however, the provision of free samples of newly released drugs is simply another example of a hidden promotional agenda by the drug industry. Familiarity with these expensive drugs by physicians who dispense them tends to enhance their local utilization and thus drives up the cost of care.[1]

Conflict that arises from journal advertising is another theme of these letters. If I had my choice, there would be no pharmaceutical advertisements in medical journals. Unfortunately, few journal owners would continue to publish without them because subscribers would be unwilling to pay the additional publishing costs. Editors spend their energy ensuring that advertisements meet certain standards, for example, the US Food and Drug Administration's requirements, and that they look like advertisements and not like editorials. Editors also struggle to keep advertisements and editorial pages on the same topic separate and isolated and to keep the editorial content free of any commercial influences.[2] Those who wish to complain about the small number of journals that make huge profits from pharmaceutical advertisements should not direct their grievances to the journal's editors, but to their owners and publishers.

I am saddened and disheartened by the correspondents who defend "free lunches." Is it really worth the price of a meal to be educated by people who have a vested interest in a product that they are pushing? Is potentially biased information really better than no information at all? Probably not. Even the busiest physicians want to provide the best care. They have an intrinsic drive to remain informed, and I believe that most would do so even if they did not get their information from drug or equipment company representatives. If their hospital cannot support lunches, shouldn't the attendees pay for it themselves? Dr Lohiya's inconsistencies are particularly transparent: he wants not only his free meals (his "meager compensation for his sacrifice") but his "comfortable living" too.

The cost of meals seems a small price to pay for dignity and integrity.

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RESEARCH LETTERS

Postexposure Rabies Prophylaxis in a Patient With Lymphoma

To the Editor: Neither the US Advisory Committee on Immunization Practices (ACIP)[1] nor the World Health Organization[2] recommendations for rabies postexposure prophylaxis contain specific guidelines for treating immunosuppressed patients. We present the first case report of a patient with lymphoma who was bitten by a rabid animal.

Report of a Case. Three weeks after being diagnosed with stage IV lymphocytic B-cell lymphoma, a 55-year-old man was attacked by a jackal. The patient experienced multiple bites on his right index finger, hand, forearm, and elbow and abdomen. At that time, he had not yet begun chemotherapy. Treatment in the emergency department included cleansing of the wounds and infiltration of the lacerations and abrasions with human rabies immunoglobulin (HRIG) 20 IU/kg (Berirab P; Centeon Pharma GmbH, Germany), and intramuscular injection of rabies vaccine (Rabipur; Chiron Behring GmbH, Germany). Rabies was later diagnosed in the jackal by using fluorescent brain microscopic examination. The patient received active rabies vaccine on the 3rd, 7th, 14th and 28th days after the attack, and he was advised to refrain from chemotherapy until the end of the vaccination schedule.

Two days after the fifth and final dose, the patient's antirabies antibody titer was low, 0.2 IU/mL according to the rapid fluorescent focus inhibition test (protective level, 0.5 IU/mL). Because of his immunosuppressed state, we decided to administer a second course of rabies vaccine using double-dose vaccine and single intramuscular HRIG. Two days before the fourth double dose, the patient's antirabies antibody titer rose to 2.73 IU/mL. The patient was then advised to start chemotherapy immediately after the fifth double dose and to have his antibody titer measured every 3 months.

Eight weeks after the attack the patient received chemotherapy including fludarabine phosphate, mitoxantrone hydrochloride, dexamethasone, and sulfamethoxazole. He was found to have an acceptable antibody titer of 1.93 IU/mL 4 months after beginning chemotherapy, but this fell to 0.15 IU/mL 3 months later. The level remained nonprotective after 3 standard rabies vaccine doses given during 7 days, but increased to 3.84 IU/mL after a series of 3 double doses. Nearly 2 years later, the patient has no signs of rabies and his lymphoma is in remission.

