Correspondence

Expediting Publication to Inform Political Debates

To the Editor: We firmly believe that you were correct in saying (Feb. 11 issue)[1] that editors should have the liberty to publish articles or advance the publication of articles that create "a lively forum for exposure and discussion of important issues that involve, even indirectly, health and medicine." However, we must disagree with the application of this logic to the article that you claim resulted in Dr. George Lundberg's dismissal as editor-in-chief of the *Journal of the American Medical Association* (JAMA). Advancing the publication date of the article in question did not "contribute to the development of public policy." The timing of its publication was not "critical to the public health." And, clearly, it was not an editorial expressing the opinion of the editor. The timing of the publication of this article was not even important with respect to providing substantive evidence for the Senate trial with which it was timed to coincide. Since none of the critical concepts that you use to frame this issue apply, we do not agree with either your indictment of the decision of Dr. E. Ratcliffe Anderson, the executive vice president of the American Medical Association (AMA), as "irrational" or your declaration that this is an "ominous precedent." On the basis of other public statements, we believe that Dr. Anderson responded appropriately to an act that was a culmination of problems, not a single event.

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1. Kassirer JP. Should medical journals try to influence political debates? N Engl J Med 1999;340:466-7.

To the Editor: Your editorial regarding the firing of the editor-in-chief of JAMA was correct in every regard save one: its conclusion. The conclusion that the firing was "an irrational decision and an ominous precedent" is based on the flawed initial premise that the rationale for the firing was advancing publication of an article with the goal of influencing political events. If that premise were correct, most physicians and scientists, I among them, would agree with everything you wrote. At issue, however, was not a generic political event. Lundberg intended to influence a particular kind of political event — specifically, one that has nothing to do with medicine or health care. His choice of editorial subject lay outside what Dr. Anderson, representing the AMA, believed to be proper editorial boundaries.

In support of Lundberg, you cited the *Journal*'s participation in debates regarding health policy, public health, and legal issues in health care; your own editorials on the medical uses of marijuana, a proposed federal ban on cloning experiments, and congressional practice of medicine;

and your putting on a fast-track reports and opinion pieces on starvation in Somalia, health care reform, the tobacco settlement, and the ethics of clinical research in developing countries. Every one of those publications was in some way related to health care.

Regardless of whether the article in question was poor science, as some have claimed,[1] the debate that Lundberg was trying to influence had nothing to do with health care. That gun control and domestic violence are related to health is plausible; the impeachment of a president is not. Timing publication to coincide with a Senate trial does not suggest an interest in health policy, public health, medical ethics, or health law. Rather, it bespeaks transparently partisan politics.

There are boundaries for the editorial policy of medical journals. I have not seen, nor do I expect to see, an editorial in the *Journal* or in JAMA supporting a particular candidate for public office or touting a specific common stock. One might agree, as I do, or disagree with Dr. Anderson's delineation of editorial boundaries for JAMA, but there can be no question that such a boundary exists and is necessary. The AMA is politically active and must work with both parties in achieving its health policy and public health goals. The use of JAMA to pursue partisan political goals, in my opinion, crosses the boundary of editorial propriety.

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1. McCormick B. Removal of JAMA editor draws fire. American Medical News. February 1, 1999:1.

To the Editor: . . . Your nicely documented personal approach to the topic of journalistic relevance offers a strong defense of Dr. Lundberg's editorial judgment. But it is Dr. Lundberg's judgment, not yours, that is in question. Although editorial independence is a hallowed journalistic concept, judgment is a personal characteristic. Implicit in every exercise of editorial independence is a review of editorial judgment by the readers and the publishers. Editors are not appointed for life, and editorial independence does not make them fireproof.

The medical profession and its journals are neither advanced nor ennobled by unwisely wading into the tortured semantics of an acrimonious political conflict, the outcome of which has nothing to do with public health, health care, or the medical sciences. Journals, institutions, leaders, and political candidates who strain to show their relevance to every passing issue, convinced of the illuminating nature of their comments, eventually become self-parodies, unable to tell big issues from little ones, thereby losing their effectiveness, their reputations, and ultimately their constituencies. A sharply focused sense of relevance is a signal difference between the professional journal and the common magazine.

Although you have defended Dr. Lundberg on the grounds of editorial independence, one is left to ponder whether you and the *Journal* would have expended any precious journalistic capital on the article in question. Nothing in my 30 years as a reader of the *Journal* suggests that you would have done so.

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To the Editor: I firmly agree with Dr. Anderson's decision to fire the editor-in-chief of JAMA. I believe that any political views of an organization should be left to a specified section of the organization for study and action as may become indicated. Such views should not be put forth by an editor as if they represented members' viewpoints. . . .

