Correspondence

Medicinal Marijuana?

To the Editor: With respect to your editorial on the medicinal use of marijuana (Jan. 30 issue),[1] I made it a priority, as the first director of the National Institute on Drug Abuse (1973 to 1978), to investigate the health effects of smoking marijuana and to report on them regularly to the Congress and the public. Particular chemical constituents of smoked marijuana may have medical benefits, but it is unthinkable that in the closing decade of the 20th century, American medicine would return to prescribing smoked leaves for any condition. The history of the past hundred years in medicine has been to identify chemicals that offer benefits for specific problems and then to make those chemicals available in stable, known doses. The proper mechanism for sorting out claims of safety and efficacy was established by the Pure Food and Drug Act in 1906. . . .

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1. Kassirer JP. Federal foolishness and marijuana. N Engl J Med 1997;336:366-7.

To the Editor: . . . The image of smoking marijuana, even for "medicinal" purposes, is inextricably linked to images of illicit drug use in our culture and could send the powerful message to adolescents that marijuana use is OK. Although many adolescents who experiment with marijuana will later stop using illicit drugs,[1] a substantial minority will use this drug as a gateway to more serious forms of addiction.[2]

Data are not yet available on how the passage of the medical-legalization propositions in California and Arizona have influenced adolescents' perceptions of the harmfulness of marijuana or the likelihood that they will experiment with this drug. In the interim, the debate over medical legalization must consider not only the potential benefit to patients who may obtain relief from their symptoms but also the potential harm to the public at large, including the devastation of the lives of adolescents whose experimentation progresses to serious forms of drug abuse. Should the welfare of the many be compromised in an effort to meet the needs of the very few?

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1. Kandel DB, Raveis VH. Cessation of illicit drug use in young adulthood. Arch Gen Psychiatry 1989;46:109-16.
2. Dupre D, Miller NS, Gold MS, et al. Initiation and progression of alcohol, marijuana and cocaine use among adolescent users. Am J Addict 1995;4:43-8.

To the Editor: You are to be congratulated on your thoughtful editorial on marijuana. Your review of the available scientific evidence is straight to the point; there are no data to support the current proscription of medical marijuana use. Still, I do not foresee a reversal by the attorney general or the secretary of health and human services any time soon. I base this prediction on my belief that emotion and symbolism govern the debate over marijuana, not science.

Drug abuse is an enormous problem in our country. As the parent of two teenagers, I worry about the messages society is sending them. Certainly, I am worried about "street drugs," but I am equally worried about tobacco, alcohol, and a cornucopia of prescription and nonprescription medications that seem to promise a discomfort-free life through pharmaceuticals.

I am not particularly worried about marijuana. In 1995, the *American Medical News* reported that almost 70 mil-

lion Americans older than 12 years had tried marijuana at least once.[1] Not all these 70 million lives were ruined. Although I hope my children will not try marijuana, I believe they are likely to lead normal lives even if they do experiment with it.

With all the other drug problems in our society, I am frankly dumbfounded as to why marijuana has become such an important symbol in our national psyche, but it has.

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1. Hearn W. Considering cannabis: does marijuana have medicinal value? Recent developments are reigniting a longstanding debate. American Medical News. October 2, 1995:19, 21-3.

To the Editor: In the 16th century, Juan de Cardenas, a Spanish physician, wrote, "To seek to tell the virtues and greatness of this holy herb, the ailments which can be cured by it, and have been, the evils from which it has saved thousands would be to go on to infinity . . . this precious herb [tobacco] is so general a human need not only for the sick but for the healthy."[1] Just as this 16th-century physician cited anecdotal evidence in support of his statement about tobacco, in your editorial, "Federal Foolishness and Marijuana," you advocate the use of marijuana on the basis of anecdotes and the testimony of "thousands of patients." One might reflect on the medical foolishness that might be seen in the future by those looking back at this episode in our history.

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1. Goodman J. Tobacco in history: the cultures of dependence. New York: Routledge, 1993:44.

To the Editor: It is very disturbing to realize that Giovanni Polli (1812 to 1880), the father of laboratory medicine in Italy, was more compassionate 130 years ago than many government authorities today. In 1861 he reported that he had treated a patient with rabies, who eventually died, with "haschisch" and that it provided excellent palliation. He advocated its use in terminally ill patients,[1] saying, "Very often most therapy, or even the entire therapy, is no more than palliative; therefore, the physician who finds a convenient and effective palliative treatment is lucky. . . . It is obvious that haschisch, which we tried, can always be called on for help as the most benign and sure sedative when there is no hope of a definitive cure."

