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Inflammation, Aspirin, and the Risk of Cardiovascular Disease

To the Editor: Ridker and colleagues (April 3 issue)[1] have provided important new information that will be useful in assessing the risk of cardiovascular events and in optimizing prophylaxis. Both Ridker et al. and Maseri, in his editorial,[2] speculate that the antiinflammatory effects of aspirin may be important in reducing the risk of myocardial infarction when the level of C-reactive protein is high.

It seems unlikely that the antiinflammatory effects of aspirin have an important role, since these effects are minuscule and short-lived at the dosage used in the study by Ridker et al. (325 mg every other day). Were these effects of aspirin indeed important, higher doses would be expected to confer a greater cardioprotective effect. I am not aware of any controlled study that has demonstrated a greater effect with higher doses.

An alternative possibility is that an elevated level of C-reactive protein is associated with increased coagulability (local or systemic, or both) and that the cardioprotective effects of aspirin are proportional to the magnitude of this increase in coagulability.

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1. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.

2. Maseri A. Inflammation, atherosclerosis, and ischemic events — exploring the hidden side of the moon. N Engl J Med 1997;336:1014-6.

To the Editor: The report by Ridker et al. adds further support to the response-to-injury hypothesis proposed 20 years ago by Ross et al.[1] However, the conclusion that the benefits of aspirin arise, at least in part, from its antiinflammatory activity is difficult to accept. A dose of one aspirin tablet every other day can hardly be considered an antiinflammatory regimen of the drug. The short (15-minute) biologic half-life of aspirin adds to the doubt. The salicylate resulting from the degradation of aspirin is a very weak contributor to its antiinflammatory effects.

It still seems probable that the unique properties of both aspirin and platelets — namely, aspirin's acetylation of the enzyme cyclooxygenase and a platelet's inability to synthesize the new enzyme — are responsible for all the antithrombotic effects observed.

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1. Ross R, Glomset J, Harker L. Response to injury and atherogenesis. Am J Pathol 1977;86:675-84.

To the Editor: Ridker and colleagues report that in their study the effect of aspirin on the risk of cardiovascular disease was largely confined to patients with elevated C-reactive protein levels and that an elevated level of C-reactive protein was associated with arterial but not venous thrombosis. The authors hypothesize that the benefits of aspirin in this subgroup reflect antiinflammatory rather than antiplatelet effects of this agent. We suggest an alternative hypothesis.

Platelets are inflammatory cells.[1] In evolutionary terms, platelets are derived from hemocytes — single circulatory blood cells with the combined functions of participating in the inflammatory response, oxygen carriage, and hemostasis.[2] Activated platelets secrete numerous proinflam-

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matory molecules, including thromboxane A_2, which is blocked by aspirin.

The association of platelet activation with the inflammatory process is well documented in inflammatory bowel disease.[3] Platelet activation may contribute to the microvascular thrombosis and infarction reported in association with this condition.

With regard to the link between interleukin-6 and C-reactive protein, to which the authors refer, it should be noted that interleukin-6 has a stimulatory effect on megakaryocytes[4] and may thus be linked to alterations of platelet function.

For these reasons, we propose that in further work addressing these intriguing observations, researchers should avoid a spurious dichotomy between the thrombotic and inflammatory effects of platelets.

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1. Page CP. Platelets as inflammatory cells. Immunopharmacology 1989; 17:51-9.
2. Iwanaga S. Primitive coagulation systems and their message to modern biology. Thromb Haemost 1993;70:48-55.
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4. Wong GG, Witek-Giannotti JS, Temple PA, et al. Stimulation of murine hemopoietic colony formation by human IL-6. J Immunol 1988;140: 3040-4.

To the Editor: The study reported by Ridker et al. shows that C-reactive protein, as an acute-phase reactant, predicts the risk of myocardial infarction and stroke. However, this study was mostly concerned with the serum level of C-reactive protein as an inflammatory marker, and there is no mention of its presence in the normal and atherosclerotic arterial wall in humans.[1,2] We have previously measured the level of C-reactive protein eluted from the human arterial wall with different degrees of atherosclerosis.[1] Fatty streaks and uncomplicated fibrous plaques contained the highest levels of C-reactive protein. Lower levels were found in areas of intimal thickening, and only a few normal areas contained the protein.[1,2]

The accumulation of C-reactive protein in the atherosclerotic wall suggests a local inflammatory event. It is difficult to establish whether the protein is produced locally or derived from the circulation, but both mechanisms are involved in the accumulation of most of the proteins present in the arterial wall. We found that C-reactive protein was localized around the foam cells of fatty streaks, suggesting its local synthesis.[3] For such a strongly responsive and potent acute-phase reactant as C-reactive protein, the small but constant and clinically significant increase in its plasma levels, as Ridker et al. observed in their study, may suggest its slow release from the arterial wall with atherosclerotic lesions.