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To the Editor: You decry the firing of the editor of JAMA for publishing an article on the sexual attitudes of college students. . . . Was the JAMA article intended to influence a public health issue? Hardly. This was a blatant attempt to influence a national political process that had little to do with sex and nothing to do with health. JAMA was intruding on a purely political action and doing so on the side that I seriously doubt a third of the AMA membership would have supported. At medical meetings, I often find myself the sole supporter of liberal ideas. Clearly, JAMA exists to serve and represent the membership of the AMA. Just as the former editor excoriated the prior leadership of the AMA over the doomed deal with Sunbeam because it did not represent the views of the membership, so, too, was Dr. Anderson correct to end political adventurism.

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To the Editor: The content of one controversial article in JAMA over a 17-year span is not the issue. The fundamental problem is the interference of the publisher, the AMA. In one public tantrum and cudgeling, the AMA has destroyed the editorial independence of JAMA, assaulted not only the editor-in-chief but also the journal's editorial boards, and destroyed the confidence of potential contributors to journals published by the AMA.

As a past trustee and chair of the board of the AMA, I found that it was not unusual to receive complaints from persons and organizations about articles or editorials in the journals. The boards of trustees and the executive vice presidents of the AMA with whom I was privileged to work recognized the necessity for editorial independence. This is what brought these journals unprecedented renown, only to be destroyed by the autocratic actions of the current executive vice president, with the support of the AMA's board of trustees.

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To the Editor: Bravo for your editorial echoing the sentiments of many of us rank-and-file physicians. I, too, am outraged at the firing of Dr. Lundberg for publishing a survey of college students' opinions on oral sex. It was Dr. Anderson, in his knee-jerk firing of Dr. Lundberg, who

committed an unforgivable political act within the framework of medicine. Dr. Lundberg was exerting his version of responsible judgment in a brave and timely fashion. If we disagree with the implied viewpoint of a publication, we can do so by writing letters to the editor, presenting contrary evidence in other studies, or otherwise exerting our rights to free speech and free intellectual inquiry.

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Control of HIV despite the Discontinuation of Antiretroviral Therapy

To the Editor: Eradication of the human immunodeficiency virus (HIV) is a difficult goal to achieve, because a reservoir of replication-competent HIV is established in resting CD4 T lymphocytes soon after infection and persists after years of highly active antiretroviral treatment.[1] A more realistic alternative to lifelong cumbersome, toxic, and expensive treatments is to control HIV, as occurs in patients with long-term nonprogression of the disease.

A patient, who has become known as "the Berlin patient," was treated soon after acute HIV infection, before complete seroconversion on Western blotting, with a combination of hydroxyurea (400 mg three times daily),[2] didanosine (200 mg twice daily), and indinavir (800 mg three times daily).[3] Before treatment, base-line measurements obtained seven days apart showed similar levels of HIV in the plasma (80,041 and 89,390 copies per milliliter), suggesting that the steady state of plasma viremia had already been reached. After levels of HIV RNA became undetectable in plasma, viremia recurred during a temporary suspension of treatment (Fig. 1, next page). However, no viral rebound was documented during a second temporary suspension of treatment, despite a concomitant infection with hepatitis A, which is known to activate the immune system and accelerate the rate of replication of HIV.[4]

The patient elected to stop treatment permanently after 176 days. No viral rebound was observed during the following 551 days. However, traces of HIV RNA were detected in a lymph node, and replication-competent virus[1] was isolated from resting CD4 T lymphocytes at very low frequencies (Table 1, next page), demonstrating that HIV had not been eradicated.

Despite 19 months without treatment, phenotypic markers, such as the CD4 count, the ratio of CD4 to CD8 T lymphocytes, and the proportion of naive CD4 and CD8 T lymphocytes (cells in which an immune response has not yet been activated) increased to normal levels (Table 1). No HIV-neutralizing antibodies were detected. In contrast, the vigorous HIV-specific helper T response[5] progressively increased during two years of follow-up in the absence of treatment. There was also a consistently strong response of CD8 cytotoxic T lymphocytes to a p17 gag epitope on both a tetrameric-complex assay and an enzyme-linked immunospot assay (Elispot). No responses to reverse transcriptase or envelope epitopes were observed. If cytotoxic T lymphocytes do control the rebound effect, the lack of a broad immune response to epitopes in this patient suggests the potential for future viral breakthrough.

In this patient viral control has been maintained for two years despite the discontinuation of intermittent antiretroviral treatment with hydroxyurea, didanosine, and indinavir. The presence of vigorous, HIV-specific responses of CD4 helper T lymphocytes and CD8 cytotoxic T lymphocytes in the absence of neutralizing antibodies suggests a role for the cellular arm of the immune system in keeping HIV replication under control. However, the immunologic correlates that predict control of viremia after the discontinuation of therapy, as well as the relative contribution of the elements required to induce such control, need to be analyzed in randomized, controlled clinical studies.

