Correspondence

Dietary Trends in the United States

To the Editor: Popkin et al. (Sept. 5 issue)[1] compared dietary trends among racial and socioeconomic groups in the United States between 1965 and 1989–1991. Judged on the basis of today's dietary wisdom, persons with high incomes in 1965 had especially poor diets, with improvement by 1989–1991. Persons with low incomes had less change in diet over this period.

Dietary advice to the public, of course, has changed substantially since the 1960s.[2-5] Emphasis on the four basic food groups (encouraging substantial intake of red meat and whole milk) gradually shifted to an increasing concern about saturated-fat intake. The authors' data might largely reflect greater access to evolving nutritional recommendations among those with high incomes and more disposable income to spend at the grocery store to follow changing dietary advice.

Do the authors have data comparing how well persons in high- and low-income brackets in 1965 complied with the diet recommendations then being offered to the public? Perhaps persons with high incomes were more compliant in following the best diet at the time, and what changed between 1965 and 1989–1991 was largely the advice they were following.

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2. The normal adult diet. In: Burton BT, ed. The Heinz handbook of nutrition. New York: McGraw-Hill, 1959:146-50.
3. Recommended allowances. In: Brock JF. Recent advances in human nutrition. London: J. & A. Churchill, 1961:102-7.
4. Recommended dietary allowances and the adequate diet. In: Krause MV, Mahan LK. Food, nutrition, and diet therapy: a textbook of nutritional care. 7th ed. Philadelphia: W.B. Saunders, 1984:215-37.
5. Optimal nutrition for health and well-being. In: Burtis G, Davis J, Martin S. Applied nutrition and diet therapy. Philadelphia: W.B. Saunders, 1988:234-55.

To the Editor: Popkin and his colleagues conclude that "by the 1989–1991 survey, the diets of all [socioeconomic and racial] groups had improved and were relatively similar." Although this may be true, the conclusion depends on the respondents' own recall of their diets over a one-day period — a method that is notoriously prone to error. In general, participants in dietary-recall studies tend to underestimate the number of calories they consume and overestimate their nutrient intake.

An alternative explanation for the reported similarities in diet may be that during the 25-year period between 1965 and 1989–1991 the respondents had been exposed to enough information about what constitutes a good diet to be able to report what they thought the investigators wanted to hear. Thus, these results may measure the success of educational efforts rather than any concomitant change in actual eating behavior. The epidemic of obesity in the United States, which is most severe among poorer, nonwhite groups, suggests that some of our nutritional habits have not improved. Figures about the kinds of food that were actually purchased and consumed during the study period are needed.

In 1973, Rathje and Murphy started the Garbage Project at the University of Arizona[1] in an attempt to apply state-of-the-art archeological techniques to the study of contemporary urban garbage. By 1992 the project had analyzed more than 100,000 kg of garbage, including large

amounts of food remnants and food packaging. The composition of this garbage was so at odds with what people said they were eating that Rathje and Murphy coined the term "lean cuisine syndrome." They wrote:

> People consistently underreport the amount of regular soda, pastries, chocolate, and fats that they consume; they consistently overreport the amount of fruits and diet soda. . . . In sum, the data generated by the Garbage Project in its cross-check of the USDA's [U.S. Department of Agriculture's] Nationwide Food Consumption Survey reveal that much of the information in the government's vaults about food consumption and waste may be shaky stuff indeed.[1]

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1. Rathje W, Murphy C. Rubbish! The archaeology of garbage. New York: HarperCollins, 1992:70-1.

To the Editor: Kumanyika (Sept. 5 issue)[1] has set out the two nutritional dilemmas. The first concerns well-circumstanced people, whose diet according to current guidelines should revert "in many respects [to] the traditional eating pattern of poor people throughout the world." Then there is the converse situation, "as people raise their standard of living, they may adopt eating patterns that have traditionally been associated with higher incomes but that are no longer considered desirable."

Among the white population of South Africa, causes of morbidity and mortality closely resemble those of Western populations.[2] Among rural South African blacks living traditionally, there was until recently a high rate of mortality among the very young, but among adults there was little or no increase in weight or blood pressure with age. Moreover, diabetes, coronary heart disease, and diet-related cancers (colon, prostate, and breast) were either absent or rare. There were certainly plenty of old people of 70 to 90 years of age, and some claimed to be 100. In strong contrast, nowadays, in big cities, where nearly half the black population lives, there has been an enormous fall in child mortality, resulting in a major increase in survival. However, unfortunately, with the changes in diet and other aspects of lifestyle, the prevalences of dental caries, hypertension, obesity in women, and diabetes have risen and now exceed those in whites.

