CORRESPONDENCE

CLINICAL PROBLEM-SOLVING: DIAGNOSING SPOUSAL ABUSE

To the Editor: Thomas and Lowitt (Aug. 3 issue)[1] describe a 41-year-old female cocaine abuser who presented with an ischemic stroke due to occlusion of the right middle cerebral artery, documented by angiography. As an exercise in clinical problem-solving, this report is incomplete in its presentation and flawed in its conclusions. First, the patient is described as having aphasia and left hemiparesis, a combination that would occur only in a subgroup of left-handed persons with right hemispheric speech dominance. It is therefore essential that information about handedness and characteristics of the speech disturbance be provided. Second, no other neurologic deficits are described, no description of the final location and size of the infarct on computed tomography (CT) is given, and no information about filling of the lenticulostriate vessels on angiography is provided. Therefore, it cannot be determined whether the leg weakness was due to cortical infarction in the territory of the middle cerebral artery — not an uncommon finding[2] — or to superimposed subcortical infarction.

Third, and most troubling, the evidence that links the patient's cerebral infarction to a strangulation attempt four months before her admission is tenuous and does not support the authors' lengthy commentary on domestic violence. The angiogram did not show carotid dissection. The proposal that focal injury to the endothelium of the internal carotid artery at the time of the attempted strangulation may have led to mural thrombosis and delayed embolization is at best a hypothesis, which should be entertained in the context of other, more viable hypotheses. In the Stroke Data Bank, fully 40 percent of cerebral infarcts were classified as infarcts of undetermined cause.[3] Of the patients with infarcts of undetermined cause who were evaluated with both CT and angiography, 66 percent were given a diagnosis of embolism from an undetermined source,[3] a category that may be well suited to the case under discussion. Furthermore, a history of cocaine abuse constitutes an important and increasingly prevalent risk factor for stroke[4] and should not be dismissed without toxicologic verification. In addition, information regarding oral-contraceptive use, an important risk factor in young women with stroke,[5] is lacking. Finally, if the "smooth filling defect" in the internal carotid artery was in fact believed to represent a thrombus, why was appropriate treatment (anticoagulation or surgical exploration) not undertaken to prevent further embolization?

PEYMAN PAKZABAN, M.D.
Boston, MA 02114 Massachusetts General Hospital

1. Thomas P, Lowitt NR. A traumatic experience. N Engl J Med 1995;333:307-10.
2. Mohr JP, Foulkes MA, Polis AT, et al. Infarct topography and hemiparesis profiles with cerebral convexity infarction: the Stroke Data Bank. J Neurol Neurosurg Psychiatry 1993;56:344-51.
3. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann Neurol 1989;25:382-90.
4. Klonoff DC, Andrews BT, Obana WG. Stroke associated with cocaine use. Arch Neurol 1989;46:989-93.
5. Carolei A, Marini C, Ferranti E, Frontoni M, Prencipe M, Fieschi C. A prospective study of cerebral ischemia in the young: analysis of pathogenic determinants. Stroke 1993;24:362-7.

To the Editor: A recent Clinical Problem-Solving exercise described a middle-aged woman who had had a stroke subsequent to a strangulation attempt by her ex-husband. A British report of two similar cases described the cause of the strokes as "conjugal disharmony" and suggested making "delicate and discreet" inquiries about marital discord.[1] I was happy to read the straightforward discussion of domestic violence and

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 400 words (please include a word count).**
- **It must have no more than five references and one figure or table.**
- **It should not be signed by more than three authors.**
- **Letters referring to a recent *Journal* article must be received within four weeks of its publication.**
- **Please include your full address, telephone number, and fax number (if you have one).**

You may send us your letter by post, fax, or electronic mail.

Our address:	**Letters to the Editor** ***New England Journal of Medicine*** **10 Shattuck St.** **Boston, MA 02115**
Our fax numbers:	**617-739-9864 and 617-734-4457**
Our Internet address:	**letters@edit.nejm.org**

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. We are unable to provide prepublication proofs. Please enclose a stamped, self-addressed envelope if you want unpublished material returned to you.

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 editions (print, data base, and optical disk) and in anthologies, revisions, and any other form or medium.

the clear description of the physician's responsibilities in the *Journal*, in contrast to the genteel and cautious language of the earlier report.

This woman's tragedy is an excellent wake-up call. Asking about domestic violence in the social history should no longer represent an exception, but rather a standard of care.

HOWARD A. HOLTZ, M.D.
Livingston, NJ 07039 St. Barnabas Medical Center

1. Milligan N, Anderson M. Conjugal disharmony: a hitherto unrecognised cause of strokes. BMJ 1980;281:421-2.

To the Editor: In describing the CT findings in "A Traumatic Experience," the expert clinician seems to use the term "attenuation" in a manner opposite its normal use. Attenuation usually refers to the decrease in energy of x-rays as they pass through tissue. Thus, an acute brain infarct, with the associated increase in brain water, causes a decrease (not an increase) in attenuation on CT. Acute hemorrhage or extravascular contrast material causes an increase (not a decrease) in attenuation as compared with the findings in normal brain.

WILLIAM B. THOMAS, D.V.M., M.S.
College of Veterinary Medicine,
Knoxville, TN 37901-1071 University of Tennessee

To the Editor: In the August 3 Clinical Problem-Solving article, the expert clinician advocated the use of thrombolytic therapy in a 41-year-old woman presenting with features of a middle-cerebral-artery occlusion. In the event, urokinase was given six hours after her arrival in the emergency room.