It is also important to mention that not only C-reactive protein but also other acute-phase reactants, such as complement proteins C3, C4, and C9, as well as important inflammatory cytokines, such as interleukin-6 and interleukin-8, are accumulated in the atherosclerotic wall.[1,3,4] The complement system, which is an important immune effector, is present in the arterial wall in its activated form, and this is an important observation, since C-reactive protein is one of its known potent activators.[3]

Thus, C-reactive protein seems to be directly involved in promoting local inflammation by activating other mediators. Its increased concentration in plasma and clinically predictive role should be correlated and indeed reflect, as shown by Ridker et al., events occurring at the level of the arterial wall, where inflammation is responsible for the progression of the atherosclerotic lesion.

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1. Vlaicu R, Rus HG, Niculescu F, Cristea A. Immunoglobulins and complement components in human aortic atherosclerotic intima. Atherosclerosis 1985;55:35-50.
2. Reynolds GD, Vance RP. C-reactive protein immunohistochemical localization in normal and atherosclerotic human aortas. Arch Pathol Lab Med 1987;111:265-9.
3. Niculescu F, Rus HG, Vlaicu R. Immunohistochemical localization of C5b-9, S-protein, C3d and apolipoprotein B in human arterial tissues with atherosclerosis. Atherosclerosis 1987;65:1-11.
4. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. Atherosclerosis 1996;127:263-71.

The authors reply:

To the Editor: Dr. Murray raises the intriguing possibility that our observations are attributable to an association between C-reactive protein and hypercoagulability. This hypothesis, however, is not supported by our finding that there was no association between C-reactive protein and venous thrombosis, a disease more closely linked to hypercoagulability than to atherothrombosis.

Dr. Bruno suggests that the antithrombotic effects of aspirin may explain our results and that the apparent increase in the efficacy of aspirin across quartiles of C-reactive protein simply reflects a greater benefit among those at greater risk. In prior reports on aspirin from the Physicians' Health Study, we observed no greater benefits in higher-risk subgroups.[1,2]

We concur with Drs. Murray and Bruno that the short half-life of aspirin renders a conventional antiinflammatory contribution from this agent less likely. Our data do raise the question of whether this contribution is adequate for microinflammatory inhibition. In this regard, the points made by Drs. Cahill and Perry, that platelets themselves can be considered inflammatory cells and that they secrete proinflammatory molecules, are of considerable interest.

The possibility that aspirin has different effects in different thrombotic settings, such as those associated with plaque rupture as compared with endothelial erosion,[3] is supported by the observations of Drs. Rus and Niculescu regarding the presence of C-reactive protein within the atherosclerotic arterial wall.[4] Whether this accumula-

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tion is more or less apparent in lesions associated with plaque rupture is also an important question to be investigated.

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1. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
2. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med 1991;325:373-81.
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To the Editor: Dr. Murray's timely letter offers me the opportunity to comment further on the progressive reduction of the risk of myocardial infarction with increasing levels of C-reactive protein in patients taking 325 mg of aspirin on alternate days.[1] I agree with Dr. Murray that the available evidence is against the hypothesis that aspirin acts as an antiinflammatory drug because of its short plasma half-life and because inflammatory cells can resynthesize cyclooxygenase.

Unpublished data from our group indicate that both in patients with stable angina and in those with unstable angina, the increase in serum C-reactive protein levels in response to diverse inflammatory stimuli is proportional to the base-line levels of C-reactive protein. Thus, the base-line values may be markers of a variable individual propensity for an enhanced acute-phase response. The hyperresponsiveness of acute-phase reactants can result in enhanced production and an enhanced effect of prothrombotic inflammatory cytokines, which under some conditions may contribute to the development of unstable angina, myocardial infarction, and stroke. This hypothesis may link the long-term prognostic value of C-reactive protein levels within the normal range (as observed in the Physicians' Health Study[1]) and the prognostic value of mildly elevated levels in patients with stable ischemic heart disease[2] or unstable angina at the time of hospital discharge[3] with the short-term in-hospital prognostic value of markedly elevated levels of C-reactive protein in patients with unstable angina.[4] Moreover, my colleagues and I failed to observe significant differences in cytomegalovirus and *Helicobacter pylori* serum antibody titers between patients with chronic ischemic syndromes and those with acute ischemic syndromes.[5] Therefore, the greater effect of aspirin in persons in the higher quartiles of the normal range of C-reactive protein in the Physicians' Health Study[1] is not easily explainable. Since the confidence limits for the risk reduction in the four groups may overlap, the differences may simply be due to the fact that the reduction in risk was more easily detectable in the higher-risk group than in the lower-risk group. However, this intriguing finding should be confirmed by other studies before there is extensive discussion about its possible interpretation.