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1. Polli G. Risultato di un eseprimento terapeutico dell'haschisch. Ann Univers Med 1861;155:632-7.

To the Editor: . . . It would be incorrect to transfer Schedule 1 agents to Schedule 2, permitting physicians to prescribe them. Physicians would be pressed into a state of continual vigilance with respect to the drug culture. Despite their best efforts, a substantial diversion of medically prescribed agents to the general population for personal use and sale would be unpreventable. A demand for such diversion within families would arise uncontrollably. The corruption of physicians, already a problem, would inevitably increase. The adverse medical and behavioral effects of marijuana as a schedule I agent would create social problems, as well as major problems, hitherto unstudied, in patient care. Medicolegal complications for families, physicians, and the institutions that employ physicians would multiply, and the costs of care would escalate.

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To the Editor: . . . Should hospitals waive their no-smoking rules for patients smoking marijuana cigarettes, while cracking down on those who smoke tobacco products?

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To the Editor: In your fine editorial, you did not point out an ironic contradiction in federal policy. In December the Health Care Financing Administration issued a directive that Medicare beneficiaries in health maintenance organizations (HMOs) are entitled to information from physicians on all options for medically necessary treatments. HMOs are forbidden to "gag" doctors. Yet the attorney general has threatened sanctions and criminal prosecution for a doctor who prescribes marijuana.

DAVID GRANT, M.D.
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To the Editor: . . . The recent legislation in California and Arizona is sloppy, irresponsible lawmaking. In California, marijuana can now be recommended for anyone, of any age, for any ailment. In Arizona, all Schedule 1 drugs can be prescribed, without provisions governing quality, dosage control, supervision, or compliance. These drugs are still produced by an unregulated, criminal black market.

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To the Editor: Your judgment that proscribing the use of marijuana is hypocritical, given the acceptance of narcotic analgesics for the relief of pain, does not withstand scrutiny. The latter are reproducibly effective for their primary use, to provide analgesia. Their pharmacologic and pharmacodynamic characteristics have been well studied, as have their toxicity and relative merits. I see no reason why

marijuana should be exempt from such considerations. The hypocrisy, in my opinion, is in those who dismiss demonstrably effective therapies for nausea, glaucoma, headaches, fatigue, or depression, while neglecting to admit that the preference for marijuana rests on its principal effect, euphoria. . . .

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To the Editor: As a person with AIDS who has to use medicinal marijuana in my fight to stay alive, I thank you for your support. I do not drink, nor do I use drugs, and I would not use marijuana if I did not have to. There is little hope for me after 16 years of infection with the human immunodeficiency virus (HIV). The medicinal use of marijuana is one of the only things that makes me feel generally better, and it helps me eat.

GARY ALLEN JOHNSON
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To the Editor: I was the care giver for a dear friend who died of AIDS. In his final months, he asked me to obtain marijuana for his nausea. The marijuana eased his suffering.

But this issue goes beyond marijuana. As my friend's care giver, I had to struggle with his doctor over pain control. My friend was in constant, severe pain, and it was a never-ending battle to convince the doctor to prescribe Demerol (meperidine). There was always much ado over the triplicate forms and the suspicions of government drug regulators. Everyone knew the end was near. Still, I had to battle for every drop of meperidine. The war on drugs has become the war on patients.

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To the Editor: You point to largely experiential evidence of the medicinal benefits of marijuana and the apparent absence of serious short-term toxicity. However, a note of caution is warranted. Although it is true that smoking marijuana carries no immediate risk of death, there may be serious adverse effects in the very patients for whom medicinal marijuana is most commonly considered (i.e., those whose immune defenses are already compromised by AIDS or cancer plus chemotherapy). For example, in patients with AIDS, marijuana use has been associated with the development of both fungal and bacterial pneumonias.[1,2] Moreover, among HIV-positive persons, marijuana use has been shown to be a risk factor for rapid progression from HIV infection to AIDS and the acquisition of opportunistic infections or Kaposi's sarcoma, or both.[3]

Cellular studies and studies in animals lend support to these potential health consequences of marijuana. For example, delta-9-tetrahydrocannabinol has been shown to have immunosuppressive effects on macrophages, natural killer cells, and T cells, as well as on the response of mice to opportunistic infection.[4] In our own studies,[5] (and unpublished data) we recovered alveolar macrophages from the lungs of habitual marijuana smokers and found a significant reduction in their ability to kill fungi, bacteria, and tumor cells, as well as a deficiency in their ability to produce protective inflammatory cytokines, such as tumor necrosis factor α.