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1. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997; 278:1295-300.
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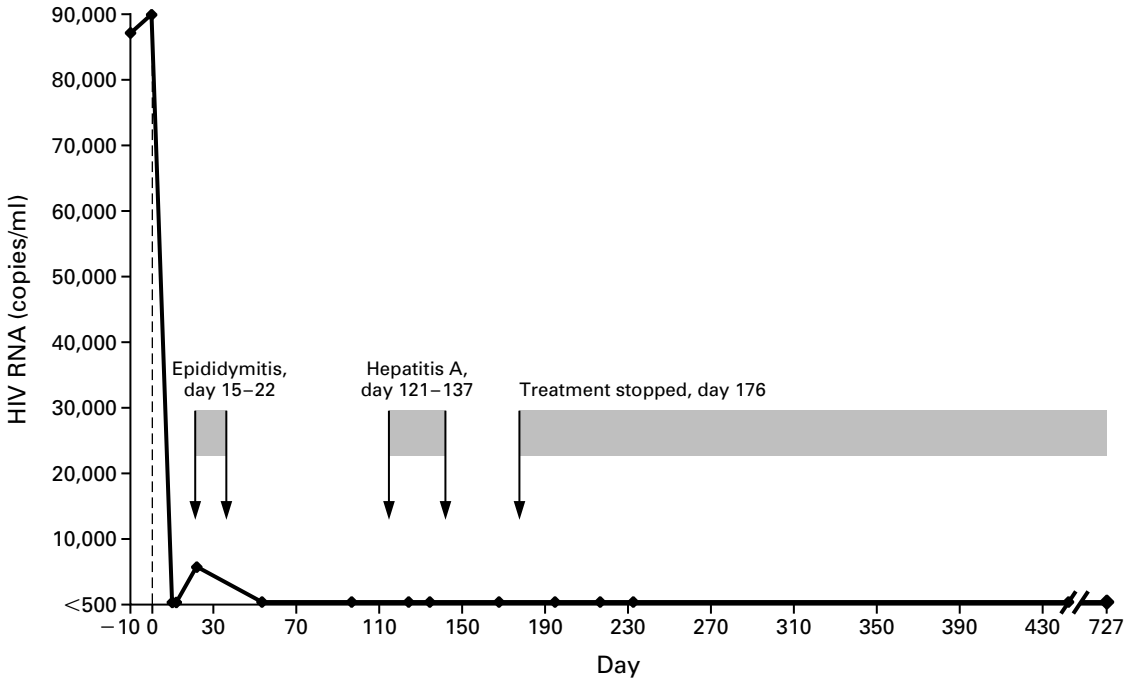

Figure 1. Plasma Levels of HIV RNA in the Patient.

Plasma levels of HIV RNA were measured by a branched-chain DNA assay with a limit of sensitivity of 500 copies per milliliter. Day 0 was the first day of treatment. Shaded areas indicate periods of no treatment.

TABLE 1. MEASUREMENTS OF CELLULAR HIV, T-LYMPHOCYTE PHENOTYPIC MARKERS, AND HIV IMMUNE RESPONSE.*

VARIABLE	DAY 0	DAY 194	DAY 564	DAY 606	DAY 727
HIV RNA (positive cells/4.4×10^7 cells)†		3			
Replication-competent HIV (virus-producing cells/10^7 PBMC)			<1		
CD4 T lymphocytes (cells/mm^3)	370				783
CD4:CD8 T lymphocytes	0.52				0.87
Naive (CD62L+,CD45RA+) CD4 T lymphocytes (% of total CD4 T lymphocytes)		24.0		49.0	
Naive (CD62L+,CD45RA+) CD8 T lymphocytes (% of total CD8 T lymphocytes)		9.8		50.3	
HIV-neutralizing antibodies				Undetectable	
Stimulation index (p24 helper T response)‡		8.0		20.2	64.2
HIV p17 cytotoxic T lymphocytes					
Tetramer assay (% of CD8 T lymphocytes)					0.39
Enzyme-linked immunospot assay (positive cells/10^6 PBMC)			2280		2309

*Day 0 was the first day of treatment. Treatment was permanently stopped on day 176. PBMC denotes peripheral-blood mononuclear cells.

†HIV RNA was measured in a lymph-node specimen by in situ hybridization.

‡The stimulation index was calculated by dividing the mean number of counts per minute of incorporated [^{3}H]thymidine from cells stimulated with p24 by the mean counts per minute from cells stimulated with baculovirus control proteins.[5]

Treatment of Esophageal Cancer

To the Editor: The negative result obtained by Kelsen et al. in their trial of preoperative chemotherapy for operable esophageal cancer (Dec. 31 issue)[1] is somewhat surprising, since Herskovic et al.[2] reported positive results for similar chemotherapy with or without radiation therapy. Patient accrual in the study by Kelsen et al. was meager (average, <1 patient per hospital per year). How did the study centers maintain high clinical quality, given the low accrual rate? Were there any differences between the centers that were major contributors of data and the rest of the hospitals? Our own results lead us to believe that induction chemotherapy for esophageal cancer is difficult to do well and requires the efforts of a complex, multidisciplinary team of committed physicians.[3] In the study by Kelsen et al., only 71 percent of patients received all three cycles of chemotherapy, and only 80 percent of patients in the chemotherapy group had surgery. Were the goals of the study more likely to be fulfilled in high-accrual centers?

