Correspondence

The Antiinflammatory Effects of Statins

To the Editor: Ridker and colleagues (June 28 issue)[1] demonstrated that the rate of acute coronary events among subjects with a base-line low-density lipoprotein (LDL) cholesterol level below 149.1 mg per deciliter and a C-reactive protein level above 0.16 mg per deciliter was higher among those given placebo than among those treated with lovastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). The authors conclude that C-reactive protein measurements may be useful in targeting statin therapy in patients with relatively low lipid levels. This conclusion is based on a difference of 15 events between the treatment groups and is unlikely to be valid. The interpretation of the C-reactive protein level is wholly dependent on the subsequent use of aspirin, as Ridker and colleagues previously demonstrated in the Physicians' Health Study.[2] The relation between the subsequent nonuse of aspirin and the inflation of the relative risk associated with the high C-reactive protein level is a form of effect modification. Once effect modification has been found, it should be handled in all future analyses by stratification — in this case, according to the use or nonuse of aspirin. Simply put, the authors must demonstrate that it was the high C-reactive protein level, and not the nonuse of aspirin, that created the 15-event difference.

It is disturbing that Ridker and colleagues continue to publish analyses of a variety of data sets and fail to account for aspirin use, hence inflating the perceived value of C-reactive protein as a tool for risk prediction. Conventional risk factors have stood the test of time because of their independence from other risk factors and concurrent therapy. Given that the relative risk associated with elevated levels of C-reactive protein is increased by the nonuse of aspirin and that the level of C-reactive protein falls with statin therapy, it is unlikely that C-reactive protein will be useful for the valid prediction of cardiovascular risk.

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1. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959-65.
2. 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. [Erratum, N Engl J Med 1997;337:356.]

To the Editor: The editorial by Munford[1] usefully adds to the stimulating debate on chronic inflammation and cardiovascular disease, exploring further the role of statin therapy. Munford rightly states that the biochemical mechanisms mediating the antiinflammatory effects of statins remain uncertain. However, two important recent observations that add substantially to the knowledge in this field were not directly addressed.

First, statins repress the induction by interferon-γ of major-histocompatibility-complex (MHC) class II by means of the class II transactivator in a variety of cells, including endothelial cells and monocyte–macrophages, thus inhibiting T-cell activation.[2] This effect is reversed by mevalonic acid, directly implicating hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase in this activity. Second, lovastatin and simvastatin inhibit the interactions between leukocyte-function–associated antigen type 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) by binding to a specific recognition site on LFA-1, independently of HMG-CoA reductase activity. Functionally, this mechanism suppresses critical T-cell costimulatory events.[3] Such cell-contact–dependent interactions between T cells and macrophages are now recognized to be of fundamental importance in promoting chronic inflammation in several autoimmune diseases[4] and may also plausibly operate in atherosclerosis. Thus, HMG-CoA reductase–independent activity may explain why Ridker et al. found no relation between a reduction in lipid fractions and C-reactive protein in patients treated with lovastatin.

These important data add to the growing evidence supporting the notion that the statin drug class may possess

immunomodulatory properties that are clinically useful in treating a variety of autoimmune diseases.

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1. Munford RS. Statins and the acute-phase response. N Engl J Med 2001; 344:2016-8.
2. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med 2000;6:1399-402.
3. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001;7:687-92.
4. McInnes IB, Leung BP, Sturrock RD, Field M, Liew FY. Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor-alpha production in rheumatoid arthritis. Nat Med 1997;3:189-95.

To the Editor: Munford offers two possible views of the role of acute-phase response in atherothrombosis. Macrophages and smooth-muscle cells within atheromas may release interleukin-6, which induces the production by the liver of C-reactive protein and other acute-phase reactants; these acute-phase reactants may or may not contribute to atherothrombosis. Alternatively, the secretion of interleukin-6 by adipose tissue or a site of smoldering infection may induce the hepatic production of C-reactive protein and other acute-phase reactants, which enter the circulation and contribute directly to atherothrombosis.

