Correspondence

Informed Consent and Approval by Institutional Review Boards in Published Reports on Clinical Trials

To the Editor: Publication of the results of biomedical research is not a mere formality in science. It is the culmination of a long process, and careful attention to every step in that process is important.[1] In randomized clinical trials, failing to obtain or forgetting to report informed consent from participants or approval of the protocol by an institutional review board (IRB) might suggest that the authors considered these steps unimportant details, if not obstacles. This is clearly a misconception, because the aim of research is to serve human subjects, not to use them.

We assessed the frequency of reporting of informed consent and IRB approval in all reports of trials published between 1993 and 1995 in the *New England Journal of Medicine,* the *Lancet,* the *Journal of the American Medical Association,* and the *British Medical Journal.* We also searched the Medline data base for all trials with at least one author from Spain that were published in other journals during the period from 1993 to 1995. We included all reports of trials involving human subjects that had two or more treatment groups and studies referred to as "clinical trials," "field trials," or "randomized trials" by the authors. When information on IRB approval or informed consent was missing in the reports, we mailed a standardized questionnaire to the corresponding authors. After two months, we repeated the mailing for authors who had not responded to the first questionnaire.

Of reports on 767 clinical trials, 543 (70.8 percent) stated that an IRB had approved the research, and 612 (79.8 percent) reported that informed consent had been requested from the participants. Both types of information were included in 64 percent of the reports. The authors explicitly stated that they had not requested the informed consent in 10 reports. In all these trials, the authors reported having obtained IRB approval. Many of these trials were studies of cardiopulmonary resuscitation for patients with cardiac arrest.

The response rate for authors of reports that lacked information on IRB approval was 73.7 percent (165 of 224), and the rate for authors of reports that lacked information on informed consent was 70.3 percent (102 of 145). Thirty-seven of the 165 respondents who did not report on IRB approval (22.4 percent) stated that they had not sought approval, and 21 of the 102 who did not report on informed consent (20.6 percent) stated that they had not requested informed consent.

There were no significant differences in the proportion of reports that included information on IRB approval or informed consent according to the year of the survey or the number of participating centers. We constructed a logistic-regression model with failure to disclose either IRB approval or informed consent as the outcome (Table 1). Among other findings, reports published in the *New England Journal of Medicine* as compared with other journals, those with authors from European countries (excluding Spain and the United Kingdom) as compared with other countries, and those involving trials funded by the pharmaceutical industry as compared with other sources of funding were more likely to report IRB approval or informed consent.

Similar surveys have been reported elsewhere.[2-5] They assessed a smaller number of trials (range, 37 to 279). In general, our survey showed a higher rate of reporting of IRB approval and informed consent than the other surveys did. However, our results suggest that, even in the leading general medical journals, closer attention to the conduct of clinical research, as well as the reporting of its ethical aspects, is needed.

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INSTRUCTIONS FOR LETTERS TO THE EDITOR

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TABLE 1. FAILURE TO REPORT ON INFORMED CONSENT OR APPROVAL BY AN INSTITUTIONAL REVIEW BOARD (IRB), 1993 THROUGH 1995.*

VARIABLE	NO. OF TRIALS	BOTH INFORMED CONSENT AND IRB APPROVAL REPORTED	INFORMED CONSENT REPORTED BUT NOT IRB APPROVAL	IRB APPROVAL REPORTED BUT NOT INFORMED CONSENT	ADJUSTED OR (95% CI) FOR FAILURE TO REPORT EITHER OR BOTH†
		percent			
All trials	767	12.9	16.3	6.9	
Journal					
New England Journal of Medicine‡	219	4.1	14.2	3.7	1.00
Journal of the American Medical Association	81	9.9	8.6	11.1	1.72 (0.89–3.30)
British Medical Journal	105	21.0	24.8	9.5	4.74 (2.31–9.74)
Lancet	203	11.8	13.8	8.9	2.15 (1.21–3.83)
Other journals (with Spanish authors)§	159	22.6	20.8	5.0	1.78 (0.65–4.92)
Country of authors¶					
Europe (except United Kingdom and Spain)‡	136	8.8	11.8	4.4	1.00
Spain	187	20.9	20.3	5.3	4.14 (1.53–11.20)
United Kingdom	127	18.1	19.7	9.4	2.33 (1.26–4.30)
United States	240	7.1	13.3	8.3	2.49 (1.30–4.74)
Other	77	10.4	18.2	6.5	2.44 (1.21–4.91)
No. of subjects in trial					
≤50‡	196	15.8	12.8	4.1	1.00
51–500	399	10.5	18.3	7.0	1.61 (1.00–2.59)
501–2000	116	13.8	18.1	8.6	2.77 (1.43–5.38)
>2000	56	17.9	10.7	12.5	2.14 (0.93–4.97)
End point					
Efficacy‡	554	11.4	17.9	6.0	1.00
Pharmacologic end point	59	10.2	8.5	5.1	0.44 (0.20–0.95)
Safety	37	13.5	10.8	2.7	0.74 (0.32–1.71)
Prevention	75	18.7	10.7	10.7	0.93 (0.50–1.74)
Diagnostic or other end point	42	26.2	21.4	19.0	1.76 (0.79–3.93)
Source of funding					
Pharmaceutical industry‡	225	7.1	8.0	7.1	1.00
Public agency	199	13.6	18.6	9.5	1.38 (0.80–2.37)
Other	143	7.0	17.5	9.1	1.71 (1.04–2.81)
Not reported	200	23.0	22.5	2.5	2.13 (1.25–3.62)