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1. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.
2. Thompson SG, Kienast J, Pyke SDM, Haverkate F, van de Loo JCW. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Engl J Med 1995;332:635-41.
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Hepatitis-Associated Aplastic Anemia

To the Editor: Brown et al. (April 10 issue)[1] summarize the main features of hepatitis-associated aplastic anemia and conclude that the hepatitis in patients with this disorder is not likely to be caused by any of the known hepatitis viruses, including hepatitis G virus (HGV). These findings support recent reports questioning the role of HGV in liver disease.[2,3] In their discussion, Brown et al. also mention that HGV did not appear to cause aplastic anemia.

The article by Brown et al. addresses two different issues: the role of HGV in causing liver disease and the role of HGV in causing aplastic anemia. We agree that HGV is most likely not associated with any liver disease. However, we would like to caution against premature conclusions regarding the role of HGV in causing aplastic anemia. The authors studied serum samples from only 10 patients with hepatitis-associated aplastic anemia and did not report on the prevalence of HGV in serum samples from patients with aplastic anemia not associated with hepatitis.

We have studied the prevalence of HGV RNA in a well-characterized cohort of 16 patients with hepatitis-associated aplastic anemia,[4] as well as 47 concurrent patients with idiopathic aplastic anemia not related to hepatitis, who were matched for age, year of transplantation, and transfusion status. Our results confirmed that transfusions were the main source of HGV RNA in serum from both patients with hepatitis-associated aplastic anemia and those with idiopathic aplastic anemia (26.1 percent of 23 patients without transfusions and 67.5 percent of 40 with transfusions had positive tests for HGV RNA, $P = 0.001$). However, there was also an increased prevalence of HGV RNA in serum from patients with aplastic anemia who did not receive transfusions (26.1 percent), whether or not the anemia was associated with hepatitis (2 of 4 patients with hepatitis-associated aplastic anemia and 4 of 19 with idiopathic aplastic anemia had HGV RNA), as compared with the prevalence (1.7 percent) in serum from normal blood donors.[5] These results suggest a possible role of HGV in the development of aplastic anemia in some patients. The

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findings also underscore the need for prospective studies of patients who have not received transfusions, in order to investigate the possible etiologic role of HGV in aplastic anemia.

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1. Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-associated aplastic anemia. N Engl J Med 1997;336:1059-64.
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The authors reply:

To the Editor: A possible relation between hepatitis GB virus C (GBV-C), also known as HGV, and aplastic anemia was first suggested by the reports of viremia in a few patients with bone marrow failure who had apparently not received transfusions at the time.[1,2] Kiem et al. report viremia in two additional patients with hepatitis-associated aplastic anemia and four with idiopathic aplastic anemia. Although the specific viral cause of post-hepatitis aplastic anemia was not a major subject of our article, we have performed more extensive investigations of the relation of GBV-C to aplastic anemia.

GBV-C viral sequences were present in blood samples from 26 percent of 57 patients with aplastic anemia, as compared with 23 percent of 52 controls who had received multiple transfusions.[3] Similar results have been reported by Moriyama et al.[4] for patients with aplastic anemia and by other groups for patients who have received multiple blood transfusions because of other diseases. We would be interested to know whether Kiem et al. have determined the rate of hepatitis G viremia in controls with multiple transfusions. Gene-amplification techniques must be carefully controlled because of the susceptibility to contamination. Furthermore, in our experience some of the primers and probes used to detect HGV also have positive results in specimens containing *Escherichia coli* DNA sequences.

Neither we nor Moriyama et al. found GBV-C in patients with aplastic anemia who had not received transfusions. However, GBV-C is not transmitted only as a result of blood transfusion. The virus is highly prevalent in some normal populations: we found that almost 6 percent of normal Vietnamese persons had viral sequences in plasma,[5] and a similar proportion of normal American children may also have viremia (unpublished data).