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1. Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 1991;324:654-62.
2. Caiaffa WT, Vlahov D, Graham NM, et al. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. Am J Respir Crit Care Med 1994;150:1493-8.
3. Tindall B, Cooper DA, Donovan B, et al. The Sydney AIDS Project: development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. Aust N Z J Med 1988;18:8-15.
4. Newton CA, Klein TW, Friedman H. Secondary immunity to *Legionella pneumophilia* and Th1 activity are suppressed by delta-9-tetrahydrocannabinol. Inject Infect Immun 1994;62:4015-20.
5. Sherman MP, Campbell LA, Gong H Jr, Roth MD, Tashkin DP. Antimicrobial and respiratory burst characteristics of pulmonary alveolar macrophages recovered from smokers of marijuana alone, smokers of tobacco alone, smokers of marijuana and tobacco, and nonsmokers. Am Rev Respir Dis 1991;144:1351-6.

Dr. Kassirer replies:

Let's set the record straight. I recommend that only desperately ill patients be allowed to use marijuana, that only physicians prescribe it, and that the government regulate it. Like some of the writers, I am opposed to the referendums in California and Arizona, and I stated publicly on several occasions that I would have voted against them. My argument for prescribing marijuana for seriously ill patients without requiring further research was based on compassion for these suffering people and on the grounds that short-term use of the agent is virtually harmless. If the only effect in these patients is to produce euphoria, so what? In fact, I did support more research on the effectiveness of marijuana in comparison with available agents, but I made two points: first, that such research is extremely difficult because the outcomes that are evaluated are entirely subjective, and second, that the government — despite nearly a century of mechanisms for assessing safety and efficacy — almost never permits clinical research on marijuana.

Reasonable people differ on the possible consequences of my proposal. I disagree that the compassionate provision of marijuana to very sick people would lead to more widespread abuse of marijuana; such abuse is a function of the availability of street drugs, not prescription drugs. There is no comparable epidemic of morphine or meperidine use. Similarly, though putting physicians in charge of prescribing marijuana would increase their burden somewhat, making decisions about who should receive which drugs (and how often) is precisely what doctors do well. It is hard to imagine why malpractice claims and costs would increase if physicians were made responsible for prescribing just one more controlled substance.

It is true that smoking is not a traditional means of delivering a medication, yet inhalers are used for many conditions, and the pulmonary route of absorption is extremely effective for many agents. I am sure that we could find some way of dealing with smoking in hospitals, maybe by allowing patients to use marijuana in other forms.

Finally, I believe that the influence of marijuana on immunity in humans requires far more confirmation. The scattered anecdotal reports of an association of marijuana with aspergillus infections in patients with HIV infection are worrisome, but an association alone does not prove causality. Aspergillus species are also found in the air, the soil, and plant matter such as tobacco. In addition, all the patients in the *Journal* article who were infected with aspergillus must have been severely immunosuppressed, because they had already had serious infections with other opportunistic organisms. Needless to say, claiming cause and effect in such patients is treacherous.

JEROME P. KASSIRER, M.D.

Intralesional Human Chorionic Gonadotropin for Kaposi's Sarcoma

To the Editor: Gill et al. (Oct. 24 issue)[1] reported that they induced apoptosis of two nodular cutaneous Kaposi's sarcoma lesions in each of 36 patients by administering human chorionic gonadotropin (hCG) intralesionally three times a week for two weeks; they noted that the efficiency of treatment was dose-dependent, with superior tumor responses in patients receiving 2000 IU per lesion as compared with those receiving 250, 500, or 1000 IU per lesion. As Krown stated in her editorial,[2] this treatment had a "limited and primarily cosmetic role," and there is no "evidence that uninjected lesions benefit."

Over the past several years, my colleagues and I have administered hCG systemically (intramuscularly) at doses ranging from 150,000 IU to 700,000 IU three times a week to patients with life-threatening cutaneous Kaposi's sarcoma lesions or a combination of cutaneous and visceral lesions. This therapy, which was remarkably well tolerated, resulted in the remission of all lesions.[3,4]

I do not see the rationale for giving local therapy for a systemic disease; it is now widely accepted that Kaposi's sarcoma is caused by a systemic infection with a unique herpeslike virus.[5] The administration of hCG to patients with Kaposi's sarcoma does indeed hold promise, but as with all pharmacologic interventions, the therapeutic benefit depends on the appropriate dosage and route of administration.