We previously reported that plasma interleukin-6 levels are increased in patients with acute myocardial infarction[1] and that interleukin-6 messenger RNA (mRNA) is expressed in human atherosclerotic lesions.[2] We also found that coronary-sinus interleukin-6 levels are significantly increased after coronary angioplasty.[3] The source of this increase is the heart itself, since interleukin-6 levels in samples of peripheral arterial blood obtained at the same time are not increased. Therefore, we speculate that the main source of plasma interleukin-6 in patients with coronary artery disease is vascular tissue rather than extravascular tissue.

Munford also states that the biochemical mechanisms of statin-induced reductions in C-reactive protein levels are uncertain. We previously studied the effects of statins on the production of interleukin-6 by cultured human monocytes and smooth-muscle cells. The addition of statins significantly decreased interleukin-6 production by these cells.[4] Therefore, we speculate that the reduction in plasma levels of C-reactive protein that occurs with the use of statins is attributable to the inhibition by the drugs of interleukin-6 synthesis in vascular tissue.

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1. Ikeda U, Ohkawa F, Seino Y, et al. Serum interleukin 6 levels become elevated in acute myocardial infarction. J Mol Cell Cardiol 1992;24:579-84.
2. Seino Y, Ikeda U, Ikeda M, et al. Interleukin 6 gene transcripts are expressed in human atherosclerotic lesions. Cytokine 1994;6:87-91.
3. Hojo Y, Ikeda U, Katsuki T, et al. Interleukin 6 expression in coronary circulation after coronary angioplasty as a risk factor for restenosis. Heart 2000;84:83-7.
4. Ikeda U, Shimada K. Statins and monocytes. Lancet 1999;353:2070.

The authors reply:

To the Editor: We respectfully disagree with Dr. McCullough that the relations we describe among C-reactive protein, LDL cholesterol, and statin efficacy are confounded by aspirin use. First, as stated in our article, less than 20 percent of the participants in AFCAPS/TexCAPS were taking aspirin, and the proportion of those taking aspirin was identical among those randomly assigned to statin therapy and those assigned to placebo. A differential effect of statin therapy caused by a maldistribution of aspirin use would thus seem implausible.

Second, the results for C-reactive protein, lipids, and statin efficacy are virtually identical if the participants who were taking aspirin are excluded from the analysis — the post hoc approach favored by Dr. McCullough. We further disagree that our choice to include rather than exclude those who were taking aspirin led to a false inflation of the estimates of risk associated with C-reactive protein. Quite to the contrary, our inclusion of all subjects — including those who were taking aspirin — is both appropriate epidemiologically and highly conservative, since it would tend, if anything, to lead to an underestimate of the risks associated with C-reactive protein.

Third, if the nonuse of aspirin were a valid explanation for the observed effect of C-reactive protein, it would be difficult to explain similar findings in the Cholesterol and Recurrent Events trial, in which more than 90 percent of the participants were taking aspirin. In that study, C-reactive protein was also predictive both of future coronary events and of statin efficacy.[1,2] That statins lower the level of C-reactive protein in an LDL-independent manner among those who are taking aspirin and those who are not has also been clearly demonstrated in the Pravastatin Inflammation/CRP Evaluation.[3]

Findings from all available prospective cohort studies must be taken into account in order to determine whether or not C-reactive protein will be useful in the prediction of cardiovascular risk. To date, there have been more than a dozen such studies, and all have been highly consistent in this regard.[4] We nonetheless concur with Dr. McCullough that, despite the large sample in AFCAPS/TexCAPS, the absolute number of events in each subgroup was small. Thus, we hold that randomized trials of statin therapy among persons without overt hyperlipidemia but with evidence of elevated C-reactive protein levels are now needed to test these hypotheses directly.

Finally, we concur with Dr. McCarey and colleagues that the lipid-independent effects of statins on C-reactive protein represent an important observation with biochemical as well as clinical implications.

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1. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998;98:839-44.
2. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999;100:230-5.
3. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64-70.
4. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199-204.