We were surprised by the comments made regarding thrombolytic therapy and concerned that they may be interpreted uncritically to support the routine use of such therapy in thrombotic stroke. As yet, there have only been small trials suggesting benefit from the use of thrombolytic agents in acute ischemic stroke.[1] Many of the major studies of thrombolysis have been stopped prematurely because of the increased incidence of early death in patients treated with streptokinase.[2,3] Furthermore, the Australian Streptokinase Trial found that patients receiving treatment three to four hours after the onset of symptoms fared worse than those treated before three hours[3]: 46 of 106 patients given streptokinase died, as compared with 27 of 122 randomly assigned to placebo ($P<0.001$). For this reason the study has stopped recruiting patients who present more than three hours after the onset of symptoms.

It is therefore premature to advocate thrombolysis for cerebral-artery thrombosis except under special circumstances. We believe that thrombolytic therapy should not be recommended for the treatment of cerebral thrombosis except as part of a trial. This position should be reviewed once these trials are completed and their findings published.

W. SUNMAN, M.R.C.P.
C. JACK, M.D.
Liverpool L69 3BX, M. LYE, M.D.
United Kingdom University of Liverpool

1. Boysen G, Overgaard K. Thrombolysis in ischaemic stroke — how far from a clinical breakthrough? J Intern Med 1995;237:95-103.
2. Hommel M, Boissel JP, Cornu C, et al. Termination of trial of streptokinase in severe acute ischaemic stroke. Lancet 1995;345:57.
3. Donnan GA, Davis SM, Chambers BR, et al. Trials of streptokinase in severe acute ischaemic stroke. Lancet 1995;345:578-9.

To the Editor: I am puzzled by what may have been inadvertent omissions in the Clinical Problem-Solving case of a 41-year-old woman who was brought to the emergency room with aphasia and left hemiparesis. The expert clinician starts out by wondering about the patient's use of medications, drugs, nicotine, and alcohol and whether she or her family had a history of vascular disease. Exploration of risk factors is, of course, important in efforts to prevent an occurrence or a recurrence of disease, but when confronted with acute illness, as in this case, should not the clinician focus first on the underlying pathologic process?

The differential diagnosis of stroke includes cerebral hemorrhage, cerebral thrombosis, cerebral embolus, subarachnoid hemorrhage, subdural hematoma, brain tumor, brain abscess, and meningitis. As part of a systematic approach, would an expert not ask about physical findings, such as a stiff neck and tendon reflexes? In order to rule out the conditions requiring the most urgent attention (including dangerously high cerebrospinal fluid pressure), would an expert not consider performing a lumbar puncture? If, as seems likely in this case, the result of the lumbar puncture was negative, the diagnostic possibilities would have been reduced to thrombosis and embolus. I submit that a CT scan of the head would then not have been required. When the arteriogram discloses a lesion of the right internal carotid artery, should one not consider exploring this lesion? When the patient's mother reported that the patient's ex-husband had recently tried to strangle her, should a clinician not have asked whether there were any bruises on the patient's neck, particularly the right side, and whether anyone else could verify the mother's account?

I would certainly agree that an opportunity for effective intervention was missed 18 months earlier when the patient had undergone what is described as a routine checkup. I wonder, however, whether what seemed routine to the physician may not have been so for the patient. Perhaps she was looking for help with a problem (e.g., domestic violence) that was too difficult and too embarrassing for her to verbalize or even conceptualize. Identifying and dealing with such patients is an art. What is called for is genuine caring and open-mindedness on the part of the physician, not just another routine question.

I suggest that physicians would practice this art more if there were more widespread public recognition that this is a legitimate part of the physician's role and a willingness by third-party payers to place a value on it.

ERWIN O. HIRSCH, M.D.
Milwaukee, WI 53226 Medical College of Wisconsin

To the Editor: In their discussion of the case presented in "A Traumatic Experience," Thomas and Lowitt raise very important issues about the deficiencies in our medical system with respect to recognizing and addressing domestic violence. The clot in the patient's right internal carotid artery was attributed to previous physical abuse. The authors discuss how abuse was not originally considered in the differential diagnosis of this patient.

I would like to add inappropriate use and incorrect interpretation of laboratory studies as additional areas of concern. In this case, protein C, protein S, and antithrombin studies were ordered to identify a hypercoagulable condition before the thrombosis was verified. The studies themselves would not have influenced the initial care of the patient. Later it is stated that the normal levels of protein S and protein C and

a negative test for lupus anticoagulant "seem to rule out a primary hematologic abnormality." This is not correct. It has been well documented that only a minority of patients whose condition fits the hypercoagulable diagnosis will have an identifiable laboratory abnormality.[1,2] Although the percentage of patients with a laboratory abnormality will increase with the use of studies to identify the newly discovered inherited abnormality in factor V, called factor V Leiden, at least 50 percent will remain without a laboratory-based diagnosis.[3]

Certainly, this patient's medical care was influenced most by a complete history. We need to teach our future clinicians to use laboratory studies more prudently and the medical history more extensively.

JAMIE E. SIEGEL, M.D.
Medical College
Philadelphia, PA 19129 of Pennsylvania

1. Bauer KA. Management of patients with hereditary defects predisposing to thrombosis including pregnant women. Thromb Haemost 1995;74:94-100.
2. Nachman RL, Silverstein R. Hypercoagulable states. Ann Intern Med 1993; 119:819-27.
3. Svensson PJ, Dahlbäck B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 1994;330:517-22.

The authors reply:

To the Editor: We thank the letter writers for their careful reading of "A Traumatic Experience." Our intent was not to write a detailed clinical case presentation, but rather to present a case that would trigger a thoughtful extension of the diagnostic decision making required by the presentation of a young woman with acute stroke. We recognize that the clinical information was limited and regret omissions that may have been misleading.