The white population has virtually no intention of conforming to a "prudent" lifestyle, dietarily or otherwise. Yet, ironically in recent years, the mortality rate from coronary heart disease has decreased by half.[3] The urban black population, with its increase in socioeconomic status, is determined to emulate the lifestyle of the whites, with rising intakes of energy and fat and falling intakes of fiber-containing foods.

Kumanyika affirms that "as we learn more about diet-related risks to health, we should not forget to use this knowledge to guide public policy." However, according to Popkin et al., in the last generation, despite strong encouragement, the intake of energy from fat among those of medium socioeconomic status has fallen only slightly, and the number of servings of fruit and vegetables consumed has remained virtually unchanged. As is the case regarding the control of cancer, the knowledge is there but not the will to apply it.[4]

How much does it matter? Although life span in developed and developing urban populations is at its highest point ever, little improvement is likely to occur in the number of disease-free or "well" years.

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1. Kumanyika S. Improving our diet — still a long way to go. N Engl J Med 1996;335:738-40.
2. Walker ARP. Nutrition-related diseases in Southern Africa: with special reference to urban African populations in transition. Nutr Res 1995;15:1053-94.
3. Walker AR, Adam A, Küstner HG. Changes in total death rate and in ischaemic heart disease death rate in interethnic South African populations, 1978-1989. S Afr Med J 1993;83:602-5.
4. Muir CS, Sasco AJ. Prospects for cancer control in the 1990's. Annu Rev Public Health 1990;11:143-63.

The authors reply:

To the Editor: Nusbaum and Eshleman suggest that dietary trends may reflect respondents' adherence to the dietary guidelines of the time. From 1916 to 1976, nutritional recommendations relative to the basic food groups were fairly stable.[1] The basic five food groups of 1916 were reduced to the basic four (two daily servings of milk and of meat, poultry, or eggs and four daily servings of fruits and vegetables and of breads and grains) in the 1960s. Not until the introduction of the U.S. Dietary Goals in 1977 did dietary guidelines explicitly recommend nutrient limitations for fats, sugars, and cholesterol. Neither our group nor others have attempted to quantify the dietary guidelines of the 1960s or to ascertain who followed the guidelines most closely.

Eshleman is correct that obesity increased significantly during the period we studied and that methods of collecting dietary-intake data underestimate total intake for individual subjects. Experiments using doubly labeled water to measure energy expenditure versus intake measured by alternative dietary-assessment methods concluded that people differ in the degree to which they underreport or overreport consumption.[2] These experiments suggested that most methods and people underestimated intake, but underreporting was more common among those who were or had been obese.

The many comparisons of the relative validity of dietary-assessment methods concludes that although the use of a single 24-hour period of recall is not an appropriate tool for assessing a person's usual diet, the method is quite acceptable for assessing the average intake of groups of people.[3] With regard to the use of these data to analyze trends, there is little evidence of a systematic increase in the rate of underestimation of food consumption over time, since the methods used in the U.S. Department of Agriculture surveys are quite comparable.[4]

We agree with Walker — knowledge alone is inadequate without systematic programs and policies and a major shift in public will. He is correct about the shifts in nutritional status in South Africa, especially with respect to the in-

crease in obesity and other factors linked with insulin resistance among the black population.[5]

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1. Boyle MA, Morris DH. Community nutrition in action: an entrepreneurial approach. St. Paul, Minn.: West Publishing, 1994:139-57.
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To the Editor: Walker's comments are too pessimistic. He implies that a decent standard of living is inevitably characterized by an unhealthy lifestyle and that policy initiatives will not work. Should we then not attempt prevention among black South Africans who, like U.S. blacks in 1965, may still eat the way we consider prudent? Having a long way to go does not mean that we have made no progress, but that progress is not fast enough. The potential for achieving lifestyle changes and improving wellness through policy initiatives has not been fully exploited.[1]

Walker's suggestion that dietary changes are unnecessary because gains are being made anyway seems ill advised if, in South Africa as in the United States, gains are driven by treatment rather than prevention. Relying on treatment while leaving detrimental lifestyles unchallenged is neither feasible nor acceptable; it makes us a population of patients. Chronic-disease–related disabilities are costly and compromise quality of life for many older adults, especially blacks.[2] Moreover, if the U.S. experience is any indication, it is unrealistic to assume that factors responsible for improved health in white South Africans will necessarily apply to black South Africans. As Walker himself notes, once chronic diseases become present in groups of blacks, their frequency rises on a steeper trajectory.

