Correspondence

Placebo Surgery in Trials of Therapy for Parkinson's Disease

To the Editor: The Sounding Board articles by Freeman et al.[1] and Macklin[2] (Sept. 23 issue) provided an excellent discussion of sham surgery for patients with Parkinson's disease. However, Freeman et al. seem overenthusiastic about downplaying the risks of sham surgery. Their statement that these procedures are easier to perform, standardize, and reproduce than traditional surgical procedures does not do justice to the neurosurgical skills involved in performing stereotactic brain surgery. It is probable that the wide range of outcomes regarding the effectiveness of and morbidity associated with pallidotomy is related to the varying skills of the operating neurosurgeon.

Freeman et al. present the cogent argument that sham surgery is the only solution for proving the validity of the neurosurgical procedures discussed in relation to Parkinson's disease. Not only are there important clinical questions that need to be answered, but society also needs to know whether any surgical therapy for Parkinson's disease provides substantial enduring benefit.

Macklin is no doubt correct that the informed-consent process is less than perfect. Rather than turn our backs on objectively evaluating surgical procedures, however, we should be more diligent in obtaining consent. In the end, the patients with Parkinson's disease who give informed and valid consent to participate in trials in which sham surgery is used are truly brave pioneers who are helping to advance the frontier of research. We should not prevent such trials from taking place.

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1. Freeman TB, Vawter DE, Leaverton PE, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. N Engl J Med 1999;341:988-92.
2. Macklin R. The ethical problems with sham surgery in clinical research. N Engl J Med 1999;341:992-6.

To the Editor: Macklin's argument against sham surgery in clinical research is fundamentally flawed in two important respects. First, there is no ethical requirement to minimize absolutely the risk of harm to research subjects. The ethical requirements are that there be a reasonable balance between the potential risks and the potential benefits to the subject or to society[1] and that the subject make a fully informed choice about participating in the research.[2] Within the context of a reasonable overall risk–benefit ratio, risks should be minimized by using medically and scientifically appropriate procedures.[1]

Second, preventing subjects from deciding what risks they are willing to take is a direct violation of the principle of autonomy. We should not declare research unethical because the process of informed consent can be imperfect; instead, we should concentrate on improving that process. Medical paternalism, in which physicians decide what risks to expose patients to, is ethically unacceptable. A medical maternalism in which research subjects are protected from all risks and from the autonomous exercise of their right to choose is no better.

(The opinions expressed in this letter are those of the author and do not necessarily represent the policy of the Department of Veterans Affairs.)

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1. 45 CFR 46.111.
2. 45 CFR 46.116.

To the Editor: In 1993, when we proposed the idea of a double-blind design for fetal-cell transplantation for Parkinson's disease, our plan was met with a good deal of skepticism by members of the scientific community, including Dr. Freeman's coauthor Dr. Olanow.[1] Because no neurosurgical trial had been performed with a double-blind de-

sign, it was unclear whether such a protocol could or should be carried out. Our double-blind study of 40 patients (20 patients who received implants and 20 control subjects) has been completed.[2,3]

It is particularly challenging to do a double-blind surgical study in patients with Parkinson's disease. Because it would be unethical to discontinue antiparkinsonian drugs in these patients, neurotransplants have to add substantially to the best pharmacologic treatment of each patient. It is likely, though not sure, that the effects of transplantation would be much easier to demonstrate in a placebo-controlled design in which the placebo group did not receive drug therapy. Because of the great value of levodopa and other drugs, such a placebo design could not be justified. Double-blind studies are undertaken to demonstrate the value of a treatment in a small group of patients with reasonable, but not zero, risk. In our study, the patients who received implants were exposed to more risk than the patients who had placebo surgery, because of needle penetrations of the brain. Whether the patients who received implants benefited more than the patients who underwent placebo surgery could be answered only with the double-blind design.

We were not surprised that our design produced controversy seven years ago. Even as discussion continues about the role of double-blind surgical studies, review groups of the Food and Drug Administration and National Institutes of Health have embraced the concept, and several such studies are now under way.

