

Correspondence



Pulmonary Dead Space and Survival

To the Editor: Nuckton and associates (April 25 issue)¹ report an abnormally high dead-space fraction (the ratio of dead-space ventilation to tidal volume, or V_D/V_T) early in the clinical course of the acute respiratory distress syndrome. Their inference of a heretofore unrecognized functional abnormality is unwarranted, because V_D/V_T was assessed on the basis of carbon dioxide excretion with the usual Bohr–Enghoff equation. By definition, the patients had refractory hypoxemia, which reflects a severe imbalance between alveolar ventilation (V_A) and perfusion (Q), leading to a reduction in the efficiency of intrapulmonary gas transfer for both oxygen and carbon dioxide.² Thus, assessment of V_D/V_T on the basis of carbon dioxide excretion is sensitive to any imbalance in V_A/Q — notably, in the midrange of values for V_A/Q — and even shunt, although to a lesser extent.^{3,4} This fact depends on the carbon dioxide blood–air partition coefficient’s being relatively close to the normal range of V_A/Q .⁴ Specific assessment of high V_A/Q areas and “true” dead space is possible, although practical only in small numbers of subjects, with the multiple inert gas elimination technique. We found that in eight patients with the acute respiratory distress syndrome, the mean (\pm SD) value for V_D/V_T as measured on the basis of carbon dioxide excretion was considerably higher (0.64 ± 0.03) than the value as measured with the multiple inert gas elimination technique (0.37 ± 0.04).⁵ In only one of these subjects did we detect areas with high values for V_A/Q (range, 10 to 100). That V_D/V_T was more closely correlated with the outcome than was the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) remains a novel and highly relevant finding of the study by Nuckton et al. that may be due to the greater influence on the latter

index of factors not intrinsic to the lung — notably, FiO_2 and mixed venous oxygen content.

FRANÇOIS FEIHL, M.D.
University Hospital
1011 Lausanne, Switzerland
francois.feihl@chuv.hospvd.ch

CHRISTIAN MELOT, M.D.
SERGE BRIMIOULLE, M.D.
Erasmus University Hospital
1070 Brussels, Belgium

1. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346:1281-6.
2. West JB. State of the art: ventilation-perfusion relationships. *Am Rev Respir Dis* 1977;116:919-43.
3. Coffey RL, Albert RK, Robertson HT. Mechanisms of physiological dead space response to PEEP after acute oleic acid lung injury. *J Appl Physiol* 1983;55:1550-7.
4. Hlastala MP, Robertson HT. Inert gas elimination characteristics of the normal and abnormal lung. *J Appl Physiol* 1978;44:258-66.
5. Feihl F, Eckert P, Brimiouille S, et al. Permissive hypercapnia impairs pulmonary gas exchange in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000;162:209-15.

To the Editor: Nuckton et al. report an association between an elevated physiological dead-space fraction and a high mortality rate among patients with the acute respiratory distress syndrome. Although these results are consistent with those I have reported,¹ I am concerned that the method the authors used to measure dead-space fraction is inaccurate. In their report, the effect of compressed volume on the measurement of the dead-space fraction was poorly addressed. In the patients who died, as compared with those who survived, quasistatic respiratory compliance was much lower, indicating that more volume was compressed in the ventilator, and hence more dilution of mixed gases took place, resulting in an overestimation of the dead-space fraction. In some patients, the authors tried to correct this effect by applying a correction factor. Instead, the compressed volume should have been separated by using a Frumin valve.²

Also, the effect of intrapulmonary shunt on the measure-

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article and 400 words in all other cases (please provide a word count). •The letter must have no more than five references and one figure or table. •The letter must be signed by no more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Include your full mailing address, telephone number, fax number, and e-mail address. •Letters to the editor may be submitted over the Internet at <http://secure.nejm.org/letters>. You may also send us your letter by standard mail or fax.

Our address: **Letters to the Editor • New England Journal of Medicine • 10 Shattuck St. • Boston, MA 02115**

Our Web address: <http://secure.nejm.org/letters>

Our fax numbers: **617-739-9864** and **617-734-4457**

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.

ment of the dead-space fraction was completely ignored. In the presence of intrapulmonary shunt, Enghoff's modification of the Bohr equation overestimates the dead-space fraction.³ Since the ratio of PaO₂ to FiO₂ was higher in the patients who died, indicating higher shunt, an overestimation of the dead-space fraction would be more significant. Considering that the mean difference in the dead-space fraction between the two groups was only 0.09, which was the same as 1 SD, correction for the two effects, gas compression and intrapulmonary shunt, may nullify the difference. Nevertheless, in acute respiratory failure, right ventricular function is the chief determinant of the dead-space fraction.^{1,4}

CHARLES HER, M.D.
New York Medical College
Valhalla, NY 10595

1. Her C. Right ventricular stroke-work: an index of distribution of pulmonary perfusion in acute respiratory failure. *Chest* 1983;84:719-24.
2. Forbat AF, Her C. Correction for gas compression in mechanical ventilators. *Anesth Analg* 1980;59:488-93.
3. Kuwabar S, Duncalf D. Effect of anatomic shunt on physiologic dead-space-to-tidal volume ratio: a new equation. *Anesthesiology* 1969;31:575-7.
4. Her C, Lees DE. Accurate assessment of right ventricular function in acute respiratory failure. *Crit Care Med* 1993;21:1665-72.

To the Editor: The study performed by Nuckton et al. was a prospective cohort study. They report an alarming escalation in the risk of death, an odds ratio of 1.45 (95 percent confidence interval, 1.15 to 1.83), for every 0.05 increase in the dead-space fraction.

Odds ratios are increasingly being reported because of widespread use of logistic regression. However, the odds ratio is a difficult concept, and clinicians often interpret it as an approximation of the relative risk. Although it is best to think of the odds ratio as a measure in its own right, the relative risk should be reported whenever it is feasible to do so, especially when the prevalence of the outcome of interest in the unexposed group is high.^{1,2} In fact, except in case-control studies, the relative risk can be estimated in most studies.^{3,4}

With the use of the method suggested by Zhang and Yu,⁴ the relative risk and its 95 percent confidence interval can be estimated on the basis of the odds ratio generated from a logistic-regression model: relative risk = odds ratio ÷ [(1 - PO) + (PO × odds ratio)], where PO represents the prevalence of the outcome of interest in the unexposed group.

