

Correspondence



Homocysteine and Dementia

To the Editor: Seshadri and colleagues (Feb. 14 issue)¹ report that high homocysteine levels are a risk factor for Alzheimer's disease. The effect of homocysteine on brain tissue is influenced by the absence within this tissue of two of the major metabolic routes for the elimination of homocysteine: betaine-mediated conversion and transsulfuration.^{2,3} Consequently, under conditions of folate deprivation, homocysteine can be eliminated only by export from the neuron. Increased export is problematic, however, as the authors point out, since homocysteine activates *N*-methyl-D-aspartate receptors and potentiates glutamate excitotoxicity.⁴ Minimizing homocysteine export may therefore be critical for nervous tissue, and it may be for this reason that folate is substantially more concentrated in spinal fluid than in plasma.⁵ Moreover, the decline in spinal fluid folate levels in Alzheimer's disease, but not in normal aging,⁵ may contribute to neurodegeneration. Folate levels considered adequate under normal circumstances may not be adequate in the face of a chronic degenerative condition such as Alzheimer's disease.

Studies in cultured neurons demonstrate not only that homocysteine potentiates β -amyloid-peptide neurotoxicity⁶ but also that potentiation of β -amyloid-peptide-induced neuronal apoptosis may be enhanced by homocysteine levels that are themselves benign.⁷ These findings suggest that homocysteine may have major effects on the onset and progression of neurodegeneration in Alzheimer's disease.

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1. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346:476-83.

2. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr* 1998;157:Suppl 2:S40-S44.
3. McKeever MP, Weir DG, Molloy A, Scott JM. Betaine-homocysteine methyltransferase: organ distribution in man, pig and rat and subcellular distribution in the rat. *Clin Sci (Lond)* 1991;81:551-6.
4. Kruman II, Culmsee C, Chan SL, et al. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J Neurosci* 2000;20:6920-6.
5. Serot JM, Christmann D, Dubost T, Bene MC, Faure GC. CSF-folate levels are decreased in late-onset AD patients. *J Neural Transm* 2001;108:93-9.
6. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. *J Neurochem* 2001;76:1509-20.
7. Ho PI, Collins SC, Dhitavat S, et al. Homocysteine potentiates amyloid beta neurotoxicity: role of oxidative stress. *J Neurochem* 2001;78:249-53.

To the Editor: In their study of plasma homocysteine as a risk factor for dementia and Alzheimer's disease, Seshadri et al. do not provide complete details about the collection of blood samples for measurement of homocysteine. The measurement of total plasma homocysteine can be done while the subject is fasting or not fasting and before or after oral methionine loading.¹ Total plasma homocysteine levels differ substantially between the fasting and nonfasting states and before and after a methionine challenge. For example, hyperhomocysteinemia after methionine loading is usually defined as a total plasma homocysteine level that is more than 2 SD above the mean.² It is usually recommended that total plasma homocysteine be measured after the subject has fasted for at least 12 hours to avoid the increases in homocysteine levels that may occur after a meal. The day-to-day variation in fasting plasma homocysteine levels is small, so it is reasonable to obtain a single measurement.³

The majority of clinical studies involving homocysteine have relied on the measurement of total plasma homocysteine during fasting.⁴ Variations in the preparation of subjects for blood-sample collection, either with respect to the rest of the study population or over time, could introduce errors and invalidate the results of analysis.

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1. Guttormsen AB, Schneede J, Fiskerstrand T, Ueland PM, Refsum HM. Plasma concentrations of homocysteine and other aminothiol compounds are related to food intake in healthy human subjects. *J Nutr* 1994;124:1934-41.
2. Dudman NP, Wilcken DE, Wang J, Lynch JF, Macey D, Lundberg P. Disordered methionine/homocysteine metabolism in premature vascular disease: its occurrence, cofactor therapy, and enzymology. *Arterioscler Thromb* 1993;13:1253-60.
3. Garg UC, Zheng ZJ, Folsom AR, et al. Short-term and long-term variability of plasma homocysteine measurement. *Clin Chem* 1997;43:141-5.
4. Auer J, Berent R, Eber B. Homocysteine: a novel risk factor in vascular disease. *Coron Health Care* 2001;5:89-99.

