year decreased from 7.9% in 1988 to 3.1% in 1992, while LSD use increased from 4.8% to 5.6%. These data also suggest an increased acceptance of LSD use among seniors; disapproval of LSD experimentation fell from 91.6% in 1987 to 88% in 1992. Along with decreased disapproval of LSD experimentation, LSD is now perceived to be less harmful than cocaine; only 42.3% of high school seniors report that there is "great risk" associated with LSD experimentation compared with 56.8% for cocaine. Perception of danger, integral to successful cocaine education and decreased cocaine use,[3] does not appear to have been applied to LSD.

Data from the Drug Enforcement Administration suggest that LSD appears to have been reformulated at a lower dose, 20 to 80 μg per dose today compared with 100 to 200 μg in the 1960s.[4] Reformulation may decrease the incidence of emergency department visits or "bad trips" related to single doses taken by naive users. However, total LSD dose may be increasing as students report taking enough LSD to become "bombed." Also, data from animal studies suggest that LSD is exceptionally potent in low doses, producing long-lasting effects on important neuronal systems.[5]

Already, emergency department visits related to LSD use are increasing in the United States.[6] The recent increase in LSD use may be related to a decrease in perceived danger and decreased social stigma associated with LSD experimentation. This increase may indicate that the lessons learned from the recent US cocaine epidemic have been limited to cocaine and crack and apparently not applied to all drugs.[7]

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1. Gold MS, Schuchard K, Gleaton T. LSD in the USA: deja vu again? *Biol Psychiatry.* 1993;33:431.
2. *National Survey on Drug Use: Monitoring the Future Study, 1975-1992: National High School Senior Survey.* Rockville, Md: University of Michigan/National Institute on Drug Abuse, 1993. NIH Publication No. 93-3597.
3. Gold MS. Prevention, education and drug therapy in cocaine abuse and dependence. *Biol Psychiatry.* 1991;2:60-62.
4. National Narcotics Intelligence Consumers Committee (NNICC). *The NNICC Report 1990: The Supply of Illicit Drugs to the United States.* Washington, DC: Drug Enforcement Administration; June 1991.
5. Garratt JC, Alreja M, Aghajanian GK. LSD has high efficacy relative to serotonin in enhancing the cationic current Ih: intracellular studies in rat facial motoneurons. *Synapse.* 1993;13:123-134.
6. *National Drug Control Strategy.* Washington, DC: The White House; 1992.
7. Gold MS. Cocaine. In: *Drugs of Abuse: A Comprehensive Series for Clinicians, III.* New York, NY: Plenum Publishing; 1993.

Opiates for Pain: Patients' Tolerance and Society's Intolerance

To the Editor.—The cloning of the μ opioid receptor is a breakthrough. It is unfortunate that the Medical News and Perspectives[1] report on this contains misinformation about the use of opiates in the treatment of chronic pain. Unfortunate emphasis is given to the "possibility of finding a powerful analgesic that does not become so quickly tolerated by the body as does morphine, which could bring pain relief to people who suffer from chronic pain, patients who are not normally given morphine because of the problems of tolerance." This is not especially tantalizing to those of us familiar with the clinical treatment of (and literature on) chronic pain and drug dependence. Tolerance and physical dependence should not be barriers to use of opioids in the treatment of chronic pain.[2,3]

The reason that patients with chronic pain are not given opiates when indicated is not tolerance but rather the intolerance in our society to any ongoing use of opiates in nonterminal patients. This has been described as "opiophobia" and is a major medical problem. Some opiophobia may be due to a prevalent confusion between the phenomena of physical dependence and tolerance vs the phenomenon of addiction. Physical dependence and tolerance occur in any patient given opioids, no matter how appropriately, for a long enough period of time. However, in patients with no drug abuse history, after withdrawal from long-term opiates that are no longer clinically indicated, there is seldom any further seeking for opiates. Addiction, on the other hand, is a neurobehavioral syndrome of compulsive seeking and continuing use of a drug despite increasing evidence of adverse effects. The addict will almost always return to the drug of abuse even long after detoxification has alleviated all symptoms of withdrawal. The nonaddicted patient weaned from narcotics after a long period of indicated use will experience some (generally easily managed) withdrawal symptoms and have no subsequent desire to renew his or her acquaintance with opiates.