Dr. Pakzaban correctly notes that the patient was left-handed with rare right hemispheric speech dominance. She did not use oral contraceptives, her history of inhaled cocaine use was remote, and the results of toxicologic screening were negative, as reported. We thank Dr. Thomas for clarifying the language of the CT reports. We are informed that use of the phrase "subtle increase in attenuation" in the original CT report refers to an increased density of the right middle cerebral artery when it is lodged with clot, relative to surrounding brain tissue, occasionally referred to as a "dense middle cerebral artery sign."[1]

The angiogram showed total occlusion of the M1 segment of the right middle cerebral artery, including several lateral lenticulostriate vessels. Subsequent CT scans have confirmed infarction of the putamen and globus pallidus, with sparing of the head of the caudate nucleus.

The description of the case as it was managed in our center was not meant to be interpreted as an endorsement of thrombolytic therapy. We agree with Sunman et al. that caution in the use of thrombolytic agents is indicated, as this case unfortunately illustrates with the complication of hemorrhage. Given this event, further anticoagulation was withheld. The patient was discharged on aspirin therapy.

Finally, we disagree with Dr. Pakzaban's conclusion that "infarct of undetermined cause" is an appropriate diagnosis here, and we wonder whether the 40 percent figure he quotes with regard to this diagnosis includes diagnostic workups as extensive as in our case. The angiogram revealed a smooth clot just above the bifurcation and failed to show stenotic disease or fibromuscular dysplasia. It was the consulting neurologist's opinion that a clot from the heart would not lodge in this location, but, rather, more distally. Thus, the clot apparently formed in situ, and the remaining history supplied evidence of the trauma that may have caused this process. As general internists, we value the context of history in which illness presents itself and hope that this case reaffirms the points that Drs. Hirsch and Siegel make, that the critical diagnostic test was the physician's interviewing skill and the critical time for prevention was a moment in the health-maintenance visit 18 months before the stroke.

PATRICIA A. THOMAS, M.D.
NANCY RYAN LOWITT, M.D.
Johns Hopkins Bayview
Baltimore, MD 21224-2780 Medical Center

1. Zorzon M, Mase G, Pozzi-Mucelli F, et al. Increased density in the middle cerebral artery by nonenhanced computed tomography: prognostic value in acute cerebral infarction. Eur Neurol 1993;33:256-9.

ESCHERICHIA COLI O157:H7

To the Editor: There is a growing need for an honest analysis of what we do and do not know about emerging infections such as enterohemorrhagic *Escherichia coli* and for cost-effective incentives to produce a safe food supply. Despite impressive progress in some areas (such as reductions in salmonella and listeria infections since the late 1980s[1,2]), the report by Boyce et al. on enterohemorrhagic *E. coli* infections (Aug. 10 issue),[3] which are estimated to account for over 20,000 infections and 250 deaths each year in the United States, raises the question of how best to prevent the potentially serious threat to health posed by contaminated food (especially meat).

At a recent conference sponsored by the U.S. Department of Agriculture (USDA) ("An Evaluation of the Role of Microbiological Criteria in Establishing Food Safety Performance Standards in Meat and Poultry Products"), the consensus emerged that although salmonella may be the best marker organism for contamination of poultry, *E. coli* is a better indicator of contamination of meats other than poultry. The organism is readily quantifiable, best reflects fecal contamination (at present), and is probably better than specific pathogens such as *E. coli* O157 that are more difficult to test for and present in much smaller numbers and that testing for may cause other important enteric pathogens to be missed. Despite the frequent presence of moderate numbers of *E. coli* in contaminated food, however, the information currently available simply does not permit definitive standards.

Perhaps the best solution, when one does not have all the answers, is simple honesty. Instead of pretending to know how many of which organism represents a threat, perhaps we could provide information about the "microbiologic quality" of a product (from either current or recent lots), just as the food industry provides exhaustive data on the numbers of calories and grams of fat, cholesterol, sodium, vitamins, and so forth. In product information collected by the USDA, this information could be expressed as a USDA microbiologic-quality grade based on the mean *E. coli* counts. The industry could then advertise Grade A as being within 1 SD of the USDA mean, Grade AA as more than 1 SD below the USDA mean, and Grade AAA as more than 2 SD (or z scores) below the USDA mean for the previous year. Grades B, C, and D could be assigned for z scores above the mean.

Such a grading system would provide incentives for companies with products of the highest microbiologic quality to use this information in marketing the products, with the recogni-

tion that at present we do not know the absolute quantities of organisms that should be allowed. In addition, this grading system would allow consumers to make informed choices when buying food. This approach might also allow us to learn about levels of microbiologic quality that are readily achievable and levels at which health risks arise. Such an approach may be acceptable to parties with opposing political viewpoints and may actually help provide a safer food supply.

RICHARD L. GUERRANT, M.D.
University of Virginia
Charlottesville, VA 22908 School of Medicine

DAVID M. THENO, PH.D.
San Diego, CA 92123 Jack-in-the-Box Restaurants

1. National *Salmonella* surveillance summary, 1994. Atlanta: Centers for Disease Control and Prevention, 1994.
2. Tappero JW, Schuchat A, Deaver KA, Mascola L, Wenger JD. Reduction in the incidence of human listeriosis in the United States: effectiveness of preventive efforts? JAMA 1995;273:1118-22.
3. Boyce TG, Swerdlow DL, Griffin PM. *Escherichia coli* O157:H7 and the hemolytic–uremic syndrome. N Engl J Med 1995;333:364-8.

To the Editor: Boyce and colleagues provide a comprehensive review of *E. coli* O157:H7 and the hemolytic–uremic syndrome in North America. In England and Wales, *E. coli* O157:H7 is also an emerging problem, with laboratory isolations having risen from 6 (0.01 per 100,000 residents) in 1983 to 411 (0.8 per 100,000 residents) in 1994.

