

Correspondence



Responses to Smallpox Vaccine

To the Editor: I am alarmed by the high rate of vaccinia-vaccine-associated morbidity (>30 percent) in the study by Frey et al. (April 25 issue).¹ In their study, there were three deviations from prior standard procedures for vaccinia vaccination²⁻⁵ that may account for the unusually high rate of morbidity as compared with the rate at our clinic.⁶ First, their use of 15 scratches (part of the investigational-new-drug [IND] protocol for the vaccine) instead of the previously recommended 5 scratches for persons without prior vaccination results in a higher inoculum, which was previously reserved for persons with a prior vaccination.

Second, their use of an occlusive dressing may retard scab formation, and the resultant increased cutaneous permeability may foster local bacterial invasion.

Finally, as I reported in ProMED on November 1, 2001 (<http://www.fas.org/promed>), at our clinic, my colleagues and I have observed the emergence, since January 2001, of cellulitis — a complication of vaccinia vaccination that was previously rare in first-time vaccinees. This same phenomenon was also observed by the Centers for Disease Control and Prevention during their vaccinia-immunization effort in December 2001. There are several possible reasons for the emergence of this complication,⁶ but its rapid resolution with antibiotic therapy strongly argues for a bacterial cause. At our clinic, the rate of apparent cellulitis as a complication of vaccination jumped from 3.9 percent (in 11 of 279 persons) in 2001 to 10.2 percent (in 12 of 118) after the switch in February 2002 to the IND vaccinia protocol with the use of 15 scratches.

In contrast to the results reported by Frey et al., only 2 of 12 persons at our clinic required one or two days of medical leave. We believe the difference in morbidity rates is primarily due to the fact that we followed the standard procedures for vaccinia vaccination rather than the new procedure.

MICHAEL A. SAURI, M.D., M.P.H.&T.M.
Occupational Health Consultants
Rockville, MD 20850

1. Frey SE, Couch RB, Tacket CO, et al. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002;346:1265-74.
2. Sauri MA, Sibley C, Monk B, Nichols M, Lai S. Durability of vaccinia immunization based on reaction at the rechallenge site. *Md Med* 2002; 3(2):44.
3. WHO Expert Committee on Smallpox Eradication: second report. WHO Tech Rep Ser 1972;493:5-64.
4. Krugman S, Ward R. Infectious diseases of children: smallpox and vaccinia. 4th ed. St. Louis: C.V. Mosby, 1968.
5. Smallpox. In: Christie AB. Infectious diseases: epidemiology and clinical practice. 2nd ed. Edinburgh, Scotland: Churchill Livingstone, 1974:204-58.
6. Lane JM, Ruben FL, Abrutyn E, Millar JD. Deaths attributable to smallpox vaccination, 1959 to 1966, and 1968. *JAMA* 1970;212:441-4.

To the Editor: How durable are the immune responses after smallpox vaccination? Little direct evidence exists; however, some early studies suggest a long-term effect mediating resistance to fatal disease.¹ There is little or no quantitative evidence of the durability of the cell-mediated response induced by vaccination against smallpox with the standard vaccinia virus.

During the course of other investigations,² we tested the CD8+ T-lymphocyte responses to vaccinia virus in persons who had been recently vaccinated (within the previous five years because of work-related potential exposures), unvaccinated persons, and persons who had been vaccinated 6 to 35 years earlier or more than 35 years earlier. Figure 1 shows the results of intracellular interferon- γ staining of CD8+ lymphocytes from persons in each of these groups, as determined by overnight culture with vaccinia-virus-infected, autologous B-lymphocyte cell lines. Vaccinia induces a robust CD8+ T-lymphocyte response in healthy persons, and this

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.

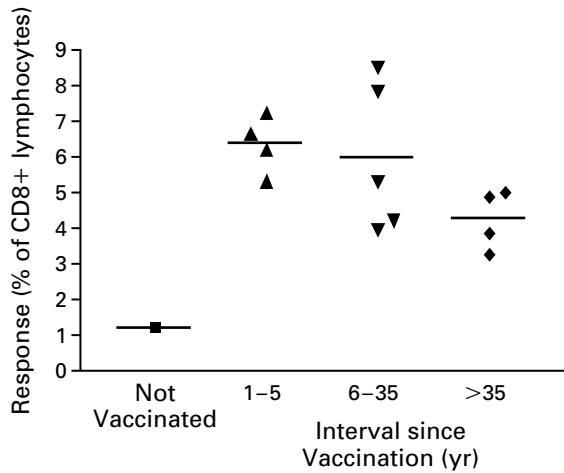


Figure 1. Responses to Vaccinia Virus by CD8+ T Lymphocytes at Different Times after Vaccination.

One person was unvaccinated, and four had been vaccinated for occupational exposure during the previous five years.² The remaining nine persons had been vaccinated between 6 and 35 years earlier or more than 35 years earlier. Responses were measured as previously described.² Bars represent mean values.

response is of long duration. It is striking that the loss of reactivity over a period of more than 35 years was very low — by a factor of less than two in persons with a remote history of vaccination (4 percent of CD8+ T lymphocytes), as compared with recently vaccinated persons (6.5 percent of CD8+ T lymphocytes). The durability of vaccinia-specific CD8+ T-lymphocyte responses is very good, suggesting that those previously vaccinated still have a significant measure of protection.

JEFFREY A. FRELINGER, PH.D.
 MOHAMMED L. GARBA, M.D.
 University of North Carolina
 Chapel Hill, NC 27599-7290
 jfrelin@med.unc.edu

1. Cohen J. Bioterrorism: smallpox vaccinations: how much protection remains? *Science* 2001;294:985.
2. Garba ML, Pilcher CD, Bingham AL, Eron J, Frelinger JA. HIV antigens can induce TGF-beta(1)-producing immunoregulatory CD8+ T cells. *J Immunol* 2002;168:2247-54.