The prevalent confusion between physical dependence and addiction is a pernicious influence among physicians, policymakers, and the general public. It significantly lowers the quality of life in patients who are unable to find adequate pain treatment and in some cases may even cause loss of life.[4,5] An iatrogenic syndrome resulting from inadequate analgesia has been described, called "opioid pseudoaddiction."[6] The patient with undertreated pain may become progressively more demanding and hostile, exhibiting behavioral changes that appear to the untrained eye as being those exhibited by a drug-seeking addict rather than a frustrated patient seeking pain relief.

The elucidation and cloning of the different opioid receptors will have major clinical ramifications in many areas. Perhaps the excitement generated by this discovery will lead to greater familiarity and a better understanding among practicing physicians of the important tools already available for the treatment of chronic pain. Major improvements in the utilization of existing medications could be just as important as the new analgesic drug discoveries that will flow from this seminal biomolecular breakthrough.

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1. Randall T. Morphine receptor cloned—improved analgesics, addiction therapy expected. *JAMA.* 1993;270:1165-1166.
2. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25:171-186.
3. Zenz M, Strumpf M, Tryba M. Long term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage.* 1992;7:69-77.
4. Fishbain DA, Goldberg M, Rosomoff RS, Rosomoff HL. Homicide-suicide and chronic pain. *Clin J Pain.* 1989;5:275-277.
5. Fishbain DA, Goldberg M, Rosomoff RS, Rosomoff HL. Completed suicide in chronic pain. *Clin J Pain.* 1991;7:29-36.
6. Weismann DE, Haddox JD. Opioid pseudoaddiction: an iatrogenic syndrome. *Pain.* 1989;36:363-366.

The Pathogenesis of Disseminated Intravascular Coagulation in Sepsis

To the Editor.—We read with interest the excellent article by Levi et al[1] reviewing the pathogenetic mechanisms of the activation of coagulation and fibrinolysis in sepsis. It is noted that plasminogen activator activity can result from the activation of the contact-activated (intrinsic) coagulation pathway. However, several studies are cited that suggest that the activation of fibrinolysis was independent of activation of the coagulation system in sepsis. The temporal relationship between the appearance of tumor necrosis factor-α (TNF-α) after endotoxin and the increase in fibrinolytic activity as well as the abolition of fibrinolytic activation in endotoxin-treated chimpanzees given pentoxifylline, suggested that TNF-α was the mediator of this effect. We would like to suggest further

insight into the mechanism of TNF-induced fibrinolytic activation.

In a phase I (uncontrolled) study of TNF-α in human cancer patients, we have recently demonstrated the release of tissue-type plasminogen activator (t-PA, an endothelial product as determined by molecular weight analysis and enzyme-linked immunosorbent assay) at 1 hour after intravenous TNF initiation.[2] The t-PA release was immediately preceded by leukopenia in the peripheral blood at 30 minutes after TNF initiation as previously described.[3] Simultaneous measurements confirmed a temporal relationship between the leukopenia and t-PA release in three patients.[2] Prior to the leukopenia, increased CD11b expression was noted on circulating polymorphonuclear leukocytes and monocytes at 7 to 15 minutes after TNF initiation. CD11b has been associated with granulocyte-endothelial adhesion in vitro.[4] These preliminary findings suggest a TNF-induced granulocyte-endothelial interaction in vivo that is temporally related to the release of t-PA and fibrinolytic activation. This would potentially implicate circulating white blood cells in the activation of fibrinolysis in vivo.

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1. Levi M, ten Cate H, van der Poll T, van Deventer SJH. Pathogenesis of disseminated intravascular coagulation in sepsis. *JAMA*. 1993;270:975-979.
2. Logan TF, Virji MA, Gooding WE, Bontempo FA, Ernstoff MS, Kirkwood JM. Plasminogen activator and its inhibitor in cancer patients treated with tumor necrosis factor. *J Natl Cancer Inst*. 1992;84:1802-1810.
3. Logan TF, Kaplan SS, Bryant JL, Ernstoff MS, Krause JR, Kirkwood JM. Granulocytopenia in cancer patients treated in a phase I trial with recombinant human tumor necrosis factor (TNF). *J Immunother*. 1991;10:84-95.
4. Gamble JR, Harlan JM, Klebanoff SJ, Vadas MA. Stimulation of the adherence of neutrophils to umbilical vein endothelium by human recombinant tumor necrosis factor. *Proc Natl Acad Sci U S A*. 1985;82:8667-8671.