The authors reply:

To the Editor: Auer and colleagues express concern about the conditions of blood-sample collection. They recommend that plasma homocysteine levels be measured after an overnight fast. In our study, all the study samples were drawn in a uniform manner from subjects who were not fasting. The subjects were permitted a light breakfast or lunch. None of the samples were drawn after oral methionine loading. Several previous studies have obtained samples from nonfasting subjects.^{1,2} Thirup and Ekelund found no significant difference between the levels of plasma homocysteine measured during fasting and the postprandial levels in the same person.³

As we acknowledged in our article, the use of samples from nonfasting subjects may have "resulted in estimates of plasma homocysteine levels that were up to 20 percent higher than they would have been in fasting subjects, but any increase in the variability in plasma homocysteine values caused by this approach is likely to be random." Random variability is more likely to lead to underestimation of a true effect than to a finding of a spurious association.⁴ None of our subjects had dementia at the time that blood was drawn for plasma homocysteine measurements; hence, a systematic bias is unlikely.

We concur with Shea and Rogers that the limited capacity of the brain to metabolize homocysteine may increase its vulnerability to small elevations in plasma homocysteine. In cell cultures, homocysteine not only sensitizes hippocampal neurons to β -amyloid-peptide-induced damage; it also enhances β -amyloid-peptide generation by the induction of a stress protein located in the endoplasmic reticulum.⁵

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2. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 1998;55:1449-55.
3. Thirup P, Ekelund S. Day-to-day, postprandial, and orthostatic variation of total plasma homocysteine. *Clin Chem* 1999;45:1280-3.
4. Clarke R, Lewington S, Donald A, et al. Underestimation of the importance of homocysteine as a risk factor for cardiovascular disease in epidemiological studies. *J Cardiovasc Risk* 2001;8:363-9.
5. Sai X, Kawamura Y, Kokame K, et al. Endoplasmic reticulum stress-inducible protein, Herp, enhances presenilin-mediated generation of amyloid beta-protein. *J Biol Chem* 2002;277:12915-20.

Leptin-Replacement Therapy in Lipodystrophy

To the Editor: Oral et al. (Feb. 21 issue)¹ demonstrate convincingly that treatment with leptin decreases triglyceride levels, improves insulin resistance, and ameliorates diabetes in patients with lipodystrophy and leptin deficiency. Minokoshi et al. have recently demonstrated that leptin can activate the enzyme AMP-activated protein kinase in skeletal muscle, thereby increasing lipid combustion and glucose uptake and establishing a molecular basis for the lipid-lowering and insulin-sensitizing effect of leptin described in this study.²

In the light of their results, Oral et al. suggest that leptin is the chief fat-derived hormone required for glucose homeostasis. Used at physiologic levels, however, leptin did not totally reverse the diabetic phenotype. Similarly, in transgenic mouse models of severe lipodystrophy, insulin resistance and diabetes are not entirely reversed by physiologic levels of leptin.³ In these models, complete reversal of the diabetic phenotype is obtained with pharmacologic levels of leptin⁴ or by fat transplantation,⁵ suggesting that in the absence of fat, leptin is not sufficient to maintain glucose and lipid homeostasis. Like leptin, adiponectin is an adipocytokine that stimulates muscle lipid oxidation and prevents liver steatosis, thereby improving sensitivity to insulin. Indeed, insulin resistance in lipodystrophic mice is completely reversed by the combination of physiologic doses of leptin and of adiponectin but is only partially reversed by either cytokine alone.⁶ Since patients with lipodystrophy and transgenic mouse models of the disorder have similar responses to treatment with leptin, it is possible that they would have similar responses to the administration of adiponectin. Determination of the adiponectin level in this subgroup of patients might be of interest for future clinical trials involving both leptin and adiponectin in patients with lipodystrophy.

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1. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002;346:570-8.
2. Minokoshi Y, Kim YB, Peroni OD, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 2002;415:339-43.
3. Gavrilova O, Marcus-Samuels B, Leon LR, Vinson C, Reitman ML. Leptin and diabetes in lipodystrophic mice. *Nature* 2000;403:850-1.
4. Ebihara K, Ogawa Y, Masuzaki H, et al. Transgenic overexpression of leptin rescues insulin resistance and diabetes in a mouse model of lipodystrophic diabetes. *Diabetes* 2001;50:1440-8.
5. Gavrilova O, Marcus-Samuels B, Graham D, et al. Surgical implantation of adipose tissue reverses diabetes in lipodystrophic mice. *J Clin Invest* 2000;105:271-8.
6. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;7:941-6.