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1. Cohen J. New fight over fetal tissue grafts. Science 1994;263:600-1.
2. Freed CR, Breeze RE, Greene PE, et al. Double-blind placebo-controlled human fetal cell transplants in advanced Parkinson's disease. Soc Neurosci 1999;1:212. abstract.
3. Fahn S, Greene PE, Tsai W-Y, et al. Double-blind controlled trial of human embryonic dopaminergic tissue transplants in advanced Parkinson's disease: clinical outcomes. Neurology 1999;52:Suppl 2:A405.

To the Editor: Macklin states, "An alternative research design that did not involve sham surgery . . . would be less rigorous from a methodologic point of view." That a placebo procedure in a clinical trial be manifestly harmless is not only an ethical requirement but also a fundamental requirement for clinically relevant, generalizable inferences to be drawn from the trial. Even if the implanted material is found to improve the patient's condition, it may not fully counter any damage that may have occurred as a result of the surgery. In other words, a positive effect of treatment in a trial involving a potentially harmful control may result in the adoption into clinical practice of a treatment that results in more harm to patients than if they had received no intervention at all.

Some may argue that a trial that compares a treatment involving surgery and implantation with conservative management and finds a beneficial effect also admits the possibility that the implantation itself added nothing to, or even detracted from, a beneficial placebo effect. If this is truly a possibility, then perhaps the three-group trial that Macklin describes at the end of her article is the only clinically informative option. However, the assumption that sham surgery is likely to have a positive effect on health requires careful examination.

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To the Editor: The advantages of a new treatment are often vastly overestimated, in spite of the most objectively written notice of information, as a result of the combined effects of the physician-investigator's expectations and the patient's hopes. Therefore, many patients not only agree to participate but also eagerly desire participation in studies of such treatments, which represent the only hope offered to them. Under these circumstances it is likely that the consent will not really be freely given, and therefore the study may not be ethically acceptable.

I suggest the following solution: when participation in a randomized study with a sham-procedure group is proposed to a patient, the patient must be offered, in addition to the alternative of agreeing or refusing to participate in the randomized study, the possibility of receiving the new experimental treatment without participating in the randomized study. Obviously, when offered this choice, fewer patients will agree to enter the study. However, if the investigator presents the possible outcome in a realistic way, with all the uncertainties about the outcome of the new treatment, some patients will agree to participate for purely altruistic reasons, and even more patients will want to participate if all the patients are offered the possibility of receiving the new treatment later if it is proved to be effective.

This design will force the investigator to present the possible outcomes of the two groups of the study in a realistic and balanced way: if the investigator exaggerates the expected benefits of the new treatment, no patients will agree to participate in the randomized study. This approach would make the recruitment of patients more difficult, but there are good reasons why this type of study should not be easy to carry out.

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The authors reply:

To the Editor: It is affirming to note that all the correspondents support the use of placebo-surgery controls under certain conditions. We agree with Burris that it is neither required nor reasonable to expect surgical trials to involve no risk. As with all trials, patients must be informed of the potential risks, and risks must be reasonable in relation to the possible benefits to the individual patient as well as to society.[1-3] We believe it is a mistake to hold surgical trials to a standard more stringent than that required for the study of nonsurgical interventions.

Horisberger recommends that patients be offered access to the experimental treatment without participating in the study in order to minimize exaggerated estimates of ben-

efit and to ensure that informed consent is freely given. Offering the patient such access to an unproved intervention implies that the investigator condones the procedure and that it is beneficial when this is not known to be the case. It would therefore serve to exaggerate benefit and to induce a less informed decision about receiving the intervention. We believe it is inappropriate for an investigator to offer an intervention as a therapy while at the same time asserting that it is necessary to perform a placebo-controlled trial to determine whether it is effective.

We agree with Weiner that differences in surgical methods and skills can affect the outcome of surgical procedures. However, it is easier to standardize surgical methods used with nonablative and minimally invasive procedures, as in the case of cellular transplantation. It is because of the variability that can occur even with a single surgeon that randomized clinical trials are necessary.[4]

Freed et al. assert that we were skeptical about the use of a placebo control in their trial design. Rather, we argued for multiple trials in which different variables with regard to transplantation were used, so that negative or inconclusive results with a single protocol would not adversely affect the entire field.[5] We were not opposed to the use of placebo controls. In our article, we cited numerous examples of such studies (including neurosurgical trials) that predated both of our trials.