The authors reply:

To the Editor: Dr. Sauri is concerned about the high rate of vaccinia-related adverse events in our studies.^{1,2} It is true that the current protocol differs from previous methods of administering vaccinia. We used 15 skin punctures, the current recommendation of the Advisory Committee on Immunization Practices,³ in previously unvaccinated subjects rather than the 5 previously used. We also now use semi-

permeable membrane dressings to provide protection against accidental inoculation with vaccinia. A randomized comparative trial would be required to determine the contribution — if any — of the current methods to adverse events. Our opinion is that the modern clinical-trial design and careful observations of minor as well as major events give us an accurate picture of the common acute viral syndrome associated with infection with vaccinia virus caused by vaccination. Other vaccines are not as reactogenic, and we, as a medical community, have forgotten or never saw vaccine reactions of the frequency reported.

The dose of vaccinia varied by a factor of 100 in one study and by a factor of 10 in the other, yet there was no difference in the frequency of systemic events across groups. There were differences in local inflammation (greater with undiluted vaccinia) and formation of local satellite lesions (greater with diluted vaccinia), and we speculate on the mechanism behind these events in our Discussion section. With 15 skin punctures as compared with 5 skin punctures, the dose would not be expected to vary by a factor of more than three. A comparison of vaccinations with dressings and without dressings has not been undertaken.

We disagree with the assertion that the extensive erythema observed in some vaccinated subjects represents bacterial cellulitis and that an apparent response to antibiotics argues for bacteria as a cause. Even without antibiotic treatment, the commonly observed extensive erythema and induration are short-lived and resolve rapidly, usually in two to three days. Extensive erythema does not appear to be toxic, and affected persons do not have more pain than those without extensive erythema. In addition, maximal erythema is reached on days 10 to 12; erythema due to bacterial cellulitis should develop much sooner. We believe the most likely cause of the erythema is a cellular inflammatory response to vaccinia itself.

ROBERT B. BELSHE, M.D.
 SHARON E. FREY, M.D.
 Saint Louis University School of Medicine
 St. Louis, MO 63110

1. Frey SE, Newman FK, Cruz J, et al. Dose-related effects of smallpox vaccine. *N Engl J Med* 2002;346:1275-80.
2. Frey SE, Couch RB, Tacket CO, et al. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002;346:1265-74.
3. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *MMWR Morb Mortal Wkly Rep* 2001;50(RR-10):1-25.

Diagnosis of Smallpox

To the Editor: In Table 1 of their article, Breman and Henderson (April 25 issue)¹ list secondary syphilis as a maculopapular eruption, noting that it has frequently been confused with smallpox. In general, it is more difficult to differentiate chickenpox from smallpox than it is to distinguish secondary syphilis from smallpox. Osler described the consequences of a misdiagnosis: “[S]ometimes it is not easy to distinguish between them. . . . It is stated that the . . . starting-point in Montreal of the epidemic of 1885, was regarded as varicella and not isolated. If so, the mistake . . . led to one of the

most fatal modern outbreaks of the disease.”² In *Arrowsmith*, Sinclair Lewis (with the help of Paul de Kruif) depicted the converse misdiagnosis when his protagonist was ridiculed after sounding the smallpox alarm for patients who had only chickenpox.³ The Centers for Disease Control and Prevention has made available a poster, “Evaluating Patients for Smallpox,”⁴ designed to reduce the risk of either misdiagnosis.

THOMAS D. REGAN, B.S.
SCOTT A. NORTON, M.D., M.P.H.
Walter Reed Army Medical Center
Washington, DC 20307
scott.norton@na.amedd.army.mil

1. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002;346:1300-8.
2. Osler W. The principles and practice of medicine. New York: Appleton, 1892:57-8.
3. Lewis S. *Arrowsmith*. New York: New American Library, 1980:186-7.
4. Health care providers. Atlanta: Centers for Disease Control and Prevention, 2002. (Accessed August 9, 2002, at <http://www.cdc.gov/nip/smallpox/Providers.htm#Posters>.)

Smallpox and Smallpox Vaccination

To the Editor: Bicknell’s Sounding Board article (April 25 issue)¹ includes some factual errors. Smallpox is not transmitted during its preeruptive period. It spreads only from overtly ill persons.^{2,3} Ring vaccination is not just for small outbreaks. It was the method that eradicated smallpox from the areas of India, Bangladesh, and Indonesia where the disease was hyperendemic.

The number of cases spread from each case in the German and Yugoslav outbreaks did not vary from 11 to 38. The majority of cases yielded zero spread. Even in the completely missed first generation of the Yugoslav outbreak, only two patients spread smallpox to more than four others.

The suggestion that 100,000 to 1 million deaths might occur from smallpox in the United States is implausible. The cumulative annual rates of attack in areas of the Asian subcontinent where the disease was hyperendemic were never more than 180 per million per year.² Isolation and ring vaccination would rapidly contain an outbreak once recognized. Finally, Dark Winter has been discredited as a portrayal of smallpox epidemiology by the work of Meltzer et al.⁴ (which is cited by Bicknell) and by other models.

Today, widespread infection with the human immunodeficiency virus, post-transplantation immunosuppression, and increasingly prevalent eczema would raise the number of deaths from vaccination to a value considerably higher than the 180 that Bicknell estimates from 1968 data. In the absence of a creditable terrorist threat, the risks of vaccination continue to outweigh its benefits.

J. MICHAEL LANE, M.D., M.P.H.
869 Clifton Rd.
Atlanta, GA 30307-1223
mikelane869@yahoo.com

1. Bicknell WJ. The case for voluntary smallpox vaccination. *N Engl J Med* 2002;346:1323-5.

2. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization, 1988.
3. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002;346:1300-8.
4. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modeling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis* 2001;7:959-69.

Dr. Bicknell replies:

To the Editor: Resuming smallpox vaccination is a necessary strategic decision. Lane assumes that the risk of smallpox is very small and that ring vaccination after an attack would work — a best-case scenario. Terrorism, when the risk of attack is unknown but not trivial, requires planning for a worst case.

A 25 percent death rate from smallpox is not avoidable. However, preexposure vaccination risks can be minimized by using a semipermeable membrane dressing and by excluding children under 10 years of age, immunocompromised persons, and those with dermatitis.¹ Vaccinating now would make any postattack control strategy easier, could deter an attack, and would be safer for everyone than acting later, in crisis. Vaccination is a proven, specific preventive measure. The federal government should endorse voluntary vaccination and allow people to make their own decisions as to risk.