The prevalence of death in the cohort studied by Nuckton et al. was fairly high (42 percent). With the use of the above equation, the relative risk of death in this study would be 1.22 (95 percent confidence interval, 1.08 to 1.36) for every 0.05 increase in the dead-space fraction. This figure is significantly lower than the odds ratio reported by Nuckton et al. and provides a clearer interpretation of the actual relative risk associated with an elevated dead-space fraction in patients with the acute respiratory distress syndrome than does the odds ratio.

KWOK M. HO, M.B., B.S.
North Shore Hospital
Auckland 1309, New Zealand
mingk@whl.co.nz

1. Deeks J. When can odds ratios mislead? Odds ratios should be used only in case-control studies and logistic regression analyses. *BMJ* 1998;317:1155-6.
2. Altman DG, Deeks JJ, Sackett DL. Odds ratios should be avoided when events are common. *BMJ* 1998;317:1318. [Erratum, *BMJ* 1998;317:1505.]
3. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ* 1998;316:989-91.
4. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-1.

To the Editor: Nuckton et al. demonstrate the use of measurements of pulmonary dead space in patients with the acute respiratory distress syndrome as a disease-specific index of risk stratification. Although injury to the pulmonary microcirculation with resulting thrombosis has been well described in this syndrome,¹ another mechanism for increased dead space is low cardiac output. As cardiac output declines, the fall in lung perfusion yields lung units that are ventilated without perfusion. In the setting of mechanical ventilation, cardiac output is often reduced because of decreased venous return caused by positive intrathoracic pressure. Thus, an elevated dead-space fraction may be a reflection of inadequate volume resuscitation. Increased pulmonary dead space early in the acute respiratory distress syndrome should prompt a search for the underlying cause (e.g., excessive extrinsic or intrinsic positive end-expiratory pressure, relative hypovolemia, microcirculatory thrombosis, or pulmonary embolus), with therapy targeted to the identified cause. This measurement could be used as a simple screening technique early in the course of the acute respiratory distress syndrome to identify patients who may benefit from interventions. Maximization of cardiac output with early aggressive resuscitation can lead to a significant reduction in mortality.² Late in the disease, however, increases in oxygen delivery are probably unhelpful, because of mitochondrial failure in tissues.^{3,4} This simple, safe, and inexpensive measurement deserves further study.

SANJAY R. PATEL, M.D.
R. SCOTT HARRIS, M.D.
ATUL MALHOTRA, M.D.
Harvard Medical School
Boston, MA 02115
spatel@partners.org

1. Tomaszefski JF Jr, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol* 1983;112:112-26.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
3. Schwartz DR, Malhotra A, Fink MP. Cytopathic hypoxia in sepsis: an overview. *Sepsis* 1999;2:279-89.
4. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995;333:1025-32.

To the Editor: Nuckton et al. calculated the dead-space fraction by measuring the mean expired carbon dioxide fraction with the use of a bedside metabolic monitor, at a standard tidal volume of 10 ml per kilogram of ideal body weight. Tidal volumes for some patients were altered for 10 minutes before and during the period of measurement. We wonder why the authors used a tidal volume of 10 ml per kilogram. It is troubling, since the use of a tidal volume of 6 ml per kilogram has been shown to improve survival and decrease

the number of days of ventilatory support in patients with the acute respiratory distress syndrome.¹

Although it has not been proved that a temporary change in the tidal volume, to 10 ml per kilogram, may be deleterious, it is disturbing that the researchers, as well as their institutional review board, did not consider such a change important enough to require informed consent. It is an axiom of good research and protection of patients' rights that even an apparently trivial and noninvasive measurement should be explained to the patient, a surrogate, or both. Such measurements should be clearly outlined in the informed-consent document. The authors' suggestion that noninvasive measurement of the dead-space fraction is routinely used for nutritional assessment does not relieve them of their obligation to obtain informed consent when the measurement is performed for research purposes. Furthermore, when the dead-space fraction is measured for the purpose of nutritional assessment, it is not necessary to measure it routinely at a tidal volume of 10 ml per kilogram.

TAEK SANG YOON, M.D.
YIZHAK KUPFER, M.D.
SIDNEY TESSLER, M.D.
Maimonides Medical Center
Brooklyn, NY 11219
stessler@maimonidesmed.org

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.

The authors reply:

To the Editor: As several of the letters suggest, the mechanisms that account for the increase in V_D/V_T early in the course of the acute respiratory distress syndrome need to be more thoroughly determined. We could not assess the contribution of cardiac output and intrapulmonary shunt because it was not feasible to insert pulmonary-artery catheters in the 179 patients in our study. Future studies should more clearly define the relation between V_D/V_T and cardiac output, shunt, and perhaps most important, pulmonary vascular resistance early in the course of the acute respiratory distress syndrome.

Patel and colleagues cite a recent study that demonstrated the value of volume resuscitation in patients with sepsis,¹ not the acute respiratory distress syndrome. The value of an increase in cardiac output in patients with the acute respiratory distress syndrome is not known. The Acute Respiratory Distress Syndrome Clinical Network of the National Institutes of Health is carrying out a large, prospective, multicenter trial to evaluate a conservative fluid strategy as compared with a liberal fluid strategy, guided by hemodynamic measurements with either a pulmonary-artery catheter or a central venous catheter, in patients with acute lung injury (<http://www.ardsnet.org>). The results of this study should provide new information about the relations among cardiac output, intravascular volume, and mortality in patients with the acute respiratory distress syndrome.