Our concern is that patients may undergo operations performed by surgeons who stand to benefit financially, academically, and by reputation but who fail to disclose that the operations have unproved benefits and undefined risks. If the safety and efficacy of a new surgical procedure are not established in controlled trials involving patients who give informed consent, thousands of future patients may be subjected to the risks and costs of an unproved operation in uncontrolled studies, without their full knowledge and consent.

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To the Editor: The claim that my argument against sham surgery in clinical research is "fundamentally flawed in two important respects" is mistaken on both counts. Burris contends that "there is no ethical requirement to minimize absolutely the risk of harm to research subjects." I do not know what he intends by "absolutely"; it is a term without meaning in this context. However, a look at the U.S. Code of Federal Regulations reveals the following as the first of the requirements that institutional review boards must determine are satisfied in order to approve research: "Risks to subjects are minimized."[1]

The second alleged flaw is that "preventing subjects from deciding what risks they are willing to take is a direct violation of the principle of autonomy." But the role of the institutional review board in our system for the protection of human subjects is precisely to determine the acceptability of risks. Once the institutional review board has determined that risks to subjects are minimized and that "risks to subjects are reasonable in relation to anticipated benefits,"[1] then potential subjects are asked to provide their voluntary, informed consent. If subjects' informed consent were the only ethical requirement for research, there would be no need for institutional review boards to make risk–benefit determinations before approving research protocols.

Weiner endorses the view that "sham surgery is the only solution for proving the validity of the neurosurgical procedures" and concludes that we should not prevent such trials from taking place. Although I acknowledge that using sham surgery as a control may be the best way to seek proof, it is not the only "objective" way to demonstrate efficacy. There are other, albeit less rigorous, ways. Slattery questions whether it is even the best way, since harm produced in a control group of a trial prevents investigators from determining whether there is a benefit from the experimental treatment.

Freed et al. note that review groups of the Food and Drug Administration and National Institutes of Health have embraced the concept of trials that involve sham surgery and that several such studies are under way. This means that the trials were approved by institutional review boards, an important procedural requirement in our system for the protection of human subjects. However, approval by an institutional review board does not make a study ethically acceptable. It is evidence only that the institutional review board found the research to be ethically acceptable, a judgment with which another institutional review board might reasonably disagree.

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1. 45 CFR 46.111.

Outbreaks of Enterovirus 71 Infection

To the Editor: The outbreak of enterovirus 71 infection in Taiwan, reported by Ho et al. (Sept. 23 issue),[1] occurred almost a year after the outbreak in Malaysia. Though both outbreaks occurred in Asia and both involved large numbers of deaths, it was not known whether the two outbreaks were related. We studied the nucleotide sequence and secondary RNA structure of some of the isolates, using the sequence of the 5′ untranslated region (UTR).

Enterovirus 71 isolates from patients in Singapore (seven isolates), Taiwan (two isolates), and Japan (one isolate) were examined and compared with those previously report-

ed in Malaysia[2,3] or with sequences deposited in GenBank. A phylogenetic tree that we constructed using the aligned 5′ UTR sequences revealed at least two major clusters of enterovirus 71 isolates. Cluster 1 included the isolate from Japan and six of the seven isolates from Singapore, together with isolates found predominantly in Malaysia during the 1997 outbreak. The isolates in this cluster had at least 89 percent sequence homology with enterovirus 71 MS isolates. The isolates in cluster 1 formed two subclusters. The isolate from Japan and five of the six isolates from Singapore were clustered with isolates from the Malaysian peninsula, forming one subcluster, and the remaining isolates, which included others from the Malaysian peninsula, Sarawak, and Singapore, formed the other subcluster.