Comment. The ACIP guidelines recommend postponing preexposure vaccination, if possible, in immunosuppressed patients and refraining from immunosuppressive agents, if possible, during postexposure rabies prophylaxis.[1]

Turner[3] found that the ability to mount delayed-type hypersensitivity reactions in mice was restored 3 days after cyclophosphamide treatment, while antibody production to *Escherichia coli* antigen and rabies vaccine was restored only if the immunization of cyclophosphamide-treated mice was delayed for 7 to 10 days. Thisyakorn et al[4] found significantly lower antirabies antibody levels in HIV (human immunodeficiency virus)-infected children compared with healthy subjects. Briggs et al[5] found very low postexposure antirabies antibody titers in symptomatic HIV-infected patients in India, and protective antibody titer was achieved only on day 37. They concluded that HRIG should be given to immunocompromised patients and that symptomatic patients usually do not respond to rabies vaccine. These authors did not recommend doubling the

vaccine dose because of a theoretical risk of increasing the viral load. Doubling the rabies vaccine dose was performed successfully in healthy Israeli soldiers who were exposed to bites of rabid animals and were given a higher HRIG dose than recommended.[6]

Our patient responded to a second double-dose series of vaccine, but his antibody titer decreased rapidly after chemotherapy. We suggest that the postexposure treatment schedule in such cases should include doubling the dose, close monitoring of antirabies antibody titers for at least 1 year, and postponing chemotherapy, whenever possible, until a protective antibody titer is achieved.

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Transforming Growth Factor-β1 Gene Polymorphism and Bone Mineral Density

To the Editor: Transforming growth factor β1 (TGF-β1) regulates bone metabolism by acting under partial control of estrogen and cooperatively with vitamin D.[1,2] The Leu10→Pro polymorphism of the *TGF-β1* gene is located in the signal peptide sequence,[3] which is thought to target newly synthesized protein molecules to the endoplasmic reticulum. Our previous observation that the serum concentration of TGF-β1 increases with the number of *C* alleles suggests that the Leu10→Pro polymorphism may affect the function of the signal peptide, possibly influencing intracellular trafficking or export efficiency of the protein.[4]

In a previous case-control study we found that a T869→C (Leu10→Pro) polymorphism of the *TGF-β1* gene is associated with reduced bone mineral density (BMD) at the lumbar spine and increased rate of bone loss in postmenopausal Japanese women. Thus, the *T* allele appears to represent a genetic risk factor for the development of osteoporosis.[4,5] We report a test of this hypothesis in a population-based cohort study.

Methods. The Japanese National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS-LSA) is a population-based prospective cohort study of aging and age-related diseases that began in 1997. We measured the association of the T869→CC polymorphism of the *TGF-β1* gene with BMD in 2241 NILS-LSA participants (1115 women and 1126 men) who were community-dwelling Japanese individuals aged 40 to 79 years and who were randomly recruited from regions close to the National Institute for Longevity Sciences.

Bone mineral density at the distal radius was measured by peripheral quantitative computed tomography and expressed as D50 (BMD for the inner 50% of the cross-sectional area, which mostly comprises cancellous bone) and D100 (BMD for the entire cross-sectional area, including both cancellous and cortical bone). The *TGF-β1* genotype was determined with an allele-specific polymerase chain reaction assay.[4]

Results. The distribution of *TGF-β1* genotypes was 30% *TT*, 52% *TC*, and 18% *CC* in women, and 27% *TT*, 51% *TC*, and 22% *CC* in men; both distributions are consistent with a Hardy-Weinberg equilibrium. Age, height, body weight, body mass index, physical activity, and smoking status did not differ by *TGF-β1* genotypes in women or men. Both D50 and D100 were similar in women with the *TC* and *TT* genotypes, but D50 was significantly lower in women with the *T* allele than in those with the *CC* genotype (TABLE). Evaluation of BMD by succes-

Table. Characteristics of 1115 Community-Dwelling Women Stratified by Age and Transforming Growth Factor-β1 Genotype*

	Total Sample		Age, y							
			40-49		50-59		60-69		≥70	
	TT + TC (n = 918)	CC (n = 197)	TT + TC (n = 233)	CC (n = 46)	TT + TC (n = 222)	CC (n = 56)	TT + TC (n = 231)	CC (n = 49)	TT + TC (n = 232)	CC (n = 46)
Age, y	59.3 (0.4)	59.0 (0.8)	45.1 (0.2)	45.9 (0.4)	54.3 (0.2)	53.8 (0.4)	64.0 (0.2)	63.7 (0.4)	73.6 (0.2)	73.5 (0.4)
Height, cm	151.4 (0.2)	151.0 (0.4)	154.9 (0.3)	154.5 (0.7)	153.4 (0.3)	152.7 (0.7)	150.2 (0.4)	149.9 (0.8)	146.8 (0.4)	146.5 (0.9)
Body weight, kg	52.6 (0.3)	52.7 (0.6)	54.5 (0.6)	54.1 (1.2)	54.1 (0.5)	52.8 (1.0)	52.3 (0.5)	53.2 (1.1)	49.3 (0.5)	50.8 (1.2)
D50 BMD, mg/cm^3	182 (3)	198 (5)†	245 (4)	262 (8)	199 (5)	207 (10)	151 (4)	160 (8)	135 (4)	165 (9)‡
D100 BMD, mg/cm^3	482 (4)	502 (9)	604 (6)	628 (12)	518 (7)	525 (14)	424 (6)	445 (12)	384 (6)	406 (13)