To the Editor: We found that when food intake was restricted in patients with lipodystrophy, elevated glucose and triglyceride levels returned to virtually normal values within days.¹ In persons who lack a storage organ for surplus calories, the result, although welcomed, was not en-

tirely unexpected. The caloric intake of the patients in the study by Oral et al. decreased and they lost weight while receiving leptin. The possible influence of food restriction was studied in only one of their patients. However, the reduction in the values for triglycerides, insulin, and glucose when leptin was given coincided with the appearance of pancreatitis and, presumably, a decrease or cessation of oral intake. Until there is more substantial evidence of the favorable effect of leptin in patients with lipodystrophy, we suggest that restricted caloric intake remains a simpler yet effective therapeutic tool.

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To the Editor: The optimal dose of recombinant leptin in patients with lipodystrophy and possibly in those with other insulin-resistant states remains to be carefully determined. In the study by Oral et al., the patients receiving leptin had a marked decrease in mean (\pm SE) food intake (from 2680 ± 250 kcal per day at base line to 1600 ± 150 kcal per day after four months), which was associated with a significantly decreased resting metabolic rate, in contrast to an expected increase. The mean weight loss was 3.6 ± 0.9 kg. Because both animals and humans with congenital leptin deficiency are supersensitive to leptin treatment,¹⁻³ such a negative energy balance might be a limiting factor for long-term use of leptin in patients with lipodystrophy.

One patient had an exacerbation of hypertension during the course of treatment, despite the marked decrease in food (and thus probably salt) intake. Leptin is known to have sympathoexcitatory actions leading to hypertension.⁴ Because leptin may also be involved in the control of reproduction, thyroid and adrenal axes, and gastrointestinal and immune functions, even physiologic doses of leptin should be carefully monitored in leptin-deficient patients.

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1. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 1999; 341:879-84.

2. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763-70.

3. Inui A. Feeding and body-weight regulation by hypothalamic neuropeptides — mediation of the actions of leptin. *Trends Neurosci* 1999;22: 62-7.

4. Correia ML, Haynes WG, Rahmouni K, Morgan DA, Sivitz WI, Mark AL. The concept of selective leptin resistance: evidence from agouti yellow obese mice. *Diabetes* 2002;51:439-42.

The authors reply:

To the Editor: As Dr. Mauvais-Jarvis states, activation of the enzyme AMP-activated kinase by leptin may be a key mechanism in the explanation of the effects observed in our patients. This hypothesis requires further testing. The effect of leptin in any species may be modified by the genetic background. We stated in our discussion that leptin is the main adipocyte hormone that maintains insulin sensitivity; however, we acknowledge that it is not the only one.¹ The effect of other adipocyte hormones in humans is an open and important question.

We agree with Dr. Wolfsdorf and colleagues that dietary control is the central tenet of treatment in all diabetic and metabolic syndromes. However, in our patients, the best metabolic control we could achieve with diet and antidiabetic therapy was indicated by the base-line data we presented. Hyperphagia is a strong drive that is hard to overcome by medical advice and rational discussion with these patients, like the hyperphagia observed in patients with a congenital absence of leptin² or leptin receptor.³ The administration of leptin clearly had an effect in ameliorating the extreme hyperphagia as well as improving the metabolic values in our patients. The pancreatitis-like syndrome occurred when leptin was withdrawn in one patient, while food intake was kept constant, and the occurrence of the syndrome coincided with the apparent increase in triglyceride levels. The withdrawal of leptin resulted in a clear rise in fasting insulin and triglyceride levels despite the constant caloric intake until the development of pancreatitis-like symptoms. Although our data are not sufficient to prove the direct effects of leptin on total-body insulin sensitivity and lipid metabolism alone, taken together with the results of pair-feeding experiments in animal models,⁴ they support the hypothesis that leptin is an insulin sensitizer in addition to its effect on food intake.

Finally, we would like to make the following points about the safety of leptin therapy, in response to Dr. Inui's comments. All the patients we described have continued to receive leptin therapy for up to a year without further weight loss and with stable energy expenditure at rest. We did not expect the resting energy expenditure to increase with leptin therapy, since this observation is limited to rodents, as we stated in our discussion. We have not noted any adverse effects on the hypothalamic-pituitary-adrenal⁵ or thyroid axis and have noted only favorable effects on the reproductive system,⁵ as well as the immune system. The exacerbation of hypertension in one patient that we noted in our report was an isolated event that occurred on the first day of treatment and did not recur in the patient, despite continued therapy.

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2. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin defi-

ciency is associated with severe early-onset obesity in humans. *Nature* 1997;387:903-8.

3. Clement K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998;392:398-401.

4. Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature* 1999;401:73-6.

5. Oral EA, Ruiz E, Andewelt A, et al. Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. *J Clin Endocrinol Metab* (in press).