Three other isolates examined, one from Singapore and two from Taiwan, were in cluster 2, which consisted mostly of isolates from the 1998 outbreak in Taiwan. Cluster 2 also had two subclusters, with all the isolates from Taiwan, including the two sequenced in this study, in one subcluster and the remaining isolates from the Malaysian peninsula and Singapore in the other. The isolates in these two subclusters had at least 97 percent homology with each other and approximately 85 percent homology with the coxsackievirus A9 5′ UTR sequence rather than with the enterovirus 71 MS group, which contained the other enterovirus 71 strains found predominantly in Malaysia and Singapore. A comparison of the 5′ UTR secondary RNA structure, which has been associated with the degree of virulence, in the cluster 2 isolates revealed no significant differences in the structure of the three domains within the 5′ UTR sequence.

These findings suggest that the 5′ UTR features of the enterovirus 71 strains from the Taiwanese outbreak were almost identical to those of the coxsackievirus A9–like strains isolated previously in the Malaysian peninsula.[3] Because of these similarities and the high frequency of travel between Malaysia and Taiwan, it is tempting to speculate that the predominant enterovirus 71 strains in the Taiwanese outbreak may have been accidental imports.

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The authors reply:

To the Editor: In response to AbuBakar et al., we refer first to a phylogenetic study of enterovirus 71 isolates from 1997 and 1998, reported by Shimizu et al.,[1] in which one of us participated as a coinvestigator. Eleven isolates from Japan, 5 from Malaysia, and 13 from Taiwan were analyzed. The isolates were classified as genotype group A (subgroup A_1 or A_2) or genotype group B. Six strains from Japan, 1 strain from Malaysia, and 10 strains from Taiwan were in group B, and 5, 4, and 3 strains, respectively, were in group A (subgroup A_2). Although the isolates were not homogeneous, the majority of the Malaysian isolates were in group A, whereas the Taiwanese isolates were in group B.

Shimizu et al. arrived at this classification by analyzing the VP4 and VP2 regions.[1] By analyzing, as did AbuBakar et al., the 5′ noncoding region, two of us also found that the majority of the Taiwanese and Malaysian strains were clustered in different groups. In a study of 60 enterovirus 71 isolates from patients in various parts of Taiwan, one of us found that only 5 isolates were in group A, whereas 55 were clustered in group B.

To date, enterovirus 71 group B consists mainly of Japanese and Taiwanese isolates of recent origin. It is unclear whether the Malaysian isolates studied by AbuBakar and colleagues have been available to other investigators. If they have not been available, many of the Malaysian isolates, contrary to our findings and those of Shimizu et al.,[1] may belong to group B. If this is the case, the findings of AbuBakar et al. need to be confirmed, and more strains should be studied. Even so, it would not be possible to conclude that the Taiwanese strains came from Malaysia. They could just as well have come from Japan. It is premature to reach definite conclusions about the precise geographic movements of the Japanese, Malaysian, and Taiwanese strains.

We and our coauthors, many of whom are in the Taiwan Department of Health, would like to acknowledge with gratitude the assistance of the Centers for Disease Control and Prevention in the investigation of the enterovirus 71 epidemic in Taiwan. Specifically, we would like to thank Drs. Anthony W. Mounts, Umesh P. Parashar, and Wun-Ju Shieh of the investigative team, who were in Taiwan in June 1998.

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Enterovirus 71 Infection and Neurologic Complications

To the Editor: In their article on neurologic complications associated with enterovirus 71 infection, Huang et al. (Sept. 23 issue)[1] reported the presence of severe brain-stem lesions, as evidenced by findings on magnetic resonance imaging in many patients and by autopsy findings in one. Our own pathological findings (unpublished data), based on a detailed autopsy examination of four patients,[2] also showed inflammation confined to the gray matter of the spinal cord and medulla and the tegmentum of the midbrain and pons. In all our patients, as in theirs, there was no inflammation in

pontine nuclei. We noted inflammation in the dentate nucleus, hypothalamus, and thalamus but not in the cerebrum.