Of the patients who underwent surgery, the chance of a potentially curative resection (R0) increased from 62 to 78 percent with preoperative chemotherapy. This difference is probably both clinically and statistically significant. The finding that survival was essentially equivalent in the two groups, even though surgery was performed in 16 percent fewer patients in the chemotherapy group than in the immediate-surgery group (80 percent vs. 96 percent, respectively) suggests that a survival advantage is associated with chemotherapy.

What the clinician (and the patient) really want to know is whether, if induction treatment is given before surgery, there will be a benefit. Kelsen et al. could advance this debate by performing a subgroup analysis of patients who received all three cycles of chemotherapy and had surgery. If there is a benefit in this group of patients, attention should be directed to reducing the toxicity of the induction treatment so as to maximize the number of patients who receive all prescribed treatments.

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2. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
3. Wright CD, Wain JC, Lynch TJ, et al. Induction therapy for esophageal cancer with paclitaxel and hyperfractionated radiotherapy: a phase I and II study. J Thorac Cardiovasc Surg 1997;114:811-6.

To the Editor: Kelsen et al. are to be congratulated on their study, which reflects the culmination of more than 20 years of effort by the primary investigator to improve the survival of patients with esophageal cancer by the use of preoperative chemotherapy. Although the study convincingly shows that preoperative chemotherapy does not improve overall survival among patients with localized esophageal cancer, several reports indicate that the subgroup of patients who respond to preoperative therapy may still benefit from this approach,[1] whereas neoadjuvant therapy in patients who do not respond may actually be detrimental.[2] An analysis of the subgroups who do and do not have a response to preoperative chemotherapy in comparison with those who undergo primary resection is therefore warranted.

Furthermore, in the study by Kelsen et al., a bias toward more favorable tumor stages in the group undergoing surgery alone, a bias that cannot be excluded, would mask a beneficial effect of neoadjuvant chemotherapy. For example, the number of patients who were not recruited into the program during the trial period and the treatments they received are not given. Perhaps only patients with more advanced disease were included at some of the participating centers. Furthermore, the number of registered but ineligible patients was significantly higher in the chemotherapy-plus-surgery group than in the surgery-only group ($P<0.001$ by Fisher's exact test). Finally, the expertise of surgeons, and consequently the quality and extent of surgical resection and lymphadenectomy,[3] must have varied substantially, since a wide range of more or less radical surgical procedures were "considered acceptable" and the surgical resections were performed at more than 120 different institutions.

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1. Roth JA, Pass HI, Flanagan MM, Graeber GM, Rosenberg JC, Steinberg S. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, videsine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg 1988;96:242-8.
2. Law S, Fok M, Chow S, Chu KM, Wong J. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 1997;114:210-7.
3. Miller JD, Jain MK, de Gara CJ, Morgan D, Urschel JD. Effect of surgical experience on results of esophagectomy for esophageal carcinoma. J Surg Oncol 1997;65:20-1.

To the Editor: The results reported by Kelsen et al. are difficult to interpret for several reasons. The study was originally designed for the treatment of epidermoid cancer, but 18 months later it was modified to include adenocarcinoma of the esophagus. No reason is given for this decision, nor is the type of involvement of the gastroesophageal junction specified. Thus, some patients may actually have had a cardiac carcinoma.

Furthermore, the recruitment of patients was slow. It took more than five years to register 467 patients. Moreover, surgeons were required to perform at least four esophagectomies per year, but fewer than four patients per participating center were entered into the study. We assume that other patients were treated differently, even if they were eligible. Kelsen et al. state that one of the most common reasons why the full dose of chemotherapy was not administered either before or after surgery was the decision of the physician. This point should be clarified. The study included substantial weight loss and cell type (epidermoid cancer or adenocarcinoma) as stratifying variables. Weight loss is said to be a predictor of poor outcome and to occur more often in cases of epidermoid cancer. However, there was no difference in outcome according to these distinct

histologic subtypes. This raises the question whether this study simply lacked the statistical power to detect a difference in overall survival, despite the large number of patients.

Most important, the status of the lymph nodes was not included in the stratification. In our opinion, patients with lymph-node metastasis are not ideally suited for surgery, because this tumor stage often "represents systemic disease beyond the limits of resection."[1] These additional data should be given, although we believe that a post hoc subgroup analysis cannot definitively answer our questions.

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1. Roth JA, Putnam JB Jr, Rich TA, Forastiere AA. Cancer of the esophagus. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer — principles & practice of oncology. 5th ed. Vol. 1. Philadelphia: Lippincott-Raven, 1997:980-1021.

To the Editor: I would like to suggest two possible reasons why preoperative chemotherapy failed to benefit patients with operable esophageal carcinoma in the study by Kelsen et al. One is that patients assigned to receive chemotherapy before surgery were less likely to receive surgery. The authors report that 217 of 227 patients assigned to the surgery group underwent surgery, but only 171 of 213 assigned to the chemotherapy-plus-surgery group actually underwent surgery. The authors do not report why the latter 42 patients did not have surgery. It would be useful to know the exact reasons.