Correction for compressible volume of the ventilator circuit was performed with the use of established methods in

all patients, not just some patients, as Her suggests. We repeated the statistical analysis using corrected values for all patients; as we reported, the results remained significant. Previous studies, including one by Forbat and Her,² have shown that measurement of V_D/V_T without the Frumin valve is accurate. Furthermore, Forbat and Her suggested that the Frumin valve may cause expiratory obstruction and compromised cardiac output when positive end-expiratory pressure is applied.² Although intrapulmonary shunt was not measured, the ratio of PaO_2 to FiO_2 was entered into all multiple logistic-regression models, and the association between V_D/V_T and mortality was independent of the degree of hypoxemia.

Measurements of expired carbon dioxide are safe, routine, and noninvasive, and the requirement for informed consent was waived. All patients were studied before publication of the results of the low-tidal-volume trial of the National Institutes of Health,³ at a time when there was no clear evidence that lower tidal volumes were efficacious. In fact, one group had reported that ventilation with a lower tidal volume (7 ml per kilogram) was not beneficial.⁴ Thus, at the time of our study, 10 ml per kilogram was considered to be an intermediate and safe tidal volume for patients with the acute respiratory distress syndrome.

We chose to report odds ratios, which is standard practice for reporting the results of logistic-regression analyses. The formula used by Dr. Ho to calculate the relative risk⁵ was designed for use with dichotomous predictor variables, not with continuous predictor variables such as V_D/V_T .

THOMAS J. NUCKTON, M.D.
MARK D. EISNER, M.D., M.P.H.
MICHAEL A. MATTHAY, M.D.
University of California, San Francisco
San Francisco, CA 94143-0130
tomnuc@itsa.ucsf.edu

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
2. Forbat AF, Her C. Correction for gas compression in mechanical ventilators. *Anesth Analg* 1980;59:488-93.
3. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
4. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998;338:355-61.
5. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-1.

Neuroblastoma Screening in Early Life

To the Editor: In their discussion, Schilling et al. (April 4 issue),¹ noting that screening for neuroblastoma at six months of age in Japan was reported to result in high survival rates among patients whose disease was detected by screening, as well as in reduced mortality as compared with that in a historical control group, expressed the concern that the ascertainment of cases among the screened cohorts in Japan was not complete. We have addressed this question and found no differences in the cumulative incidence of ad-

vanced-stage neuroblastoma and the cumulative mortality rates for neuroblastoma between screened and unscreened children in the Kyushu area in Japan.² We concluded that mass screening at six months of age in Japan did not substantially improve the unfavorable prognosis for patients with neuroblastomas that were identified after one year of age, which is the primary purpose of such mass screening. Thus, the results of our study in Japan are consistent with the conclusions of Schilling et al. and Woods et al. (April 4 issue).³

SACHIYO SUITA, M.D., PH.D.

Kyushu University
Fukuoka 812-8582, Japan
suito@pedsurg.med.kyushu-u.ac.jp

- Schilling FH, Spix C, Berthold F, et al. Neuroblastoma screening at one year of age. *N Engl J Med* 2002;346:1047-53.
- Suita S, Tajiri T, Akazawa K, et al. Mass screening for neuroblastoma at 6 months of age: difficult to justify. *J Pediatr Surg* 1998;33:1674-8.
- Woods WG, Gao R-N, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med* 2002;346:1041-6.

To the Editor: Schilling et al. and Woods et al. report substantial overdiagnosis, a high incidence of false negative cases (i.e., negative results on screening in children who subsequently presented with disease), and a high mortality rate among the children with false negative results. We conducted a similar study in Austria between 1991 and 2000, targeting infants between 7 and 12 months of age.¹ The rates of false negative cases (3.5 per 100,000 screened infants) and mortality (0.95 per 100,000) were similar to those in the study by Schilling et al., but the follow-up time was longer. There were 3 deaths in our screened cohort (a total of 313,860 children); all 3 children who died had been screened in the early years of the study (between 1991 and 1994), and all the deaths were related to therapy.

We are concerned about the relatively high mortality rate in the screened cohort in the study by Schilling et al. within a short follow-up period. The authors do not report how many of these deaths were due to the disease itself and how many were due to complications of therapy.

Given our own observations¹⁻³ and the excess of cases of stage 4 disease in patients who did not undergo screening in the trial by Schilling et al. although they were living in a screening area, we conclude that a good proportion of neuroblastomas that are likely to progress may be detected at a preclinical phase.

It may be speculated that high rates of complications of therapy and therapy-related deaths may diminish the potential benefit of screening for neuroblastoma. This problem could perhaps be overcome by careful consideration of less life-threatening, "patient-tailored" therapies (e.g., less aggressive surgery and chemotherapy, as well as additional non-cytotoxic treatment).

REINHOLD KERBL, M.D.
CHRISTIAN E. URBAN, M.D.

University of Graz
A-8036 Graz, Austria

PETER F. AMBROS, PH.D.
Children's Cancer Research Institute
A-1090 Vienna, Austria

- Kerbl R, Urban CE, Ladenstein R, et al. Neuroblastoma screening in infants postponed after the sixth month of age: a trial to reduce "overdiagnosis" and to detect cases with "unfavorable" biologic features. *Med Pediatr Oncol* 1997;29:1-10.
- Ambros PF, Ambros IM, Kerbl R, et al. Intratumoural heterogeneity of 1p deletions and MYCN amplification in neuroblastomas. *Med Pediatr Oncol* 2001;36:1-4.
- Powell JE, Esteve J, Mann JR, et al. Neuroblastoma in Europe: differences in the pattern of disease in the UK. *Lancet* 1998;352:682-7.

To the Editor: Woods et al. and Schilling et al. report that screening for neuroblastoma at 3 weeks, 6 months, or 12 months of age does not reduce mortality from neuroblastoma. The authors believe that screening detected tumors that would have regressed or would have matured into ganglioneuromas. Can the authors ascertain from their data bases — or that in Japan, where screening of newborns for neuroblastoma is required — whether the incidence of ganglioneuroma in fact decreases in screened populations?

MARGARET H. COLLINS, M.D.