An infected terrorist is likely to have no visible disease, to feel well enough to travel, and to transmit disease actively to others. As the prodromal fever drops, the smallpox rash is not visible inside the mouth. The terrorist temporarily feels better and is very infectious. The rash becomes obvious several days later.² A plausible scenario is that of terrorists traveling to multiple cities and disseminating smallpox in subways and airports, resulting in hundreds of thousands to millions of cases. Multiple releases from an aerosol container would be far worse.

Ring vaccination in the eradication program worked relatively slowly, was applied to populations with high levels of immunity and less mobility than Americans have today, and was applied in situations where there was no malicious intent. Kaplan et al., in a quantitative comparison of ring vaccination and immediate postattack mass vaccination, demonstrate that a moderate attack would overwhelm ring vaccination, even when the supply of vaccine is plentiful.³

The jurisdictional and management lessons of Dark Winter remain valid. Outbreaks in Yugoslavia and elsewhere teach us that one case can lead to the infection of many others. With malicious dissemination, particularly in the first round of infection, we must expect rates of spread that are substantially higher than 1 terrorist to 10 victims. Subsequent rounds are likely to have lower rates of spread.

J. Donald Millar, a former director of the smallpox-eradication program of the Centers for Disease Control and Prevention, has made the following statement: “The idea that the government would withhold the only effective means of protecting the population from a terrible disease until an epidemic is confirmed is new to public health. Prevention, in this new concept, obviously has no meaning for the ‘sentinel’ Americans who will become ill and die of smallpox as trigger for the government’s response. That is not good public health, and is certainly not good protection from bioterrorism.”⁴ Selective, step-by-step, voluntary preexposure

vaccination is a low-risk, high-benefit approach that would make any postexposure strategy easier.

WILLIAM J. BICKNELL, M.D., M.P.H.
Boston University School of Public Health
Boston, MA 02118-2526
wbicknel@bu.edu

1. Frey SE, Couch RB, Tackett CO, et al. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002;346:1265-74.
2. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002;346:1300-8.
3. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: the case for mass vaccination. *Proc Natl Acad Sci U S A* (in press).
4. Millar JD. It's bad policy to hold back smallpox vaccine. *Milwaukee Journal Sentinel*. December 27, 2001:15A.

Clinical Investigation in the 18th Century

To the Editor: Boylston (April 25 issue)¹ reminds us that clinical trials have been around a long time and that they are available to all, and he cites William Watson's contribution to the understanding of smallpox in 1767 as perhaps the first. But I offer James Lind's *A Treatise of the Scurvy*,² published in 1753, as an even earlier report of a clinical trial. It was simple and controlled and was not burdened by P values, review boards, or other impediments of modern science. Lind's two oranges and one lemon saved lives on his ship and soon saved lives the world over. He reports:

On the 20th of May 1747 I took twelve patients in the scurvy on board the Salisbury at sea. Their cases were as similar as I could have them . . . and had one diet common to all. Two of these were ordered each a quart of cyder a day. Two others took 25 gutts of elixir vitriol [sulfuric acid] three times a day. . . . Two others took two spoonfuls of vinegar three times a day. . . . Two of the worst patients . . . were put under a course of sea water. Of this they drank half a pint every day. . . . The two remaining patients took the bigness of a nutmeg three times a day of an electuary of garlic, mustard seed, *rad. raphan*, balsam of Peru and gum myrrh. . . . The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of six days, fit four [sic] duty.²

FRANK J. LEPREAU, M.D.
74 Old Harbor Rd.
Westport, MA 02790

1. Boylston AW. Clinical investigation of smallpox in 1767. *N Engl J Med* 2002;346:1326-8.
2. Lind J. A treatise of the scurvy: in three parts, containing an inquiry into the nature, causes, and cure of that disease: together with a critical and chronological view of what has been published on the subject. London: A. Millar, 1753.

Dr. Boylston replies:

To the Editor: Dr. Lepreau prefers Lind; I prefer Watson, for the reasons outlined in the last paragraph of my article. Lind clearly understood the principles of controlled trials, as did Boylston and Jurin before him. Unfortunately, the

Royal Navy, Lind's employer, did not appreciate the importance of his findings. Citrus supplements did not become mandatory on His Majesty's ships until 1795.

ARTHUR W. BOYLSTON, M.D.
University of Leeds
Leeds LS9 7TF, United Kingdom
boylston@btinternet.com

Brachytherapy and Saphenous-Vein Grafts

To the Editor: Radiation treatment undoubtedly reduces the risk of recurrence of in-stent restenosis. However, the findings of Waksman et al. (April 18 issue)¹ should be taken in the context of two facts. First, although the greatest need for target-lesion revascularization (that is, restenosis) occurs within the first 8 months after the procedure, the risk of restenosis after vein-graft intervention continues to rise until 18 to 24 months after the procedure, suggesting a phenomenon of late restenosis that is unique to vein-graft intervention.^{2,3} Therefore, longer follow-up (perhaps with follow-up angiography at 24 months) would be helpful in judging the magnitude of the beneficial effect of radiation. Second, clinical recognition of restenosis after vein-graft intervention is often difficult because of coexisting multivessel disease and the presence of collaterals, which limit the interpretation of myocardial-perfusion studies and symptoms.⁴ Although this effect was equal in the two groups (since the study was randomized and blinded), it would be helpful to know whether target-lesion revascularization was driven by ischemia or by symptoms.

SANJIV SHARMA, M.D.
WILLIAM NYITRAY, M.D.
BRIJESH BHAMBI, M.D.
Bakersfield Heart Hospital
Bakersfield, CA 93301
sanjiv1122@yahoo.com

1. Waksman R, Ajani AE, White RL, et al. Intravascular gamma radiation for in-stent restenosis in saphenous-vein bypass grafts. *N Engl J Med* 2002; 346:1194-9.
2. Hong MK, Mehran R, Dangas G, et al. Comparison of time course of target lesion revascularization following successful saphenous vein graft angioplasty versus successful native coronary angioplasty. *Am J Cardiol* 2000; 85:256-8.
3. Le May MR, Labinaz M, Marquis J, et al. Predictors of long-term outcome after stent implantation in a saphenous vein graft. *Am J Cardiol* 1999;83:681-6.
4. Safian RD, Freed MS, eds. The manual of interventional cardiology. 3rd ed. Royal Oak, Mich.: Physicians Press, 2001:324.