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1. Gill PS, Lunardi-Iskandar Y, Louie S, et al. The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. N Engl J Med 1996;335:1261-9.
2. Krown SE. Kaposi's sarcoma — what's human chorionic gonadotropin got to do with it? N Engl J Med 1996;335:1309-10.
3. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. Lancet 1995;346:118-9.
4. *Idem.* Intramuscular administration of human chorionic gonadotropin to treat Kaposi's sarcoma. AIDS Patient Care STDs 1996;10:154-61.
5. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and those without HIV infection. N Engl J Med 1995;332:1181-5.

To the Editor: The findings reported by Gill et al. confirm the tumoristatic effect of hCG that we have reported in cultures of both rat mammary carcinomas and human breast epithelial cells.[1,2] Their findings add a new dimension to the understanding of the tumoristatic effect of this hormone, in a different model and in tumors with a different cause.

I understand that Kaposi's sarcoma is far removed from breast cancer and chemically induced carcinogenesis, but the tumoristatic effect of hCG on mammary epithelial cancers may open new avenues in our understanding of the role of this hormone in seemingly unrelated organs.

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1. Russo J. Basis of cellular autonomy in the susceptibility to carcinogenesis. Toxicol Pathol 1983;11:149-66.
2. Russo IH, Russo J. Role of hCG and inhibin in breast cancer. Int J Oncol 1994;4:297-306.

To the Editor: In her editorial, Krown speculates on possible indirect antitumor activities of hCG that may explain the relative infrequency of Kaposi's sarcoma in women. However, the excess of Kaposi's sarcoma among men in Western countries can be explained by the high rates of Kaposi's sarcoma in homosexual men with AIDS; epidemiologic data do not support Krown's clinical observation of a higher incidence of Kaposi's sarcoma among men with "all forms of Kaposi's sarcoma."

In the United States[1] and Europe,[2] among injection-drug users, African-born heterosexuals, and those infected with the human immunodeficiency virus (HIV) through transfusions, equal proportions of men and women present with Kaposi's sarcoma as their first AIDS-defining illness. In the United States,[1] the only other group with high rates of Kaposi's sarcoma was men recorded as having acquired HIV through "other heterosexual" contact, some of whom may not have acknowledged homosexual contact. The people with AIDS who have the lowest risk of Kaposi's sarcoma are those infected with HIV through blood products, and they are overwhelmingly male (hemophilia being a male disorder). In Africa, the male-to-female ratio of AIDS-associated Kaposi's sarcoma has fallen dramatically since the beginning of the AIDS epidemic and is now thought to be around 2:1.[3] Kaposi's sarcoma that is associated with chemical immunosuppression after transplantation appears to be no more common in men than in women, with the published sex ratios ranging from 0.5 to 2.7.[2]

In contrast, before the AIDS epidemic Kaposi's sarcoma was more frequent in men than in women. Population-based series gave male-to-female ratios ranging from 1 to 6 in Western countries.[2] In Africa, Kaposi's sarcoma appears to have been much more common in men than in women before the AIDS epidemic, with a male-to-female ratio of about 10.[2]

Population-based data therefore do not support the frequent claim that Kaposi's sarcoma is always more common

in men than in women. Before the AIDS epidemic, it was clearly more common in men in both Africa and the West. Among people with AIDS, the higher incidence of the sarcoma in men seems to be related to male homosexuality rather than sex in itself. We believe that a factor associated with male homosexual contact is more likely than female sex hormones to explain the excess of AIDS-associated Kaposi's sarcoma among men. Recent work suggests that this factor may be infection with human herpesvirus 8, the epidemiology of which is consistent with transmission by male homosexuals.[4] Although a potential role of sex hormones in treating AIDS-associated Kaposi's sarcoma should not be dismissed, epidemiologic data on the occurrence of Kaposi's sarcoma do not provide consistent support for their use.