Efforts to establish a relation between GBV-C and any disease have been frustrating. A member of the expanding Flaviviridae family has been proposed as a candidate for a viral cause of aplastic anemia.[6] However, GBV-C does not appear to be the agent responsible for either the common form of fulminant hepatitis of childhood or seronegative acute "viral" hepatitis. In our opinion, these syndromes and hepatitis-associated aplastic anemia probably share a single infectious cause. Hepatitis viruses commonly "travel" together, and GBV-C viremia may reflect exposure to another, as yet undiscovered pathogenic hepatitis virus.

Caution is indicated in the interpretation of laboratory results until we have a better understanding of GBV-C infection in humans and especially of the importance of viremia in apparently well adults and children.

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1. Byrnes JJ, Banks AT, Piatack M Jr, Kim JP. Hepatitis G-associated aplastic anaemia. Lancet 1996;348:472.
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High-Dose Pulsed Dexamethasone for Immune Thrombocytopenia

To the Editor: An important and unresolved problem is the treatment of patients with idiopathic thrombocytopenic purpura in whom severe thrombocytopenia persists despite splenectomy. In the June 2, 1994, issue, Andersen reported excellent results in 10 patients with refractory idiopathic thrombocytopenic purpura (5 men and 5 women) who were treated with high-dose dexamethasone.[1] In all the patients who completed six cycles of dexamethasone therapy (40 mg daily for 4 consecutive days every 28 days), platelet counts not only increased but remained above 100×10^9 per liter for at least 6 months after the last cycle of treatment.

We treated 10 consecutive patients with refractory idiopathic thrombocytopenic purpura (Table 1, next page). All 10 patients had undergone splenectomy and had had relapses after several different treatments. The mean ($\pm$SD) age of our patients was similar to the mean age of the patients described by Andersen (36 ± 13 and 41 ± 12 years, respectively; $P>0.05$), and the mean duration of disease was also similar (43 ± 14 months and 46 ± 22 months, respectively; $P>0.05$).[1] All 10 patients underwent six cycles of the high-dose dexamethasone protocol. The patients were followed for 10 to 22 months after the completion of the trial. As Table 1 shows, none of our patients had a significant increase in the platelet count.

Caulier et al. used a similar protocol,[2] and none of their patients had a stable increase in the platelet count to a level

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TABLE 1. CHARACTERISTICS OF THE PATIENTS AND PLATELET COUNTS BEFORE AND AFTER THE COMPLETION OF PULSED HIGH-DOSE DEXAMETHASONE THERAPY AND AT THE END OF FOLLOW-UP.

PATIENT NO.	AGE (YR)	SEX	DURATION OF DISEASE (MO)	THERAPY*		PLATELET COUNT ($\times 10^{-9}$/LITER)		
				PRIOR	ASSOCIATED	BEFORE THERAPY	AT 6 MO	AT END OF FOLLOW-UP (MO)
1	32	M	28	Pred,† splen,† vcr,† aza‡	None	21	27	25 (22)
2	23	F	39	Pred,† splen,† dan,‡ cyc‡	Pred	14	17	16 (20)
3	41	F	58	Pred,‡ splen,† vcr,‡ IVIG†	None	17	15	14 (19)
4	29	M	43	Pred,‡ splen,‡ vcr,‡ aza,‡ IVIG‡	None	15	20	18 (17)
5	36	M	35	Pred,‡ splen,† vcr,† cyc‡	None	28	36	34 (16)
6	65	F	46	Pred,† splen,† aza,† IVIG†	None	22	27	28 (14)
7	31	F	51	Pred,† splen,† cyc,‡ IVIG‡	Pred	17	16	14 (14)
8	23	M	26	Pred,† splen,† aza,‡ IVIG†	cyc	11	15	15 (12)
9	30	F	30	Pred,‡ splen,‡ vcr,‡ dan‡	Pred	19	18	21 (11)
10	52	M	71	Pred,‡ splen,‡ dan,‡ cyc‡	None	12	16	16 (10)
Mean	36.2	—	42.7	—	—	17.6	20.7	20.1
SD	13.2	—	14.3	—	—	5.1	7	6.8
SE	4.2	—	4.5	—	—	1.6	2.2	2.1

*Pred denotes prednisone, splen splenectomy, vcr vincristine, aza azathioprine, dan danazol, cyc cyclophosphamide, and IVIG intravenous immune globulin. For patients receiving associated therapy, the drugs were tapered and discontinued after the first cycle of pulsed high-dose dexamethasone.