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1. Milio N. Nutrition policy for food-rich countries: a strategic analysis. Baltimore: Johns Hopkins University Press, 1990.
2. National Center for Health Statistics. Health, United States, 1993. Washington, D.C.: Government Printing Office, 1994. (DHHS publication no. (PHS) 94-1232.)

Enoxaparin as Prophylaxis against Thromboembolism after Total Hip Replacement

To the Editor: We are concerned about the report of Bergqvist et al. (Sept. 5 issue)[1] and the implications it may have for patient care. They reported that among patients who had total hip arthroplasty, the rate of venography-confirmed deep-vein thrombosis was substantially reduced in those who had continuing prophylaxis with the low-molecular-weight heparin enoxaparin after hospital discharge, compared with a control group that received enoxaparin prophylaxis only while hospitalized. Although we do not question the validity of these findings, we do challenge the clinical significance of the results. Venography-confirmed deep-vein thrombosis after orthopedic surgery is an excellent end point for determining the relative efficacy of antithrombotic agents, since a high rate of events is observed. However, the clinical significance of these largely asymptomatic thrombi is uncertain. If untreated, how many will lead to thromboembolic complications?

Before a strategy of extending the duration of prophylaxis after joint arthroplasty beyond discharge from the hospital is developed, possibly increasing the risk of bleeding, we feel that large, randomized, controlled trials are required to determine whether prolonging prophylaxis reduces the rate of clinically important venous thromboembolic complications, such as symptomatic deep-vein thrombosis and pulmonary embolism. Venography, because of its high sensitivity to small deep-vein thrombi, may not be the appropriate test to diagnose symptomatic deep-vein thrombosis in such studies.

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1. Bergqvist D, Benoni G, Björgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med 1996;335:696-700.

To the Editor: I found the article by Bergqvist et al. to be a welcome documentation of the prolonged risk of venous thromboembolism after total hip replacement. Readers should note some important features of this paper, however. In the study, enoxaparin was given subcutaneously once every 24 hours in a 40-mg dose. Current marketing suggests giving 30 mg every 12 hours; in the United States, enoxaparin can be purchased only in 30-mg prefilled syringes.

In addition, the cost of 40 mg of enoxaparin, administered subcutaneously each day, would be 300 times that of daily warfarin sodium, a most acceptable alternative for prophylaxis against venous thromboembolism in outpatients ($15.00 vs. $0.05 per day). Although monitoring warfarin sodium would require an occasional measurement of the prothrombin time, the expense of this would be far less than that of daily injections.

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Dr. Bergqvist replies:

To the Editor: In one respect, our study does not differ from many other studies of thromboprophylaxis — we do not fully know the clinical relevance of asymptomatic deep-vein thrombosis. Besides our study, three additional studies have arrived at similar conclusions — that prolonged prophylaxis does significantly reduce the frequency of venographically diagnosed deep-vein thrombosis after hip arthroplasty.[1] Obviously, there is much that is still unknown: the clinical relevance of late thrombosis for pulmonary embolism and the post-thrombotic syndrome, the reproducibility of our findings in a routine clinical setting, economic implications, and detailed definition of risk groups, among others. An indication that prolonged prophylaxis may be of benefit is the reduction in the rate of symptomatic deep-vein thrombosis in our study from 8 to 2 percent and in the study by Planes et al.[2] from 8 to 3 percent. However, in our paper we did not recommend the widespread use of prolonged prophylaxis until more information is obtained. In the past, most studies of thromboprophylaxis focused on clinical end points, then attention switched to "objective" diagnostic methods such as venography and the fibrinogen-uptake test, and now we have returned to studying clinical end points.