Malposition of a Pacemaker Lead

To the Editor: Firschke and Zrenner (Feb. 7 issue)¹ describe a case of inadvertent malposition of a right ventricular pacing lead in the left ventricle. The patient was taking aspirin for coronary artery disease. Surprisingly, the authors state, "No action was taken, since there had been no complications during the previous four years and the pacemaker and lead functions were normal." Patients with left ventricular leads are at significant risk for systemic embolization from thrombus formation on the lead, even when they are receiving antiplatelet therapy.² Therefore, if timely removal of a malpositioned lead in the left ventricle is not performed, lifelong anticoagulation therapy with warfarin should be instituted.

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1. Firschke C, Zrenner B. Malposition of dual-chamber pacemaker lead. *N Engl J Med* 2002;346:e2. (Available at <http://www.nejm.org>.)

2. Van Gelder BM, Bracke FA, Oto A, et al. Diagnosis and management of inadvertently placed pacing and ICD leads in the left ventricle: a multi-center experience and review of the literature. *Pacing Clin Electrophysiol* 2000;23:877-83.

The authors and a colleague reply:

To the Editor: Dr. Farzaneh-Far refers to the summary of 28 case reports involving patients with a pacemaker lead inadvertently placed in the left ventricle.¹ Eleven of the 28 patients had cerebral ischemia, in most cases two years or less after implantation of the lead. Cerebral ischemia occurred in 3 of 6 patients who were receiving antiplatelet medication, in none of 2 who were receiving warfarin, in 6 of 16 who were not receiving medication, and in 1 of 4 who were receiving unknown medication ($P=0.36$). Of four patients with cerebral ischemia, subsequently treated with warfarin, one had a recurrence of cerebral ischemia. The period of follow-up and the prevalence of concomitant risk factors, such as atrial fibrillation and valvular or vascular disease, were not reported. On the basis of these data, no conclusions can be drawn with regard to either the risk of thromboembolism associated with a left ventricular lead or a general therapeutic strategy for this condition.

In our patient, who was asymptomatic during a period of four years after implantation of the pacemaker, without evidence of thrombus on echocardiography and with no additional risk factors for cardiogenic thromboembolism,

the risk of thromboembolism with continued use of aspirin was considered too low to justify surgical removal of the lead or initiation of oral anticoagulant therapy. In addition, the risk of bleeding complications associated with anticoagulation in a 78-year-old person with arterial hypertension has to be taken into consideration.² Longer follow-up of the patients in the study described above¹ may help to determine the most appropriate therapy for patients with a pacemaker lead inadvertently placed in the left ventricle.

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2. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996;348:423-8.

Direct-to-Consumer Marketing

To the Editor: There is a conflict between the conception of health care as a free-market economic process and the notion that health care represents one of society's obligations to its citizens. We cannot have it both ways. Physicians are also caught between these two incompatible views.

In a free-market system, physicians charge whatever the market will bear and limit the amount of charity care they provide in order to maintain profitability. Those who cannot pay simply do without care. Drug companies and owners of high-technology machines hawk their wares in any way they wish (including direct-to-consumer marketing as discussed in the Feb. 14 issue¹⁻⁴), and for consumers, the watchword is "Buyer beware."

If society recoils from the heartless consequences of a free-market system, we must cope with providing necessary care without regard to ability to pay. If every citizen is entitled to all types of medical care when they are needed, then we need a system that taxes all of us in order to support that entitlement. We need to determine which services, supplies, drugs, and tests must be included and which will be excluded. We need to determine what the payment to physicians will be, remembering that if the payment is too low, we will lose good physicians. We should use evidence-based studies to educate physicians and consumers about the costs and benefits of services, drugs, and tests.

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1. Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. *N Engl J Med* 2002;346:498-505.

2. Wolfe SM. Direct-to-consumer advertising — education or emotion

promotion? *N Engl J Med* 2002;346:524-6. [Erratum, *N Engl J Med* 2002;346:1424.]

3. Holmer AF. Direct-to-consumer advertising — strengthening our health care system. *N Engl J Med* 2002;346:526-8.

4. Lee TH, Brennan TA. Direct-to-consumer marketing of high-technology screening tests. *N Engl J Med* 2002;346:529-31.

To the Editor: Pharmaceutical firms and medical entrepreneurs are not the only ones marketing directly to consumers. Recently, many professional societies have expanded their advocacy agendas. The purpose of these campaigns is in part to inform consumers and in part to increase demand for the services offered by members of the professional society. The American College of Gastroenterology produced a television announcement urging people over 50 years of age to be screened for colon cancer. The American College of Physicians created advertisements promoting their “brand” of doctors (internists) and distinguishing them from family practitioners. The American Dental Association launched a national campaign warning consumers, “Don’t let it grow up to be oral cancer”; the campaign was funded by OralScan Laboratories, the manufacturer of a brush-biopsy test. Because consumers may not discern self-interest in advice from doctors, these advertisements can be more ethically and legally troubling than the practices described by Rosenthal et al.¹ and Lee and Brennan.²