*Trials whose authors originally acknowledged not having obtained IRB approval or informed consent are included with trials whose authors did not originally disclose information about these issues. For comparisons of the failure to disclose information on one or both issues, the percentages of authors who failed to report on both must be added to the percentages of authors who failed to report on one.

†A higher odds ratio (OR) means a higher probability of failing to provide information about either or both issues in the original report. Odds ratios have been adjusted (by logistic regression) for all variables shown in the table and also for the length of the article and the methodologic characteristics of the trial. CI denotes confidence interval.

‡This was the reference category.

§There were 103 other journals that published reports with authors from Spain. The most frequently reviewed journals in this group (and the number of trials included in the study) were *Hepatology* (12 trials), *Gut* (6), the *Journal of Hepatology* (6), *Antimicrobial Agents and Chemotherapy* (6), the *American Journal of Hypertension* (3), *Annals of Oncology* (3), *Intensive Care Medicine* (3), and the *Journal of Pharmacology and Experimental Therapy* (3).

¶In the case of international trials, the country (or group of countries) was assigned according to the following order: Spain, the United States, the United Kingdom, other European countries, and other. For example, a trial with Spanish participation was assigned to Spain, and a collaborative American–British trial was assigned to the United States.

1. Relman AS. Publishing biomedical research: roles and responsibilities. Hastings Cent Rep 1990;20(3):23-7.
2. Rennie D, Yank V. Disclosure to the reader of institutional review board approval and informed consent. JAMA 1997;277:922-3.
3. Olson CM, Jobe KA. Reporting approval by research ethics committees and subjects' consent in human resuscitation research. Resuscitation 1996; 31:255-63.
4. Olde Rikkert MG, ten Have HA, Hoefnagels WH. Informed consent in biomedical studies on aging: survey of four journals. BMJ 1996;313: 1117.
5. Matot I, Pizov R, Sprung CL. Evaluation of institutional review board review and informed consent in publications of human research in critical care medicine. Crit Care Med 1998;26:1596-602.

Pravastatin and Coronary Heart Disease

To the Editor: The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial (Nov. 5 issue)[1] is the third study, after the Scandinavian Simvastatin Survival Study[2] and the Cholesterol and Recurrent Events study,[3] on the use of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors for secondary prevention of coronary disease. The positive results of this trial are as marginal as those of the studies that preceded it.

The authors calculated relatively high values for risk re-

duction with pravastatin as compared with placebo, those being between 11 and 23 percent, which might tempt the inexperienced physician to use statins universally. The relevant values with respect to the reduction of events are, however, much lower and demonstrate a small treatment effect. However, the data on the "number needed to treat" are the most informative for the expert. It can be deduced, for example, that 316 patients have to be treated in order for one coronary event to be averted in 1 patient. Yet, 315 patients would be burdened with a medication, the dangers of which cannot be foreseen in the case of treatment over a period of 20 to 30 years. Pravastatin has no particular advantage over placebo, even for certain subgroups at higher risk (those ≥70 years of age and those with hypertension, diabetes, or total cholesterol levels ≥251 mg per deciliter).

The optimistic conclusion of the authors that "the current low rate of use of cholesterol-lowering therapy among patients with CHD [coronary heart disease] can no longer be accepted" is not defensible when the appropriate measures (reduction of events and number needed to treat) are considered. Incidentally, Krumholz et al.[4] already called for patients over 70 years of age not to be burdened with lipid-lowering agents, and Weverling-Rijnsburger et al.[5] demonstrated that, in the case of the very elderly, life expectancy shows a positive correlation with cholesterol values.

Healthful living, a varied diet, physical activity, not smoking, and adequate social integration are of greater use than statins for increasing life expectancy. Statins are rather fragile props.

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1. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
2. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;334:1383-9.
3. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-9.
4. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA 1994;272:1335-40.
5. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350:1119-23. [Erratum, Lancet 1998;351:70.]

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To the Editor: The LIPID Study Group concludes, "The current low rate of use of cholesterol-lowering therapy among patients with CHD can no longer be accepted"; however, less than 50 percent of the patients in their study received β-adrenergic blockers. No comment was made about this fact. Beta-blocker therapy effectively reduces the incidence of myocardial infarction in patients with coronary artery disease,[1] yet many patients for whom beta-blocker therapy would be ideal are not prescribed these drugs at the time of their discharge from the hospital after acute myocardial infarction.[2]

Given that pravastatin is much more expensive than beta-blockers and aspirin and that cost constraints are a concern, we ought to try aspirin and beta-blockers before we prescribe a 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor.