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1. Beral V. Epidemiology of Kaposi's sarcoma. Cancer Surv 1991;10:5-22. [Erratum, Cancer Surv 1992;12:225.]
2. Grulich A, Kaldor J. The sex ratio of AIDS-associated Kaposi's sarcoma does not provide evidence that sex hormones play a role in pathogenesis. AIDS (in press).
3. Brettle RP, Leen CL. The natural history of HIV and AIDS in women. AIDS 1991;5:1283-92.
4. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med 1996;2:918-24.

The authors and a colleague reply:

To the Editor: We are aware of the work by Harris,[1] who treated six patients with high doses of hCG (up to 700,000 IU) — amounts derived from doses we used in mice given human Kaposi's sarcoma cells in transplantation.[2] Harris used various preparations of hCG but failed to define the relative activity of each. This is critical, since we have evidence that the active moiety is not the native hCG heterodimer. She suggests that since Kaposi's sarcoma–related herpesvirus (KSHV) has been described, local therapy has no place in the treatment of patients with Kaposi's sarcoma. This logic is flawed. If a tumor is caused by a virus, there is no reason the tumor cannot be treated locally. Harris's claim that KSHV causes Kaposi's sarcoma is inappropriate. Although correlative data suggest that KSHV is associated with Kaposi's sarcoma, no cause-and-effect relation has been established.

We are aware of the important work of Russo and associates.[3] But their experiments were limited to rodents and cell lines, whereas ours were in humans. Their studies were limited to the effects of a preparation of hCG on the mammary gland and mammary tumors, whereas ours was on a sarcoma. Russo and her colleagues limited their investigation to the prevention of mammary-tumor carcinogenesis, whereas we showed direct antitumor effects. They showed that hCG induces the differentiation of human breast epithelium and rat mammary tissue; the effects we showed are not of the induction of differentiation but of cell killing. Most important, our findings show that only certain preparations of hCG have anti–Kaposi's sarcoma activity and that highly purified and recombinant hCG has little or no activity; the active moiety against Kaposi's sarcoma tumor cells in commercial preparations of hCG is not hCG itself.

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1. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. Lancet 1995;346:118-9.
2. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. Nature 1995;375:64-8. [Erratum, Nature 1995;376:447.]
3. Russo IH, Koszalka M, Russo J. Human chorionic gonadotropin and rat mammary cancer prevention. J Natl Cancer Inst 1990;82:1286-9.

To the Editor: Lunardi-Iskandar et al.[1] cited a higher frequency of Kaposi's sarcoma in men than in women as a rationale for investigating the antineoplastic potential of hormones in this tumor. Their subsequent observations — that Kaposi's sarcoma tumors failed to grow in pregnant mice and that tumor growth was inhibited by hCG — led directly to the clinical trials that were the subject of the editorial in question. The reference in the editorial to an excess of Kaposi's sarcoma among men was intended, therefore, to explain the investigators' own rationale for conducting these studies. It constituted neither an endorsement of a hormone-based therapeutic strategy nor a comment on the role of hormones or other factors in the development of this tumor.

That said, there is substantial evidence among immunosuppressed patients that the higher risk of Kaposi's sarcoma among men is not restricted to HIV-infected homosexual men. Among 730 Saudi kidney-transplant recipients, for example, Kaposi's sarcoma developed in 6.1 percent of the men and 3.1 percent of the women.[2] Among 7923 French organ recipients, only 1 of 41 patients in whom Kaposi's sarcoma developed was a woman.[3] In U.S. AIDS cases reported through December 1994, Kaposi's sarcoma was more frequently a presenting diagnosis of men than of women among injection-drug users (by a factor of 1.7), heterosexuals (by a factor of 2.6), and transfusion recipients other than persons with hemophilia (by a factor of 2.5).[4] In Kampala, Uganda, where over 90 percent of cases of Kaposi's sarcoma are AIDS-related, the age-standardized incidence rates of the sarcoma were 30.1 in men and 11 in women,[5] despite a male-to-female ratio of AIDS cases that is close to 1. These data do not prove that hormones have a role in the development of Kaposi's sarcoma among the immunosuppressed, or in protecting them from it, but they do not rule out a hormonal contribution. Hormones are not the only feature that distinguishes women from men, however, and environmental or genetic differences could also account for the unequal frequencies of Kaposi's sarcoma in the two sexes. We would note that Grulich and Kaldor base their argument on the frequency with which Kaposi's sarcoma appears as the initial AIDS-defining illness, but this is not a surrogate for the overall

incidence, which includes both initial and secondary presentations.