The authors reply:

To the Editor: In published trials of intracoronary radiation therapy for in-stent restenosis, the majority of target-lesion revascularizations were performed within the first six to nine months after the initial procedure. Angiographic analysis at this time allows assessment of the efficacy of treatment, in addition to that provided by clinical follow-up.¹⁻³ Although late restenosis in patients who receive radiation can occur after this period, judicious clinical follow-up will identify the majority of patients with restenosis who require

repeated intervention. Assessment of vein-graft failure is challenging because many of these grafts have diffuse disease and because totally occluded grafts do not necessarily represent the status of the target lesion, since other blockages could have contributed to the occlusion. Therefore, it is encouraging that the data in our article continue to hold for target-vessel revascularization.

In all the cases in our series, the decision to perform target-lesion revascularization was driven either by symptoms refractory to medical therapy or by evidence of ischemia on functional testing (exercise testing or myocardial-perfusion studies). We agree that clinical recognition of restenosis after vein-graft intervention may be challenging because of the presence of multivessel disease and collaterals; however, these confounders should have occurred equally in the two treatment groups, since the study was randomized and blinded. Revascularization was performed only when angiographic restenosis correlated with the clinical assessment — an approach that we believe reflects “real-world” clinical management.

RON WAKSMAN, M.D.
ANDREW E. AJANI, M.D.
Washington Hospital Center
Washington, DC 20010
ron.waksman@medstar.net

1. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;101:2165-71.
2. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;336:1697-703.
3. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;344:250-6.

Volume and Outcome

To the Editor: The attempt of Birkmeyer et al. (April 11 issue)¹ to correlate low procedure-specific hospital volume with increased mortality has methodologic and interpretive problems. The investigators used data from the Medicare Provider Analysis and Review (excluding those for Medicare patients enrolled in health maintenance organizations) and from the Nationwide Inpatient Sample, without verification, to estimate procedure-specific hospital volume. The correlation between Medicare volume and hospital volume (correlation coefficient, 0.97) probably resulted from mathematic coupling,^{2,3} which occurs when variables are shared. Were the relations between outcome and volume significant when only Medicare volumes were analyzed?

No proof of validation of the regression models is presented. For most procedures, lower-volume institutions had higher percentages of nonelective admissions, patients over 75 years of age, and black patients (a fact that the authors erroneously interpret as indicating that black patients were more likely to be treated at low-volume hospitals). These three variables are included in the regression analysis, but they are the tip of the iceberg made up of a multitude of other unreported confounders — such as preoperative selection of patients, intraoperative management, and postoperative care. Obviously, it is impossible to assign patients randomly to hospitals, but without robust, validated regres-

sion equations, the relative importance of volume may be overestimated or underestimated.

JAMES E. BARONE, M.D.
Stamford Hospital
Stamford, CT 06902
drjbarone@stamhosp.chime.org
DONALD A. RISUCCI, PH.D.
JOHN A. SAVINO, M.D.
New York Medical College
Valhalla, NY 10595

1. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128-37.
2. Archie JP Jr. Mathematic coupling of data: a common source of error. *Ann Surg* 1981;193:296-303.
3. Barone JE, Lowenfels AB. Maximization of oxygen delivery: a plea for moderation. *J Trauma* 1992;33:651-3.

To the Editor: The article by Birkmeyer et al. advances our understanding of the relation between hospital volume and outcome. We are curious, however, about whether the authors attempted to analyze surgical mortality according to the patient's level of surgical risk. In the case of coronary-artery bypass grafting, we have shown that differences in mortality rates between low-volume hospitals and high-volume hospitals might be driven predominantly by differences among patients at high surgical risk.¹ Patients who are at low risk, in contrast, might receive little or no benefit from obtaining their care at high-volume centers. This possibility has clear implications for regionalization policies, in general, and for high-volume procedures such as coronary-artery bypass grafting, in particular.² To avert an estimated 314 annual deaths related to coronary-artery bypass grafting, for example, very-high-volume centers would need to double their capacity by absorbing more than 31,000 additional cases per year. If high-risk patients who would clearly benefit from the expertise available at high-volume centers could be identified preoperatively and then selectively sent to such regional centers, these logistic problems would be greatly diminished.

Finally, we would caution against extrapolation of these data to patients younger than 65 years of age. Advanced age — both directly and in association with coexisting conditions — clearly increases a patient's base-line risk of death related to surgery. The population studied by Birkmeyer et al. therefore represents a high-risk group of patients, as reflected in the relatively high 30-day mortality reported for patients undergoing coronary-artery bypass grafting: 4.8 percent at very-high-volume centers, as compared with a national average of 2.9 percent.³

BRAHMAJEE K. NALLAMOTHU, M.D., M.P.H.
University of Michigan Medical Center
Ann Arbor, MI 48109-0022
bnallamo@umich.edu
SANJAY SAINT, M.D., M.P.H.
Ann Arbor Veterans Affairs Medical Center
Ann Arbor, MI 48105
KIM A. EAGLE, M.D.
University of Michigan Medical Center
Ann Arbor, MI 48109-0022

1. Nallamothu BK, Saint S, Ramsey SD, Hofer TP, Vijan S, Eagle KA. The role of hospital volume in coronary artery bypass grafting: is more always better? *J Am Coll Cardiol* 2001;38:1923-30.
2. Luft HS. Better for whom? Policy implications of acting on the relation between volume and outcome in coronary artery bypass grafting. *J Am Coll Cardiol* 2001;38:1931-3.
3. Grover FL. The Society of Thoracic Surgeons National Database: current status and future directions. *Ann Thorac Surg* 1999;68:367-73.