The editorialist replies:

To the Editor: McCarey et al. call attention to the possibility that statins may have HMG-CoA reductase–independent antiinflammatory effects. They note that certain statins, such as lovastatin and simvastatin, inhibit leukocyte adhesion to ICAM-1 by binding to a discrete site on LFA-1.[1] This mechanism has been studied principally in vitro, but it might explain simvastatin's ability to inhibit local inflammation and to prevent atherosclerosis in mice without altering blood lipid levels.[2] On the other hand, statin-induced reductions in levels of C-reactive protein have correlated poorly with reductions in blood lipid levels in clinical trials of pravastatin,[3,4] which does not inhibit LFA-mediated leukocyte adhesion.[1] The effect on leukocyte adhesion is thus unlikely to be the only explanation for the lack of correlation.

Ikeda and Shimada note that interleukin-6 can be produced within atherosclerotic arteries. The evidence for this statement comes largely from studies performed during coronary arteriography or angioplasty for acute ischemic heart disease. In these advanced stages of coronary artery disease, active inflammation is often present within the affected vessels. In contrast, the pathogenesis as the disease develops over many years is less clear. Does the inflammation originate in the coronary artery, triggered by oxidized LDL cholesterol, phospholipid, or both, or is it mainly extravascular and able to accelerate the progression of coronary artery disease by inducing proatherosclerotic and prothrombotic acute-phase phenomena? As discussed in my editorial, there are arguments that favor each viewpoint; in some patients, the intravascular and extravascular inflammatory influences could be additive or even synergistic.

Ikeda and Shimada also suggest that statins may lower C-reactive protein levels by diminishing interleukin-6 production in vascular tissue. This suggestion is consistent with the prominent role of interleukin-6 in inducing C-reactive protein production,[5] which occurs mainly in the liver. However, a recent study found that three different statins lowered serum C-reactive protein levels in human volunteers without altering the resting blood levels of immunoreactive interleukin-6 or soluble interleukin-6 receptor.[3] Although this result does not exclude a statin effect on local or circulating interleukin-6 levels (which may occur, for example, through a dampening of stress-induced or circadian peaks in the interleukin-6 level without affecting basal interleukin-6 production), it suggests that establishing the causative link proposed by Ikeda and Shimada may be very difficult.

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2. Sparrow CP, Burton CA, Hernandez M, et al. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol 2001;21:115-21.
3. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 2001;103:1933-5.
4. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999;100:230-5.
5. Bataille R, Klein B. C-reactive protein levels as a direct indicator of interleukin-6 levels in humans in vivo. Arthritis Rheum 1992;35:982-4.

The Ecology of Medical Care Revisited

To the Editor: Green et al. (June 28 issue)[1] may have severely underestimated how the changes in medicine and society have affected emergency medicine. In their reanalysis of the monthly prevalence of illness in the community and the roles of various sources of health care, they report that 13 of 1000 persons visit an emergency department per month. That would mean for the U.S. population of 280 million a total of approximately 43 million visits per year. This number is very different from a report from the Centers for Disease Control and Prevention on use of emergency departments from the 1999 National Hospital Ambulatory Medical Care Survey, which reported that in 1999 there were 102.8 million emergency department visits.[2] Emergency department overcrowding has become a significant national problem. An underestimation of the number of emergency department visits might distract attention and divert resources that should be dedicated to the delivery of emergency care.

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1. Green LA, Fryer GE Jr, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. N Engl J Med 2001;344:2021-5.
2. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 1999 emergency department summary. Advance data from vital and health statistics. No. 320. Hyattsville, Md.: National Center for Health Statistics, 2001.

To the Editor: I was heartened to see "The Ecology of Medical Care Revisited," by Green et al., which presented a view as vital as ever to the reorientation of medical care, education, and policy. It also unexpectedly implies the depth of health disparities in the United States.