I have no comments regarding the dosage question raised by Dr. Pedell. The dose we used is the common regimen in Europe.

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1. Bergqvist D. The postdischarge risk of venous thromboembolism after hip replacement: the role of prolonged prophylaxis. Drugs 1996;52:Suppl 7:55-9.
2. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. Lancet 1996;348:224-8.

Prophylaxis against Venous Thromboembolism after Major Trauma

To the Editor: We view with concern the claim of Geerts et al. (Sept. 5 issue)[1] that the potent anticoagulant low-molecular-weight heparin can safely be used as routine prophylaxis against deep venous thrombosis in trauma victims. The study compared low-dose heparin with low-molecular-weight heparin in a cohort of 265 patients. The authors found that deep venous thrombosis occurred at a higher rate in the low-dose–heparin group (60 of 136 patients, or 44 percent) than in the low-molecular-weight–heparin group (40 of 129, or 31 percent; $P = 0.014$). Thus, 18 (60 minus 31 percent of 136) cases of deep venous thrombosis may have been prevented in the group that received low-molecular-weight heparin. This reduction in the rate of deep venous thrombosis was purchased, however, at the price of five episodes of severe hemorrhage in the low-molecular-weight–heparin group, including one subdural hematoma requiring operative drainage. Geerts et al. note that only one episode of bleeding (a nosebleed) occurred in the low-dose–heparin "control" group but claim that there was no difference between the two groups on the basis of a Fisher's exact test P value of 0.12.

The real concern in patient care is not deep venous thrombosis but pulmonary embolism. Ironically, the single pulmonary embolism that occurred in this study was in a member of the low-molecular-weight–heparin group. Other therapies have been proposed to deal with potential pulmonary embolism that do not pose the risk of anticoagulation. The Greenfield vena caval filter has been successfully employed in several prospective studies with minimal morbidity and a significant reduction in the incidence of pulmonary embolism.[2,3]

Thus, the authors have misunderstood the risks that trauma patients face. Deep venous thrombosis is usually asymptomatic and rarely fatal. Hemorrhage is the constant and paramount risk. Anticoagulation therapy for such patients has led to complications in these authors' hands. Overall, 18 probably asymptomatic deep venous thromboses were prevented by a therapy that caused five clinically relevant episodes of hemorrhage.

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1. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 1996;335:701-7.
2. Rogers FB, Shackford SR, Ricci MA, Wilson JT, Parsons S. Routine prophylactic vena cava filter insertion in severely injured trauma patients decreases the incidence of pulmonary embolism. J Am Coll Surg 1995;180:641-7.
3. Rodriquez JL, Lopez JM, Proctor MC, et al. Early placement of prophylactic vena cava filters in injured patients at high risk for pulmonary embolism. J Trauma 1996;40:797.

The authors reply:

To the Editor: Unfortunately, Osler and Rogers misconstrue both the objectives of our study and its results. We designed an efficacy trial using total deep-vein thrombosis, detected by contrast venography, as the primary outcome. While we clearly demonstrated the superior efficacy of the low-molecular-weight heparin enoxaparin over low-dose heparin in reducing the total rate of deep-vein thrombosis, we also emphasized enoxaparin's 58 percent reduction in the risk of proximal deep-vein thrombosis — an outcome of greater clinical importance. Eventually, we hope that investigators will demonstrate in effectiveness studies that thromboprophylaxis decreases the rate of clinically important thromboembolic events. However, our important first step involved performing a double-blind, randomized trial with a sensitive and objective measure of outcome.

Despite the early use of anticoagulant prophylaxis, bleeding was uncommon (occurring in less than 2 percent of patients). We described the six bleeding episodes so that readers could make their own decision about which were clinically relevant. "Severe hemorrhage" occurred in only one patient, and there were no significant differences between the bleeding studies in the two groups. The observed bleeding rate, according to the same definition, was also equivalent to that in studies of elective arthroplasty. This low risk of clinically significant bleeding is important, since

it provides strong reassurance that anticoagulant prophylaxis can be safely used in patients with major trauma.

We do not misunderstand the risks that trauma patients face. On the contrary, the two primary authors have personally seen and followed until discharge every trauma patient at our center for more than five years. Although we and our surgical colleagues share the concern about the potential for bleeding in these patients, we have been impressed with the absence of clinical bleeding associated with an aggressive prophylaxis regimen based primarily on the use of enoxaparin. To date, we have not encountered serious bleeding complications in these patients that could be attributed to the prophylaxis.