Should professional societies recuse themselves from speaking out on important health issues? Not necessarily. Offering information to health care consumers can improve health, even as it increases the demand for medical services. For example, marketing immunizations both gets children into pediatricians’ offices and serves public health. Explaining the competencies and expertise of their members also seems to be a proper role for professional societies. But when professionals recommend specific actions to consumers, they should be certain that these actions are grounded in firm evidence of medical efficacy and cost effectiveness. When the balance tips toward financial self-interest, consumers and regulators may appropriately start treating professionals no differently from the way they treat for-profit companies.

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To the Editor: Although there may be advantages and disadvantages to direct-to-consumer advertising of prescription drugs, the main point to be considered is that such advertising helps to promote the empowerment of patients. Direct-to-consumer advertising of prescription drugs is il-

legal in many countries, including Portugal. Recently, an advertising campaign was launched by Portuguese authorities promoting the prescription of generic drugs. The campaign included advertising on television and in newspapers. For example, in one major newspaper, three complete pages were used to advertise generic drugs that are currently on the market. Such advertisements may be taken as a subtle form of direct-to-consumer advertising of prescription drugs that probably aims to reduce the pharmaceutical budget of the Portuguese state.

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To the Editor: Despite the statistics that are quoted by Alan Holmer of the Pharmaceutical Research and Manufacturers of America in his editorial,¹ I do not believe many of the statements he makes. For instance, I do not believe that advertising a drug on television does not increase the cost of the drug to the patients who use it. If a pharmaceutical company believes that, then it needs new auditors. I do not believe that advertising a drug on television always leads to a useful discussion between the patient and his or her doctor. Even when the discussion does take place, the doctor may have trouble talking the patient out of using the “new and better” drug. After all, the patient discovered the miracle drug in a good magazine and “learned” a lot about it when it was presented on television. The artwork was so beautiful and the message so clear that the patient believes every word of the advertisement and assigns little value to what the doctor says. Holmer states that the purpose of the advertising is “rather to encourage an informed discussion between patient and physician.” I believe that the purpose of the advertisements on television and in magazines is to sell drugs — just as companies use such advertisements to sell soap and toothpaste.

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1. Holmer AF. Direct-to-consumer advertising — strengthening our health care system. *N Engl J Med* 2002;346:526-8.

To the Editor: Drs. Lee and Brennan state that screening tests must have a high sensitivity, have a low false positive rate, and be useful for therapeutic decisions or reassurance, depending on the results. These criteria are understood by preventive cardiologists and lipid specialists who practice in this field to be salient features of electron-beam computed tomography (CT). Such “plaque imagers” have asserted that electron-beam CT produces essentially no false positives while offering virtually 100 percent sensitivity for detecting coronary calcium, a recognized marker of atherosclerosis. In outcome studies¹ (except for a heavily criticized report involving high-risk elderly adults), the calcium score has been shown to be a powerful predictor of coronary events and to have incremental prognostic value

beyond the identification of conventional risk factors.² The unfortunate use of angiography as a gold standard by a writing group of the American College of Cardiology and the American Heart Association (only one of whose members had actual experience in coronary imaging) was roundly criticized by the Society of Atherosclerosis Imaging. Before a coronary event, electron-beam CT of the typical asymptomatic person would demonstrate a calcium score in the top quartile and would reveal no substantial obstruction.³ The authors would therefore misconstrue the test result as a false positive. Greenland et al.⁴ suggest that clinicians consider noninvasive testing for approximately 40 percent of adults in order to target for clinical risk-reduction measures those with “true risk” (who otherwise might be mischaracterized according to the guidelines of the National Cholesterol Education Program). If physicians referred patients for electron-beam CT when such examinations were indicated,⁵ instead of prescribing doctor-owned stress tests for patients with class III indications, the need for marketing might largely disappear.

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Editor's note: Dr. Ehrlich is the medical director of and a shareholder in three imaging centers that use electron-beam CT. Dr. Rumberger is the medical director of an imaging center that uses electron-beam CT and derives a salary from that center. Dr. Wasserman is the cardiology director of an imaging center that uses electron-beam CT and is paid by that center to read studies.

1. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36:1253-60.
2. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;86:495-8.
3. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850-5.
4. Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation* 2001;104:1863-7.
5. Hecht HS. Practice guidelines for electron beam tomography: a report of the Society of Atherosclerosis Imaging. *Am J Cardiol* 2000;86:705-6, A9.

Dr. Rosenthal and colleagues reply:

To the Editor: We agree with Ackman and Glied that the recommendations made by health care professionals and the organizations that represent them may affect their own financial interests. This is true both under traditional fee-

for-service payment plans and in an environment in which physicians are paid by capitation, although the incentives are obviously different in the two situations. Self-regulation is a central tenet of professionalism. Physicians must be especially wary in situations in which the potential effect of their advice on their own financial interests is great.

The letter from Nunes is a reminder that direct-to-consumer advertising could contribute to improved patient care and, in some situations, could even reduce the cost of care. One can imagine similar educational campaigns by managed-care organizations or the generic-drug industry in the United States to promote the use of less expensive medications.

Finally, we share Weinberg's support for universal coverage but believe that it could be accomplished without the elimination of “the market,” at least in terms of delivery. Many countries have achieved this goal while maintaining market incentives. The key is a nationally shared commitment to providing health care for all our citizens.

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Drs. Lee and Brennan reply:

To the Editor: We agree with Ehrlich and colleagues that use of electron-beam CT should be targeted at patients for whom it is most likely to provide information that will improve their care. However, we do not believe that any such population of patients has been identified through rigorous research to date. There is little question that calcium scores correlate with prognosis for asymptomatic patients, but two questions remain unanswered: Can electron-beam CT improve risk predictions that are based on the thoughtful analysis of clinical data? And does treatment of asymptomatic patients with high scores on electron-beam CT reduce their risk of complications of coronary heart disease? Until both of these questions can be answered in the affirmative, we believe that it is inappropriate for physicians to be marketing electron-beam CT directly to consumers or performing electron-beam CT outside of research protocols.

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Dr. Wolfe replies:

To the Editor: Nunes implicitly discusses the difference between direct-to-consumer advertising, the main purpose

of which is to sell brand-name prescription drugs, and accurate direct-to-consumer information, the purpose of which is to empower patients with information that will be of benefit to them. The case of the Portuguese government's campaign to educate the public about the economic advantages of generic drugs is an excellent example of the latter — one that the U.S. government should replicate. Other examples would be widely publicized government campaigns, involving the Food and Drug Administration and the National Institutes of Health, to educate patients and physicians with accurate and up-to-date information about the preferred treatments for various common diseases.

Ackman and Glied point out that the concept that financial conflicts of interest may cloud the veracity of information is not limited to the pharmaceutical industry but has infected what I believe must be the overwhelming majority of organizations for physician specialties and subspecialties. As medicine increasingly becomes a business, with money too often trumping the basic, historical service ethic of our profession, the credibility of medical organizations and physicians themselves is endangered by the increasing documentation of decisions made not solely on the basis of what is in the best interest of the health of the patient but also on the basis of what may be most beneficial financially to doctors and their organizations.

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Debt Repayment for Trainees

To the Editor: Ley and Rosenberg (Jan. 31 issue)¹ fail to note that a high average debt load is common among physicians entering private practice and those training for careers in medical science. What differentiates the two pathways financially is salary. Since money is fungible, loan repayment simply increases the net compensation of the selected recipients. As the authors admit, there is no proof that educational-loan repayment itself is especially compelling, yet this is the only rationale offered to justify bestowing a (relative) windfall on certain trainees. Ironically, the repayment program will create an incentive for students considering careers as physician-scientists to accumulate educational debt, whether they need the loans or not.

Nathan (Jan. 31 issue)² admits that the category “clinical investigator” is “vaguely defined.” Under the current definition, the experimental methods that a scientist uses matter as much as the questions he or she is trying to address. This definition thus creates a compelling and ethically problematic financial incentive for grant applicants to find justifications for incorporating human subjects into their study design. Physician-scientists should be able to ask important questions about human biology and disease without having to worry about whether the design of their experiments will cause them to receive much lower compensation than their peers. Nathan worries about a “barrier of jealousy” between M.D. and Ph.D. researchers, but both Sounding Board articles overlook the effect on mo-

rale of allowing some M.D. researchers to receive increased income in the form of loan repayment while others, by dint of their study design or the way their finances are structured, are deemed ineligible to apply for better compensation.

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1. Ley TJ, Rosenberg LE. Removing career obstacles for young physician-scientists — loan-repayment programs. *N Engl J Med* 2002;346:368-72.
2. Nathan DG. Educational-debt relief for clinical investigators — a vote of confidence. *N Engl J Med* 2002;346:372-4.