Between 1992 and 1994, 1266 laboratory isolations were reported, the majority of cases being sporadic. During this period, 159 persons were infected in 18 outbreaks; 40 percent of those infected persons were admitted to the hospital, 18 percent had the hemolytic–uremic syndrome, and 2.5 percent died — all much higher percentages than those reported by Boyce et al. for the United States. Of the 18 outbreaks, 9 were transmitted through the consumption of contaminated food, 4 through both the consumption of contaminated food and person-to-person contact, 2 through contact with cattle, 1 through person-to-person contact, and 2 by unknown routes.

E. coli O157 is the most common verocytotoxin-producing *E. coli* in England and Wales.[1] Many laboratories test fecal specimens for *E. coli* O157 only if the patient has bloody diarrhea, but about half the patients who are infected do not have blood in their stools.[2] A government working group has recently issued recommendations for the surveillance of infections in humans and farm animals, improvement of subtyping methods, evaluation of procedures for testing food and environmental samples, and implementation of a monitoring system (Hazard Analysis and Critical Control Points) for the storage, handling, and heat treatment of raw foodstuffs.[1]

E. coli O157 infection has become an important public health problem in recent years. The organism can cause serious morbidity and mortality among those affected, particularly children, with long-term residual impairment in renal function reported in a substantial proportion of childhood survivors of the hemolytic–uremic syndrome.[3] The introduction of effective prevention and control measures is essential.

MICHAEL J. RYAN, M.B., M.P.H.
PATRICK G. WALL, M.B., M.V.B.
THOMAS CHEASTY, B.SC.
London NW9 5DF, Public Health Laboratory
United Kingdom Service Board

1. A Working Group of the Advisory Committee on the Microbiological Safety of Food. Report on Vero cytotoxin producing Escherichia coli. London: Her Majesty's Stationery Office, 1995.
2. Vero cytotoxin producing *Escherichia coli:* which specimens should be tested? Commun Dis Rep CDR Wkly 1995;5:147.
3. Fitzpatrick MM, Shah V, Trompeter RS, Dillon MJ, Barratt TM. Long term renal outcome of childhood haemolytic uraemic syndrome. BMJ 1991;303:489-92.

The authors reply:

To the Editor: Ryan and colleagues report an increase in the rate of laboratory isolation of *E. coli* O157:H7 in England and Wales from 1983 to 1994, which may reflect a true increase in the incidence of *E. coli* O157:H7 infections, as well as greater awareness on the part of physicians and more thorough laboratory screening and reporting. The rates given for hospitalization, death, and development of the hemolytic–uremic syndrome among 159 persons affected in 18 outbreaks in England and Wales are all higher than the rates reported among 1557 persons affected in 19 outbreaks in the United States.[1,2] Differences in case definitions and in the thoroughness of case finding may make these rates difficult to compare. For example, if the case definition included a culture-confirmed infection or if case finding focused on patients with bloody diarrhea, only severe cases would be likely to be detected, which would result in higher rates of hospitalization, death, and development of the hemolytic–uremic syndrome.

Ryan and colleagues note that a government working group in England and Wales has made specific recommendations concerning surveillance of *E. coli* O157:H7 infections. Recently, a consensus panel on *E. coli* O157:H7 infections in the United States issued a similar statement,[3] including the recommendation that all diarrheal stools submitted for the examination of bacterial enteric pathogens also be cultured for *E. coli* O157:H7.

Drs. Guerrant and Theno's suggestion that meat be graded for microbiologic quality is intriguing and might allow market forces to improve the processing of meat in order to decrease contamination levels. Performance-based grading,[4] a similar approach that has been proposed, would rate processing plants on the basis of compliance with industry standards for processing, as well as past and current microbiologic testing for products. The USDA recently proposed a regulation that would modify the current system of meat and poultry inspection, which is based on physical inspection, supplementing it with the science-based monitoring system called Hazard Analysis and Critical Control Points, which would include microbiologic testing at critical steps during processing. Implementation of such a system would be an important step toward improving the safety of meat in the United States. Decreasing the number of infections due to *E. coli* O157:H7 and other foodborne pathogens will require safer methods of production, slaughter, processing, storage, and distribution of meat to reduce contamination, as well as education about the need to cook ground beef thoroughly.

THOMAS G. BOYCE, M.D.
DAVID L. SWERDLOW, M.D.
PATRICIA M. GRIFFIN, M.D.
Centers for Disease Control
Atlanta, GA 30333 and Prevention

1. Boyce TG, Swerdlow DL, Griffin PM. *Escherichia coli* O157:H7 and the hemolytic–uremic syndrome. N Engl J Med 1995;333:364-8.
2. Griffin PM. *Escherichia coli* O157:H7 and other enterohemorrhagic *Escherichia coli.* In: Blaser MJ, Smith PD, Ravdin JI, Greenberg HB, Guerrant RL, eds. Infections of the gastrointestinal tract. New York: Raven Press, 1995:739-61.
3. Brotman M, Giannella RA, Alm PF, et al. Consensus conference statement: *Escherichia coli* O157:H7 infections — an emerging national health crisis, July 11–13, 1994. Gastroenterology 1995;108:1923-34.
4. Bjerklie S. A not-so-modest proposal. Meat Poultry 1995;41:6.

IMMUNOSUPPRESSIVE THERAPY FOR MYOCARDITIS

To the Editor: Mason and colleagues report the results of a clinical trial of immunosuppressive therapy for myocarditis (Aug. 3 issue).[1] Ventricular function improved to the same extent among the patients randomly assigned to receive conventional therapy plus immunosuppressive treatment as among those who received conventional therapy alone. McKenna and Davies, in an accompanying editorial, observe that many patients with dilated cardiomyopathy have immunohistochemical evidence of inflammation, even though they may not meet the Dallas criteria for the histologic diagnosis of myocarditis, and the authors allude to the question of a potential role for immunosuppression in the treatment of dilated cardiomyopathy.[2]

Six years ago in the *Journal* we reported the results of a randomized trial of prednisone for dilated cardiomyopathy,[3] which are clearly germane to the diagnostic and therapeutic issues raised by McKenna and Davies. Of the 102 patients with dilated cardiomyopathy in our trial, only 2 met strict Dallas criteria, but another 58 had cellular infiltration with fibroblasts or lymphocytes (or both) or other potential indicators of inflammation (immunoglobulin deposition detected on endomyocardial biopsy, positive gallium scans, or elevated erythrocyte sedimentation rates). These findings, especially given the problematic variability between observers and the empiricism of the Dallas criteria,[4] underscore the clinical inadequacy of the current nosology of myocarditis and dilated cardiomyopathy. As McKenna and Davies imply, there may be subgroups of patients with dilated cardiomyopathy who could benefit from immunosuppression, but we have no definite means of identifying them.