To the Editor: Aside from the direct costs of medical care, travel to a high-volume center can be costly and is not affordable for all patients. An uninsured patient with pancreatic cancer will probably not be accepted at a high-volume institution and will most likely not even be offered the option of going to one. Those who can afford the expense of copying medical, pathological, and radiologic records, and traveling for the consultation, procedure, and any follow-up will do so, leaving those who are less fortunate at the local center. Birkmeyer et al. controlled for coexisting conditions, but I would bet that patients who are able to travel are patients with a better prognosis.

CHRISTOPHER K. SENKOWSKI, M.D.
Mercer University School of Medicine
Savannah, GA 31404
senkoch1@memorialhealth.com

To the Editor: The studies by Birkmeyer et al. and Begg et al. (April 11 issue)¹ add further evidence of the correlation between volume and quality in the delivery of certain health care services. Whereas others will certainly challenge the validity or reliability of the data sets or will question whether adequate risk adjustment would temper or invalidate the results, I instead question the policy suggestions laid out in the accompanying editorial by Epstein.² It seems much too premature to recommend broadly the diversion of selected procedures from low-volume hospitals, even as a “transitional strategy.” Certainly, experience matters, but what else is included in the equation? It is still unclear whether volume itself is a generalizable predictor of quality at all, or whether and how much such underlying factors as organizational design, streamlined data management, or multidisciplinary care act as confounders. Without such knowledge, merely stripping further volume away from low-volume centers may be strikingly counterproductive in terms of the goal of high quality overall.

DARREN M. KOCs, M.D.
University of Michigan Medical Center
Ann Arbor, MI 48109
dkocs@umich.edu

1. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med* 2002;346:1138-44.
2. Epstein AM. Volume and outcome — it is time to move ahead. *N Engl J Med* 2002;346:1161-4.

To the Editor: Although we generally agree with Epstein's support of targeted policies to decrease the proportion of surgical procedures performed at low-volume hospitals, such

policies trouble us because volume seems a fairly crude predictor of patient outcome and the closely related measure of the quality of health care. Why not try to identify the true determinants of patient outcomes or quality of health care? Such information could be used to predict the outcome for patients treated by a particular type of physician at a particular type of hospital, reveal characteristics of the physicians and hospitals from which the best outcomes could be expected, and design interventions to improve quality (for all types of health care workers and health care facilities — not just surgeons working in hospitals).

ALEXANDER K. ROWE, M.D., M.P.H.
MICHAEL S. DEMING, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA 30341
axr9@cdc.gov

To the Editor: Epstein raises some of the key dilemmas facing policy makers as they wrestle with the implications of the association between volume and outcome. In particular, interventions directed at influencing the referral of patients toward high-volume institutions, by fiat, incentive, or consumer pressure, leave unanswered the question of what to do with the lower-volume centers. It is helpful to recognize that volume alone does not presage outcome. The amount of improvement in performance that can be extracted from a given number of procedures also depends in part on how the activities related to learning are managed at a given institution.¹ We have found notable variation in the quality and quantity of management attention paid to learning in the case of the adoption of a new form of medical technology.² Perhaps part of the solution to the policy makers' dilemma is better management.

RICHARD BOHMER, M.B., CH.B., M.P.H.
AMY EDMONDSON, PH.D.
GARY PISANO, PH.D.
Harvard Business School
Boston, MA 02163

1. Pisano GP, Bohmer RMJ, Edmondson AC. Organizational differences in rates of learning: evidence from the adoption of minimally invasive cardiac surgery. *Management Sci* 2001;47:752-68.
2. Edmondson AC, Bohmer RM, Pisano GP. Disrupted routines: team learning and new technology implementation in hospitals. *Administrative Sci Q* 2001;46:685-716.

To the Editor: The editorial by Dr. Epstein is laudable in its review of recent information concerning the relation between surgical volume and outcomes, but important points are not well understood. As a case in point, six years ago, I began referring surgical and general medical patients from our small rural hospital to regional referral centers. As this practice led to what I had perceived to be improved patient care, it also created much larger problems in the community: as surgical volume decreased, the skills of the surgical team also deteriorated. The community was then left without a

general surgeon. The hospital decreased in size, and the future of this community resource appears to be in danger.

JOHN L. GHERTNER, M.D.
6055 Robinson Rd.
Sodus, NY 14551
nghertner@earthlink.net

To the Editor: I think the assumption made by Epstein that all low-volume hospitals have high mortality after high-risk surgical procedures is unjustified by the data presented. We in the medical profession have no business getting into this matter. Instead, let us use the data to look at the various hospitals and improve the quality of care. Preventing low-volume hospitals from performing surgery can have dangerous consequences. For instance, preventing low-volume surgeons from performing elective repair of abdominal aortic aneurysms will have negative consequences in the form of patients with ruptured aneurysms. Surgeons who are not performing elective aneurysm repair may not feel comfortable repairing ruptured aneurysms — a procedure requiring far more experience and skill. Patients with ruptured aneurysms may have to travel substantial distances to get to centers where the procedure is performed.

WILLIAM W. BABSON, JR., M.D.
Jordan Hospital
Plymouth, MA 02360
dkbabson@aol.com

The authors reply:

To the Editor: In our study, hospital volume was measured directly by counting Medicare procedures. To facilitate interpretation of our results, we converted hospital Medicare volumes to total hospital volumes, using data from the Nationwide Inpatient Sample to estimate the appropriate multiplier for each procedure. Because the same multiplier was applied to all hospitals, this approach does not in any way affect the magnitude of reported volume–outcome relations. Barone et al. also note the importance of accounting for potentially confounding variables, including variables related to patient selection. As we acknowledged, the extent to which data on claims capture these variables is limited. However, it would be inappropriate to adjust for variables related to operative and postoperative care. Such processes of care are most likely essential parts of the causal pathway underlying the relations between volume and outcome and thus should not be viewed as “confounders.”

Nallamothu et al. wonder whether hospital volume may be most important for high-risk patients, as their research has suggested with regard to coronary-artery bypass grafting.¹ Our (unpublished) analyses support this premise when the importance of volume is expressed in terms of absolute differences in operative mortality. Differences in mortality appear to be largest for subgroups of patients with the highest base-line risk, such as the very elderly. In terms of the relative risk of death, however, we found the effect of hospital volume to be relatively uniform among subgroups defined according to base-line risk.