In Reply.—The observation of Logan et al supports the notion that the induction of fibrinolysis and coagulation by cytokines follows different pathways. Endotoxin as well as TNF causes t-PA release in vivo, before thrombin generation can be detected, and neutralization of TNF in endotoxemia inhibits t-PA release, but not thrombin formation. The temporal relationship between neutropenia and t-PA release that occurs in TNF-infused cancer patients was also observed in healthy volunteers who received a bolus TNF injection and may indicate a causal role of activated adhering neutrophils for t-PA release by endothelial cells.

This observation merits further investigation, in particular because TNF does not cause the rapid release of t-PA from endothelial cells in vitro, even in the presence of plasma or serum, which suggests that other cells may be involved in TNF-induced activation of the fibrinolytic system in vivo.

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Sushi Syncope Schusser Gets Wedeler's Valve at Vail

To the Editor.— A 68-year-old man was involved in a severe frontal impact with another skier while "wedeling" at a high rate of speed in Vail, Colo. Medical history was unremarkable, other than having developed "sushi syncope" at 63 years of age.[1] While prior to the accident he had experienced no difficulty skiing expert trails at an elevation of over 3600 m (10 000 ft), afterward he became dyspneic while walking at the base of the mountain.

On returning to sea level, he noted continued dyspnea on exertion; examination revealed V waves in the jugulars evident at 30° and a prominent murmur of tricuspid insufficiency. Transesophageal echocardiography demonstrated a flail tricuspid leaflet, and angiography revealed wide-open tricuspid regurgitation. Fortunately, his dyspnea gradually resolved, and by 3 months after the event he had returned to playing tennis without difficulty. Serial echocardiograms reveal that his right ventricular size has remained stable, and stress tests fail to demonstrate any functional limitation.

Traumatic tricuspid valve damage—an extremely rare event—is classically related to being kicked in the chest by a horse or, most commonly, a severe motor vehicle accident.[2,3] Presumably the right ventricle must be fully inflated at the time of injury; the shock to the chest results in reflux of blood through the tricuspid valve and traumatic avulsion of the tendinae chordae or the papillary muscles as the valve is overstressed. Fortunately, repair of the defect is not always necessary; this patient has not required surgical intervention and, despite his "wedeler's valve," has just returned from another 10 days' hard skiing at Vail, where he schussed without sushi and wedeled without valvular consequences.

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1. Spitzer DE. Horseradish horrors: sushi syncope. *JAMA*. 1988;259:218-219.
2. Gayet C, Pierre B, Delahaye JP, et al. Traumatic tricuspid insufficiency: an underdiagnosed disease. *Chest*. 1987;92:429-432.
3. Dontigny L, Baillot R, Panneton J, et al. Surgical repair of traumatic tricuspid insufficiency: a report of three cases. *J Trauma*. 1992;33:266-269.

Lack of Physician Representation in Framing Policy on National Health Insurance—1938

To the Editor.—Health care reform is a major focus of the Clinton administration. The American people, the medical profession, various health-related industries, and the media are anxiously awaiting the report of Hillary Rodham Clinton's task force. Several past administrations also addressed health care reform. The debate was especially intense during the Roosevelt, Truman, and Johnson administrations when several "current" issues were the subject of controversy.

Access to health care and its cost have been discussed in America for decades. Moreover, the relative roles of politicians, physicians, and others with interest in the issues have been hotly debated in the past. Recently, many individuals and organizations expressed concern that Hillary Rodham Clinton's task force does not include adequate physician representation. In 1938, during an intense debate over national health insurance, *JAMA* editor Morris Fishbein, MD, responded to a letter from Alfred Cohn, MD, an influential clinical scientist at the Rockefeller Institute. Fishbein's comments[1] will sound familiar to those concerned about certain aspects of Hillary Rodham Clinton's task force.

August 23, 1938
Dear Doctor Cohn:

I have read with great interest your letter of August 17. It would be highly desirable to limit *The Journal* exclusively to scientific editorials and scientific material. However, the various attempts that are being made to make medicine a political issue in future political campaigns have forced us to use such material as came to hand, and thus to be able to reveal to the medical profession that not all of the public are in accord with the administration's point of view on this subject.

It was by order of the House of Delegates and the Board of Trustees that the Organization Section of *The Journal*, dealing with such matters, was established.

Indeed, it would be perfect if everyone who attempts to discuss the current status of medical practice had "the social experience or the scientific mind that entitle their views to count heavily." However,