Cincinnati Children's Hospital Medical Center
Cincinnati, OH 45229
margaret.collins@chmc.org

To the Editor: In his editorial on newborn screening (April 4 issue),¹ Dr. Cunningham underscores the need for increased federal-state coordination in establishing guidelines and systems for newborn screening. At present, the paucity of national oversight has resulted in a system that does not equitably meet the needs of all children. For example, although all states screen for phenylketonuria and congenital hypothyroidism, many infants are born in states that still do not screen for treatable disorders such as homocystinuria or congenital adrenal hyperplasia. States with inadequate screening programs put their children at avoidable risk for lifelong disability or death.

Addressing these disparities, the March of Dimes has recommended that states screen all newborns for at least a core group of eight specific metabolic disorders for which intervention is available and in which delayed treatment could adversely affect the infant.² These disorders are phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, maple syrup urine disease, galactosemia, homocystinuria, and sickle cell disease. This recommendation for minimal screening was recently updated to include testing for a ninth specific metabolic disorder, medium-chain acyl-coenzyme A dehydrogenase deficiency, as well as screening for hearing abnormalities.

NANCY S. GREEN, M.D.

March of Dimes
White Plains, NY 10605
ngreen@marchofdimes.com

- Cunningham G. The science and politics of screening newborns. *N Engl J Med* 2002;346:1084-5.
- Howse JL, Katz M. The importance of newborn screening. *Pediatrics* 2000;106:595.

The authors reply:

To the Editor: Dr. Suita correctly notes that, as discussed in our report, there have been small, retrospective studies

questioning the value of neuroblastoma screening in Japan. Unfortunately, such reports have not convinced health officials in Japan that the mandatory screening program there has not been effective in reducing mortality from neuroblastoma.

On the basis of our data, we disagree with Kerbl et al. that “a good proportion of neuroblastomas that are likely to progress may be detected at a preclinical phase.” There were no deaths in the infants in Quebec whose neuroblastomas were detected preclinically. The study by Kerbl et al.¹ evaluated 100,000 infants (27 percent of a birth cohort) in an uncontrolled fashion.

Dr. Collins raises the interesting question of whether preclinical detection of neuroblastoma reduces the incidence of ganglioneuroma. Because of the low incidence and logistic issues related to ascertainment, we did not attempt to determine the incidence of these benign tumors. Given that the incidence of ganglioneuroma is only a small fraction of that of neuroblastoma, it is likely that neither our study nor the study by Schilling et al. would have the power to support definitive statements regarding the effect of screening on the incidence of ganglioneuroma.

Screening for diseases among populations of newborns has, to varying degrees, become established policy because of both the availability of a screening test and the assumption that it will improve public health. This approach has resulted in the lack of uniformity in neonatal screening in the United States that is noted by Dr. Green. We agree with Dr. Cunningham’s recommendation that the value of various screening assays in general be investigated before a screening program is implemented.

We believe that our study and that of Schilling et al. confirm the value of large, prospective, controlled trials in answering questions regarding the efficacy of such screening. Perhaps these two population-based studies with strikingly similar results will convince health authorities in countries that require neuroblastoma screening to reconsider this policy.

WILLIAM G. WOODS, M.D.

Emory University
Atlanta, GA 30322
william.woods@choa.org

MARK BERNSTEIN, M.D.

Hôpital Sainte-Justine
Montreal, QC H3T 1C5, Canada

LESLIE L. ROBISON, PH.D.

University of Minnesota
Minneapolis, MN 55435

1. Kerbl R, Urban CE, Ladenstein R, et al. Neuroblastoma screening in infants postponed after the sixth month of age: a trial to reduce “overdiagnosis” and to detect cases with “unfavorable” biologic features. *Med Pediatr Oncol* 1997;29:1-10.

To the Editor: Suita mentions the results of a retrospective Japanese study that are similar to ours and particularly similar to those of the study by Woods et al., with a similar screening age. It is especially interesting that no improve-

ment in mortality was observed. Since a historical control group was used, at least some reduction in mortality over time related to improvement in treatments could have been expected. But a more recent study from Japan confirms these results.¹

Kerbl et al. are concerned about the relatively high mortality rate in the screened group in our study. As compared with the mortality in previous birth cohorts, that reported thus far in our study is actually somewhat lower than would be expected; it is certainly not unusually high. Most of the 33 deaths registered in the screened group up to June 30, 2001, occurred in nonparticipants (16 of the 33) or in children with a false negative result on screening (14 of the 33).

As we stated in our article, there were only three treatment-related deaths among screened patients. Even if the treatment-related deaths in the screened group had not occurred, the mortality in the screened group or in the screening area would not be significantly lower than in the control area. Although it is too early for us to draw final conclusions about mortality because follow-up for this end point is still insufficient, the similarity in the incidence of stage 4 disease in the screened and unscreened groups makes it unlikely that there will be major differences in mortality between the groups.

We fully agree with the statement that, especially in the light of the high rate of overdiagnosis, movement toward “patient-tailored” therapies is an important challenge. This issue is addressed by an ongoing German trial of neuroblastoma treatment in which chemotherapy is avoided in half the patients.²

Collins asks whether changes in the incidence of ganglioneuroma could be observed in the screened populations in Germany or Japan. Since ganglioneuroma is not classified as a malignant disease by the *International Classification of Diseases*, data that would allow us to answer this question are not collected systematically in Germany.

FREIMUT H. SCHILLING, M.D.

Olgahospital Klinikum Stuttgart
70176 Stuttgart, Germany
f.schilling@olgahospital.de

CLAUDIA SPIX, PH.D.

German Childhood Cancer Registry
55131 Mainz, Germany

FRANK BERTHOLD, M.D.

University Children’s Hospital
50924 Cologne, Germany

1. Yamamoto K, Ohta S, Ito E, et al. Marginal decrease in mortality and marked increase in incidence as a result of neuroblastoma screening at 6 months of age: cohort study in seven prefectures in Japan. *J Clin Oncol* 2002;20:1209-14.

