmonary hypertension has been demonstrated on the basis of hemodynamic data, exercise tolerance, and clinical status.

We agree that the risk of liver injury should not be underestimated. The Food and Drug Administration requires that patients taking bosentan be monitored by means of monthly liver-function tests.

Ten patients treated with 125 mg of bosentan twice a day had increases in aminotransferase levels to more than three times the upper limit of the normal range. Two of these patients had an increase in the alkaline phosphatase level that was more than twice the upper limit of the normal range, but bilirubin levels did not increase to values that were more than twice the upper limit of the normal range. Bosentan therapy was continued in all 10 patients, either at the same dose or at a dose of 62.5 mg twice a day. Aminotransferase levels returned to values that were less than twice the upper limit of the normal range in seven patients and decreased progressively in the other three patients. All 10 patients participated in the open-label extension study.

The mechanism responsible for the increase in liver aminotransferase levels has not been fully elucidated. On the basis of preclinical studies, an accumulation of bile acids in hepatocytes due to competitive inhibition of the bile-salt-export pump could play a part. However, hepatocellular injury and mixed hepatocellular and cholestatic injury have both been observed.

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FOR THE BOSENTAN RANDOMIZED TRIAL OF ENDOTHELIN
ANTAGONIST THERAPY STUDY INVESTIGATORS

Editor's note: Drs. Rubin, Galìè, and Simonneau have served as consultants and investigators for Actelion, the manufacturer of bosentan, and for several other companies involved with the development of pharmaceuticals to treat pulmonary hypertension.

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Treatment of Tobacco Use and Dependence

To the Editor: In her article on tobacco use (Feb. 14 issue),¹ Rigotti recommends that at every visit, clinicians routinely assess and record patients' smoking status and advise them to quit before assessing their readiness to change and offering stage-appropriate interventions. However well intentioned, this approach may have important adverse effects.

In a qualitative study, we found that patients were already well aware that they should quit smoking.² Being told that they should quit each time they went for health care was often counterproductive. For example, a 30-year-old woman said, "I found that when I've gone [to the doctor's office] for a bad ankle, he's said, 'You shouldn't smoke.' I think, 'Well, I haven't come about that.' There is a certain doctor I won't see . . . because of smoking. It's annoying when you go [to the doctor] for something and have a lecture." Some of our subjects avoided seeking health care at times in order to avoid anticipated interventions against their smoking. Asking patients' permission to raise the subject of smoking and establishing rapport are essential first steps. Telling patients what they already know takes time away from responding most effectively to each smoker's unique situation.³

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To the Editor: Rigotti does not address the question of smoking cessation immediately after an acute coronary event. The initiation of nicotine-replacement therapy is not advised after acute events. Although bupropion, with or without the use of nicotine patches, is recommended in the guidelines

of the American College of Cardiology and the American Heart Association as a treatment option for patients with stable cardiovascular disease,¹ its safety among patients who have had an acute coronary event has not been established, and its dopaminergic and noradrenergic effects warrant concern. A recent case report suggests that bupropion treatment may induce acute coronary syndromes and notes that the British Committee on the Safety of Medicines has received many reports of chest pain or tightness among patients for whom this medication was prescribed.² Only 20 to 60 percent of smokers who have had a myocardial infarction cease smoking without any pharmacologic intervention.³ More data are therefore needed to facilitate smoking cessation among these and other patients at high risk.

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Dr. Rigotti replies:

To the Editor: The concern raised by Drs. Butler and Rollnick is often expressed by clinicians. In contrast to their qualitative report, two quantitative studies provide reassurance that, in the aggregate, clinicians do not alienate smokers — even those who are not interested in quitting — by routinely addressing tobacco use at office visits.^{1,2} In both studies, smokers who recalled being asked about smoking and being advised to quit at their most recent office visit reported higher levels of satisfaction with their physicians and with the visit than smokers who did not recall receiving this advice. This was true even among smokers who were not interested in quitting smoking. It may be that patients have come to expect that an office visit will include an assessment of smoking status, just as they expect that their blood pressure will be measured. If there is no such assessment, they may wonder whether other important health issues are also being neglected. Nonetheless, Butler and Rollnick correctly point out that the way in which a physician addresses smoking matters. An abrupt or judgmental tone certainly alienates a smoker. Their own work suggests that physicians should take an empathic stance when delivering the message and avoid arguments, promote the patient's autonomy, and boost the patient's self-confidence.³

Drs. Gatt and Heyman correctly note that the safety of sustained-release bupropion in patients who have an acute coronary syndrome or who have recently had a myocardial infarction has not been established. This point is noted in the Food and Drug Administration's product information for the drug, which states that "care should be exercised if it is used in these groups" of patients.⁴ It is my impression

that the drug is commonly used in such patients, but as Gatt and Heyman note, data from smokers with an acute coronary syndrome or a recent myocardial infarction are lacking. Studies to address this gap are currently in progress.

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Reversible Chorea and Focal Dystonia in Vitamin B₁₂ Deficiency

To the Editor: A 71-year-old man presented in June 2000 with a two-month history of progressive right hemichorea. His medical history included a resection for gastric cancer at the age of 55 years. Neurologic examination revealed a postural, symmetric, rapid tremor of the hands; choreic movements of the right upper limb and right toes; and moderate hypopallesthesia in the four limbs. The results of laboratory tests showed a macrocytic anemia: erythrocytes, 4.15×10^6 per microliter (normal range, 4.7 to 6.1); mean corpuscular volume, 102.4 fl (normal range, 80 to 94); a normal hemoglobin level; and vitamin B₁₂, 124 pg per milliliter (normal range, 243 to 894). Tests for tumor markers; serologic tests for borrelia, *Treponema pallidum* hemagglutination, and human immunodeficiency virus types 1 and 2; and a genetic test for Huntington's disease were negative. Nuclear magnetic resonance imaging of the brain was normal.