Another, less obvious possibility is an uneven distribution of stages of disease between the two treatment groups. Because the patients were not stratified according to the stage of the disease and because the trial included patients with tumor stage 1, 2, and 3 disease, it is possible that patients who received chemotherapy had more advanced disease than patients who underwent only surgery. However, Kelsen et al. do not report the stages of disease in the two treatment groups. One potentially confounding factor is that preoperative staging may not reflect the true stage of disease at the time of surgery. Frequently, a patient's disease may be assigned a higher stage because of false positive findings on preoperative computed tomographic scans and the detection of microscopic disease in regional lymph nodes. Therefore, it is highly important to understand the distribution of stages between the two groups of patients in the study by Kelsen et al. and to analyze outcomes according to stage.

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The authors reply:

To the Editor: In response to Drs. Fleeth and Begemann: during the initial steps in the design of our study, the incidence of adenocarcinoma was controversial. When the increased incidence of this tumor became clear, the protocol was amended. Patients with cancers of the gastroesophageal junction could not have more than 2 cm of tumor extension into the stomach. Participating institutions were not required to submit a register of eligible patients who were not entered into the study, and therefore we do not have data regarding their treatment. The preference of a physician not to continue chemotherapy was adjudicated when it was clear that there was no progression of disease, no dose-limiting toxicity, and no refusal of additional treatment by the patient; 10 patients met these criteria. The study was designed to test for a treatment difference with a statistical power of 90 percent, which has been judged to be more than adequate.

Drs. Fleeth and Begemann suggest that patients with lymph-node metastasis are not ideally suited for surgery. We did not stratify patients on the basis of the status of the lymph nodes because of the inaccuracy of currently available noninvasive staging techniques. However, there were no significant differences between the groups according to the clinical nodal stage. Of the group that was treated with surgery only, 59 percent had lymph-node metastases; the corresponding figure for the chemotherapy-plus-surgery group was 49 percent. However, fewer patients in the chemotherapy-plus-surgery group underwent surgical exploration.

In response to Dr. Chang: patients in the chemotherapy group did not undergo surgery for various reasons, including death (10 patients, with death as a result of toxic effects of chemotherapy in 7), inability to tolerate surgery (6), a tumor that was clinically unresectable (5), refusal by the patient (5), development of metastatic disease (3), removal from the protocol (1), and unknown reasons (12). Significantly more patients in the chemotherapy group who underwent surgical exploration had stage 0 or 1 disease ($P=0.003$), suggesting that their disease was assigned a lower stage, but this difference was offset (for the whole group) by patients in the chemotherapy group who had progression of disease and did not undergo surgery.

Drs. Fink and Stein ask about the survival of patients who had a response to treatment and those who did not respond. Patients in the chemotherapy group who responded to treatment had a significantly better survival rate than did those in the chemotherapy group who did not respond ($P=0.002$) and those in the surgery-only group ($P<0.001$).

In response to Dr. Wright: 53 of 78 patients (68 percent) in the three high-volume centers received three courses of induction chemotherapy, as compared with 90 of 126 patients (71 percent) in the institutions with lower accrual. While R0 resections were more likely to be achieved in patients who were assigned to both chemotherapy and surgery and who underwent surgical exploration, there were no significant differences in the overall distribution of R0 resections, since 42 of 213 patients (20 percent) who received chemotherapy did not undergo surgery. We evaluated survival in the subgroup of patients who received all three cycles of chemotherapy followed by surgery as compared with those who underwent surgery only. Whereas patients who received three courses of chemotherapy had significantly better survival than patients who received fewer than three courses of treatment ($P=0.04$), there was no significant difference in survival between patients who received all three courses and those who underwent surgery only ($P=0.80$). This result may be due to the presence of pro-

gressive disease before surgery in some patients who received fewer than three courses of treatment.

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Tumorigenic Potential of Apparently Tumor-free Lymph Nodes

To the Editor: Metastatic relapse after the complete resection of an apparently localized primary tumor indicates that disseminated cancer cells, present at the time of surgery, are sometimes undetectable by current methods. Using monoclonal antibody Ber-Ep4 against an epithelial-cell surface antigen, we can detect one tumor cell in a background of 10^4 to 10^5 lymph-node cells. This finding is prognostically relevant in patients with operable lung or esophageal cancer.[1,2] However, it remains unclear whether these immunopositive cells are viable tumor cells with metastatic potential, shed tumor cells with a limited life span, or simply laboratory artifacts.[3]

We report direct evidence that immunohistochemical analysis can identify viable tumor cells with tumorigenic potential. With the use of culture methods,[4] a unique cell line (LN1590) was generated from a lymph node obtained from a patient with esophageal cancer classified as stage $pT_1pN_1M_0$, according to the tumor–node–metastasis classification of the International Union against Cancer. The node was classified as tumor-free by routine pathological methods (hematoxylin and eosin staining), but it contained 3 Ber-Ep4–positive cells per approximately 10^5 lymph-node cells (Fig. 1A). The cultured cells were transplanted subcutaneously into seven mice with severe combined immunodeficiency. Progressive tumor nodules were observed in all seven animals (Fig. 1B).