†There was an initial response followed by a relapse.

‡There was no response.

higher than 100×10^9 per liter. We do not think that high-dose dexamethasone is effective in the treatment of refractory idiopathic thrombocytopenic purpura. Controlled multicenter trials may help identify new therapeutic options for this disease.

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1. Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. N Engl J Med 1994; 330:1560-4. [Erratum, N Engl J Med 1994;331:283.]
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Dr. Andersen replies:

To the Editor: More than four years after the completion of treatment, 7 of 10 consecutive outpatients with resistant idiopathic thrombocytopenic purpura who were treated with pulsed high-dose dexamethasone[1] remain in complete clinical remission; 2 are in partial remission. One patient has had a hematologic relapse but remains asymptomatic. Table 1 (facing page) summarizes these results, as well as those for 25 additional patients with new-onset, resistant, or lupus-associated idiopathic thrombocytopenic purpura treated at Wayne State University.

Although optimal dosing schedules have not been established, it appears likely that a division of the daily dose, shortened treatment cycles, and the absence of a meaningful rise in the platelet count after three cycles of pulsed dexamethasone therapy presage a poor response. Regional or population-based variability in the response rate may reflect, in part, genetically conditioned variability in dexamethasone clearance[2,3] (and Santen RJ: personal communication). Patients with a relapse after an initial remission with pulsed dexamethasone often have a response to one or two retreatment cycles.

Not knowing the actual characteristics of the patients studied by Demiroğlu and Dündar, I cannot determine which, if any, of the above factors may explain the dramatic difference in the response rate. A natural tendency to use a newly reported regimen to achieve a benefit in patients with the poorest responses may provide a partial explanation, as may population-based differences in drug metabolism and availability.

Only randomized, prospective clinical trials in well-characterized patient populations can determine the value of a treatment for idiopathic thrombocytopenic purpura. A national multicenter group for the study of idiopathic thrombocytopenic purpura has been formed to examine critically, in patients with several different categories of immune thrombocytopenia, response rates to both conventional and newer therapies. The initial comparison will be between conventional prednisone therapy and pulsed-dexamethasone therapy in obviating the need for splenectomy in patients with newly diagnosed idiopathic thrombocytopenic purpura.

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TABLE 1. RATES OF RESPONSE TO PULSED HIGH-DOSE DEXAMETHASONE.

GROUP*	NO. OF PATIENTS	FOLLOW-UP	PLATELET COUNT ($\times 10^{-9}$/liter)			COMMENTS
			>150	50–150	<50	
		mo	no. of patients (%)			
1	10	>50	7 (70)	2 (20)	1 (10)	Resistant idiopathic thrombocytopenic purpura†
2a	15	>17	7 (47)	5 (33)	3 (20)	Resistant idiopathic thrombocytopenic purpura†
2b	8	>15	6 (75)	2 (25)	0	New-onset idiopathic thrombocytopenic purpura‡
2c	2	>26	0	0	2 (100)	Lupus-associated idiopathic thrombocytopenic purpura§

*Group 1 consists of the patients with resistant idiopathic thrombocytopenic purpura who were treated at Wayne State University and described in 1994.[1] The updated results are shown. Group 2 consists of patients subsequently treated at Wayne State University.

†These patients had symptomatic relapses of idiopathic thrombocytopenic purpura and had received previous outpatient treatment with more than two regimens (with or without splenectomy).

‡These patients had previously untreated idiopathic thrombocytopenic purpura, which had been diagnosed within the previous three months.

§These patients had immune thrombocytopenia in the setting of active systemic lupus erythematosus (with or without splenectomy).

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Stenting for Carotid Stenosis?

To the Editor: I was disappointed by "A Common Clinical Conundrum" (April 3 issue).[1] This Clinical Problem-Solving article discussed a procedure — extracranial carotid-artery stenting — that is experimental, has not been validated by published multicenter trials, and is not widely available in community hospitals. In their discussion of success rates, complications, and long-term patency, the authors do not cite any article in a peer-reviewed journal to support their claims, only sketchy abstracts presented at a scientific meeting.[2,3] They cite no study to prove cost effectiveness, referring only to their own unpublished "preliminary" work. The inclusion of carotid stenting in the Clinical Problem-Solving article has given the technique an imprimatur that it does not yet deserve.