A brief trial of amantadine was ineffective, but treatment with 300 g of tiapride daily resulted in an 80 percent reduction in the choreic movements until January 2001, when, over a period of three to four days, disabling, generalized chorea developed with blepharospasm-type focal dystonia and dysarthria in the absence of cognitive symptoms. The rest of the neurologic examination was unchanged. A new laboratory assessment showed 3.19×10^6 erythrocytes per microliter, a mean corpuscular volume of 106.1 fl, a hemoglobin level of 11.7 g per deciliter (normal range, 14 to 18), a vitamin B₁₂ level of 93 pg per milliliter, and a serum homocysteine level of 40.1 mmol per liter (normal range, <15); the blood copper level, folic acid level, and antistreptolysin ratio were in the normal range. A computed tomographic scan of the brain was normal, and no signal alteration was found on nuclear magnetic resonance imaging of the spinal cord. Electrophysiological investigation revealed a mild sensory neuropathy.

At the end of January, the patient started treatment with high doses of cyanocobalamin (5000 μ g daily for four weeks,

then twice weekly for an additional month, and once a month thereafter) in association with folic acid once a month and tiapride. A follow-up visit after two months showed residual involuntary movements of the toes, laboratory tests revealed 3.98×10^6 erythrocytes per microliter, a mean corpuscular volume of 99.3 fl, a vitamin B₁₂ level of 1306 pg per milliliter, and a serum homocysteine level of 17.6 μ mol per liter. Tiapride was stopped over a two-week period, and at follow-up visits in November 2001 and February 2002, involuntary movements were absent and the neurologic examination was normal.

Vitamin B₁₂ deficiency induces an increase in homocysteine, which is required for the methylation of the methionine.¹ The neurotoxic, *N*-methyl-D-aspartate-agonist action of homocysteine produces excitatory activity in the basal ganglia by means of the thalamocortical pathway² and leads to dystonia.³ The excess methyl levels in vitamin B₁₂ deficiency increase the levels of methyltetrahydrofolate, which acts as an agonist of kainic acid. In experiments in animals, this neurotoxin produces a pattern of damage similar to that seen in patients with Huntington's disease.^{4,5} With respect to our patient, these pathophysiological relations are only speculative, but the reversibility of the syndrome with cyanocobalamin supplementation is striking.

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Seizure Associated with Use of Visicol for Colonoscopy

To the Editor: Visicol has been prescribed more than 210,000 times since its introduction last year. The letter by Mackey et al. (June 27 issue)¹ describes four patients with seizures after the use of Visicol for colonic cleansing and suggests that the risk of seizures may be greater with this product than with other purgatives. We take issue with this suggestion.

All four patients discussed by Mackey et al. had severe hyponatremia, which was the most likely cause of their seizures. Hyponatremia could have resulted from sodium losses through gastrointestinal mechanisms or sweating, excessive free-water ingestion, and excessive secretion of antidiuretic hormone. Potential contributing factors not identified by

Mackey et al. include hypoparathyroidism, strenuous exercise during hot weather, the administration of two 20-tablet doses of Visicol two to three hours apart, and daily use of a laxative containing polyethylene glycol (PEG).

Neurologic dysfunction as a result of elevated antidiuretic hormone levels with hyponatremia has been reported after colonoscopy and the use of a PEG-containing product as a purgative.² Also, among 40 patients who received a PEG-containing product as a purgative, 25 percent had elevated antidiuretic hormone levels just before undergoing colonoscopy and 7.5 percent had hyponatremia just after undergoing colonoscopy.³ The investigators attributed the elevated antidiuretic hormone levels to the nausea, vomiting, and abdominal hyperactivity associated with the use of PEG-con-

taining purgatives; other possible causes include hypovolemia and hypotension.⁴

Neurologic symptoms of hyponatremia include confusion, somnolence, loss of consciousness, and seizures.⁴ The data base of the Food and Drug Administration indicates that all these adverse events, as well as others, have been attributed to the use of PEG-containing products (Table 1). The data suggest that sodium phosphate tablets and PEG-containing purgatives can cause hyponatremia, which in rare cases may lead to seizures. The growing adoption of a regimen involving reduced doses of sodium phosphate tablets and reduced volumes that is described by Rex et al.⁵ may further decrease the likelihood of hyponatremia and may have contributed to the apparent absence of new cases of seizures since August 2001.

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TABLE 1. SELECTED ADVERSE EVENTS IN THE FOOD AND DRUG ADMINISTRATION'S ADVERSE EVENT REPORTING SYSTEM AS OF OCTOBER 31, 2001, IN WHICH A PRODUCT CONTAINING POLYETHYLENE GLYCOL WAS THOUGHT TO BE A PRIMARY CAUSE.

ADVERSE EVENT	NO. OF PATIENTS*
Death	1
Seizure	5
Loss of consciousness	6
Stupor, somnolence, or confusion	7
Rigors	11
Water intoxication	2
Hyponatremia	3
Hypokalemia	6

*Each patient is counted only once.

Editor's note: InKine is the manufacturer of Visicol.

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