This result proves that the cultured cells indeed contained malignant tumor cells. Moreover, cytogenetic changes found in the lymph-node tumor cells with the use of a novel cytogenetic technique termed multiplex fluorescence in situ hybridization[5] directly support the concept of selection during the process of lymphatic dissemination (Kraus J, Speicher M, University of Munich: personal communication).

Our observation should have important consequences for tumor staging. If immunohistochemically identifiable cells in lymph nodes represent viable tumor cells, this information should be incorporated into the staging nomenclature of the International Union against Cancer.

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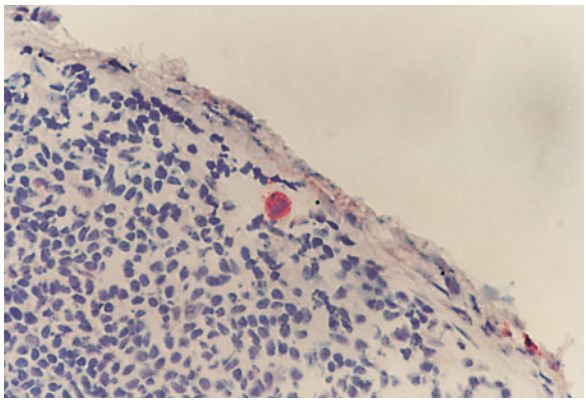

A

B

Figure 1. Cryostat Section of a Left-Sided Gastric-Artery Lymph Node with a Red-Stained, Isolated Ber-Ep4–Positive Tumor Cell (Panel A), and Local Tumor Formation after Subcutaneous Injection of LN1590 Cells into a Mouse with Severe Combined Immunodeficiency (Panel B).

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Creutzfeldt–Jakob Disease

To the Editor: The article on Creutzfeldt–Jakob disease by Johnson and Gibbs (Dec. 31 issue)[1] gives the impression that case–control epidemiologic studies have been numerous and have found no link to "dietary eccentricities." We are aware of only a small number of case–control studies, but several of these found a link between consumption of meat products and an increased risk of Creutzfeldt–Jakob disease. One study from the United States that involved 26 patients with the disease found that nine individual food items were statistically linked to an increased risk of Creutzfeldt–Jakob disease.[2] Of these foods, six came from pigs. Furthermore, with four of the pork products there was a positive association between in-

creased consumption of the products and increased risk of Creutzfeldt–Jakob disease.

A second study that is by far the largest case–control study to date, involving over 400 European patients and published just last year, found a significantly increased risk of Creutzfeldt–Jakob disease associated with the consumption of raw meat or brains.[3] The same study also found a significant increase in the risk of Creutzfeldt–Jakob disease with increasing consumption of pork.

A third case–control study of sporadic Creutzfeldt–Jakob disease in the United Kingdom, involving 206 cases, found a significant increase in the risk of Creutzfeldt–Jakob disease associated with increasing consumption of beef, veal, venison, or brains.[4]

Finally, Johnson and Gibbs point out that laboratory studies provide strong evidence that bovine spongiform encephalopathy and new-variant Creutzfeldt–Jakob disease have a common origin but conclude that the mode of transmission is not necessarily consumption of meat from cattle infected with the agent responsible for bovine spongiform encephalopathy. But many scientists would disagree with them. The fact that the same studies show that various exotic ungulate species in zoos, as well as domestic house cats, all in the United Kingdom, have died of a transmissible spongiform encephalopathy caused by an agent that appears identical to the agent that causes bovine spongiform encephalopathy strongly suggests that these animals, as well as the persons with new-variant Creutzfeldt–Jakob disease, contracted the disease from something they ate. Given these findings, and given the fact that all three case–control studies of sporadic Creutzfeldt–Jakob disease show a significant correlation between the disease and consumption of various animal products, it would make sense to conduct more detailed studies to pursue this connection.

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To the Editor: In the article by Johnson and Gibbs on Creutzfeldt–Jakob disease, it is implied that the decline in cases of bovine spongiform encephalopathy in Britain after 1991 is attributable to the preceding withdrawal of animal products from cattle feed. The authors also suggest that the four-to-five-year delay between the ban on animal products in cattle feed and the decline in the number of cases of bovine spongiform encephalopathy is consistent with the incubation period for the disease. However, they do not note that there was extensive slaughter of potentially infected animals, particularly in herds containing cattle with diagnosed bovine spongiform encephalopathy. Thus, much of the decline in the incidence of bovine spongiform encephalopathy after 1991 is due to a reduction in the population of cattle at risk for the disease.

One cannot make valid assessments of trends over time in the number of cases of bovine spongiform encephalopathy or of the duration of the incubation period without considering changes in the number of animals at risk for the disease. It would be more appropriate to express the number of cases of bovine spongiform encephalopathy as an annual rate of incidence per 1000 cattle at risk.