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To the Editor: In "A Common Clinical Conundrum" Gray and associates describe a patient with ischemic heart disease and asymptomatic carotid stenosis who underwent staged carotid-artery stenting and coronary bypass. We assert that the data they cite on morbidity after carotid stenting and endarterectomy are not representative. The data were obtained from a study by Iyer and colleagues, published as an abstract, in which the risk of stroke associated with carotid stenting was given as 3.3 percent.[1] Other articles by the same group have reported stroke rates between 6 percent[2] and 8 percent.[3] At follow-up, which was limited to six months, 6 percent of patients required reintervention (endarterectomy or balloon angioplasty) for stent deformation or restenosis.[3]

The widely published estimates of the risk of neurologic events after carotid endarterectomy from the Asymptomatic Carotid Atherosclerosis Study and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) are 2.4 percent for asymptomatic patients[4] and 5.5 percent for patients with symptoms (transient in two thirds of the latter).[5]

Furthermore, the arteriogram presented as proof of technical success after carotid stent placement demonstrated near-occlusion of the external carotid artery by the stent. This result would be unacceptable after endarterectomy because of the extensive cerebral collaterals dependent on this vessel should restenosis develop in the internal carotid artery.

In summary, the authors have described the use of carotid stenting in a high-risk patient with coronary artery

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disease. Undoubtedly, appropriate indications for this new technique will emerge for selected patients. However, at the present time, owing to the lack of long-term follow-up, increased risk of neurologic events, and uncertainties regarding its durability and long-term costs, carotid stenting is not yet appropriate for the routine management of carotid stenosis.

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1. Iyer SS, Roubin GS, Yadav JS, et al. Angioplasty and stenting for extracranial carotid stenosis: multicenter experience. Circulation 1996;94:Suppl I:I-58. abstract.
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The authors reply:

To the Editor: We strongly agree with Dr. Mittl — at this time, carotid stenting should be performed only under a strict investigational protocol with appropriate multidisciplinary support and assessment. Its experimental nature should be clearly explained to potential patients, as should alternatives such as medical or surgical management. We disagree, however, that there are no peer-reviewed data supporting carotid stenting. At least one published article, by Yadav et al.,[1] summarizes the experience with the procedure.

The representation by Estes et al. of the stroke rates in the Yadav article, which is the largest published series of its type, may be misleading. Of 126 stents implanted, there were seven strokes related to the procedure. One was a major stroke, and six were minor. A minor stroke was defined as modest deficits that resolved within a week. Because all these patients met NASCET exclusion criteria, they would not have been included in NASCET. Similar stroke rates were observed in NASCET, which involved a more highly selected patient population than that in the stent study.[2] In addition, complications of surgery in NASCET, including cranial-nerve palsy (7.6 percent), wound hematoma (5.5 percent), and infection (3.4 percent), were not seen after carotid stenting. Although the rates of restenosis after carotid surgery range from 5 to 19 percent,[3,4] only three patients received treatment for asymptomatic restenosis after carotid stenting in the study by Yadav et al.[1]

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1. Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. Circulation 1997;95:376-81.
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Osteomyelitis

To the Editor: Several comments are in order for the U.S. audience of the excellent review of osteomyelitis by Lew and Waldvogel (April 3 issue),[1] especially regarding Table 2. Many infectious-disease specialists prescribe both penicillin and nafcillin every four hours, rather than every six hours as suggested in the article. These beta-lactams have a short half-life, and consideration should certainly be given to using the higher dose (i.e., a shorter interval between doses). Clindamycin can be given effectively every eight hours because of its prolonged half-life. No clinical advantage has ever been proved for the administration of 600 mg every six hours as opposed to every eight hours. A dosing regimen involving six-hour intervals is more toxic, more expensive, and certainly much more difficult to give on an outpatient basis. Ciprofloxacin, at doses of 750 mg every 8 to 12 hours, should also be considered as an acceptable therapy for serratia or pseudomonas. (It was only listed as the treatment of choice for enteric gram-negative rods in Table 2.) Amoxicillin–clavulanate is not available in the United States as an intravenous preparation; cloxacillin is not available at all, although dicloxacillin is. Numerous other drugs can be substituted for intravenous amoxicillin–clavulanate, including ampicillin–sulbactam, ticarcillin–clavulanate, piperacillin–tazobactam, and a third-generation cephalosporin plus metronidazole. Other potential options in the United States for the treatment of methicillin-resistant *Staphylococcus aureus* in cases in which intravenous vancomycin cannot be used include agents such as trimethoprim–sulfamethoxazole, clindamycin, minocycline, and a quinolone with or without rifampin.