2. Berthold F, Hero B. Neuroblastoma: current drug therapy recommendations as part of the total treatment approach. *Drugs* 2000;59:1261-77.

Germ-Line Mutations in Nonsyndromic Pheochromocytoma

To the Editor: The article on germ-line mutations in nonsyndromic pheochromocytoma, by Neumann et al. (May 9

issue),¹ contains a common point of confusion: the terms “paraganglioma” and “glomus tumor” are used interchangeably. They are not interchangeable. The glomus tumor is a tumor of modified perivascular smooth muscle, which frequently presents as a painful subungual mass, and is unrelated to tumors of the adrenal and extraadrenal paraganglia. The tumor to which the authors are actually referring is the jugulotympanic paraganglioma, which has been mistakenly referred to as a “glomus jugulare tumor” in the past. This neoplasm, which was recognized as a distinct pathologic entity by Sadao Otani at Mount Sinai Hospital in the 1940s and is still sometimes referred to as Otani’s tumor, arises from minute, anatomically dispersed paraganglia located at the base of the skull and temporal bone and is closely related to similar tumors of the carotid body and other extraadrenal paraganglia.² Though still sometimes referred to as glomus jugulare tumor, it is unrelated to the much more common glomus tumor of skin and soft tissue.

JAMES A. STRAUCHEN, M.D.
Mount Sinai School of Medicine
New York, NY 10029
james.strauchen@msnyuhealth.org

1. Neumann HPH, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459-66.
2. Lack EE. Tumors of the adrenal gland and extra-adrenal paraganglia. *Atlas of tumor pathology*. 3rd series. Fascicle 19. Washington, D.C.: Armed Forces Institute of Pathology, 1997.

The authors reply:

To the Editor: As Dr. Strauchen points out, the term “glomus tumor” was originally used to refer only to glomus tumors of the skin. Nevertheless, there is also widespread use of this term to refer to paragangliomas of the neck and skull base, both in clinical practice and in standard textbooks of otolaryngology.^{1,2} Furthermore, at the time of this writing, a Medline search for the term “glomus” yielded 53 citations for the years 2000, 2001, and 2002, and about 60 percent of the cited articles pertain to humans. Of the latter citations, the majority refer to glomus tumors and paragangliomas interchangeably. Because the term “glomus” is the Latin word for ball, it naturally enough has been used to refer to several entities. We believe the term “glomus jugulare” evolved because some have referred to the neuroendocrine cells of carotid-body paragangliomas as glomus cells.³

HARTMUT P.H. NEUMANN, M.D.
JÖRG SCHIPPER, M.D.
Albert-Ludwigs University
D-79106 Freiburg, Germany
neumann@med1.ukl.uni-freiburg.de

CHARIS ENG, M.D., PH.D.
Ohio State University
Columbus, OH 43210

1. Cummings CW, Fredrickson JM, Harker LA, Krause CJ, Schuller DE, Richardson MA, eds. *Otolaryngology — head & neck surgery*. 3rd ed. St. Louis: Mosby, 1998:3305.

2. Zenner HP, ed. *Hals-Nasen-Ohren-Heilkunde*. Weinheim, Germany: Chapman & Hall, 1997:62.
3. Pardal R, Lopez-Barneo J. Carotid body thin slices: responses of glomus cells to hypoxia and K(+) channel blockers. *Respir Physiol Neurobiol* 2002;132:69-79.

Case 9-2002: Orbital Mucormycosis

To the Editor: In Case 9-2002 (March 21 issue),¹ the patient’s pancytopenia and subsequent splenectomy may have been considered risk factors for the development of mucormycosis, but the nasal packing also may have played a part in promoting the extension of the infection from the nasal passages to the preseptal spaces and beyond. How long was the packing in place, and was it anterior or posterior?

TRISTRAM C. DAMMIN, M.D.
Lahey Clinic
Burlington, MA 01805
drtcd@massmed.org

1. Case Records of the Massachusetts General Hospital (Case 9-2002). *N Engl J Med* 2002;346:924-9.

To the Editor: Although Dr. Bienfang arrived at the correct diagnosis, he did not relate this unusual infection to the patient’s splenectomy only 16 days before the onset of eye symptoms. The spleen has a well-recognized and important role in the prevention of infection, and infection with unusual organisms may certainly occur after splenectomy or in patients with congenital asplenia.

GORDON J. GILBERT, M.D.
500 Pasadena Ave. S.
St. Petersburg, FL 33707

To the Editor: This case report deals with “rapid development of ocular arterial disease.” Should not the differential diagnosis include cholesterol embolization?¹

CARL F. NEEDLES, M.D.
1955 Merrick Rd.
Merrick, NY 11566

1. Case Records of the Massachusetts General Hospital (Case 2-1991). *N Engl J Med* 1991;324:113-20.

Dr. Bienfang and a colleague reply:

To the Editor: Drs. Dammin and Gilbert address important considerations that were neglected in the discussion, which emphasized the level of iron in tissue. Both correspondents ask why this nondiabetic but obviously very ill woman fell prey to a mucormycosis infection. It is difficult to invoke either the pancytopenia or the splenectomy as a risk factor. The patient’s hematologic values while she was ill showed an ability to mount a fairly robust white-cell response to the infection. Although the spleen is important in complement-based reactions, trapping blood-borne foreign intruders and

responding with an immune response to non-novel infections (all features of bacterial infections), it is not thought to have much of a role in combating encapsulated organisms such as fungi.

More challenging is the question of the nasal packing. Mucorales are molds. There certainly are cases of mucormycosis, also known as zygomycosis, attributed to surgical dressings.^{1,2} In this case, retained nasal packing was indeed found at the time of surgery. Considering, however, how commonly nasal packing is performed and how rarely cases such as this one are seen, we think this patient must have had some other susceptibility factor that was never identified.