Finally, there is not a single published trial in which trauma patients were randomized to the use of a vena caval filter. We agree that the use of filters may well be associated with fewer pulmonary emboli as compared with no prophylaxis or ineffective prophylaxis. The important as yet unresolved issue, however, is the benefit and cost effectiveness of filters when added to a prophylaxis regimen proved to be efficacious. In the meantime, it is imprudent to recommend the use of an invasive, permanent, and very costly device that is associated with both short-term and long-term complications and that increases the incidence of deep-vein thrombosis until evidence from at least one methodologically sound trial demonstrates that the use of filters is necessary or cost effective.

Our data provide strong evidence that low-molecular-weight heparin is an effective, safe method of prophylaxis in this extremely high risk group of patients. We encourage physicians interested in the care of trauma patients to advocate evidence-based thromboprophylaxis strongly and to contribute to well-designed trials in this area.

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Association between Prior Cytomegalovirus Infection and the Risk of Restenosis after Coronary Atherectomy

To the Editor: The association between seropositivity for cytomegalovirus (CMV) and restenosis after coronary atherectomy reported by Zhou et al. (Aug. 29 issue)[1] is intriguing, but their analysis leaves open several questions. The authors included four patients in the CMV-positive group who, though initially seropositive, were seronegative at the six-month follow-up visit. Three of these patients had initial CMV titers just above the cutoff for seropositivity, whereas one had a midrange titer; all the titers dropped to nearly zero on follow-up. This raises the question of whether these patients in fact had CMV infection.[2] Since they all had restenosis, including them in the CMV-positive category has substantial bearing on the results. Had the infections been classified on the basis of the results of serologic testing at six months rather than before atherectomy, our calculations suggest that CMV would not have been identified as a risk factor for restenosis (odds ratio, 2.4; 95 percent confidence interval, 0.7 to 8.3). Given the uncertainty of these patients' CMV status, it would seem prudent at a minimum to omit them from the analysis.

Another problem we perceived is the use of the CMV titer as a continuous variable. Although it would be interesting to correlate titers with outcomes, only patients considered to be seropositive should be studied. Seronegativity is used to indicate the absence of prior exposure to CMV; therefore, no variation in a negative titer is meaningful. Moreover, since the distribution of titers was markedly skewed, some method of normalizing the data must be used before the parametric methods described can be employed. As presented, the use of continuous titers gives no more information than the dichotomous analysis.

Finally, we have reservations about the analyses that were conducted "by vessel" rather than "by patient." The coronary vessels of an individual patient are not independent of one another. Not only might events in one part of the heart influence events elsewhere, but the inclusion of more than one vessel from a given patient may give undue weight to unrecognized confounding factors. Other studies have shown that coronary arteries differ in their risk of restenosis, and patients with multivessel disease may also be at increased risk.[3,4] A more complete description of the vessels studied, including an indication of whether the patient had multivessel disease, would make it easier to understand what effect, if any, CMV had on the risk of restenosis.

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1. Zhou YF, Leon MB, Waclawiw MA, et al. Association between prior cytomegalovirus infection and the risk of restenosis after coronary atherectomy. N Engl J Med 1996;335:624-30.
2. Landini MP, Mach M. Searching for antibodies specific for human cytomegalovirus: is it diagnostically useful? When and how. Scand J Infect Dis Suppl 1995;99:18-23.
3. Fishman RF, Kuntz RE, Carrozza JP Jr, et al. Long-term results of directional coronary atherectomy: predictors of restenosis. J Am Coll Cardiol 1992;20:1101-10.
4. Giuliani ER, Gersch BJ, McGoon MD, Hayes DL, Schaff HV, eds. Mayo Clinic practice of cardiology. 3rd ed. St. Louis: Mosby–Year Book, 1996.

To the Editor: Zhou and colleagues report that prior CMV infection, as assessed by titers of anti-CMV IgG antibodies, is an independent risk factor for the development of restenosis six months after directional coronary atherectomy. The authors observed a 43 percent rate of restenosis in the seropositive patients, as compared with an 8 percent rate in the seronegative patients. These findings would appear to strengthen the earlier demonstration by the same group[1] of CMV DNA sequences in atherectomy samples with restenosis and the production of IE84, one of the virus's immediate early proteins, by smooth-muscle cells grown in vitro from such lesions.