Senkowski suggests that lower-income patients and those without insurance may be less likely to undergo surgery at high-volume hospitals. Although previous studies have demonstrated only moderate differences between high-volume hospitals and low-volume hospitals in the socioeconomic status of patients, we agree that more work is needed to clarify the role of patient selection in the observed relations between volume and outcome. We also agree that policy makers must be careful to ensure that less fortunate patients are not left behind as volume-based referral initiatives are implemented.

Given the hundreds of articles published over the past several decades demonstrating better outcomes with selected procedures at high-volume hospitals,^{2,3} we do not agree with Kocs that ongoing efforts to translate this information into policy are “premature.” As he points out, hospital volume may serve as a proxy for numerous organizational characteristics associated with better quality. Efforts to identify these attributes and to ensure that they are implemented broadly would be worthwhile. Meanwhile, many unnecessary deaths could be averted by policies concentrating pancreatic resections, esophagectomies, and other high-risk procedures in high-volume centers.

JOHN D. BIRKMEYER, M.D.
Dartmouth–Hitchcock Medical Center
Lebanon, NH 03756
john.d.birkmeyer@hitchcock.org

EMILY V.A. FINLAYSON, M.D.
University of California at San Francisco
San Francisco, CA 94143

1. Nallamothu BK, Saint S, Ramsey SD, Hofer TP, Vijan S, Eagle KA. The role of hospital volume in coronary artery bypass grafting: is more always better? *J Am Coll Cardiol* 2001;38:1923-30.
2. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. *JAMA* 2000;283:1159-66.
3. Halm EA, Lee C, Chassin MR. Is volume related to quality in health care? A systematic review and methodologic critique of the research literature. *Ann Intern Med* (in press).

The editorialist replies:

To the Editor: Drs. Babson, Ghertner, and Kocs all express concern about the potentially deleterious consequences of diverting patients from low-volume hospitals. I share their concern. However, the relations between volume and outcome are extraordinarily strong for some surgical procedures. For example, according to data from Birkmeyer et al., risk-adjusted mortality rates for esophagectomy varied from 8.4 percent in very-high-volume hospitals to 20.3 percent in very-low-volume hospitals. Risk-adjusted mortality rates for pancreatic resection and repair of an abdominal aortic aneurysm varied from 3.8 percent to 16.3 percent and from 3.9 percent to 6.5 percent, respectively. Clearly, we need research to understand the causes of these differences and quality-improvement interventions to improve our care and reduce these differences. But the benefit from these activities may not be seen for years. For patients receiving care now, the effect of these differences on patients' health outcomes is too large to ignore.

Policy changes can often result in unanticipated consequences. Therefore, our approach should be demonstration and evaluation with close follow-up and readjustment. I recognize Dr. Ghertner's point that rural hospitals are especially vulnerable and their loss would threaten patients' access to care. I therefore proposed that efforts to divert patients to low-volume hospitals be limited to urban areas, as well as to procedures for which the relations between volume and mortality are strongest, and to institutions at the bottom end of the spectrum with very low volume. I urge that the Leapfrog Group and others who support more aggressive policies refine their current plans as they move toward interventions that go beyond education. Broad-scale regionalization is not warranted at this time.

Dr. Bohmer and colleagues and Drs. Rowe and Deming underscore the fact that volume is merely a characteristic that is associated with differences in patient outcome rather than a direct measure of quality of care. Differences in risk-adjusted mortality arise largely from differences in clinical management. Efforts to improve clinical management, reduce mortality, and diminish differences in the quality of care should be our highest priority.

ARNOLD M. EPSTEIN, M.D.
Harvard School of Public Health
Boston, MA 02115

Bronchial Cast

To the Editor: The Image in Clinical Medicine entitled "Bronchial Cast" (March 28 issue)¹ describes a patient who had had respiratory symptoms for six months and who expectorated a bronchial cast. However, the authors do not mention the outcome. Was the patient cured after coughing up this rather large cast? Most physicians are still interested in answers to such questions.

DOUGLAS R. MIGDEN, D.O., J.D.
Virginia Mason Medical Center
Seattle, WA 98111
drmigden@aol.com

1. Studer SM, Terry PB. Bronchial cast. *N Engl J Med* 2002;346:981.

The authors reply:

To the Editor: The differential diagnosis of cough productive of bronchial casts is considerable,¹ and such coughs are often associated with pulmonary disease that may be characterized by hypersecretion of mucus. Treatment of the underlying pulmonary disease may decrease the formation of bronchial casts, but as was the case with our patient, a primary lung disease cannot always be identified. This condition of idiopathic bronchial cast formation has been termed plastic, or fibrinous, bronchitis.² Proposed treatments for plastic bronchitis include bronchodilators, antibiotics for bacterial infection, hydration, chest physiotherapy, postural drainage,³ and bronchoscopic removal of casts.⁴

Our patient received inhaled bronchodilators for several weeks, with no change in bronchial casts. Administration of

oral corticosteroids resulted in a slight decrease in cast formation. Antibiotics were not prescribed, since there was no evidence of bacterial infection, and DNase was considered but not used because histopathological examination revealed that the cast was relatively acellular in nature. Our patient moved out of the area and was lost to follow-up several months after his initial presentation, but published reports suggest that he may have periods of remission lasting months or years.³

SEAN M. STUDER, M.D.
Mount Sinai Medical Center
New York, NY 10029
sean.studer@msnyuhealth.org

PETER B. TERRY, M.D.
Johns Hopkins University
Baltimore, MD 21287

1. Kao NL, Richmond GW. Cough productive of casts. *Ann Allergy Asthma Immunol* 1996;76:231-3.
2. Bettman M. Report of a case of fibrinous bronchitis, with a review of all cases in the literature. *Am J Med Sci* 1902;123:304-29.
3. Jett JR, Tazelaar HD, Keim LW, Ingrassia TS III. Plastic bronchitis: an old disease revisited. *Mayo Clin Proc* 1991;66:305-11.
4. Liston SL, Porto D, Siegel LG. Plastic bronchitis. *Laryngoscope* 1986;96:1347-51.