The reason for this distribution of inflammation is unknown, but it may be related to the predilection of enterovirus 71 for specific neurons. Another possibility is that the virus may enter the central nervous system by way of the peripheral cranial and spinal nerves and infect the neurons it first encounters in the tegmentum of the brain stem and the gray matter of the spinal cord before spreading along neuronal pathways. Interestingly, this pattern of inflammation appears to be similar to that of bulbar poliomyelitis, in which there is also involvement of the tegmentum of the brain stem but not of the anterior pons.[3] However, although we noted that the inferior olives were inflamed, Bodian described the absence of inflammation in these areas in patients with bulbar poliomyelitis.[3] Thus, in addition to neurologic and other manifestations,[1] pathological features also appear to distinguish encephalitis of the brain stem caused by enterovirus 71 infection from bulbar poliomyelitis.

To strengthen the causal link between enterovirus 71 infection and encephalitis further, immunolocalization of viral antigens in inflamed tissues of the central nervous system was performed, and positive neuronal staining was obtained in our four patients.[4] Direct localization, by immunohistochemical methods or other means, is essential in order to confirm the presence of encephalitis caused by enterovirus 71 infection. In the series of Huang et al., only two patients had virus isolated from a clinically relevant site — the cerebrospinal fluid in one and tissues of the central nervous system in the other.[1] In a majority of their patients (95 percent), isolates of enterovirus 71 were obtained from the throat and rectum. In a major epidemic, such as the one in Taiwan, patients with other types of fulminant viral encephalitis (e.g., Japanese encephalitis) could be identified inadvertently, and the enterovirus 71 isolated from a peripheral site could, in fact, be nonpathogenic.

We agree with Huang et al. that the children with encephalitis of the brain stem caused by enterovirus 71 probably died as a result of neurogenic pulmonary edema due to destruction of the medulla.[2,5] There was no histologic evidence of myocarditis in any of the cases we examined.

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The authors reply:

To the Editor: The biphasic clinical manifestation of enterovirus 71 infection that we saw, with a prodrome of hand-foot-and-mouth disease or herpangina that lasted an average of 3.2 days followed by neurologic manifestations, clearly indicates the causal link between enterovirus 71 infection and disorders of the central nervous system. Indeed, 66 percent of our patients had isolates of enterovirus 71 obtained from throat swabs, 44 percent had isolates obtained from stool specimens, and only 5 percent had isolates obtained from cerebrospinal fluid or brain tissue. Very low rates of virus isolation in cerebrospinal fluid, ranging from 0 to 3 percent, were reported in previous outbreaks of enterovirus 71 infection in Bulgaria, Hungary, Japan, and Australia.[1] With poliovirus infections, the virus is also only occasionally recovered from cerebrospinal fluid. The diagnosis of poliomyelitis is often established on the basis of a virus recovered from a peripheral site, such as the throat or rectum.[2,3] We believe that the diagnosis of enterovirus 71–related infection of the central nervous system may be established in a similar manner. Moreover, we found high titers in our patients of enterovirus 71–specific antibody by means of a neutralization test (data not shown), which is additional evidence of recent enterovirus 71 infection. We also demonstrated by immunohistochemical methods that enterovirus 71 antigens were present in the brain-stem tissue of the patient who underwent autopsy.

Because of the effective nationwide vaccination program, an epidemic of Japanese encephalitis is no longer a cause of major concern for Taiwanese children. The clinical manifestations of Japanese encephalitis include nuchal rigidity, opisthotonos, dystonia, rigidity, convulsions, coma, and coarse tremors, which differ from the symptoms largely affecting the brain stem in our patients with enterovirus 71 infection. The majority of the survivors of Japanese encephalitis have mental retardation, seizure disorders, motor deficits, or subtle behavioral and intellectual abnormalities, effects that are quite different from those caused by enterovirus 71 infection. The characteristic findings on magnetic resonance imaging that are associated with Japanese encephalitis include lesions of the thalamus, basal ganglia, and hippocampus,[4] again in contrast with the predominant involvement of the brain stem, especially the pontine tegmentum, in patients with enterovirus 71 infection. We believe that the presence of hand-foot-and-mouth disease or herpangina, myoclonus, cerebellar and oculomotor signs, and characteristic findings on magnetic resonance imaging in the brain stem all help to distinguish rhombencephalitis caused by enterovirus 71 infection from Japanese encephalitis and other viral infections, such as bulbar poliomyelitis. We found no evidence that Japanese encephalitis had contributed to the involvement of the central nervous system in our patients with culture-confirmed enterovirus 71 infection, although serologic testing for the presence of Japanese encephalitis was not performed.