One of the many roles of the Clinicopathological Conferences is to emphasize the diagnostic importance of a particular clinical finding in the context of a patient's particular illness. In this instance, the arterial occlusion in an obvious case of sinus and orbital sepsis without severe orbital compression essentially reduced the diagnostic considerations to one: mucormycosis. The discussion emphasized how the arterial occlusion narrowed the diagnostic considerations. Dr. Needles is, of course, correct in suggesting that there are legions of local and systemic causes for arterial occlusion, including cholesterol embolization. In this case, the patient's carotid arteries and heart valves were already under close scrutiny because of her previous illnesses, and she was receiving an anticoagulant. The failure to expand the differential diagnosis of the arterial occlusion was due to a desire to make an uncluttered point and to avoid pedantry.

DON C. BIENFANG, M.D.
MARK VARVARES, M.D.
Harvard Medical School
Boston, MA 02115

1. Dennis JE, Rhodes KH, Cooney DR, Roberts GD. Nosocomial Rhizopus infection (zygomycosis) in children. *J Pediatr* 1980;96:824-8.
2. Mead JH, Lupton GP, Dillavou CL, Odom RB. Cutaneous Rhizopus infection: occurrence as a postoperative complication associated with an elasticized adhesive dressing. *JAMA* 1979;242:272-4.

Bioterrorism and Civil Liberties

To the Editor: On the basis of service as a senior public health official in four states, I believe that Annas (April 25 issue)¹ is incorrect in his conclusion that bioterrorism is primarily a federal issue. Historically and legally, state and local public health agencies in this country have had the lead role in responding to outbreaks or suspected outbreaks of communicable disease within their jurisdictions. State and local public health agencies have performed in this capacity for over 100 years. During those years, state health officials have repeatedly demonstrated their ability to use "police powers" with proper restraint. Federal health agencies can and do play a valuable part in support of state and local public health agencies that are dealing with communicable diseases.

As a state health official, I have often requested and welcomed the assistance of federal health agencies. However, I do not believe a federal takeover of the public health response to bioterrorism would be in the public's best interest. By virtue of their relationships with their communities and expertise cultivated through years of dealing with outbreaks of communicable diseases, state and local public

health agencies are better able to lead the public health response to bioterrorism within their jurisdictions.

I agree that actions to prevent and respond to bioterrorism should be a federal priority. The National Pharmaceutical Stockpile Program is an excellent example of a federal response to bioterrorism that properly integrates the public health responsibility and authority of state and federal governments. I look forward to further such development of the federal-state partnership for preparedness for bioterrorism.

MICHAEL MOSER, M.D., M.P.H.
Kansas Department of Health and Environment
Topeka, KS 66612
mmoser@kdhe.state.ks.us

1. Annas GJ. Bioterrorism, public health, and civil liberties. *N Engl J Med* 2002;346:1337-42.

To the Editor: Annas is correct that the model statutes proposed by the Centers for Disease Control and Prevention (CDC) would threaten the trust that Americans usually have in public health officials — trust that is essential for effective protection of our population. As a state health officer in Vermont and Colorado, I found the most common threat to trust to be the desire of elected officials to have public health officials reassure the public. In truth, the public is comforted only by knowing that its public health officials are more concerned about and more alert to threats to public health than are individual citizens. Public health officials are never trusted if they are perceived as offering reassurance rather than vigilance. Sadly, U.S. postal workers understand this lesson because, confronted with the peril of anthrax, a few of my public health colleagues forgot it.

ANTHONY ROBBINS, M.D.
Tufts University School of Medicine
Boston, MA 02111
anthony.robbins@tufts.edu

To the Editor: Annas's review of the proposed model legislation to combat bioterrorism presents a truly horrible scenario. The price we might pay in the loss of precious liberties for a very uncertain protection makes me wonder what is worse for the nation: the loss of life or the loss of our civilized society. Is it worthwhile to live in a society in which constitutional protections can be summarily suspended by a politician, bypassing the courts, leaving civil liberties at the discretion of ill-prepared, low-level officials, the self-appointed guardians of the common well-being?

SERGIO C. STONE, M.D.
11 Estates Dr.
Villa Park, CA 92861
scstone@pacbell.net

Professor Annas replies:

To the Editor: Dr. Moser uses the term "lead role" in a way that invites multiple interpretations. He is correct that

state and local agencies have been (and will remain) the first to respond to local outbreaks of communicable diseases. He is incorrect, however, if he believes that September 11 and the anthrax attacks did not change the jurisdictional identity of the lead agencies in trying to prevent and respond to bioterrorism. The lead agencies will be federal agencies because, as I noted, bioterrorism is inherently a matter of national security, even if the attack is confined to a single state. The precise roles of both federal and state agencies in combating bioterrorism remain to be worked out (and are complex, since the vast majority of public health problems do not involve bioterrorism).¹ Nonetheless, federal agencies such as the CDC, the Federal Bureau of Investigation, and the new Department of Homeland Security will have to take the lead in trying to prevent or mitigate a bioterrorist attack.

Of course, effective responses to a bioterrorist attack will require joint planning and close cooperation among local, state, and federal public health officials. In this regard, Dr. Robbins rightly emphasizes that public health officials must provide the public with honest and frank assessments of risk, not paternalistic reassurances. Unaccountable and untrustworthy public health agencies are not only ineffective, they can, as Dr. Stone understands, destroy both life and civil liberties.

GEORGE J. ANNAS, J.D., M.P.H.

Boston University Schools of Medicine and Public Health
Boston, MA 02118
annasgj@bu.edu

1. Parmet WE. After September 11: rethinking public health federalism. *J Law Med Ethics* 2002;30:201-11.

Medical Mystery — The Answer

To the Editor: The medical mystery in the July 25 issue¹ involved a 34-year-old woman who was receiving dialysis and who had had multiple admissions for uremic pericarditis. An abdominal radiograph (Fig. 1) was obtained during an evaluation for abdominal pain. The uremic pericarditis was the probable cause of referred abdominal pain. The patient had received two renal transplants, 18 and 20 years earlier, and had undergone partial parathyroidectomy 4 years earlier for hyperparathyroidism. The abdominal image shows two ossified renal transplants and adjacent surgical clips. There are marked changes indicative of osteomalacia. No cause of the abdominal pain is evident on the abdominal image.