Since titers of anti-CMV IgG antibodies did not change during the study period, the authors affirm that their results "are most compatible with the idea that either the virus produced an abortive infection . . . or viral replication occurred locally in the absence of systemic viremia."[2] It is conceivable, therefore, that the local detection of

CMV messenger RNA (mRNA) would be needed to prove definitively that active CMV infection has a pathogenetic role in the development of restenosis and ischemic syndromes. In this respect, we recently reported[3] that of a group of atherectomy specimens from 40 patients with stable or unstable angina, none of the 33 patients with primary lesions, and not even the 7 with restenosis, were positive for CMV IE84 mRNA. Although the small samples did not allow us to study the presence of both DNA and RNA or measure anti-CMV IgG antibodies in our patients, our findings suggest that the authors' hypothesis, that an active local CMV infection may have a pathogenetic role, should be considered with caution.

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1. Speir E, Modali R, Huang E-S, et al. Potential role of human cytomegalovirus and p53 interaction in coronary restenosis. Science 1994;265:391-4.
2. Zhou YF, Leon MB, Waclawiw MA, et al. Association between prior cytomegalovirus infection and the risk of restenosis after coronary atherectomy. N Engl J Med 1996;335:624-30.
3. Kol A, Sperti G, Shani J, et al. Cytomegalovirus replication is not a cause of instability in unstable angina. Circulation 1995;91:1910-3.

The authors reply:

To the Editor: Dr. Kol and associates are correct. Our data do not allow us to conclude that if CMV contributes to restenosis, it necessarily operates through a local effect of the virus on the vessel wall. However, their data clearly do not prove the converse, for several reasons. First, they studied only seven patients with restenosis, too few to permit definitive conclusions. Second, the virus may have expressed CMV mRNA at the time of angioplasty but not several months later, when the tissue was retrieved for analysis. Finally, atherectomy retrieves only part of the lesion, and therefore there may be false negative results. We believe that anti-CMV antibodies are a more sensitive measure of the presence of CMV than atherectomy-based sampling of lesions.

Drs. Smith and Parsonnet believe that either the four patients who were seropositive at entry into the study but seronegative at the six-month follow-up should be excluded from the analysis or the cohort should be analyzed on the basis of serologic tests at six months. Excluding the four patients is unwarranted, because the prospectively determined end point of the study was the correlation between restenosis and the base-line CMV-antibody status. Therefore, the analysis was performed without bias due to knowledge of the restenosis status. To arbitrarily omit four patients from the analysis because of an end point that was not identified prospectively would not be scientifically valid. Furthermore, if CMV does contribute to restenosis, we would expect that CMV status at the time of atherectomy would be most relevant to any CMV-induced effect on restenosis.

We analyzed the CMV titer as a continuous variable in order to deal directly with the previous point Smith and Parsonnet raise. Although we defined seropositivity prospectively, any such definition is admittedly arbitrary. We therefore wanted to ascertain whether there was a correlation between the CMV titer as a continuous variable and restenosis. This was in fact the case. It would have been inappropriate to focus only on the seropositive patients.

Smith and Parsonnet question our analyses conducted "by vessel" rather than "by patient." It is difficult to determine which approach is better. As a result, we analyzed our data both ways. Thus, 43 percent of patients who were CMV-seropositive had restenosis, as compared with 8 percent of patients who were seronegative. In addition, the analyses by vessel, a type of assessment commonly used by interventional cardiologists, showed that there was a significant correlation between the loss index and seropositivity. The point is moot, however, because of the 75 patients studied, only 10 had two-vessel angioplasty; the rest had angioplasty of a single vessel.

We would emphasize that although our article shows a strong association between prior CMV infection (as indicated by CMV seropositivity) and restenosis, our findings must be confirmed by further studies before a definite relation between CMV and restenosis can be accepted as proved.

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Heparin-Induced Skin Necrosis

To the Editor: In the September 5 Image in Clinical Medicine[1] the appearance of the skin lesion described as heparin-induced skin necrosis is also compatible with a diagnosis of ecthyma gangrenosum. The authors do not state whether the heparin injected was sterile or whether cultures of aspirates from the skin lesion grew gram-negative organisms. This information would be useful for the differential diagnosis.

