Editorials

Federal Foolishness and Marijuana

THE advanced stages of many illnesses and their treatments are often accompanied by intractable nausea, vomiting, or pain. Thousands of patients with cancer, AIDS, and other diseases report they have obtained striking relief from these devastating symptoms by smoking marijuana.[1] The alleviation of distress can be so striking that some patients and their families have been willing to risk a jail term to obtain or grow the marijuana.

Despite the desperation of these patients, within weeks after voters in Arizona and California approved propositions allowing physicians in their states to prescribe marijuana for medical indications, federal officials, including the President, the secretary of Health and Human Services, and the attorney general sprang into action. At a news conference, Secretary Donna E. Shalala gave an organ recital of the parts of the body that she asserted could be harmed by marijuana and warned of the evils of its spreading use. Attorney General Janet Reno announced that physicians in any state who prescribed the drug could lose the privilege of writing prescriptions, be excluded from Medicare and Medicaid reimbursement, and even be prosecuted for a federal crime. General Barry R. McCaffrey, director of the Office of National Drug Control Policy, reiterated his agency's position that marijuana is a dangerous drug and implied that voters in Arizona and California had been duped into voting for these propositions. He indicated that it is always possible to study the effects of any drug, including marijuana, but that the use of marijuana by seriously ill patients would require, at the least, scientifically valid research.

I believe that a federal policy that prohibits physicians from alleviating suffering by prescribing marijuana for seriously ill patients is misguided, heavy-handed, and inhumane. Marijuana may have long-term adverse effects and its use may presage serious addictions, but neither long-term side effects nor addiction is a relevant issue in such patients. It is also hypocritical to forbid physicians to prescribe marijuana while permitting them to use morphine and meperidine to relieve extreme dyspnea and pain. With both these drugs the difference between the dose that relieves symptoms and the dose that hastens death is very narrow; by contrast, there is no risk of death from smoking marijuana. To demand evidence of therapeutic efficacy is equally hypocritical. The noxious sensations that patients experience are extremely difficult to quantify in controlled experiments. What really counts for a therapy with this kind of safety margin is whether a seriously ill patient feels relief as a result of the intervention, not whether a controlled trial "proves" its efficacy.

Paradoxically, dronabinol, a drug that contains one of the active ingredients in marijuana (tetrahydrocannabinol), has been available by prescription for more than a decade. But it is difficult to titrate the therapeutic dose of this drug, and it is not widely prescribed. By contrast, smoking marijuana produces a rapid increase in the blood level of the active ingredients and is thus more likely to be therapeutic. Needless to say, new drugs such as those that inhibit the nausea associated with chemotherapy may well be more beneficial than smoking marijuana, but their comparative efficacy has never been studied.

Whatever their reasons, federal officials are out of step with the public. Dozens of states have passed laws that ease restrictions on the prescribing of marijuana by physicians, and polls consistently show that the public favors the use of marijuana for such purposes.[1] Federal authorities should rescind their prohibition of the medicinal use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule 1 drug (considered to be potentially addictive and with no current medical use) to that of a Schedule 2 drug (potentially addictive but with some accepted medical use) and regulate it accordingly. To ensure its proper distribution and use, the government could declare itself the only agency sanctioned to provide the marijuana. I believe that such a change in policy would have no adverse effects. The argument that it would be a signal to the young that "marijuana is OK" is, I believe, specious.

This proposal is not new. In 1986, after years of legal wrangling, the Drug Enforcement Administration (DEA) held extensive hearings on the transfer of marijuana to Schedule 2. In 1988, the DEA's own administrative-law judge concluded, "It would be unreasonable, arbitrary, and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record."[1] Nonetheless, the DEA overruled the judge's order to transfer marijuana to Schedule 2, and in 1992 it issued a final rejection of all requests for reclassification.[2]

Some physicians will have the courage to challenge the continued proscription of marijuana for the sick. Eventually, their actions will force the courts to adjudicate between the rights of those at death's door and the absolute power of bureaucrats whose decisions are based more on reflexive ideology and political correctness than on compassion.

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REFERENCES

1. Young FL. Opinion and recommended ruling, marijuana rescheduling petition. Department of Justice, Drug Enforcement Administration. Docket 86-22. Washington, D.C.: Drug Enforcement Administration, September 6, 1988.