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1. Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med 1997;336:999-1007.

To the Editor: Drs. Lew and Waldvogel barely commented on the usefulness of oral antibiotics in the treatment of this infection. Certainly, the use of oral antimicrobial therapy, when based on sound pharmacodynamic principles, is a "current concept" that we should not ignore.

Although oral beta-lactam agents have limited bioavailability, as the authors pointed out, they have been used quite successfully in the treatment of osteomyelitis and septic arthritis, when given in appropriate doses.[1] Although the quinolones have revolutionized the approach

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to treating severe infections in the outpatient setting, other oral agents such as clindamycin, trimethoprim–sulfamethoxazole, metronidazole, doxycycline, and minocycline also offer excellent bioavailability, favorable dosing schedules, good tissue penetration, long-term tolerability, and low cost. . . .

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1. Black J, Hunt TL, Godley PJ, Matthew E. Oral antimicrobial therapy for adults with osteomyelitis or septic arthritis. J Infect Dis 1987;155:968-72. [Erratum, J Infect Dis 1987;156:541.]

The authors reply:

To the Editor: Dr. Glatt makes some valuable comments on treatment recommendations. Table 2 of our article was not exhaustive, and obviously other antibiotics may be prescribed as he suggests. Parenteral penicillins may indeed be prescribed every four to six hours, although in some cases such as the antipseudomonas penicillins the interval between doses can be extended successfully to eight hours.[1] Clindamycin may be prescribed every six to eight hours (which is more convenient for oral administration) as indicated by the severity of symptoms and infecting microorganisms. In our opinion the glycopeptides are often the only available therapeutic agents for methicillin-resistant *Staphylococcus aureus.* The other alternatives proposed (trimethoprim–sulfamethoxazole and minocycline) may be used for minor infections with methicillin-resistant *S. aureus.* Unfortunately, a large proportion of methicillin-resistant *S. aureus* are resistant to quinolones.

Dr. Shea raises the issue of the role of oral antibiotics in the treatment of osteomyelitis. Although oral treatment of acute osteomyelitis in children has been an accepted approach for many years, the approach to the treatment of acute or chronic osteomyelitis in adults has traditionally been intravenous. In our opinion, for beta-lactam antibiotics intravenous therapy remains the standard for osteomyelitis in adults. Among other agents, clindamycin may be a reasonable alternative for sequential intravenous–oral therapy because of its excellent bone penetration and good bioavailability.

Several good-quality comparative trials have shown the equivalence of oral quinolones and parenteral therapy. We have performed a cumulative analysis of published comparative trials of quinolones to treat osteomyelitis.[2] With oral ciprofloxacin, success rates of 92 percent for Enterobacteriaceae (even higher if serratia are excluded), 72 percent for *Pseudomonas aeruginosa,* and 75 percent for *S. aureus* were found.[2] On treatment with quinolones osteomyelitis due to *P. aeruginosa* or *S. aureus* was associated with a fourfold increase in the failure rate, as compared with the failure rate in osteomyelitis due to other pathogens.[2] Thus, in the case of osteomyelitis due to Enterobacteriaceae the success rate is so good that no further trials appear to be necessary. This is not the case for *S. aureus* and *P. aeruginosa.*

Figure 2B of our article was printed upside down. Therefore, the T_1-weighted image appears on the right and the image after the intravenous injection of gadolinium on the left.

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1. Quintiliani R, Nightingale CH, Sullivan MC. Use of pharmacodynamic concepts in developing a cost-effective dosing method for piperacillin. Clin Ther 1993;15:Suppl A:44-9.
2. Lew DP, Waldvogel FA. Quinolones and osteomyelitis: state-of-the-art. Drugs 1995;49:Suppl 2:100-1.

Cellulitis Due to Botfly Larvae

To the Editor: I report a case of cellulitis complicated by what turned out to be botfly larvae.

A 36-year-old woman presented with erythema, swelling, and pain in both shins. The lesions had developed two weeks after she returned from Peru. Cellulitis was diagnosed, and cephalexin was prescribed. The cellulitis improved somewhat, but two weeks after the initial presentation new lesions developed. On examination, the patient had seven tender, erythematous, indurated subcutaneous lesions 2 to 3 cm in diameter, each with a central punctum. A course of dicloxacillin was started. The same night, the patient saw a larva crawl out of a lesion (Fig. 1). She called for advice and was told to apply petroleum jelly to force the other larvae out for air. She tried this briefly, but became impatient and eventually squeezed out the larvae manually. She obtained a total of seven larvae in this man-



Figure 1. Botfly Larva from the Patient (×75).