Although human herpesvirus 8 is present in all forms of Kaposi's sarcoma, including its classic and African endemic forms, homosexually acquired infection is unlikely to account for the consistent excess among men in these varied populations. This suggests that multiple factors contribute, in varying degrees, to the development and progression of different forms of Kaposi's sarcoma. Evidence of the involvement of any one factor (such as infectious agents, cytokines, or hormones) does not rule out a role for others.

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1. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. Nature 1995;375:64-8. [Erratum, Nature 1995;376:447.]
2. al-Sulaiman MH, al-Khader AA. Kaposi's sarcoma in renal transplant recipients. Transplant Sci 1994;4:46-60.
3. Farge D. Kaposi's sarcoma in organ transplant recipients. Eur J Med 1993;2:339-43.
4. AIDS public information data set. (Data through December 1994.) Atlanta: Centers for Disease Control and Prevention, 1994.
5. Wabinga HR, Parkin DM, Wabwire-Mangen F, Mugerwa JW. Cancer in Kampala, Uganda, in 1989-91: changes in incidence in the era of AIDS. Int J Cancer 1993;54:26-36.

Sertraline and Breast-Feeding

To the Editor: Postpartum depression occurs in approximately 10 percent of women who give birth and is associated with substantial morbidity in mothers and their children. For some women, treatment with an antidepressant drug may be necessary but complicated by their desire to continue to breast-feed. Unfortunately, there is a dearth of information on the safety of treatment with various antidepressant drugs, including the selective serotonin-reuptake inhibitors, during breast-feeding. During gestation, serotonin (5-hydroxytryptamine) influences neurogenesis and morphogenesis, and in the neonatal period it modulates synaptogenesis.[1] The effects of 5-hydroxytryptamine on early neurodevelopment arouse special concern about the use of selective serotonin-reuptake inhibitors by nursing mothers. Although plasma drug levels in infants exposed to serotonin-reuptake inhibitors in breast milk are reported to be generally quite low,[2] it is not known whether 5-hydroxytryptamine transport in infants is affected.

In humans, platelet and neuronal 5-hydroxytryptamine transporters are identical,[3] and studies in animals indicate that reuptake inhibitors cause similar central and peripheral blockade. We measured 5-hydroxytryptamine levels in whole blood from four mothers and their nursing infants before and during treatment with sertraline for postpartum depression. Because of the extremely low levels of plasma free 5-hydroxytryptamine, whole-blood levels are equivalent to platelet levels.[4] Since platelet 5-hydroxytryptamine is exogenously derived, these values should reflect the relative extent of the inhibition of 5-hydroxytryptamine transport in mother and infant.

Whole-blood 5-hydroxytryptamine levels in the mothers and their infants were determined before and after treatment of the mothers with sertraline for 9 weeks at a maximal dose of 100 mg per day (mothers of Infants 1 and 3) or 12 weeks at a maximal dose of 50 mg per day (mothers of Infants 2 and 4).[4] Plasma sertraline levels were measured at the time of postexposure sampling. Two infants (Infants 1 and 2) were fully breast-fed, whereas the other two infants were breast-fed three or four times daily. At the start of the study, Infant 1 was 15 days old; Infant 2, 26 days; Infant 3, 12 months; and Infant 4, 6 months.

As expected,[5] marked declines in platelet 5-hydroxytryptamine levels (to 10.2±2.9 percent of the base-line value) were observed in the mothers after treatment with sertraline. In contrast, little or no change was seen in the levels in the infants exposed to sertraline through breast milk (Fig. 1). The data indicate that platelet 5-hydroxytryptamine levels and, hence, transport were not reduced in the infants. Although knowledge of the relation between platelet and neuronal blockade is incomplete, the results also suggest that little central reuptake inhibition occurred. This tentative conclusion is consistent with the low plasma concentrations of sertraline in the nursing infants.