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To the Editor: In the article by Johnson and Gibbs on prion diseases, there is only passing mention of "suspected" transmission of Creutzfeldt–Jakob disease in 1974 through a corneal transplant. The authors state further that "human transmission was more . . . convincingly demonstrated . . . after . . . surgery to excise epileptic foci." However, in the case of the corneal transplant, specimens from both the donor and the recipient were later reviewed by knowledgeable neuropathologists, and the diagnosis was reconfirmed.[1] Furthermore, inoculation of brain tissue from the donor produced clinical Creutzfeldt–Jakob disease in primates after extended incubation, and secondary transmission was pathologically confirmed.[2] Recently, two additional cases of probable and possible transmission have also been reported in the literature from Japan and Germany.[3]

The most important new case of the transmission of prion disease through corneal transplants, however, occurred recently in Great Britain. In February 1997, a 53-year-old woman died of lung cancer. For several weeks before her death, she was described by one of her daughters as "falling over," having a "staggering gait," and "acting like a senile old lady"[4]; symptoms were attributed to presumed metastasis of the cancer to the central nervous system. In early March 1997, both of the woman's corneas were transplanted to two recipients; a third received sclera from the donor. In November 1997, the donor's brain was examined, revealing a spongiform encephalopathy typical of sporadic Creutzfeldt–Jakob disease, later confirmed by neuropathologists at the United Kingdom Creutzfeldt–Jakob Disease Surveillance Unit. The transplant recipients were notified, the transplanted tissues were removed, and surveillance continues.[3] These three cases arouse particular concern, since the infectivity (expressed as the median infective dose) of corneal tissue in scrapie, the prototypic prion disease of animals, was reported as 5.4 log units per milliliter, as compared with 8.9 log units per milliliter for brain and 8.4 log units per milliliter for retinal tissue.[3] Other animal studies have also shown that corneal tissue harbors the agent and can transmit disease.[5]

The possibility of a recent increase in iatrogenic cases of Creutzfeldt–Jakob disease resulting from the transplantation of prion-infected corneas has created heightened medical and public sensitivity regarding U.S. donor-screening practices for the more than 40,000 corneas transplanted annually. On the basis of recent events, additional measures for tightening inclusion criteria with respect to the medical history have been proposed for potential donors of ocular tissue.[3] Fortunately, the criteria introduced in the 1980s have been adequate, and with additional safeguards

in place, they should ensure the best possibility of continued safety. Because of the large numbers of patients involved, however, we hope that a reliable and specific laboratory screening method will become available in the near future and will eliminate these issues of concern.

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1. Brown P, Cervenakova L, Goldfarb LG, et al. Iatrogenic Creutzfeldt–Jakob disease: an example of the interplay between ancient genes and modern medicine. Neurology 1994;44:291-3.
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The authors reply:

To the Editor: Dr. Hansen is correct that several studies have implicated a history of consumption of various meat products in Creutzfeldt–Jakob disease. In a disease in which patients frequently are demented or have died, dietary histories are limited and subject to bias. This problem is graphically demonstrated in a study cited by Hansen, the British Surveillance Report (available to readers at http://www.cjd.ed.ac.uk/report97.html). This report contains an analysis of the dietary histories of 80 patients in whom the suspected diagnosis of Creutzfeldt–Jakob disease was not subsequently confirmed. Comparison of these cases with confirmed cases of sporadic Creutzfeldt–Jakob disease showed no differences in the consumption of beef or brains. The report concludes that dietary associations "may reflect recall bias rather than a real, underlying link."

The absence of geographic differences in incidence is more convincing evidence against major dietary factors, since large populations eschew pork and some consume no meat or meat products. We are unaware of studies of the incidence of Creutzfeldt–Jakob disease in populations of lifelong vegetarians; such a study would be of interest. In the meantime, we hold to our conclusion that, as yet, diet has not been convincingly linked to causation in sporadic cases of Creutzfeldt–Jakob disease.

The second issue raised by Dr. Hansen concerns the mode of transmission of new-variant Creutzfeldt–Jakob disease. The prions of the new human disease and bovine spongiform encephalopathy are closely related, as demonstrated by several methods of comparison discussed in our review. They appear to have a common origin, which could be related to the consumption of contaminated beef, but it could also be due to common exposure of cattle and humans to the contaminated products of the rendering process. Cosmetics, soap, bonemeal–based food for roses, and myriad other products of rendering could lead to human exposure by different routes of inoculation. It is imprudent at this time to conclude that eating meat or even oral exposure is the mode of transmission of the new-variant disease.

Dr. Gray's point is well taken. The elimination of older animals in herds would decrease the incidence of disease, since animals under five years of age are rarely affected clinically. The selective slaughter of affected herds might have little effect, however, since there is no evidence of horizontal spread within herds. Nevertheless, figures expressed as annual cases per cattle at risk would be preferable.