2. Department of Justice, Drug Enforcement Administration. Marijuana scheduling petition: denial of petition: remand. (Docket No. 86-22.) Fed Regist 1992;57(59):10489-508.

Silence of the Leukemic Clone

THE success of treatment for childhood acute lymphoblastic leukemia (ALL) has been justifiably lauded. Some 70 percent of patients who receive optimal therapy and support can now expect to have a long-term remission and probable cure.[1] Most current therapeutic protocols use not only early induction and consolidation phases of combination therapy but also a two-year maintenance phase with methotrexate and other drugs. Clinical trials have clearly demonstrated that this protracted treatment is necessary; a shorter duration of maintenance therapy results in more relapses.[2] After the cessation of chemotherapy, a minority of patients unpredictably relapse within a year or two. Overall, the likelihood of relapse 5 and up to 15 years after diagnosis has been approximately 10 percent.[3] Survivors sometimes have long-term side effects of the treatment but are generally considered to be cured of their leukemia.

It has been expected that the advent of clonotypic polymerase-chain-reaction (PCR) methods for tracking small numbers of leukemic cells would make it possible to monitor the efficacy of therapy, identify residual or reemerging disease, and hence anticipate clinical relapses as a guide to management. Several studies have demonstrated persistence of the leukemic clone for 12 to 18 months after diagnosis, thereby providing a rationale for maintenance therapy.[4,5] Others have shown an impressive correlation between the rapidity or extent of the reduction in the number of leukemic cells after induction therapy and the subsequent outcome[6] or between persistently positive results on PCR testing or the presence of minimal residual disease and subsequent relapse.[7] The addition of quantification of the PCR test with clonotype-specific primers derived from rearranged immunoglobulin or T-cell–receptor genes or leukemia-related fusion genes promises to improve the accuracy and value of molecular monitoring. Current large-scale studies in Europe and the United States are attempting to determine how to optimize, simplify, and standardize PCR-based predictive screening.

The report by Roberts et al.[8] in this issue of the *Journal* extends these earlier studies by showing that patients who relapse relatively late can be identified on the basis of increases in the level of a clonotypic marker detectable by PCR. In accord with earlier findings, the authors report that the level of PCR-detectable minimal residual disease in individual patients was at its nadir or nonexistent 15 to 21 months after diagnosis. Strikingly, however, and in contrast to patients in previous reports, patients who remained in extended remission had an increase in presumptive leukemic cells after this period, up to a ratio of leukemia-cell DNA to normal bone marrow–cell DNA of 0.001. The increase appeared to be sustained or stable. Fifteen of the 17 patients who had completed 2 years of therapy and were in clinical and hematologic remission 2 to 35 months after the cessation of treatment still had cells in bone marrow with the genotypic marker of the leukemic clone — namely, a specific rearranged sequence (*DNJ*) of the immunoglobulin heavy-chain (*IgH*) gene — detected by PCR. Furthermore, cells with this clonotypic sequence were detectable in 7 of 12 of these patients after bone marrow cells were cloned in an assay developed by the investigators to detect self-renewing ALL blast cells. The authors conclude that cure does not require the complete elimination of the leukemic clone.

What should we make of these new data? There are some technical issues to consider. The authors are well aware of the inherent risk of contamination in PCR tests and have taken the necessary precautionary steps and included essential controls to rule out trivial explanations for the observations. The reported sensitivity or threshold of their limiting-dilution PCR assay is about 5×10^{-6}. This is a substantial improvement (of 10-fold or more) over that reported by most other groups, and its technical basis has been described by the authors. The PCR data appear to be reinforced by the cell-cloning results, although it is disappointing that few of the primary data are provided. Extraordinary claims require extraordinary evidence, and the authors should share this information.

The cell-cloning data are less than entirely clear for another reason. In previous papers the authors stated that colonies with a compact refractile appearance are unique to ALL cells and that normal committed progenitors do not renew themselves.[9] The latter statement appears to be based on an assumption rather than on evidence. Transplantation experiments with murine progenitors marked with a retrovirus provide formal proof that there are some B-lineage–restricted cells with self-renewal potential.[10] Human lymphoid progenitors are likely to renew themselves under some circumstances, especially in very young persons and in regenerating bone marrow. This phenomenon is perhaps reflected by the increased numbers of cells with the common ALL immunophenotype in regenerating bone mar-