To the Editor: After the National Institutes of Health (NIH) Director's Panel on Clinical Research released its report in December 1997, private grant-making organizations sprang into action. Several quickly developed innovative programs to address the acute shortage of clinical investigators. To aid in this process, 11 prominent foundations that support medical research joined together to form the Clinical Research Alliance, which provided a platform for members to brainstorm and share best practices. In July 2001, we met as a group with NIH leaders to stress our shared concern and to press for implementation of their extramural loan-repayment program.

The response of private organizations has been substantial. A survey of Alliance members revealed that our collective investment in the pipeline of clinical investigators (as defined by the NIH) has more than doubled since 1997 and now exceeds \$78.5 million annually. Special features of awards for new investigators include debt repayment, “protected time,” longer award periods, and stipends for mentors. The Clinical Research Alliance continues to meet in order to focus on other initiatives, such as exposing medical students to clinical investigation and recruiting members of underrepresented minority groups for careers in clinical research.

Historically, private grant-making organizations have not been known to collaborate. However, urgent needs call for creative responses. Any impediment to the flow of scientific discovery to patients must be addressed rapidly and effectively. We hope our efforts are just the beginning of new partnerships and innovative solutions to this urgent problem.

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To the Editor: Shortly after receiving a favorable score on an NIH K08 grant application, I elected to pursue private

practice, weighing my debt and continued need to moonlight against my limited salary increase and the uncertainty of academic success. I needed to look no further than my mentors to reaffirm the prudence of my choice. Few faculty members were, as I was, the sole breadwinners in their families; many were partners in dual-physician relationships or were otherwise financially secure and more insulated against monetary worries. Still, if I had had an opportunity for debt forgiveness, I might have chosen otherwise.

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Drs. Ley and Rosenberg reply:

To the Editor: Chessler notes that the debt for all graduating M.D.s is the same, but the salaries in practice and academia are different. The debt figures cited in our article do indeed refer to all medical school graduates, not just those contemplating careers in science. The salary reduction and delayed earning potential of “late bloomers” who choose to become physician-scientists can never be recovered with loan-repayment contracts. Their purpose is not to correct a salary differential but to remove a career obstacle that has affected the pipeline of physician-scientist trainees. We believe that the issue is compelling enough that substantial steps must be taken now. Loan-repayment programs should be seen as one part of a comprehensive strategy to encourage young physicians to consider a career in science. These programs are indeed considered experimental by all who advocate them. We will learn during the next few years just how much incentive they provide. We hope it is considerable.

We applaud the actions of the foundations that Egan, Gallin, and Sung represent and the many others who have participated in the collaboration they describe. The rapid response of medical-research foundations to this problem has been visionary and should have an enormous effect.

We wish that loan-repayment programs had been available to Gronski when he made his career choice, which was based on compelling economic considerations. Loan repayment was not a big consideration for either of us, since our entire tuition bills for medical school were less than the salary that each of us received as an intern. Things have changed. The obstacles to a career in science are real, and the proof is in the numbers. Early steps to address this problem are under way and must be monitored carefully for their effectiveness and modified rapidly if they are insufficient.

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Dr. Nathan replies:

To the Editor: Chessler makes several interesting points. It is true that there are no hard data to prove that educa-

tional debt influences the career choices of physicians, but there is a massive “clinical impression” among division chiefs and department chairs that it does. I doubt very much that students will amass debt whether they need loans or not. The risk would be very high, because only a fraction of the applicants will actually be funded in this program. I also doubt that it is unethical to offer incentives to medical students to pursue careers in clinical research. By offering M.D.–Ph.D. programs, we already offer them incentives to be interested in basic research. I would remind Chessler that I do not favor restriction of this program to M.D.s, but if educational debt is keeping M.D.s out of clinical research, I do hope to alleviate that problem.

Egan, Gallin, and Sung correctly point out that private foundations have certainly stepped up to the plate and greatly alleviated the problem with extremely effective granting programs. Difficult problems are best solved by effective collaborations, and the entire medical community is grateful to them and to the boards of trustees of the Damon Runyon Cancer Research Foundation, the Doris Duke Charitable Foundation, and the Burroughs Wellcome Fund. The Howard Hughes Medical Institute has also entered the field with an excellent program in clinical research.

Gronski emphasizes the first point in my response to Chessler. We have not conducted a formal study to prove the point, but if we did, I believe its results would be strongly positive.