Drs. Cavanagh and Hogan feel we gave short shrift to transmission by corneal transplantation. Such an oversight was not intended. Twenty-five years ago both of us were involved in the case and studies of the initial patient who acquired the disease through corneal transplantation. The very thought of human-to-human transmission of a degenerative disease by physicians was so unspeakable that some detractors suggested that the presence of disease in the donor and the recipient might have been coincidental. The report three years later of illness in two young persons implanted with the same electrode and the subsequent transmission to a nonhuman primate through the implantation of the same electrode convinced the doubters. The subsequent report of transmission through corneal transplantation added further confirmation. The report of additional cases by Cavanagh and Hogan (in a report published subsequent to our review) provides yet more documentation. We heartily endorse their advocacy of cautious screening of corneal donors.

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Disclosure Statements Regarding Hormonal Treatment of Prostate Cancer

To the Editor: In compliance with the *Journal*'s editorial rules regarding disclosure of affiliations and according to my understanding of those rules, I provided a single institutional affiliation when I submitted a letter to the editor concerning hormonal treatment of prostate cancer (March 11 issue).[1] At the request of the Editors after the submission of my letter, I am providing the following information: in addition to being clinical professor of medicine (part-time) at Harvard Medical School and the Beth Israel Deaconess Medical Center, I am also chief medical officer of Praecis Pharmaceuticals, a company involved in the development of a gonadotropin-releasing hormone antagonist.

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1. Garnick MB. Hormonal treatment of prostate cancer. N Engl J Med 1999;340:812.

Editor's note: We regret that because of an editorial error, the disclosure statement sent to us by Dr. Mario Eisenberger was omitted from the published article "Bilateral Orchiectomy with or without Flutamide for Metastatic Pros-

tate Cancer" (1998;339:1036-42). Dr. Eisenberger provided the following information: "Mario Eisenberger and E. David Crawford have received educational grants from Schering-Plough, or serve as scientific advisors to the company, or both. Schering-Plough donated the flutamide and placebo used in this study. Schering-Plough also provided a grant to support data management for this trial, but all data analyses were carried out at the statistical center of the Southwest Oncology Group."

Excessive Blood Drawing for Laboratory Tests

To the Editor: I was recently hospitalized in a major university hospital for the Guillain–Barré syndrome. While there, I had blood drawn, usually twice a day. During my two weeks in the intensive care unit, my hematocrit dropped from 43 to 31.

As chair of the Department of Laboratory Medicine at a well-known children's teaching hospital, I was shocked at the amount of blood drawn for my tests. I asked the phlebotomist to draw less blood, but she refused, saying that her instructions had to be followed. While I was completely paralyzed, I began to think about why hospitals draw so much blood. I knew that this practice went back 20 years, to when most instruments required large quantities of serum. I decided that when I recovered, I would conduct a survey of blood-drawing practices.

After my recovery, I sent a questionnaire to 24 hospitals in the United States and received responses from 19 — 2 large community hospitals, 10 major university hospitals, and 7 children's hospitals. On the questionnaire, each hospital was asked to list the amount of blood it drew for the following tests: basic metabolic panel (blood urea nitrogen, sodium, potassium, chloride, carbon dioxide, glucose, and creatinine), comprehensive metabolic panel (blood urea nitrogen, sodium, potassium, chloride, carbon dioxide, calcium, glucose, creatinine, bilirubin, albumin, protein, aspartate aminotransferase, and alkaline phosphatase), automated complete blood count, complete blood count with manual differential, and a liver panel (bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase). The questionnaire also asked what equipment the hospital used for each of these tests.

The results showed that all the community hospitals and university hospitals drew far more blood for each test than did the children's hospitals. Table 1 summarizes these practices. For the basic metabolic panel, the amount of blood required by any university or community hospital laboratory was 2.5 to 10 times as much as the maximum required by any children's hospital, even though the tests were the same and the instruments used were the same or similar.

TABLE 1. BLOOD-DRAWING PRACTICES AT 19 HOSPITALS IN THE UNITED STATES.

TYPE OF HOSPITAL	BASIC METABOLIC PANEL	COMPREHENSIVE METABOLIC PANEL	AUTOMATED COMPLETE BLOOD COUNT	COMPLETE BLOOD COUNT WITH MANUAL DIFFERENTIAL	LIVER PANEL
	blood requested (ml)				
University (n=10)	2.5–10.0	2.5–10.0	2.5–7.0	2.5–7.0	2.5–10.0
Community (n=2)	5.0–7.0	5.0–7.5	2.5–5.0	2.5–5.0	5.0–7.5
Children's (n=7)	0.2–1.0	0.4–1.5	0.3–1.0	0.3–1.0	0.3–1.0

For the comprehensive metabolic panel, the situation was similar. For the automated complete blood count or the complete blood count with manual differential, the community and university hospitals drew 2.5 to 7 times as much blood as did the children's hospitals, again despite the fact that all the hospitals used the same or similar equipment. For the liver panel, the community and university hospitals drew 2.5 to 10 times as much blood as did the children's hospitals, again using the same equipment for the analyses.

I am concerned that in the United States we are drawing far more blood from adults than is necessary. This issue is of particular importance for the increasing number of older persons. It is the responsibility of all physicians and laboratorians to change this practice.

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