LESLIE A. KORY, M.D.

Jacobi Medical Center
Bronx, NY 10461

1. Kory LA. A medical mystery. *N Engl J Med* 2002;347:260.

Editor's note: We received 116 responses to this medical mystery. Sixty-two of the respondents (53 percent) indicated that the image showed calcified renal transplants. The remaining respondents suggested a wide range of calcified structures and calcification mechanisms.



Figure 1. Abdominal Radiograph Showing Two Ossified Renal Transplants and Adjacent Surgical Clips.

Hyperosmolar Metabolic Acidosis and Intravenous Lorazepam

To the Editor: In their letter about a patient with severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam (April 18 issue),¹ Tayar et al. err in attributing the observed acidosis and osmolality to polyethylene glycol and overlook the greater contribution of propylene glycol. Each milliliter of Ativan injection (2 mg of lorazepam per milliliter, Wyeth–Ayerst Laboratories) contains 0.8 ml of propylene glycol.² We calculate that the cumulative lorazepam dose of 1696 mg would include 704 g or 678 ml of propylene glycol (molecular weight, 76) in addition to the 153 ml of polyethylene glycol (mean molecular weight, 400) noted by Tayar et al. In any dose of parenteral lorazepam, propylene glycol contributes nearly 23 times as many osmotically active particles as polyethylene glycol.

Propylene glycol (1,2-propanediol) undergoes oxidation to lactate and pyruvate, which can also contribute to the persistent lactic acidosis described. The association of propylene glycol in lorazepam and other drugs with lactic acidosis, hyperosmolality, and renal failure has been described in case reports.³⁻⁵ Tayar et al. also describe fomepizole as “a polyethylene glycol antagonist.” Fomepizole is a potent

inhibitor of alcohol dehydrogenase that is used in treating ethylene glycol poisoning and methanol poisoning. However, there is no clear indication for using fomepizole in a patient with suspected exposure to either polyethylene glycol or propylene glycol. To the extent that the lorazepam infusion contributed to the hyperosmolar metabolic acidosis in this case, propylene glycol had a much greater role than polyethylene glycol.

MICHAEL E. MULLINS, M.D.

Washington University School of Medicine
St. Louis, MO 63110
mullinsm@msnotes.wustl.edu

BRIAN J. BARNES, PHARM.D.

Barnes-Jewish Hospital
St. Louis, MO 63110

1. Tayar J, Jabbour G, Saggi SJ. Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002;346:1253-4.
2. Toxicity of propylene glycol in Ativan injection. Philadelphia: Wyeth-Ayerst Pharmaceuticals, November 1998 (package insert).
3. Arbour RB. Propylene glycol toxicity related to high-dose lorazepam infusion: case report and discussion. *Am J Crit Care* 1999;8:499-506.
4. Cawley MJ. Short-term lorazepam infusion and concern for propylene glycol toxicity: case report and review. *Pharmacotherapy* 2001;21:1140-4.
5. Reynolds HN, Teiken P, Regan ME, et al. Hyperlactatemia, increased osmolar gap, and renal dysfunction during continuous lorazepam infusion. *Crit Care Med* 2000;28:1631-4.

The authors reply:

To the Editor: Although we agree with the calculations of Mullins and Barnes, we did not overlook the role of propylene glycol. Propylene glycol is in fact metabolized to lactic and pyruvic acid, and its association with hyperosmolarity and lactic acidosis has been described in previous reports. In our patient, however, the lactate levels were decreasing while the patient was still receiving a large dose of lorazepam and had a rapidly increasing osmolar gap (up to 165 mOsm per liter). Furthermore, blood tests for propylene glycol and pyruvate were negative. These findings contrast with those of Arbour and Esparis, whose patient had new-onset lactic acidosis after a lorazepam infusion was begun and had high propylene glycol and pyruvate levels.¹ Reynolds et al. found that the rise and fall of the serum lactate level and osmolality (which they attributed to propylene glycol) were closely correlated with the lorazepam infusion.² Although the use of fomepizole seemed reasonable under the circumstances, we agree that there is no clear indication for its use in polyethylene glycol or propylene glycol intoxication.

JEAN TAYAR, M.D.

SUBODH J. SAGGI, M.D.

Staten Island University Hospital
Staten Island, NY 10305

1. Arbour R, Esparis B. Osmolar gap metabolic acidosis in a 60-year-old man treated for hypoxemic respiratory failure. *Chest* 2000;118:545-6.
2. Reynolds HN, Teiken P, Regan ME, et al. Hyperlactatemia, increased osmolar gap, and renal dysfunction during continuous lorazepam infusion. *Crit Care Med* 2000;28:1631-4.

Gastrointestinal Angiodysplasia and Aortic Stenosis

To the Editor: For unknown reasons, bleeding from gastrointestinal angiodysplasia in patients with severe aortic stenosis (Heyde's syndrome¹) usually ceases after aortic-valve replacement.² We have proposed that this bleeding disorder may be explained by acquired type IIA von Willebrand's syndrome,³ which is a deficiency of high-molecular-weight multimers of von Willebrand factor associated with aortic stenosis. We now report two cases of Heyde's syndrome in which abnormal von Willebrand factor–multimer profiles normalized after aortic-valve replacement.

Two women, one 65 years old and one 70 years old, underwent aortic-valve replacement for severe aortic stenosis (estimated valve area, 0.67 and 0.50 cm², respectively); each received a 21-mm bioprosthesis. Preoperatively, both patients had bleeding from endoscopically proven angiodysplasia involving the jejunum (in one) or the colon (in the other), and both required blood transfusions and iron-replacement therapy. The preoperative platelet count, activated partial-thromboplastin time, and factor VIII coagulant level were normal in both patients. The level of von Willebrand factor antigen (0.82 and 0.73 U per milliliter) and the activity of von Willebrand factor ristocetin cofactor (0.50 and 0.72 U per milliliter) were also normal (normal range for both variables, 0.5 to 1.5 U per milliliter). The bleeding time was prolonged (14 minutes) in only the second patient. However, both patients had a severe deficiency of high-molecular-weight multimers of von Willebrand factor (less than 2 percent of the total multimers; normal range, 17 to 27 percent). Postoperatively, the bleeding time normalized in the patient whose bleeding time had been prolonged, and in both patients all the other hemostasis values remained normal. In both patients, the von Willebrand factor–multimer profiles also normalized after surgery, and they have remained normal during 10 years of follow-up (Fig. 1). In neither patient has recurrent bleeding or anemia developed, and neither patient has needed iron supplements.