The Medical Expenditure Panel Survey and the Gallup poll assume a household and a telephone. The Federal Communications Commission estimates that 94 percent of U.S. households have a telephone[1]; thus, 6 percent of households, or 14 million people, are excluded. The authors state that 2 million inmates were excluded. There are 700,000 to 2 million homeless people in the United States. There are an estimated 3.5. million migrant workers. The California Farm Workers found that 60 percent of migrant workers live in impermanent dwellings (abandoned cars, labor camps, and so forth); thus, 2.1 million are excluded. Subtracting these migrants from the 5 million undocumented immigrants in

the United States leaves 2.9 million. By estimating (conservatively) that 50 percent of them would decline participation in a government-sponsored survey, an additional 1.5 million are excluded. This leaves 22.4 million to 23.8 million people, nearly 10 percent of the U.S. population, who are not represented in the sample. The National Cancer Institute estimates that there are currently 8.9 million victims of cancer in the United States, or 3 percent of the population.[2]

We know little of the ecology of this unrepresented decile. However, it is probably quite different from that of the general population. For instance, more than a third of the migrant workers in California reported that they had never seen a physician in their entire lives.[3] My intent is not to criticize the authors' methods but rather to call for comprehensive investigation of the ecology of health care of this population that has been, literally, decimated.

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1. Stroup C. Telephone subscribership in the United States. Washington, D.C.: Federal Communications Commission, 2000.
2. Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER cancer statistics review, 1973-1998. Bethesda, Md.: National Cancer Institute, 2001.
3. Villarejo D, Lighthall D, Williams D III, et al. Suffering in silence: a report of the health of California's agricultural workers. Davis: California Institute for Rural Studies, November 2000.

The authors reply:

To the Editor: Smith appropriately points out the limits of telephone surveys. We concur with his claim. For this reason, we based most of our analyses on the Medical Expenditure Panel Survey, which relies on personal interviews conducted in a nationally representative sample of U.S. households. We also agree that we know less about the people who lack a home address. However, we are unaware of surveys or other information sources that provide reliable data on health care utilization in a nationally representative sample of homeless or migrating populations. Were such data available, the ecology model could be applied to these populations, perhaps constructively quantifying health care disparities that matter.

We share the concern of Goldberg and Goldfrank about potential misuse of our findings to overemphasize or underemphasize the importance and role of particular segments of the health care system. Apparently, they derived from our results an estimate of 43 million emergency visits per year by assuming that each person who visited an emergency department in a single year did so only once. The resulting estimate would be the smallest possible number of visits to emergency departments by those persons during the year. We reported findings based on the number of individual persons involved in a particular type of health care in a month, not their total number of visits or encounters during the month. It is well known that the same individual persons revisit emergency rooms. This is one explanation for the larger number of visits to the emergency department in a year as reported in the National Hospital Ambulatory Medical Care Survey. As pointed out by Smith, higher rates of health care utilization by people who were excluded from the surveys we analyzed, such as prisoners, could be another explanation. Thus, we believe our estimate of the number of people obtaining care in an emergency department in an average month is actually consistent with estimates of annual visits reported in the National Hospital Ambulatory Medical Care Survey.

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Chelation Therapy in Children Exposed to Lead

To the Editor: Rogan et al. (May 10 issue)[1] conclude that chelation therapy with succimer for children with lead levels of 20 to 44 μg per deciliter is valueless. However, an important methodologic weakness of their study is that succimer therapy failed to achieve a timely, enduring reduction in the lead level, producing a difference in blood lead levels between treatment groups of only 2.7 μg per deciliter over a one-year period. There is no evidence (e.g., measurement of erythrocyte protoporphyrin) that succimer effected any significant reduction in the body burden of lead. The authors assert without reference that there is no better chelator than succimer. However, efficacy has been reported with penicillamine[2-4] and with 2,3-dimercaptopropane-1-sulfonate.[5] Finally, the authors ignore the other toxic effects of lead poisoning that can be reversed by chelation — e.g., normalization of 1,25-dihydroxyvitamin D, δ-aminolevulinic acid dehydratase, and erythrocyte protoporphyrin activity.[6] Collectively, these shortcomings leave open the possibility that individualized case management for children with lead poisoning may have a role in treatment, which may in some cases include chelation therapy.