*Data are presented as mean (SE). D50 BMD indicates bone mineral density (BMD) for the inner 50% of the cross-sectional area of the distal radius; D100 BMD, BMD for the entire cross-sectional area of the same. *P* values computed by Kruskal-Wallis test.
†*P* = .04.
‡*P* = .01 (Kruskal-Wallis test).

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In Reply: Parents should be informed of the risks and benefits of immunization, including both the risks of severe adverse events related to vaccination (which have been shown in multiple studies to be rare) and the risks of not vaccinating. Pertussis and even measles infections still occur in the United States and pose risks both to the individual and to the community, especially in the setting of reduced frequencies of vaccination against these diseases. We chose to use the years 1987-1998 for the measles analysis because we had data from those years. Moreover, the relative risk of measles among vaccinated and unvaccinated children would not be affected by the outbreak period. In mentioning the 55622 cases of measles that occurred during 1989-1991, Dr Orient highlights the threat of measles in the absence of an effective vaccination program. She incorrectly suggests that most of the 67% of vaccinated children in measles outbreaks who had an unknown exposure source were not exposed to exemptors but rather to internationally imported cases. In fact, few of these individuals were likely exposed to imported cases since these only accounted for 5% of measles cases among children in Colorado during 1987-1998 while exemptors accounted for 22% of cases. Orient also points out that the risk of disease among exemptors in our study was several times higher than that imposed by exemptors on vaccinated children. Although she asserts that the risk of measles in a vaccinated child exposed to an exemptor is small, this does not mean that it is acceptable. This risk would most likely be greater for other vaccine-preventable diseases that are more common than measles, such as pertussis, varicella, and pneumococcal diseases.

We concur with Dr Swan that "immunization programs will be more appreciated by the public if they are based on science that is explained to the public. . . ." We hope our results will contribute to this. When we referred to strength of conviction in claiming personal exemptions, we did not intend to legitimize religious exemptions over philosophical exemptions. We meant that parents should not be making decisions about vaccination based on convenience but, rather, should be given adequate information and counseling before deciding to withhold vaccination from their children.

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Postexposure Rabies Prophylaxis in Immunosuppressed Patients

To the Editor: In their Research Letter describing treatment for rabies in a patient with lymphoma, Dr Hay and colleagues[1] recommended doubling the dose of rabies vaccine and postponing chemotherapy. However, we believe that several issues surrounding rabies postexposure prophylaxis (PEP) require clasification.

First, an assay for antibodies is used to detect an immune response against rabies virus, not to define protection.[2] Therefore, "acceptable" response is a more preferred term than "protective" response. The rapid fluorescent focus inhibition test is the current viral neutralization test of choice for human sera.[3,4] The Advisory Committee on Immunization Practices (ACIP) has recommended that complete neutralization of virus at a serum dilution of 1:5 is acceptable.[3] The World Health Organization recommends a more conservative level of 0.5 IU/mL (a titer of approximately 1:50 by serum dilution).[4] Both of these values are arbitrary laboratory standards and neither equates with protection.

Second, when needed, serum should be collected 2 to 4 weeks after PEP is completed to correspond with a peak titer.[5] The patient described by Hay et al had a titer of 0.2 IU/mL (a titer of approximately 1:20 by serum dilution) 2 days after completing PEP. This titer provides evidence of an antibody response (assuming no prior rabies vaccination) acceptable by ACIP recommendations. If titers had been determined using serum drawn 2 to 4 weeks later, they may have been even higher.

Third, although the authors suggest using a double dose of vaccine for immunosuppressed patients, there is no evidence that this dosage will increase the likelihood of successfully mounting an adequate antibody response.