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Adult T-Cell Leukemia–Lymphoma during Pregnancy

To the Editor: Human T-cell lymphotropic virus type I (HTLV-I) infection is uncommon in the United States. During the period from 1991 to 1996, the incidence of seropositivity for HTLV-I or human T-cell lymphotropic virus type II (HTLV-II) in U.S. blood donors was 1.59 per 100,000 person-years.¹ This virus causes adult T-cell leukemia–lymphoma.² We report a case of adult T-cell leukemia–lymphoma during pregnancy.

A 23-year-old woman was admitted to a hospital in South Carolina because of a 7-day history of sore throat, fever, and fatigue during the 26th week of gestation. There was no history of intravenous drug use, foreign travel, transfusion, or sexual promiscuity. Exudative tonsillitis and tender, enlarged lymph nodes of the head and neck were present. An enlarged spleen (20 cm) and stable fetal status were confirmed on ultrasonography. The white-cell count was 55,900 per cubic millimeter (with 74 percent unclassified cells). Serum aminotransferase levels were normal; a Monospot test, a test for antistreptolysin O titers, a polymerase-chain-reaction (PCR) assay for human immunodeficiency virus type 1, and tests for IgM antibodies against Epstein–Barr virus, human cytomegalovirus, and *Toxoplasma gondii* were negative. The patient was given supportive care.

On the fourth hospital day, the white-cell count rose to 75,000 per cubic millimeter, the serum calcium level was

20.2 mg per deciliter, and the lactate dehydrogenase level was 7056 U per liter. Flow-cytometric analysis showed increased numbers of CD3+CD4+ and CD3-CD25+ T cells in the blood, and examination of a specimen from a bone marrow biopsy showed 34 percent atypical, intermediate-size lymphocytes. IgG anti-HTLV-I or HTLV-II antibodies were present, and HTLV-I was detected by a PCR assay performed on the whole-blood sample. The patient was treated with hydroxyurea (1 g) and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; the white-cell count fell to 12,700 per cubic millimeter. On the eighth day, a healthy boy was delivered by cesarean section. Eleven days after admission, the patient died from *Staphylococcus aureus* septicemia.

HTLV-I is endemic on the islands of the Caribbean basin and in Japan, South America, and West and Central Africa. In the United States, most cases of HTLV-I or HTLV-II infection are reported on the East and West Coasts.³ We do not know how this patient became infected with HTLV-I.

In the United States, the rate of vertical transmission of HTLV-I from infected mothers to offspring is approximately 2.7 percent. Adult T-cell leukemia-lymphoma develops in approximately 5 of 100 patients with chronic HTLV-I infection, and the risk of adult T-cell leukemia-lymphoma among children born to women who are seropositive for HTLV-I ranges from 0.1 percent to 1 percent.⁴ Breast-feeding is the main route of transmission, and prolonged exposure to breast milk (>3 months) increases the rate of postpartum transmission of HTLV-I by approximately 20 percent.⁵ Prenatal HTLV-I screening of high-risk women in the coastal regions of the United States may provide critical information, since the cessation of breast-feeding by HTLV-I-infected women may prevent retroviral transmission to the child.

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1. Glynn SA, Kleinman SH, Schreiber GB, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. *JAMA* 2000;284:229-35.
2. Siegel R, Gartenhaus R, Kuzel T. HTLV-I associated leukemia/lymphoma: epidemiology, biology, and treatment. *Cancer Treat Res* 2001;104:75-88.
3. Poiesz BJ, Papsidero LD, Ehrlich G, et al. Prevalence of HTLV-I-associated T-cell lymphoma. *Am J Hematol* 2001;66:32-8.
4. Ades AE, Parker S, Walker J, Edginton M, Taylor GP, Weber JN. Human T cell leukaemia/lymphoma virus infection in pregnant women in the United Kingdom: population study. *BMJ* 2000;320:1497-501.
5. Takezaki T, Tajima K, Ito M, et al. Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. *Leukemia* 1997;11:Suppl 3:60-2.

Failing

Your sunken eyes plead with me
Volcanic orbits wasted of sculptured fat
Burned in failure's fire
Your listless gaze pleads with me
To offer a clue —
We both know your cancer
Sneaks about within you
Evading my mortal knife —
On this day as dusk settles
With its flippant breach of faith
In this inhospitable hospice place
I visit you with apology
Faint on my awkward tongue —
Pain claws your innards
Casting you closer to your fate
Even as my narcotic needle
Bites with a measure of reprieve —
Your eyes flutter now
Eternity approaches within inches
And I measure my deceit —
I didn't know you were this close

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