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1. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med 2001;344:1421-6.
2. Marcus SM. Experience with D-penicillamine in treating lead poisoning. Vet Hum Toxicol 1982;24:18-20.
3. Shannon M, Graef J, Lovejoy FH Jr. Efficacy and toxicity of D-penicillamine in low-level lead poisoning. J Pediatr 1988;112:799-804.
4. Shannon M, Grace A, Graef JW. Use of penicillamine in children with small lead burdens. N Engl J Med 1989;321:979-80.
5. Chisolm JJ Jr, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate

in treatment of lead poisoning in children. J Pharm Exp Ther 1985;235:665-9.
6. Rosen JF, Chesney RW, Hamstra A, DeLuca HF, Mahaffey KR. Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N Engl J Med 1980;302:1128-31.

To the Editor: Rogan et al. cite a meta-analysis by Pocock et al.[1] demonstrating the association between increased blood lead level and decreased IQ. They do not, however, reveal the conclusion of the authors of the meta-analysis: "However, the inherent limitations of observational epidemiology in pinpointing the reasons for this association mean that uncertainty remains as to the real impact that lead makes on children's neuropsychological development."

Given this uncertainty, a very reasonable explanation for the findings in the study by Rogan et al. — i.e., that lowering blood lead levels did not improve scores on tests of cognition, behavior, or neuropsychological function — is that lead exposure was not responsible for impairment in the first place. This possibility was not even broached by the authors.

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1. Pocock SJ, Smith M, Baghurst P. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ 1994;309:1189-97.

The authors reply:

To the Editor: Shannon et al. propose the use of other oral chelating agents and the treatment of biochemical responses to lead exposure. We evaluated the use of penicillamine when we planned our trial and came to the same conclusion that the American Academy of Pediatrics did: "The overall toxicity profile of penicillamine relegates it to a third-line agent, indicated only when unacceptable reactions have occurred to succimer and CaNa2EDTA."[1] We are not aware of any controlled, long-term data on the reduction of any measure of lead exposure by penicillamine. Concurrent, preferably randomized controls are necessary because of the strong effects of age on blood lead levels, as seen in our study. Similarly, studies showing the efficacy of chelation for protoporphyria[2] and abnormalities of vitamin D metabolism[3] have not been randomized, controlled trials, and their results are consistent with regression to the mean or spontaneous resolution as the blood lead level falls. As for 2,3-dimercaptopropane-1-sulfonate, it is not commercially available in the United States.

Mandelbaum is of course correct in saying that if lead does no damage, then treating lead exposure will do no good. For the purposes of both public health and clinical trials, however, we think that the debate about whether lead causes cognitive deficits at relatively low levels of exposure is settled. Major organizations, including the Centers for Disease Control and Prevention[4] and the World Health Organization,[5] treat the association as causal. Lead is the best studied of the environmental chemical agents thought to produce cognitive deficits at commonly encountered levels, with a huge clinical and laboratory literature showing unquestionable neurotoxicity. The only question is the dose at which the toxic effects become measurable. The relation between lead and neurotoxicity was sufficiently established that we and our advisors thought that a trial attempting to reduce or prevent lead-associated cognitive deficits by means of chelation was needed, and we still believe that to have been true.

We note with sadness the death of our senior colleague, J. Julian Chisholm, Jr., on June 20, 2001.

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1. American Academy of Pediatrics Committee on Drugs. Treatment guidelines for lead exposure in children. Pediatrics 1995;96:Part 1:155-60.
2. Marcus SM. Experience with D-penicillamine in treating lead poisoning. Vet Hum Toxicol 1982;24:18-20.
3. Rosen JF, Chesney RW, Hamstra A, DeLuca H, Mahaffey KR. Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N Engl J Med 1980;302:1128-31.
4. Screening young children for lead poisoning: guidance for state and local public health officials. Atlanta: Centers for Disease Control and Prevention, 1997.
5. Inorganic lead. Vol. 165 of Environmental health criteria. Geneva: World Health Organization, 1995.

Acquired Bleeding Diathesis in a Patient Taking PC-SPES

To the Editor: PC-SPES is a commercially available nutritional supplement containing eight herbs that is used by many patients with prostate cancer. It has potent estrogenic activity and substantial antineoplastic effects in patients with prostate cancer.[1,2] We describe a patient with profound bleeding diathesis after one month of unsupervised use of this compound.