Forty-nine of the patients in our trial received conventional therapy plus prednisone (60 mg daily for three months), and 52 received conventional therapy alone. Among these patients (as among those described by Mason et al.), ventricular function improved regardless of whether they received immunosuppressive therapy. After three months, the left ventricular ejection fraction had increased slightly more in the prednisone group (from 17.9 to 22.2 percent) than in the control group (from 17.1 to 19.3 percent, $P=0.054$). In the prospectively defined subgroup of 60 patients with some evidence of myocardial or systemic inflammation, the left ventricular ejection fraction had increased (i.e., risen 5 percent or more) in 67 percent of the patients given prednisone but in only 28 percent of the controls ($P=0.004$). These data emphasize the need for further research to identify subgroups of patients with dilated cardiomyopathy who may benefit from immunosuppressive therapy.

ROBERT E. CUNNION, M.D.
Bethesda, MD 20892 National Institutes of Health

JOSEPH E. PARRILLO, M.D.
Rush–Presbyterian–St. Luke's
Chicago, IL 60612 Medical Center

1. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:269-75.
2. McKenna WJ, Davies MJ. Immunosuppression for myocarditis. N Engl J Med 1995;333:312-3.
3. Parrillo JE, Cunnion RE, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989; 321:1061-8.
4. Shanes JG, Ghali J, Billingham ME, et al. Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 1987; 75:401-5.

To the Editor: "Cardiac inflammation is difficult to diagnose and even if diagnosed, can we then treat it more effectively?" This could be the conclusion of the Myocarditis Treatment Trial but was actually written 223 years ago by Jean Baptiste Sénag, physician to Louis XV. Since then, too much has changed for us to accept willingly the negative results of this trial.

The criteria for the diagnosis of myocarditis were based solely on the results of light microscopy. Today even Billingham, from the Dallas panel of pathologists, states that "these criteria have been misrepresented as a classification that is used as a *sine qua non* of the histological diagnosis of acute myocarditis."[1] Advances in immunohistochemistry (the identification of lymphocyte subpopulations, expression of major-histocompatibility-complex antigens, adhesion molecules, and immunoglobulin binding in biopsy specimens) have greatly increased specificity and sensitivity.[2] Light microscopy is no longer the standard. It may even identify the wrong patients in the florid viral phase of myocarditis. In addition, necrosis, which is indispensable for the diagnosis of active myocarditis, is almost impossible to detect in a tiny biopsy specimen, and its use as a diagnostic criterion may have excluded patients with chronic forms and autoreactive features, who might have profited most from immunosuppression.[3]

Other diagnostic tools used in the trial were inadequate as well. The presence of enteroviral RNA or DNA from adenovirus, cytomegalovirus, Epstein–Barr virus, and influenza virus in the biopsy specimens was not determined. Their presence would rule out immunosuppressive therapy,[4] since mortality in coxsackievirus-B3–infected animals with persistent virus is increased exponentially.[3]

In addition, the duration of the immunosuppressive treatment was too short. An extrapolation of the data in Figure 2 of the article by Mason et al. shows that there were nine deaths in the control group and four in the immunosuppression group at six months, when treatment was discontinued. The positive trend was already obvious at this time. Moreover, not all immunosuppressive agents are alike. Reviews of controlled trials[3,4] suggest that azathioprine and prednisone are more beneficial than other agents.

BERNHARD MAISCH, M.D.
D-35033 Marburg, Germany Philipps University

FULVIO CAMERINI, M.D.
I-34100 Trieste, Italy Ospedale Riuniti

HEINZ-PETER SCHULTHEISS, M.D.
D-12200 Berlin, Germany Benjamin Franklin University

1. Billingham ME. The histopathological diagnosis and morphological features of acute myocarditis. In: Banatvala JE, ed. Viral infections of the heart. London: Edward Arnold, 1993:32-58.
2. Kühl U, Noutsias M, Seeberg B, Schanwell M, Welp LB, Schultheiss H-P. Chronic inflammation in the myocardium of patients with clinically suspected dilated cardiomyopathy. Cardiac Failure 1994;1(1):13-25.
3. Maisch B, Herzum M, Schönian U. Immunomodulating factors and immunosuppressive drugs in the therapy of myocarditis. Scand J Infect Dis 1993; Suppl 88:149-62.
4. Maisch B, Schönian U, Hengstenberg C, et al. Immunosuppressive treatment in autoreactive myocarditis — results from a controlled trial. Postgrad Med J 1994;70:Suppl 1:S29-S34.

To the Editor: Mason et al. conclude that immunosuppression is not an effective treatment for lymphocytic myocarditis. We are concerned that readers may falsely conclude that endomyocardial biopsy has no role in cases of suspected myocarditis.

Giant-cell myocarditis may resemble lymphocytic myo-

carditis on presentation. Giant-cell myocarditis usually begins with congestive symptoms during a period of several weeks to months, often with ventricular arrhythmias, but has a worse prognosis than lymphocytic myocarditis.[1] There is usually a rapid progression to cardiogenic shock and death, unless a heart transplantation is performed. The diagnosis can be made only by endomyocardial biopsy.