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Acute Myeloid Leukemia

To the Editor: In their otherwise informative review of new developments in the diagnosis and treatment of acute myeloid leukemia (AML), Löwenberg and colleagues (Sept. 30 issue)[1] state that before the 1970s, the five-year survival rate among patients with AML was less than 15 percent but that survival among patients under the age of 65 years is currently 40 percent. These statistics differ markedly from U.S. population–based survival rates among patients with AML from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute,[2] a consortium of 11 geographically defined cancer registries. Data from the SEER program indicate that five-year overall (observed) survival among all patients with AML was 5 percent for patients given a diagnosis in the mid-1970s, the earliest period for which data are available (Table 1). Although this survival rate has improved steadily over time, it reached only 11 percent for patients given a diagnosis in the most recent years for which five-year follow-up is complete (1988 to 1991). Moreover, for patients under the age of 65, the most recent five-year survival rate was 21 percent, according to the data from the SEER program — about half that cited for this age group by Löwenberg and colleagues (although they did not specify whether they were reporting a five-year overall rate).

Table 1 also highlights the striking association between age and survival among patients with AML. Over the past 20 years, improvements in survival have been realized almost entirely by persons under the age of 65, with equivalent gains among patients up to 19 years old and those 20 to 64 years old. In contrast, five-year observed survival is exceedingly poor and has not improved with time among patients 65 and older, who account for half of all cases of AML.

TABLE 1. FIVE-YEAR OVERALL SURVIVAL RATES AMONG PATIENTS WITH ACUTE MYELOID LEUKEMIA, ACCORDING TO AGE AND YEAR OF DIAGNOSIS.*

AGE AT DIAGNOSIS	YEAR OF DIAGNOSIS			
	1973–1977	1978–1982	1983–1987	1988–1991
	total no. of patients (% surviving)			
≤19 yr	192 (18)	162 (25)	143 (32)	133 (40)
20–64 yr	1016 (6)	1015 (10)	1044 (15)	838 (18)
≥65 yr	1055 (2)	1170 (1)	1255 (1)	1118 (2)
Total	2263 (5)	2347 (7)	2442 (9)	2089 (11)

*Data were obtained from the Surveillance, Epidemiology, and End Results program.[2] All patients were followed through 1996. The number of patients represents the total number of patients at the beginning of the five-year period in question, and the percentage represents the percentage surviving after five years.

Löwenberg et al. do not give the source of the survival rates presented in their review. If these statistics were derived from a clinical setting, they may very well be more favorable than those observed in a geographically defined area, which summarize outcomes of disease among an entire population. With regard to general observations about the outcome of cancer, survival data from the population-based SEER program have the distinct advantages of large numbers of patients, uniform follow-up, and demographic representativeness. In addition, up-to-date data on incidence and survival can be obtained easily through the Internet at http://www-seer.ims.nci.nih.gov.

Regardless of the source of the data, the survival statistics for patients with AML convey the fact that grave outcomes continue to be associated with this disease, particularly in older patients.

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The authors reply:

To the Editor: Drs. Clarke and Glaser raise the important issue of difference in survival rates between patients in the general population who are given a diagnosis of acute myeloid leukemia and those who are enrolled in clinical trials. They suggest that a survival rate of 40 percent for patients under the age of 65 years is overly optimistic.

We agree that most published data on survival among patients with AML are derived from clinical trials and that there are too few population-based data available. This issue has been addressed in a limited way by Stiller et al. through regional surveys of patients under 30 years of age in the United Kingdom.[1] The population survival rate is virtually the same as that among the patients enrolled in the national trial[2] — 42 percent at 5 years and 39 percent at 10 years. There was no difference in survival between patients who were enrolled in the national trial and those who were not — possibly because patients who were not enrolled tended to follow the schedule of the trial. A high proportion of younger patients (<55 years old) in the United Kingdom entered the national trial.