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1. Christiaens GCML, Nieuwenhuis HK. Heparin-induced skin necrosis. N Engl J Med 1996;335:715.

To the Editor: With respect to the image of heparin-induced skin necrosis, the authors should have considered other causes, since the initial injections of heparin apparently did not result in similar lesions. The morphology and clinical course of a cutaneous lesion resulting in ulceration requiring skin grafting resemble those of ecthyma gangrenosum observed in cases of *Pseudomonas aeruginosa* septicemia. Was the patient immunosuppressed? Did she have any associated systemic symptoms or neutropenia? Did she receive any antibiotic therapy before or after the appearance of the skin lesion?

Similar lesions are also possible in primary cutaneous infections with *P. aeruginosa* (primary *P. aeruginosa* pyoderma), other gram-negative rods such as *Escherichia coli,* klebsiella, or even fungi. Did the authors perform Gram's staining and culture of the aspirate from the lesion? Secondary infection from a contaminated needle or some other source is always a possibility in hospitals. Biopsy of the lesion might have documented large numbers of bacteria invading the blood vessels, with few inflammatory cells in the case of ecthyma gangrenosum.[1]

Furthermore, the estimations of protein C and protein S mentioned in the report seem irrelevant, since deficiencies of these proteins predispose patients to skin necrosis after warfarin therapy and not heparin. Warfarin given alone in those situations causes a further decrease in protein C or protein S concentrations (since they are dependent on vitamin K), leading to thrombosis of veins and capillaries supplying blood to the skin and resulting in extensive necrosis.

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1. Pollack M. Pseudomonas infections. In: Isselbacher KJ, Martin JB, Braunwald E, Fauci AS, Wilson JD, Kasper DL, eds. Harrison's principles of internal medicine. 13th ed. Vol. 1. New York: McGraw-Hill, 1994:665-71.

To the Editor: Do the authors know for a fact that heparin was given? Could the patient have received a subcutaneous injection of a vasoactive, vasoconstrictive agent, such as epinephrine?

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To the Editor: The image of heparin-induced skin necrosis is a striking and instructive example of this clinical problem. However, the report would have been made more complete by the inclusion of skin-biopsy findings on this bullous lesion for both routine hematoxylin-and-eosin staining and immunofluorescence microscopy to establish the diagnosis.

Despite the clear-cut history of recent heparin injections at the lesion site, the lesion might have had other causes — bullous erythema multiforme, pemphigus vulgaris, and bullous impetigo to name just a few. Since a skin graft was necessary to repair the lesion, a definitive diagnosis is imperative. Histologic findings in heparin-induced necrosis include extensive thrombosis of the dermal and subcutaneous vessels, with hemorrhage and focal epidermal necrosis but no evidence of vasculitis or an inflammatory infiltrate.[1]

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The authors reply:

To the Editor: We agree with Drs. McCloskey and Kumar that infectious causes should be considered in the differential diagnosis of erythematous, necrotic skin lesions after an injection. In this case there were no indications of an infection, the patient was otherwise healthy and was not immunocompromised, and cultures were negative for pathogens.

With respect to the comment of Dr. Schechter, we believe it is very unlikely that the patient was given an injection of epinephrine instead of heparin. A skin biopsy may be helpful if one is doubtful about the diagnosis of a heparin-induced skin lesion, but it is usually not necessary. Heparin-induced skin lesions at injection sites typically begin five or more days after the initiation of treatment. The lesions may appear as painful erythematous plaques or skin necrosis. Heparin-dependent platelet-activating antibodies may be present. This adverse effect is not uncommon; Warkentin[1] observed it in six patients over a 30-month period.

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Heroin Inhalation and Progressive Spongiform Leukoencephalopathy

To the Editor: We report two cases of a progressive spongiform leukoencephalopathy that, to our knowledge, has not been reported previously in the United States. The disease occurred after the patients inhaled heated heroin vapor, a practice known as "chasing the dragon."