We established the Multicenter Giant Cell Myocarditis Study Group in January 1995 to address the many unresolved questions about this rare and rapidly fatal disease. We have enrolled 50 patients with giant-cell myocarditis from U.S. and international medical centers in this ongoing study and have reported on the first 5.[2] We know of several cases of giant-cell myocarditis that responded to treatment with cyclosporine, including two cases reported in the literature.[3] The only well-documented treatment for giant-cell myocarditis remains heart transplantation. Of the 14 patients in our study who received heart transplants, 9 are well up to 11 years after transplantation.

Giant-cell myocarditis should be suspected in patients with rapidly progressive, refractory heart failure and ventricular arrhythmias. We recommend a heart biopsy as part of the evaluation. Patients should be placed on waiting lists for heart transplants as soon as the diagnosis of giant-cell myocarditis is established.

LESLIE T. COOPER, JR., M.D.
RALPH SHABETAI, M.D.
University of California,
San Diego, CA 92103-8411 San Diego, Medical Center

1. Davidoff R, Palacios I, Southern J, Fallon JT, Newell J, Dec GW. Giant cell versus lymphocytic myocarditis: a comparison of their clinical features and long-term outcomes. Circulation 1991;83:953-61.
2. Cooper LT Jr, Berry GJ, Rizeq M, Schroeder JS. Giant cell myocarditis. J Heart Lung Transplant 1995;14:394-401.
3. Desjardins V, Pelletier G, Leung TK, Waters D. Successful treatment of severe heart failure caused by idiopathic giant cell myocarditis. Can J Cardiol 1992;8:788-92.

The authors reply:

To the Editor: We agree with Cunnion and Parrillo that there is no gold standard for the diagnosis of myocarditis. They cite the study by Shanes et al. as evidence of interobserver variability and the empiricism of the Dallas criteria. That study was flawed by technically inadequate histologic preparations and lack of training of the observers in the use of the criteria. Our pathology panel reported excellent consensus using the Dallas criteria.[1] The criteria were developed to define myocarditis rigidly for our trial. The internal consistency of the study population is a hallmark of a meaningful clinical trial. The biopsy criteria were not intended to define myocarditis exclusively, since it has many potential histologic, immunologic, and clinical manifestations.

We also agree with the primary point that Cooper and Shabetai make about giant-cell myocarditis. With the help of Dr. Shabetai, a coinvestigator in our trial, we designated giant-cell myocarditis as a criterion for exclusion from enrollment and a form of myocarditis to which the results of the trial do not apply. We have previously pointed out the differences between lymphocytic myocarditis and giant-cell myocarditis, as well as the need to consider immunosuppressive therapy for the latter.[2] We do not agree, however, that a biopsy should be performed to rule out giant-cell myocarditis in all patients with heart failure of uncertain cause, because it is a rare entity that will declare itself in its rapid progression. It is also not clear that transplantation is the best treatment, since giant-cell myocarditis may recur in the graft.[3]

Maisch et al. point out the conundrum that myocarditis can be diagnosed by multiple means because its pathogenesis is unknown. However, they imply that their methods constitute a new standard for the diagnosis of this disorder. We disagree. Standard diagnostic criteria for myocarditis (which do not yet exist) should identify one or more disease entities, each with uniform clinical characteristics and responsiveness to therapy. Thus far, light microscopy has not met these requirements, but neither have any of the new techniques cited by Maisch et al. Our experience with such techniques, which were not available when the trial was initiated, in a subgroup of our patients justifies tempered enthusiasm.[4,5]

Maisch et al. also suggest that there was a trend toward the efficacy of immunosuppressive therapy in the trial. At six months the difference between the two groups was not significant, and the effect did not persist. But we accept the possibility that a longer period of immunosuppressive therapy or use of other immunosuppressive drugs and doses might have yielded different results.

JAY W. MASON, M.D.
University of Utah
Salt Lake City, UT 84132 Medical Center

JOHN B. O'CONNELL, M.D.
Jackson, MS 39216 University of Mississippi

BRUCE M. MCMANUS, M.D., PH.D.
Vancouver, BC V6T 2B5, University of
Canada British Columbia

1. Aretz HT, Billingham ME, Edwards WD, et al. The utility of the Dallas criteria for the histopathological diagnosis of myocarditis in endomyocardial biopsy specimens. Circulation 1993;88:Suppl:I-552. abstract.
2. Mason JW. Distinct forms of myocarditis. Circulation 1991;83:1110-1.
3. Kong G, Madden B, Spyrou N, Pomerance A, Mitchell A, Yacoub M. Response of recurrent giant cell myocarditis in a transplanted heart to intensive immunosuppression. Eur Heart J 1991;12:554-7.
4. Tracy S, Chapman NM, McManus BM, Pallansch MA, Beck MA, Carstens J. A molecular and serologic evaluation of enteroviral involvement in human myocarditis. J Mol Cell Cardiol 1990;22:403-14.
5. Weiss LM, Movahed LA, Billingham ME, Cleary ML. Detection of Coxsackievirus B3 RNA in myocardial tissues by the polymerase chain reaction. Am J Pathol 1991;138:497-503.

STRUT SEPARATIONS IN BJÖRK–SHILEY MITRAL VALVES

To the Editor: O'Neill et al. (Aug. 17 issue)[1] described a radiographic method for the detection of strut separation in Björk–Shiley convexo-concave mitral valves that had a reasonable sensitivity (83 percent) and high specificity (99.7 percent). The authors suggest that this method may be useful for screening patients with this type of mechanical heart valve, since the elective removal of valves with a defect in one leg of the outlet strut will prevent death from subsequent mechanical failure of the second leg.