A 62-year-old man with hormone-refractory prostate cancer and nodal metastases (stage D1 disease) presented to the emergency department after an episode of syncope. This episode had been preceded by one day of epistaxis, abdominal pain, hematuria, and the passage of maroon stools. The patient denied a family history of bleeding or bruising, and the prothrombin time and activated partial-thromboplastin time had previously been normal. The only medications were 12 capsules of PC-SPES daily (twice the manufacturer's recommended dosage) for one month, in addition to multivitamins. The initial vital signs were notable for a pulse of 120 beats per minute and a blood pressure of 112/82 mm Hg. Physical examination revealed extensive ecchymoses, and a computed tomographic scan showed a large retroperitoneal hematoma. The results of laboratory analysis and mixing studies with normal plasma are shown in Table 1. Hepatic-function variables were within normal limits. Initial treatment included the transfusion of 2 units of packed red cells and 6 units of fresh-frozen plasma and the adminis-

TABLE 1. HEMATOLOGIC AND COAGULATION VARIABLES.

VARIABLE	ON ADMISSION	MIXING STUDY*	AFTER TRANSFUSION	DAY 3	DAY 7	DAY 21
Hemoglobin (g/dl)	7.3		9.6	10	12.2	11.9
Platelet count (per mm^3)	629,000		286,000	308,000	356,000	230,000
Prothrombin time (sec)	>106	15.8	17.1	16.5	13.0	12.1
Activated partial-thromboplastin time (sec)	>120	32.1	38	29	22	25
Thrombin time (sec)	7.5					
Fibrinogen (mg/dl)	611	539				698
D-Dimer (ng/ml)	500–1000					500–1000
Fibrin-degradation product (μg/ml)	<5					

*The patient's plasma was mixed in a 1:1 ratio with normal plasma to determine whether a clotting-factor deficiency or a clotting-factor inhibitor was present.

tration of vitamin K. On follow-up testing three weeks and again three months later, the prothrombin time and activated partial-thromboplastin time were normal. Laboratory studies on admission also unexpectedly revealed a serum warfarin level of 0.69 μg per milliliter (therapeutic range, 2 to 8).

The use of PC-SPES has been associated with increased rates of deep venous thrombosis and pulmonary embolism, but to our knowledge its use has never been linked to hemorrhage. Two isolates of the herb Baikal skullcap (*Scutellaria baicalensis Georgi*), one of the components of PC-SPES, are coumarins (compounds structurally related to warfarin, a synthetic coumarin) and have been shown to act as vitamin K reductase inhibitors in a manner similar to that of warfarin.[3] In this case, the history and laboratory variables were most consistent with the presence of an acquired coagulation-factor deficiency, and the measured warfarin level was insufficient to have induced the described changes in coagulation variables.

To investigate the possibility that a phytocoumarin was contained in the PC-SPES, two mice were given the PC-SPES preparation procured from the patient at a dosage of 500 mg per kilogram of body weight per day, administered orally as previously described.[4] After three days, the mean (±SD) measured serum warfarin level was 0.87 ±0.2 μg per milliliter. These results indicate that the PC-SPES preparation that this patient took contained a component that comigrates with warfarin on high-performance liquid chromatography. The transient, severe bleeding diathesis in this patient was probably the result of unsupervised use of PC-SPES and was probably related to a phytocoumarin or other compound in the PC-SPES. Patients should be counseled that PC-SPES has multiple thrombotic and hemorrhagic side effects, that these potentially harmful complications must be balanced with the antineoplastic effects of PC-SPES, and that unsupervised use of this preparation is not recommended.