Combined Blood Substitute and Erythropoietin Therapy in a Severely Injured Jehovah's Witness

To the Editor: We disagree strongly with the conclusions of Cothren et al. (April 4 issue)¹ about the benefits of the polymerized hemoglobin-based oxygen carrier PolyHeme in critically ill patients with anemia who refuse transfusions. Hemoglobin-based oxygen carriers are administered in such patients to increase oxygen delivery to the tissues, in order to maintain or restore oxygen uptake. Yet no data on tissue oxygen balance before and after the administration of the product are presented. Such products may not be associated with increased oxygen delivery when they cause vasoconstriction in the peripheral circulation and decrease cardiac output.^{2,3} Finally, in order for oxygen uptake to improve with hemoglobin-based oxygen carriers, the condition of oxygen supply dependency must be present,⁴ which did not seem to be the case in this patient.

We believe that the recovery of the native hemoglobin concentration followed a pattern more compatible with simple hemoconcentration than with red-cell regeneration, negating the presumed "bridge to transfusion" effect of the hemoglobin-based oxygen carrier. When high doses of erythropoietin are used to treat anemia in patients with severe organ dysfunction, reticulocyte counts begin to improve only after two to three weeks.⁵ Reticulocytosis was not documented. Moreover, by extrapolating from the values given in Figure 1 in the letter by Cothren et al., we estimate that the hemoglobin concentration should have risen to 10 g per deciliter within the next two to three days if erythropoiesis had been responsible for the recovery.

Finally, the literature is replete with cases of patients who were Jehovah's Witnesses who refused transfusions

and survived despite hemoglobin concentrations of less than 5 g per deciliter. Hemoglobin-based oxygen carriers are an interesting concept, but so far, there are few data (including the case presented by Cothren et al.) supporting their use in humans.

JEAN-FRANÇOIS HARDY, M.D.
SYLVAIN BÉLISLE, M.D.
University of Montreal
Montreal, QC H3C 3J7, Canada
jean-francois.hardy@umontreal.ca

PHILIPPE VAN DER LINDEN, M.D., PH.D.
Centre Hospitalier Universitaire Charleroi
B-6040 Jumet, Belgium

1. Cothren C, Moore EE, Offner PJ, Haenel JB, Johnson JL. Blood substitute and erythropoietin therapy in a severely injured Jehovah's Witness. *N Engl J Med* 2002;346:1097-8.
2. Kasper SM, Grune F, Walter M, Amr N, Erasmi H, Buzello W. The effects of increased doses of bovine hemoglobin on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. *Anesth Analg* 1998;87:284-91.
3. Tsai AG. Influence of cell-free Hb on local tissue perfusion and oxygenation in acute anemia after isovolemic hemodilution. *Transfusion* 2001;41:1290-8.
4. Sielenkamper AW, Chin-Yee IH, Martin CM, Sibbald WJ. Diaspirin crosslinked hemoglobin improves systemic oxygen uptake in oxygen supply-dependent septic rats. *Am J Respir Crit Care Med* 1997;156:1066-72.
5. Gabriel A, Kozek S, Chiari A, et al. High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome. *J Trauma* 1998;44:361-7.

The authors reply:

To the Editor: To address the first point raised by Hardy et al., we do not insert pulmonary-artery catheters unless it is anticipated that they will be critical for therapy. This patient did not have a catheter inserted because her base deficit was corrected from -12 to -1.8 with the administration of PolyHeme; consequently, oxygen transport and cardiac indexes were not available. Although Hardy et al. state that hemoglobin-based oxygen carriers cause vasoconstriction, in fact, PolyHeme, a stroma-free polymerized and pyridoxalated hemoglobin solution with a tetrameric concentration of less than 1 percent, does not produce systemic or pulmonary hypertension.¹⁻³

Our patient was given a combination of PolyHeme and erythropoietin. The response to erythropoietin is dose-related, with an increase in reticulocytosis by the second or third dose.⁴ The dose for our patient was chosen on the basis of studies that have shown few complications associated with administration of high doses.⁵ We agree that measuring the response to this high-dose regimen by means of reticulocyte counts is important. However, we made every effort to minimize iatrogenic blood loss through nonessential blood sampling. The only available reticulocyte count was obtained on the 10th hospital day, and it was 6.6 percent. Furthermore, hemoconcentration was not a confounding factor in this patient. There was no negative net fluid balance or weight loss during the period on which we reported; the patient's weight was 60 kg at both the beginning and the end of that period.

Although the literature may contain several cases of pa-

tients surviving with a hemoglobin concentration of less than 5 g per deciliter, there are few reports of patients who are Jehovah's Witnesses surviving with a hemoglobin concentration close to 3 g per deciliter, as it was in our patient. A recent review of the literature reveals that although there is a 20 percent mortality rate associated with a hemoglobin concentration of 5 g per deciliter, most patients with a hemoglobin concentration of 3 g per deciliter die.²

CLAY COTHREN, M.D.
ERNEST E. MOORE, M.D.
JEFFREY L. JOHNSON, M.D.
Denver Health Medical Center
Denver, CO 80204-4507
ernest.moore@dhha.org

Editor's note: The authors are supported by an educational grant from Northfield Laboratories.

1. Gould SA, Moore EE, Moore FA, et al. Clinical utility of human polymerized hemoglobin as a blood substitute after acute trauma and urgent surgery. *J Trauma* 1997;43:325-31.
2. Gould SA, Moore EE, Hoyt DB, et al. The life-sustaining capacity of human polymerized hemoglobin when blood may be available. *J Am Coll Surg* (in press).
3. Johnson JL, Moore EE, Offner PJ, Haenel JB, Hides GA, Tamura DY. Resuscitation of the injured patient with polymerized stroma-free hemoglobin does not produce systemic or pulmonary hypertension. *Am J Surg* 1998;176:612-7.
4. Goodnough LT, Verbrugge D, Marcus RE, Goldberg V. The effect of patient size and dose of recombinant human erythropoietin therapy on red blood cell volume expansion in autologous blood donors for elective orthopedic operation. *J Am Coll Surg* 1994;179:171-6.
5. Price TH, Goodnough LT, Vogler WR, et al. The effect of recombinant erythropoietin administration on the efficacy of autologous blood donation in patients with low hematocrits: a multicenter, randomized, double-blind, controlled trial. *Transfusion* 1996;36:29-36.