The alternatives to screening are direct elective surgery without screening on the one hand, and expectant management (observation) on the other. Direct surgery carries a risk of operative mortality, and observation carries a cumulative risk of mechanical failure with an associated high mortality. For a 61-year-old patient with no coexisting condition and a valve with a risk of mechanical failure of 0.99 percent per year (averages from O'Neill et al.[1]), the mortality rate associated with reoperation may be estimated as 2 percent[2] and the cumulative mortality caused by failure as 4.5 percent.[3] There-

fore, screening may result in a mortality reduction of at most 2 percent, as compared with direct surgery. This maximal benefit will not be achieved for several reasons. First, strut separation and mechanical failure may occur between two consecutive screening visits, even with short intervals such as every six months.[1] Furthermore, the estimated sensitivity of the screening method may be too optimistic, since some strut separations were undetected. Moreover, the reproducibility of the method in other centers may be low, as indicated by the poor kappa values for outside observers.[1] Finally, surgical mortality will increase during follow-up, because of increasing age and the possible development of additional coexisting conditions.

We conclude that the case for selective screening as a useful alternative to observation or direct elective surgery remains to be proved.

EWOUT W. STEYERBERG, M.SC.
MARINUS J.C. EIJKEMANS, M.SC.
J. DIK F. HABBEMA, PH.D.
Erasmus University
3000 DR Rotterdam, the Netherlands

1. O'Neill WW, Chandler JG, Gordon RE, et al. Radiographic detection of strut separations in Björk–Shiley convexo-concave mitral valves. N Engl J Med 1995;333:414-9.
2. Piehler JM, Blackstone EH, Bailey KR, et al. Reoperation on prosthetic heart valves: patient-specific estimates of in-hospital events. J Thorac Cardiovasc Surg 1995;109:30-48.
3. van der Meulen JH, Steyerberg EW, van der Graaf Y, et al. Age thresholds for prophylactic replacement of Björk-Shiley convexo-concave heart valves: a clinical and economic evaluation. Circulation 1993;88:156-64.

Dr. O'Neill replies:

To the Editor: We concur with Steyerberg et al. that radiographic screening of Björk–Shiley convexo-concave valves has not been shown to decrease the risk of outlet-strut fracture. Unfortunately, sample size and logistic considerations preclude prospective, randomized testing of this technique. We hope that the completion of screening of 900 patients and the subsequent follow-up of this cohort will show a decreased incidence of outlet-strut fracture as compared with historical controls.

We strongly disagree with Steyerberg et al. regarding the value of routine explantation of these valves. Since most patients have had these valves in place for more than 10 years, on average the patients are older than when they had their original operations (61 ± 11 years in our study).[1] Older age alone will increase operative mortality. The risk of surgery is in fact greater in this cohort. To date, 805 patients have undergone radiographic screening and 27 patients have undergone prophylactic explantation because of abnormal results of radiographic examinations. There have been four operative deaths (15 percent mortality). De Mol et al.[2] reported that no deaths occurred in 27 operations. The patient group was younger (mean age, 51), and their surgery was performed at one highly regarded center. Although no deaths occurred, 3 patients had protracted postoperative courses, and 16 patients underwent needless surgery, since the valves were fully intact. Given the known clinical risk of explantation and the continuously aging patient population, reliable predictors of valve failure must be developed before prophylactic explantation. We are confident that radiographic screening will prove to be such a test.

WILLIAM W. O'NEILL, M.D.
William Beaumont Hospital
Royal Oak, MI 48073

1. O'Neill WW, Chandler JG, Gordon RE, et al. Radiographic detection of strut separations in Björk–Shiley convexo-concave mitral valves. N Engl J Med 1995;333:414-9.
2. de Mol BA, Kallewaard M, McLellan RB, van Herwerden LA, Defauw JJ, van der Graaf Y. Single-leg strut fractures in explanted Björk-Shiley valves. Lancet 1994;343:9-12.

SOY PROTEIN AND SERUM LIPIDS

To the Editor: In reporting the results of a meta-analysis of the effects of soy protein on serum lipid levels (Aug. 3 issue), Anderson et al.[1] commented on the position of the American Heart Association (AHA) on this issue. The conclusion of the 1993 AHA Rationale of the Diet–Heart Statement was that although there is good evidence that soy protein can lower cholesterol levels in animal models, the effects in humans, with a few exceptions, are not nearly so convincing.[2] Indeed, most studies included in the analysis by Anderson et al. did not show a significant reduction in levels of low-density lipoprotein cholesterol, as was the case with a well-controlled study that was excluded from the meta-analysis but cited in the AHA report.[3] Furthermore, the meta-analysis fails to show a significant effect in subjects with plasma cholesterol levels below 200 mg per deciliter, the principal population group to whom the AHA report was directed. Regardless of the validity of the meta-analysis, it is not prudent to use such "averaged" information to make specific dietary recommendations for the public, rather than for people with high serum cholesterol concentrations.

On the other hand, the moderate use of soy protein is consistent with the dietary guidelines of the AHA if soy-based food products are included in a diet that is balanced overall. On the basis of stronger and more extensive evidence than that included in the meta-analysis, these recommendations call for limiting the intake of animal fat, which is associated with animal protein, and consuming more vegetables and fruits. The article by Anderson et al. may appropriately serve to call readers' attention to considering soy protein as a food option. As with other studies of specific foods, however, the AHA is concerned about the potential for medical reports to focus on a single nutrient and in so doing to deflect attention from established, broader-based principles of nutrition.

In addition, more information is needed on the mechanisms of the presumed effects of soy protein on serum lipids. For example, if plant estrogen components of soy products are important, as suggested,[1] it will be necessary to understand their overall biologic effect, including the conceivable risks associated with high intake, as well as the variability of soy preparations with respect to the content of such estrogens. The AHA's Nutrition Committee can be expected to develop more specific guidelines for the intake of soy products as information accumulates from research.