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ner, which were identified as *Dermatobia hominis,* commonly called the human botfly.

D. hominis has a fascinating life cycle.[1] It is found widely in humid areas of Mexico, Central America, and South America. Its larvae can survive only in vertebrate tissue; infestation with them is known as myiasis. The adult female botfly deposits eggs on the abdomen of a bloodsucking fly or mosquito, which in turn deposits the eggs on an animal host. The growth of each larva can provoke severe ulceration and secondary infection. Once mature, the larvae erupt through the host's skin and fall to the ground, where they develop into pupae and subsequently into adult flies.

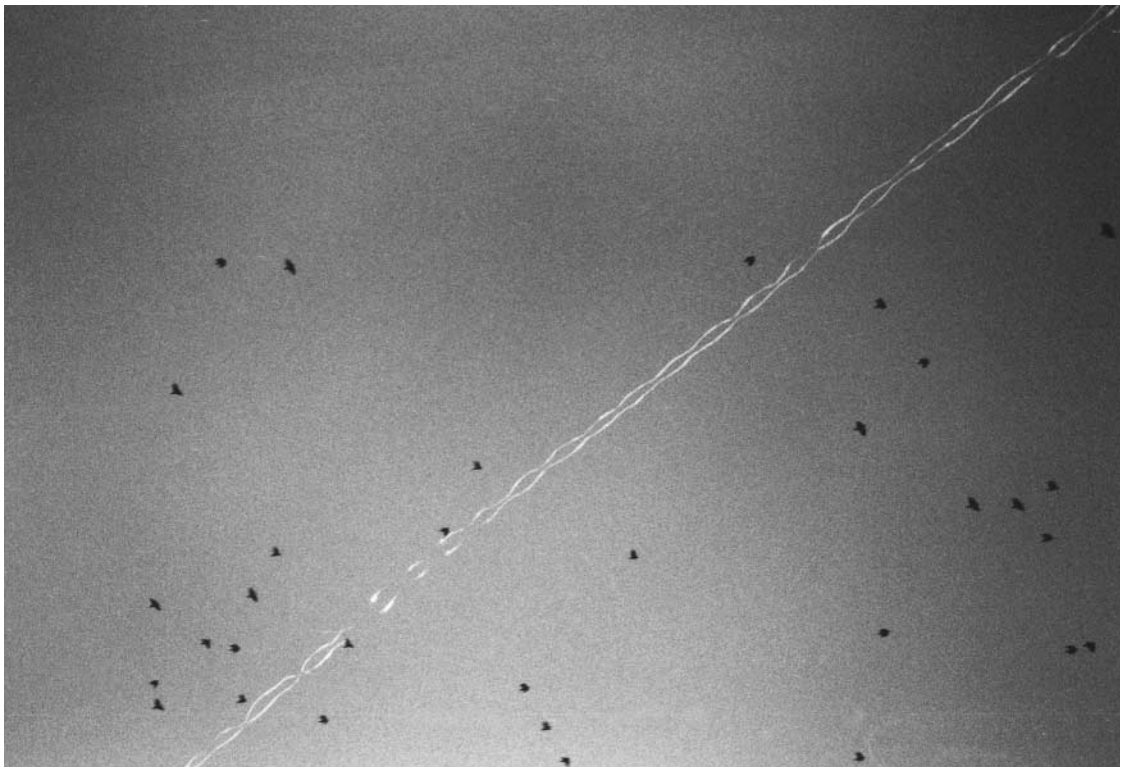
Myiasis has been reported previously,[2-4] but this case was remarkable in two respects. The first was that multiple larvae were present. Previous reported cases have involved infestations of at most a few larvae each. The presence of seven larvae in this patient should alert practitioners to look for multiple sites of infestation.

The second interesting aspect was the mode of treatment. Standard recommendations are to apply petroleum jelly or raw meat to draw the larvae out,[5] or to extract them with mosquito forceps. Nowhere does the literature recommend simply squeezing them out. In fact, one may wonder whether such an approach might worsen the problem by crushing the larvae. However, in this patient the procedure was expedient and effective for all seven lesions, and she recovered without sequelae.

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Birds, Sky, and Plane Gone By STEPHAN MOLL, M.D.

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