Acute Babesiosis Caused by *Babesia divergens* in a Resident of Kentucky

To the Editor: *Babesia divergens* is the primary cause of human babesiosis in Europe, resulting in fatality rates of 42 percent among persons who have undergone splenectomy and 5 percent among persons with intact spleens.¹ The known vector tick, *Ixodes ricinus*,² is not indigenous to North America. We report what we believe to be the first human case of babesiosis caused by *B. divergens* in North America.

A 56-year-old man presented with a fever (temperature, 40°C), a hemoglobin level of 13.7 g per deciliter, a platelet count of 43,000 per cubic millimeter, and hemoglobinuria. He had had headaches for two weeks and had been treated with amoxicillin, without improvement. The history included splenectomy in 1993, a Caribbean cruise nine months earlier, and deer and rabbit hunting four weeks previously, but he had no recollection of a tick bite. Doxycycline therapy (100 mg twice daily) was initiated. The Giemsa-stained blood smear revealed characteristic *B. divergens* organisms (30 to 35 per 100 red cells) in singles, pairs, and tetrads (Fig. 1). Therapy with clindamycin (900 mg intravenously every eight hours) and oral quinidine (650 mg three times a day) was instituted. Defervescence began after 72 hours. Hemoglobinuria cleared by day 7. Polymerase-chain-reac-

tion tests for *Ehrlichia chaffeensis* and *B. microti* were negative (MRL Reference Laboratories). When he was discharged on day 12 while continuing to take medication, he had a parasite count of 5 to 10 per 100 oil-immersion fields; he has not had a relapse for over a year.

The parasite small subunit ribosomal RNA gene was amplified from extracted DNA, cloned, and sequenced^{3,4} after appropriate measures were taken to prevent cross-contamination of samples. The resulting 1724-bp sequence differed at three nucleotide positions (99.8 percent homology) from that of *B. divergens* GenBank accession number U16370 (99.3 percent and 98.2 percent homology to *B. divergens* GenBank accession number V07885 and European Molecular Biology Organization accession number Z48751.1, respectively), as compared with less than 92 percent iden-

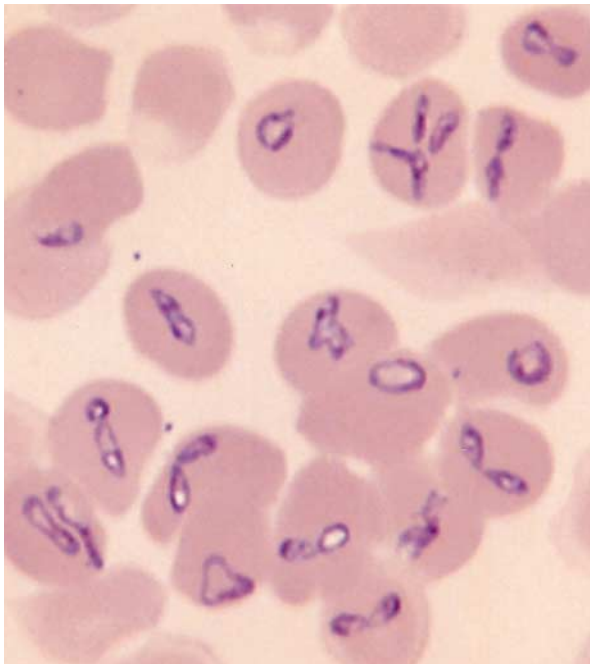


Figure 1. *Babesia divergens* in a Giemsa-Stained Blood Smear ($\times 1470$).

tity with *B. microti* (numbers AB032434, AF231349, AF231348, and U09833 according to the National Center for Biotechnology Information basic local alignment search tool [BLAST]).

This case is disturbing because it suggests that *B. divergens* infections may be emerging in North America. Although the source of this infection is unconfirmed, recent reports of molecular evidence of *B. divergens* in rabbits (27 percent of those tested) and ixodes species ticks on Nantucket Island, Massachusetts,⁵ suggest that the parasite was acquired while the patient was hunting rabbits.

Our findings indicate that *B. divergens* has caused human babesiosis in North America, that rapid, accurate diagnosis and treatment are lifesaving, and that blood banks must be aware of the potential for infection with babesia species in areas where such infections are not endemic. Physicians must consider the possibility of *B. divergens* infection in patients presenting with a rapid onset of fever, chills, intravascular hemolysis, and hemoglobinuria.

JAMES F. BEATTIE, M.D.

MARIE L. MICHELSON, M.D.

Medical Center at Bowling Green
Bowling Green, KY 42102

PATRICIA J. HOLMAN, PH.D.

Texas A&M University
College Station, TX 77843
pholman@cvm.tamu.edu

1. Gorenflot A, Moubri K, Precigout E, Carcy B, Schettters TP. Human babesiosis. *Ann Trop Med Parasitol* 1998;92:489-501.
2. Telford SR III, Spielman A. Babesiosis of humans. In: Cox FEG, Kreier JP, Wakelin D, eds. *Topley and Wilson's microbiology and microbial infections*. 9th ed. Vol. 5. London: Edward Arnold, 1998:349-59.
3. Chae J-S, Lee J-M, Kwon O-D, Holman PJ, Waghela SD, Wagner GG. Nucleotide sequence heterogeneity in the small subunit ribosomal RNA gene variable (V4) region among and within geographic isolates of *Theileria* from cattle, elk and white-tailed deer. *Vet Parasitol* 1998;75:41-52.
4. Elwood HJ, Olsen GJ, Sogin ML. The small-subunit ribosomal RNA gene sequences from the hypotrichous ciliates *Oxytrichia nova* and *Stylonychia pustulata*. *Mol Biol Evol* 1985;5:399-410.
5. Goethert HK, Telford SR. Enzootic transmission of *Babesia divergens* in cottontail rabbits on Nantucket Island. *Am J Trop Med Hyg* 2000;62: Suppl:185. abstract.

Correspondence Copyright © 2002 Massachusetts Medical Society.