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1. de la Taille A, Buttyan R, Hayek O, et al. Herbal therapy PC-SPES: in vitro effects and evaluation of its efficacy in 69 patients with prostate cancer. J Urol 2000;164:1229-34.
2. DiPaola RS, Zhang H, Lambert GH, et al. Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. N Engl J Med 1998;339:785-91.
3. Liu XF, Liu ML, Iyanagi T, Legesse K, Lee TD, Chen SA. Inhibition of rat liver NAD(P)H:quinone acceptor oxidoreductase (DT-diaphorase) by flavonoids isolated from the Chinese herb scutellariae radix (Huang Qin). Mol Pharmacol 1990;37:911-5.
4. Kubota T, Hisatake J, Hisatake Y, et al. PC-SPES: a unique inhibitor of proliferation of prostate cancer cells in vitro and in vivo. Prostate 2000;42:163-71.

Thalidomide for Malignant Melanoma

To the Editor: A 63-year-old man with a dense left hemiplegia from a stroke two and a half years earlier was seen in the clinic in May 2000 with clinical evidence of relapsed malignant melanoma of the scalp. Stage II malignant melanoma over the vertex had first been diagnosed in March 1999. In July 1999, the lesion was widely excised, with a 1-cm margin of normal tissue. The diameter of the melanoma was 1 cm and its depth 4 mm. The margin was tumor-free. He received no adjuvant therapy. In March 2000, two lesions developed, one measuring 10 by 8 mm over the right parietal region and the other measuring 4 by 4 mm over the scalp and forehead in the midline; each was accompanied by three satellite nodules measuring 2 by 2 mm. He was not considered to be a candidate for aggressive therapy and was referred to us for a second opinion in May 2000. A fine-needle aspiration biopsy confirmed the presence of recurrent malignant melanoma (Fig. 1), with the cells staining positive for the antigens S-100 and HMB-45. The lesions were judged to be in-transit metastases, since they were both more than 2 cm away from the site of the primary lesion. Imaging studies confirmed that the disease was localized to the scalp.

The patient was mentally sound but required a wheelchair on account of his hemiplegia. He also had a tonic–clonic seizure disorder as a result of his stroke. He was not believed to be a candidate for aggressive surgery, chemotherapy, or immunotherapy. He was given a four-week trial of immunotherapy consisting of twice-weekly perilesional in-

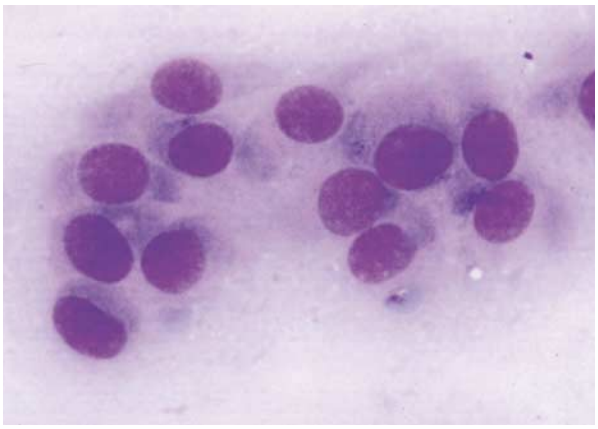

Figure 1. Single, Discohesive Malignant Melanoma Cells (Modified Wright–Giemsa Stain, ×600).

jections of bacille Calmette–Guérin; there was no local response, and the tumor progressed. He was then empirically treated with 200 mg of thalidomide daily. Within six weeks, the lesions had shrunk substantially, and after six months they had resolved completely. Confirmatory skin biopsies revealed only scar tissue. Imaging studies showed no disease elsewhere. Currently, the patient remains in complete remission while receiving thalidomide, although the dose has been reduced (to 100 mg) because of constipation.

Thalidomide has been used in clinical trials to treat advanced malignant melanoma, with some evidence of a response.[1-3] In this patient, we observed a complete response with the use of thalidomide alone. The sequence of events in this case makes both spontaneous remission and a response to the vaccination with bacille Calmette–Guérin extremely unlikely.

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1. Eisen T, Boshoff C, Mak I, et al. Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. Br J Cancer 2000;82:812-7.
2. Eisen TG. Thalidomide in solid tumors: the London experience. Oncology (Huntingt) 2000;14:Suppl 13:17-20.
3. Hwu WJ. New approaches in the treatment of metastatic melanoma: thalidomide and temozolamide. Oncology (Huntingt) 2000;14:Suppl 13: 25-8.

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