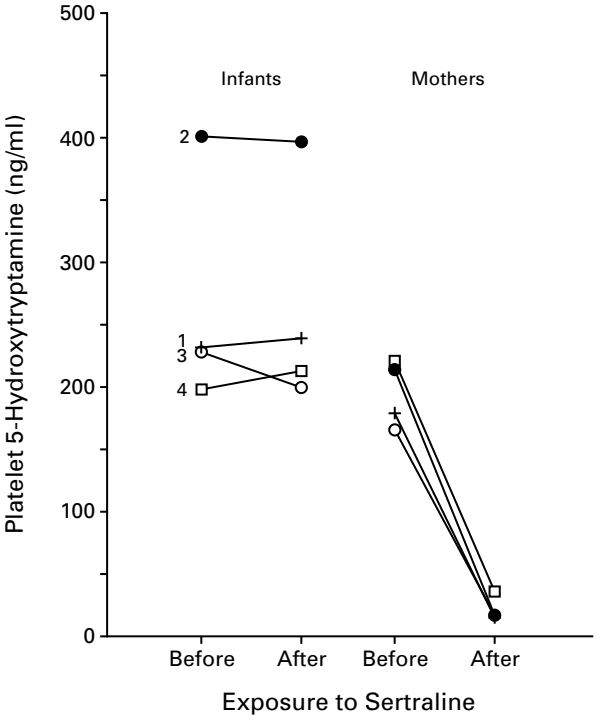

Figure 1. Effect of Sertraline on Platelet 5-Hydroxytryptamine Levels in Four Breast-Fed Infants and Their Mothers.

After maternal treatment, sertraline and desmethylsertraline levels were less than 2.5 ng per milliliter and less than 5 ng per milliliter, respectively, in all four infants. In the mothers of Infants 1, 2, 3, and 4, sertraline levels were 46.1, 48.2, 20.5, and 10.3 ng per milliliter, and desmethylsertraline levels were 31.1, 64.5, 37.4, and 19.7 ng per milliliter, respectively.

Although the possible reuptake-inhibiting effects of sertraline can be assessed on the basis of platelet 5-hydroxytryptamine measurements, it is difficult to completely rule out other, nonspecific pharmacologic effects such as direct receptor stimulation or enzyme activation. The situation is particularly complex because of possible developmental differences in receptor affinities and expression. Thus, conclusions about the safety of sertraline treatment during breast-feeding will always depend somewhat on the assumption that the drug's principal site of action is the 5-hydroxytryptamine transporter. Our data are reassuring, but larger studies are needed to determine conclusively whether mothers receiving sertraline or other selective serotonin-reuptake inhibitors can breast-feed without exposing their infants to physiologically meaningful doses of the drugs.

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1. Lauder JM. Neurotransmitters as growth regulatory signals: role of receptors and second messengers. Trends Neurosci 1993;16:233-40.
2. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. Am J Psychiatry 1996;153:1132-7.
3. Lesch KP, Wolozin BL, Murphy DL, Reiderer P. Primary structure of the human platelet serotonin uptake site: identity with the brain serotonin transporter. J Neurochem 1993;60:2319-22.
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Should One Reinsert the Stylet during Lumbar Puncture?

To the Editor: The post–lumbar puncture syndrome may be due to prolonged leakage of cerebrospinal fluid because of delayed closure of a dural defect, which causes low cerebrospinal fluid pressure. The reported frequency of the syndrome ranges from less than 1 percent to 70 percent. Its incidence depends on the diameter of the needle,[1] the shape of the needle,[2] and whether a diagnostic lumbar puncture is performed or spinal anesthesia is administered.[3] The incidence of the post–lumbar puncture syndrome is much lower after spinal anesthesia than after diagnostic lumbar puncture.[3,4] The reason for this difference may be that a strand of arachnoid enters the needle with the outflowing cerebrospinal fluid during diagnostic lumbar puncture; when the needle is removed, the strand may then be threaded back through the dural defect and produce prolonged cerebrospinal fluid leakage along the arachnoid.

We evaluated the effect of reinserting the stylet (mandrin) before removing the needle on the incidence of the post–lumbar puncture syndrome. By reinserting the stylet to the tip of the needle, any strand of arachnoid should be pushed out or cut off, which may reduce the frequency of the syndrome. For lumbar puncture, we used Sprotte's atraumatic needle (21 gauge), a modification of Whitacre's "pencil-point needle."[5]

A total of 600 patients were randomly assigned to one of two groups. In 300 patients, the stylet was reinserted to the tip of the needle; in the other 300, it was not reinserted. We performed all the lumbar punctures. The patients were questioned about their symptoms (headache, tinnitus, dizziness, or nausea) every day for the first seven days after the lumbar puncture. Symptoms were recorded only if they were reproduced by a change in position and improved when the patient lay flat.

The post–lumbar puncture syndrome developed in 49 of the 300 patients without reinsertion (16 percent) but in only 15 of the 300 patients with reinsertion (5 percent, $P<0.005$ by the chi-square test). This significant difference supports our hypothesis.