In Patient 1, a 21-year-old woman with a six-month history of inhaling heroin vapor, progressive bradykinesia, ataxia, and slurred speech developed over a two-week period. She denied using intravenous drugs. On admission she had abulia. She followed simple, one-step commands, but there was a long period of latency before she initiated movements, which were slow and ataxic. She maintained a decorticate posture at rest, with normal tendon reflexes. Over the next two weeks she became mute, spastic, nearly quadriplegic, and unable to stand or sit.

Blood tests revealed traces of heroin, cocaine, and methadone. The results of serologic tests for the human immunodeficiency virus (HIV), routine analyses of serum chemistry, hematologic tests, and cerebrospinal fluid studies were normal. A computed tomographic scan showed diffuse lucency of the cerebellar and cerebral white matter. T_2-weighted magnetic resonance imaging (MRI) showed diffuse, symmetric areas of hyperintensity in the white matter of the cerebellum, the posterior cerebrum, the corticospinal tract, and the lemniscal pathway (Fig. 1). A brain biopsy revealed spongiform degeneration of the white matter, with relative sparing of subcortical fibers (U fibers).

Patient 2 was a 40-year-old musician with a six-month history of intranasal use of cocaine and heroin; he had inhaled heroin vapor daily with Patient 1 for two weeks,

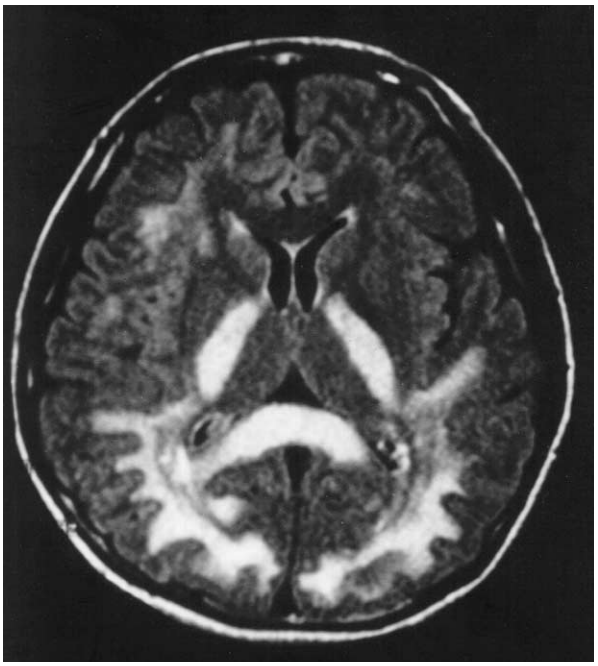

Figure 1. Modified T_2-Weighted Spin–Echo MRI Scan of the Brain in Patient 1.

There are symmetric lesions of high signal intensity in the occipital white matter, the posterior limb of the internal capsule, and the splenium of the corpus callosum. These findings are characteristic of toxic heroin-induced leukoencephalopathy.[1]

ending three weeks before admission. During the week before admission he had difficulty playing the drums and began bumping into furniture. He had dysarthric, scanning speech and saccadic-pursuit eye movements with ocular dysmetria. His arm movements were ataxic, with dysmetria, dysdiadochokinesia, and rebound. His gait was broad-based and ataxic. HIV serologic, hematologic, and cerebrospinal fluid studies were normal. Cerebral T_2-weighted MRI findings were similar to those in the first patient: diffuse, symmetric areas of white-matter hyperintensity most prominent in the cerebellum, but also involving the posterior cerebrum, the splenium of the corpus callosum, and the posterior limbs of the internal capsule. After treatment with ubiquinone (coenzyme Q; 300 mg four times daily), Patient 2 had clinical improvement.

Toxic heroin-induced progressive spongiform leukoencephalopathy has a characteristic pattern on MRI (Fig. 1). An outbreak in the Netherlands in 1982 involved 47 people.[2] Subsequent cases have been reported elsewhere in Europe.[1,3-5] In all instances, the mode of ingesting heroin was to heat the powder on aluminum foil and inhale the vapor.[1-5] There have been suspicions about possible contamination of small batches of the drug by an unknown substance that is activated by heating. The illness has no known treatment and a mortality rate of 25 percent.[1-3,5] "Dragon chasing" is gaining popularity among drug abusers in the United States as a means of ingesting heroin that averts the risk of exposure to HIV. Unfortunately, the practice puts users at risk for toxic heroin-induced leukoencephalopathy.

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