Data from the Netherlands Cancer Registry obtained during the period from 1989 through 1995 indicate five-year survival rates among patients with AML of 47 percent (for those up to 14 years of age) and 30 percent (for those 15 to 19 years of age).[3] We agree that these data are incomplete and that there has been little evidence of improved survival among older patients. In the Netherlands, patients are usually not offered suitable treatment in a trial and are usually treated according to a more obviously palliative approach. Data from trials involving older patients are relevant only to the minority of patients who are considered suitable for entry into the trials, and the results derived are not

always applicable to the majority who do not enter such trials. It is also difficult to find evidence of improvement in survival among older patients who do not enter trials.

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Growth Hormone Therapy in Adults and Children

To the Editor: In their review of growth hormone therapy (Oct. 14 issue),[1] Vance and Mauras do not mention the abuse of growth hormone by adults. Physicians should be aware that this phenomenon is well documented in athletes.[2] Abuse by physicians is also of concern. My organization has intervened in several cases in which physicians have taken growth hormone to increase their sense of well-being and physical performance.

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To the Editor: Vance and Mauras note that children with Down's syndrome, Noonan's syndrome, the Prader–Willi syndrome, or other conditions may have short stature. If so, should they be denied the benefits of growth hormone therapy? The authors' only stated objection is that no studies have prospectively assessed linear growth in children with these conditions until the achievement of final height. However, as the authors note, growth hormone therapy has not been proved to increase final height in children with chronic renal insufficiency, yet that diagnosis is an approved indication for treatment with growth hormone.

Is growth hormone too expensive to give to children with mental deficiency or developmental defects? Why is growth hormone therapy for children with chronic renal insufficiency or Turner's syndrome — conditions in which only a minority of patients have growth hormone insufficiency — more acceptable than it is for patients whose short stature is associated with other conditions?

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The authors reply:

To the Editor: There is no scientific evidence that administration of growth hormone has any beneficial effects in anyone with normal pituitary function. That some physicians take growth hormone is not surprising, since physicians are not immune to the unsubstantiated claims that it improves well-being and physical performance.

The Prader–Willi syndrome, Down's syndrome, and Noonan's syndrome are some of the many congenital conditions that impair linear growth and for which growth hormone therapy has been tried. In children with Down's syndrome, treatment for three years resulted in improved linear growth, but there was no change in either head circumference or intellectual function.[1] Children with Noonan's syndrome have had increases in growth in response to growth hormone therapy for up to four years; the responses were intermediate between those in children with idiopathic growth hormone deficiency and those with Turner's syndrome.[2,3] In children with the Prader–Willi syndrome, treatment with growth hormone for up to two years resulted in improved linear growth, decreased body fat, and increased lean body mass.[4,5] The duration of all these studies was limited, and they were not well controlled. One must be cautious not to raise parental expectations of greater height until the results of large, long-term, well-controlled studies of growth hormone therapy in children with these conditions are available.

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Acute Eosinophilic Hepatitis from Trovafloxacin

To the Editor: According to the Food and Drug Administration, trovafloxacin, a broad-spectrum quinolone antibiotic, has been associated with more than 100 cases of hepatic toxicity. Fourteen of these cases involved acute liver failure, with transplantation required in four patients; five patients died of liver disease. More than 300,000 prescriptions for trovafloxacin were written monthly in the United States before use of the drug was limited to certain serious infections in an inpatient setting.

There have been a few reports of hepatic toxicity asso-

ciated with the use of quinolones[1-3] but to our knowledge no published reports of toxicity associated with trovafloxacin. We describe a patient in whom severe acute hepatitis developed while he was receiving trovafloxacin for chronic sinusitis. This 66-year-old man presented with nausea, vomiting, malaise, and abdominal distention. He had taken 100 mg of trovafloxacin daily for four weeks for treatment of refractory chronic sinusitis. His medical history included hypertension, gout, osteoarthritis, and chronic idiopathic angioedema. He had been treated with losartan, metoprolol, hydrochlorothiazide, allopurinol, nabumetone, and doxepin for several years. He rarely drank alcohol.