Fourth, even if it was thought that this patient needed a titer of 0.5 IU/mL, once such a level was demonstrated further serologic testing was unnecessary, and additional vaccination driven by such testing would not be recommended. Unless a person is at continuous or frequent risk for rabies exposure, serologic testing for titer maintenance is unnecessary.[3]

Finally, rabies immune globulin (RIG) is given only once, preferably at the same time (day 0) as PEP initiation. The RIG injection provides a passive source of immediate virus-neutralizing antibody until active immunity ensues and can be given within 7 days of the initial vaccine dose. Administration of RIG beyond 7 days after the initial vaccination, or RIG in higher-than-recommended doses, may suppress antibody response.[3] For this reason, RIG is not given to those who have had preexposure vaccination or prior PEP, or to those patients beyond 7 days of initiating PEP.

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In Reply: We agree with Drs Gibbons and Rupprecht that the term "acceptable antibody titer" is preferable to "protective." The Israel Ministry of Health adopted the World Health Organization recommendations for an acceptable antirabies antibody titer of 0.5 IU/mL. It is true that blood specimens collected 2 to 4 weeks after PEP should reveal a neutralizing antibody titer. However, the recommendations of the ACIP indicate that in immunosuppressed persons, seroconversion should be detected after the third dose.[1] There is no recommendation regarding the acceptable level of seroconversion in such cases.

Our patient had a high-grade lymphoma and was scheduled to receive chemotherapy. Hematologic malignancies and chemotherapy interfere with the immune system, and chemotherapy can suppress the immune response for months.[2-5] The patient had an antirabies antibody level of 0.07 IU/mL after the third dose. Although this is considered to indicate seroconversion, compared with our experience with healthy persons who receive preexposure vaccination, this is a very low immune response. We faced a dilemma: the fatality of inadequately treated rabies vs the fatality of untreated high-grade lymphoma. We thought that waiting 4 weeks after the fifth dose to verify an acceptable antirabies antibody titer was unreasonable and risky and that the likelihood of finding a low titer after this period was high. Weighing these problems led us to double the vaccination dose. The double dose accelerated the patient's response and raised his antibody titer.

The patient received 2 courses of chemotherapy and a third course of immunotherapy. Incubation periods of rabies as long as 7 years have been described.[6] That was the reason we continued to assess his antibody titer frequently. As stated in our article, his antibody titer dropped to 0.15 IU/mL after the second chemotherapy course, as expected, and he had to continue for the immunotherapy course. His response after the third standard dose of rabies vaccination was again low (0.27 IU/mL). Doubling the dose accelerated his response and raised the antibody titer.

We agree that the effectiveness of the second rabies immunoglobulin injection is questionable and could have suppressed his immune response, but faced with this dilemma, we preferred to administer this second immunoglobulin injection. We do not routinely recommend a second immunoglobulin injection, but we do recommend assessing the immunologic response frequently in patients exposed to rabies infection who are scheduled to receive chemotherapy courses, at least during the first year of treatment.

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A Woman Experiencing Difficulty With Breastfeeding

To the Editor: In her discussion of difficulties with breastfeeding, Dr Lawrence[1] mentions that epidural analgesia during labor may contribute to breastfeeding difficulty because of transplacental drug passage and its adverse effects on early suckling. Her references to support this allegation, however, all found extremely low neonatal blood levels of anesthetic drugs, normal Apgar scores, normal umbilical vessel acid-base status, and normal neonatal neurobehavioral scores. This is particularly important because several of these references used epidural anesthesia for cesarean delivery, which requires much greater doses of local anesthetic than labor analgesia. Nonetheless, none of these maternal or neonatal examinations showed evidence of infant depression.

Several authors have reported no adverse effects of intrapartum[2,3] or postcesarean[4] epidural analgesia on early breastfeeding efforts. Maternal and neonatal blood concentrations of local anesthetics and opioids following intrapartum epidural analgesia are typically low and neonatal neurobehavioral scores are normal, even after prolonged infusions during labor.[5] There is now overwhelming evidence that modern regional analgesia for labor or cesarean delivery does not result in significant drug accumulation or adverse neonatal neurobehavioral effects.

Epidural analgesia is not risk free. Nonetheless, obstetric anesthesiologists have made considerable strides to ensure that one of the most painful events in a woman's life—childbirth—can, if the woman desires, be experienced without pain, and more importantly, with great safety for both mother and infant. In the absence of other confounding factors, transplacental drug passage of labor epidural medications should not be implicated in postpartum breastfeeding difficulties.

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