It is essential to use the stylet with insertion of the needle, but controversy persists about whether the stylet should be reinserted before removing the needle.[3] From our study, we conclude that the stylet should always be reinserted before removing the needle, since reinsertion reduces the incidence of the post–lumbar puncture syndrome.

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1. Kovanen J, Sulkava R. Duration of postural headache after lumbar puncture: effect of needle size. Headache 1986;26:224-6.
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4. Dieterich M, Brandt T. Is obligatory bed rest after lumbar puncture obsolete? Eur Arch Psychiatry Neurol Sci 1985;235:71-5.
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More on Ganciclovir-Induced "Psychosis"

To the Editor: I find no fault with the report by Hansen et al. on ganciclovir-induced psychosis (Oct. 31 issue)[1] or with their conclusions, but I do take exception to their terminology. In their case report, they clearly describe all the characteristic features of a confusional state: disorientation, incoherent speech, agitation, incontinence, hallucinations, and delusions. These are the characteristic features of a confusional state,[2] delirium, or toxic encephalopathy (all synonyms). A psychosis, however, is quite different, because it occurs in a clear sensorium,[3] as found, for example, in patients with psychosis associated with schizophrenia.

It appears that in some persons, ganciclovir may precipitate a toxic psychosis (rather than a latent psychiatric psychosis, which may not be readily reversible on withdrawal of the drug), as noted in this case.

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1. Hansen BA, Greenberg KS, Richter JA. Ganciclovir-induced psychosis. N Engl J Med 1996;335:1397.
2. Delirium and other confusional states. In: Adams RD, Victor M, eds. Principles of neurology. 5th ed. New York: McGraw-Hill, 1993:353-63.
3. Cassem NH. Massachusetts General Hospital handbook of general hospital psychiatry. 3rd ed. St. Louis: Mosby–Year Book, 1991:449.

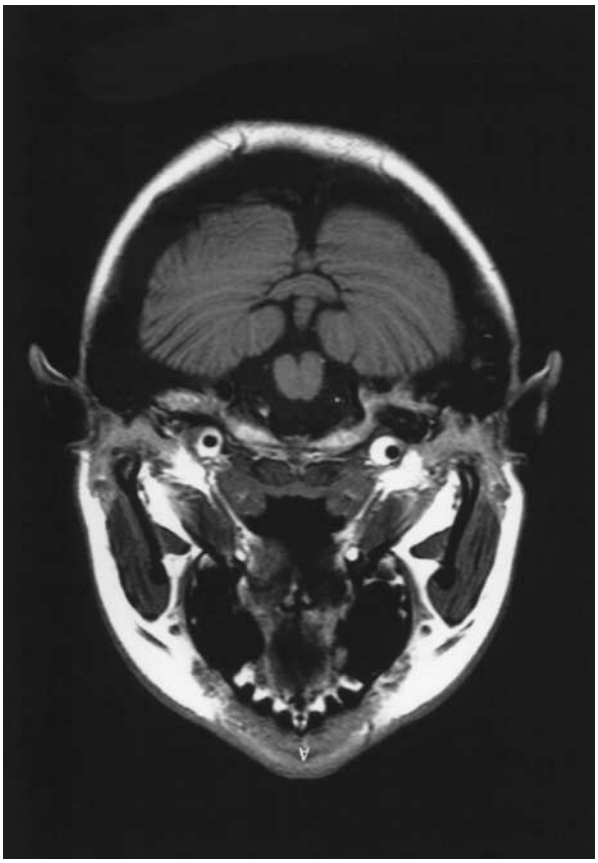

Figure 1. Traumatic Carotid-Artery Dissection.
This MRI scan is the Image to which the letters refer.

The Scary MRI

To the Editor: I must congratulate you on the wonderful reproduction of the magnetic resonance imaging (MRI) scan of traumatic carotid-artery dissection (Image in Clinical Medicine, Oct. 31 issue)[1] (Fig. 1). Perhaps you could market it as a mask for radiologists who party on Halloween.

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1. Matsumura JS, Pearce WH. Traumatic carotid-artery dissection. N Engl J Med 1996;335:1368.

To the Editor: Medicine aside, could you possibly have chosen a better item for the *Journal* dated October 31, 1996 — the day of Halloween? What great selection and timing, or was it just serendipity?

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Dr. Kassirer replies:

Not serendipity this time,[1] Dr. Leonard.

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