On examination, the patient was febrile and had mild tachypnea. His abdomen was markedly distended but not tender; bowel sounds were decreased. There was no jaundice, ascites, or organomegaly. The initial white-cell count was 8000, with 16 percent eosinophils; the serum aspartate aminotransferase level, 537 IU per liter; the serum alanine aminotransferase level, 841 IU per liter; the direct bilirubin level, 1.0 mg per deciliter; the total bilirubin level, 1.6 mg per deciliter; the alkaline phosphatase level, 111 IU per liter; the blood urea nitrogen level, 30 mg per deciliter; and the creatinine level, 3.2 mg per deciliter. Tests for hepatitis A, B, and C infection were negative. A computed tomographic scan of the abdomen showed fluid adjacent to the liver and spleen, bilateral pleural effusions, and consolidation at the base of the right lung, but no hepatic parenchymal abnormality. Ultrasonography of the abdomen showed coarse echogenicity, a finding consistent with necrosis. Neither gallstones nor ascites was seen; the bile ducts were not distended. A biopsy specimen of the liver showed centrilobular and focal periportal necrosis and eosinophilic infiltration (Fig. 1). The sinusoids were dilated and contained lymphocytes and eosinophils; many hepatocytes were undergoing mitosis. A stool sample was positive for *Clostridium difficile* toxin, which may have accounted for the persistent abdominal distention.

Use of trovafloxacin was discontinued, while use of the other medications was continued. The patient was treated with prednisone for the hepatitis and metronidazole for the *C. difficile* infection. His hepatic and renal function returned to normal, and the eosinophilia gradually resolved. This is a biopsy-proved case of hepatic toxicity associated with the use of trovafloxacin. We are indebted to Dr. Peter B. Kelsey for permitting us to study this patient.

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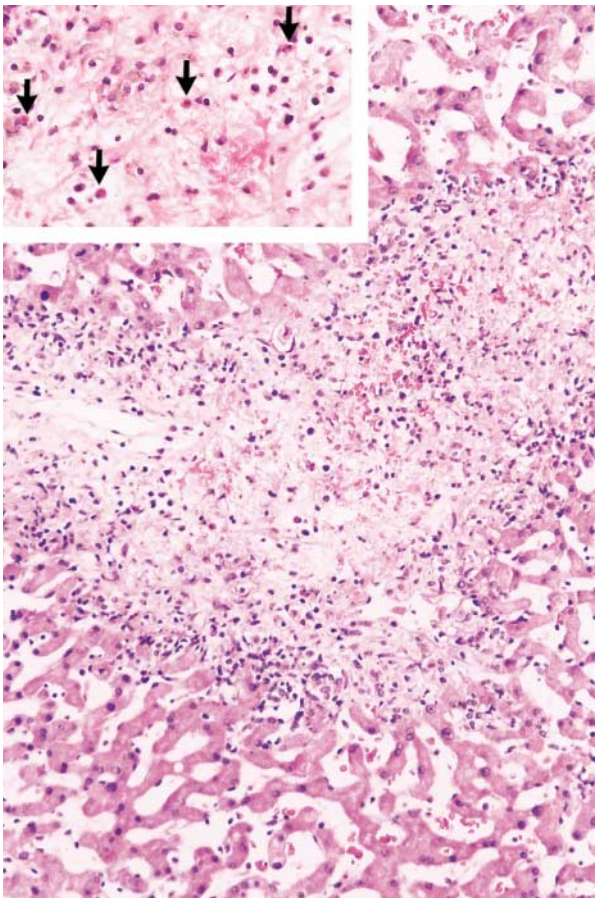

Figure 1. Biopsy Specimen of the Liver (Hematoxylin and Eosin).

The biopsy specimen of the liver (×156) shows centrilobular necrosis, with a mixed cellular infiltrate of eosinophils, polymorphonuclear leukocytes, and mononuclear cells. There is marked hepatic necrosis out of proportion to the extent of inflammation, a finding that suggests toxic injury. The inset (×312) shows four eosinophils (arrows).

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