RONALD M. KRAUSS, M.D.
Lawrence Berkeley
National Laboratory
Berkeley, CA 94720

ALAN CHAIT, M.D.
University of Washington
Seattle, WA 98195

NEIL J. STONE, M.D.
Northwestern University
Medical School
Chicago, IL 60611

1. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995;333:276-82.
2. Chait A, Brunzell JD, Denke MA, et al. Rationale of the diet-heart statement of the American Heart Association: report of the Nutrition Committee. Circulation 1993;88:3008-29.

3. Grundy SM, Abrams JJ. Comparison of actions of soy protein and casein on metabolism of plasma lipoproteins and cholesterol in humans. Am J Clin Nutr 1983;38:245-52.

The authors reply:

To the Editor: Krauss et al. note that most studies included in our report[1] did not show significant decreases in serum concentrations of low-density lipoprotein cholesterol. Meta-analyses are specifically designed to address clinical questions when there is a disparity between studies.[2] Traditional reviews rely heavily on personal judgment and are subject to the biases of the authors.[3] Meta-analyses usually focus on single clinical questions.[2] A basic objective of the approach is to increase the power of tests of significance by combining the results of different studies and thus to strengthen conclusions about the efficacy of treatment.

Often, single studies are too limited in size or scope to detect significant effects. The pooling process used in meta-analysis weights studies to maximize the precision of estimates of the average effect. Such estimates are an important index of the general efficacy of treatment and can assist in resolving inconsistencies between the results of individual studies.[4,5]

Although our conclusion that soy protein intake significantly decreases serum cholesterol concentrations is supported by the meta-analysis, trained clinical scientists would probably draw similar conclusions from these data even without statistics. In 34 of 38 controlled clinical trials (89 percent), serum cholesterol concentrations decreased more with soy protein than with the control treatment; in the 4 studies that did not report reductions, the initial serum cholesterol values averaged 185 mg per deciliter. The unweighted net reduction in serum cholesterol — the "average" reduction obtained without weighting for sample size or variance — was 10.0 percent, a figure quite similar to the weighted net reduction of 9.3 percent.

Our observations[1] that reductions in serum cholesterol concentrations in patients with soy protein intake are highly correlated with base-line serum cholesterol concentrations have important clinical implications; persons with moderate-to-severe hypercholesterolemia are likely to have substantial benefits. However, even those with serum cholesterol concentrations below 200 mg per deciliter had an estimated decrease in the serum concentration of low-density lipoprotein cholesterol of 7.7 percent.

James W. Anderson, M.D.
Bryan M. Johnstone, Ph.D.
Margaret E. Cook-Newell, M.S., R.D.
Lexington, KY 40536-0086 University of Kentucky

1. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995;333:276-82.
2. Goodman SN. Have you ever meta-analysis you didn't like? Ann Intern Med 1991;114:244-6.
3. Abramson JH. Meta-analysis: a review of pros and cons. Public Health Rev 1990/91;18:1-47.
4. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
5. National Research Council. Combining information: statistical issues and opportunities for research. Washington, D.C.: National Academy Press, 1992.

LABORATORY-ACQUIRED SABIÁ VIRUS INFECTION

To the Editor: In their editorial (Aug. 3 issue),[1] Drs. Murphy and Johnson recommend that the causes of a laboratory accident at Yale University in the summer of 1994 should be carefully reviewed. In fact, shortly after the incident Yale requested two reviews, one by an internal biologic-safety committee of distinguished Yale scientists and a second by an external review committee of distinguished U.S. scientists convened at Yale's request by the Centers for Disease Control and Prevention. Both of these helpful and constructive reviews established human error as the principal factor in the incident and recommended improvements in laboratory procedures to prevent a recurrence. Both reviews were publicly released by Yale last December, and all their recommendations have been implemented.

Robert W. Ryder, M.D.
Elan J. Gandsman, Ph.D.
Yale University
New Haven, CT 06520-8034 School of Medicine

1. Murphy FA, Johnson KM. An exotic viral disease acquired in a laboratory. N Engl J Med 1995;333:317-8.

BOOK REVIEWS

Screening the Body: Tracing medicine's visual culture

By Lisa Cartwright. 199 pp., illustrated. Minneapolis, University of Minnesota Press, 1995. $17.95. ISBN 0-8166-2290-6.

In March 1992, the editor of the *Journal* inaugurated the Images in Clinical Medicine section with an editorial pointing out the enormous variety of visual images that doctors use in their daily work. Noting how crucial these images are to clinical decisions, he argued that they are not just representations of a reality independent of viewers; instead, they induce within viewers a rich cognitive model of reality that is necessary for their interpretation. *Screening the Body* builds elaborately on this theme, arguing in a variety of ways that visual images in medicine can be understood only in relation to the physicians who view them and that these images reveal as much about the medical culture in which they are used as they do about the actual objects and processes they depict.

Cartwright, a professor of English and visual and cultural studies at the University of Rochester, attempts to recover in this book the professional attitudes and ideologies represented in the clinical images of the past. Her primary focus is on the medical cinema, by which she means medicine's "motion pictures": graphic tracings and films of dynamic physiologic processes, for example, or film studies of movement disorders, or educational public health movies. Her premise is that there is a close relation between medicine and cinema that dates back to the invention of the cinematograph in 1895 by Auguste and Louis Lumière, brothers who promoted the use of the machine in medical research. Medicine and motion pictures have influenced each other ever since, Cartwright contends, and one can find in medical films of both the past and the present a rich interaction between cultural and scientific values, especially with respect to notions of the human body. She is trying, simply stated, to put the "cine" back in medicine.

The book does not provide a complete history of the development of medical films and imaging but instead comprises essentially five loosely connected and theoretical case studies in the long tradition of image making and filmmaking in med-