These data support the hypothesis³ that acquired type IIA von Willebrand's syndrome may explain the hemorrhagic diathesis underlying Heyde's syndrome — including its potential for surgical cure — even in patients with normal results on screening tests for von Willebrand factor deficiency. Recently, Veyradier and colleagues⁴ reported selective loss of high-molecular-weight multimers of von Willebrand factor (despite normal levels of von Willebrand factor) in eight of nine patients with bleeding angiodysplasia; seven of these eight patients had aortic stenosis. In contrast, control patients with nonbleeding angiodysplasia or diverticular hemorrhage had normal multimer profiles.

The activity of the von Willebrand factor–cleaving metalloproteinase is increased and von Willebrand factor–platelet interactions are enhanced when there is increased shear stress.⁵ High shear associated with aortic stenosis could thus predispose patients to selective loss of the largest von Willebrand factor multimers. After aortic-valve replacement, cessation of gastrointestinal bleeding in our patients was accompanied by lasting recovery of high-molecular-weight multimers of von Willebrand factor. Because bleeding angiodysplasia is a common feature of type IIA von Wille-

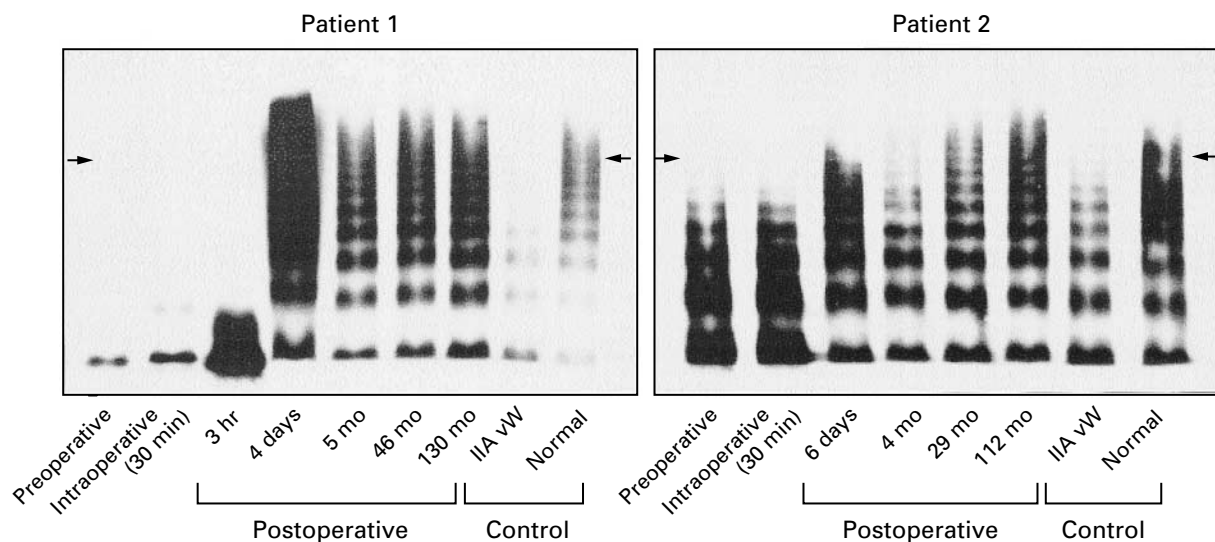


Figure 1. Analysis of von Willebrand Factor Multimers in Two Patients with Aortic Stenosis and Cessation of Bleeding Gastrointestinal Angiodysplasia after Aortic-Valve Replacement.

Blood collected in tubes containing factor–protease inhibitors was obtained before and after surgery. With the use of similar amounts of von Willebrand factor antigen from each patient, the von Willebrand–multimer profiles were analyzed by gel electrophoresis (with 1.25 percent agarose and 1 percent acrylamide) followed by immunoblotting. High-molecular-weight multimers were defined as all bands above the position of the von Willebrand factor 10-mer (arrows) and were quantitated by densitometry. Plasma from a patient with congenital type IIA von Willebrand's disease (IIA vW) and pooled normal plasma were used as controls. The preoperative deficiency of high-molecular-weight multimers that was observed in both patients normalized after valve replacement.

brand's syndrome of diverse causes,³ large von Willebrand factor multimers may play an important part in maintaining hemostasis in patients with gastrointestinal angiodysplasia.

THEODORE E. WARKENTIN, M.D.

JANE C. MOORE, B.Sc.

DAVID G. MORGAN, M.D.

McMaster University
Hamilton, ON L8L 2X2, Canada
twarken@mcmaster.ca

1. Heyde EC. Gastrointestinal bleeding in aortic stenosis. *N Engl J Med* 1958;259:196.

2. Love JW, Jahnke EJ, Zacharias D, Davidson WA, Kidder WR, Luan LL. Calcific aortic stenosis and gastrointestinal bleeding. *N Engl J Med* 1980; 302:968.

3. Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link? *Lancet* 1992;340:35-7.

4. Veyradier A, Balian A, Wolf M, et al. Abnormal von Willebrand factor in bleeding angiodysplasias of the digestive tract. *Gastroenterology* 2001; 120:346-53.

5. Pareti FI, Lattuada A, Bressi C, et al. Proteolysis of von Willebrand factor and shear stress-induced platelet aggregation in patients with aortic valve stenosis. *Circulation* 2000;102:1290-5.

Correspondence Copyright © 2002 Massachusetts Medical Society.