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1. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998;339:489-97.
2. Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of β-blockers for the treatment of elderly patients after acute myocardial infarction. JAMA 1998;280:623-9.

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The authors reply:

To the Editor: In the LIPID trial of patients with CHD, we studied the effects of pravastatin used with dietary advice and usual care, including myocardial revascularization and drugs such as beta-blockers and aspirin. Similar benefits of pravastatin treatment were seen in those who received beta-blockers and those who did not. Among the 4229 patients receiving beta-blockers at the time of study entry, pravastatin therapy resulted in a 19 percent reduction in coronary events (P=0.01), a 29 percent reduction in mortality from CHD (P=0.004), and a 30 percent reduction in total mortality (P<0.001) as compared with placebo. Consequently, the benefits of pravastatin should be regarded as additional to any benefits of beta-blocker therapy.

The cost effectiveness of pravastatin is the subject of a separate report, but a preliminary analysis has shown this treatment to be cost effective, as compared with other accepted medical interventions. The cost is less than $6,300 ($10,000 Australian) for each year of life gained.

In response to the comments of Meyer: the LIPID trial extends the results of the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events study in important ways. The results of the LIPID trial provide convincing evidence of a treatment effect on total mortality in patients with CHD and typical cholesterol levels. Although the size of the treatment effect is moderate, with an absolute reduction in mortality of 3.1 percent over 6.1 years, this rate means that 32 patients need to be treated over this period in order for one death to be prevented. If serious nonfatal events (myocardial infarction or stroke) are also considered, only 15 patients need to be treated over 6.1 years in order for one serious fatal or nonfatal event to be prevented. For a treatment with no demonstrated serious side effects and a long-term record of safety, this represents substantial clinical benefit.

The LIPID trial did not have the power to demonstrate reliable separate treatment effects for women, the elderly, or patients with diabetes. However, the results were consistent, with a similar relative reduction in CHD events for each of the prespecified subgroups. Assuming the same relative reduction, a larger absolute benefit will result for those in groups at higher risk. This is particularly so when the patients in the LIPID trial are compared with populations without CHD and those with[1] or without[2] elevated cholesterol levels. In fact, larger benefits can be expected from the treatment of patients with CHD and average cholesterol levels than from the treatment of those without CHD but with elevated cholesterol levels.

We accept that the LIPID study has not ruled out the

possibility of long-term complications associated with treatment over the course of decades. We continue to follow the entire LIPID cohort, with approximately 85 percent of the patients continuing to receive pravastatin therapy. We plan to analyze results after a further two years of follow-up and again after five years.

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1. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.
2. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615-22.

Implantable Defibrillators, Pacemakers, and Electronic Antitheft Devices

To the Editor: The report by Santucci et al. (Nov. 5 issue)[1] provides another example of sources of interference with implantable defibrillators.[2] That this should occur is not surprising to anyone familiar with the sensing function of medical devices. Indeed, such systems have been falsely triggered by devices such as radio-controlled model cars and slot machines,[3] electrocautery for unrelated surgery, and neural stimulators for pain control. Other devices and procedures that may be expected to inhibit the output of pacemakers or initiate inappropriate discharge of defibrillators include hair-removal (depilation) units and rapid-stimulation electromyography studies. In two patients with implantable cardioverter–defibrillators who were treated at my facility, the devices discharged while they were jumpstarting a car with battery cables.

That such events may occur is not in question; up to 20 percent of all firings of implantable cardioverter–defibrillators are estimated to be inappropriate. However, readers should not interpret isolated case reports as representing a trend, and patients can take comfort in the infrequency with which such externally triggered events apparently occur. The reality is that several hundred thousand recipients of medical devices pass through electronic antitheft systems each day, yet there are but a handful of documented episodes of interference. Of the hundreds of thousands of Holter-monitoring studies performed each year, many in patients with implanted cardiac devices, the occurrence of such interference is all but unknown. Although it is easy to have discussions of who is responsible for minimizing such interactions (the electronic-field producer or the implanted-device producer),[2] a simple technical solution is elusive. "Don't linger, don't lean" is an easy, practical remedy that

was recently recommended by the Food and Drug Administration (FDA),[4] and the American Heart Association has made similar recommendations.

In the same issue of the *Journal,* Drs. McIvor and Sridhar[5] report on interactions between cardiac pacemakers and antishoplifting security systems. In Figure 1 of their report, the first two native QRS complexes suggest that the patient is in atrial flutter, which if sensed, can initiate pacing at the upper tracking rate of the device. The recorded rhythm strip is 18 seconds long, and, contrary to what is implied in the figure, it seems unlikely that the patient walked through the gate. An elderly person on crutches could navigate this space in half the time.

Each of us in the field of device therapy must take notice of such reports and strive to confirm the absence of any clinically significant consequences. The average patient, when passing through such a system, is exposed to the signal source for a period that is equivalent to one or two heartbeats, and little more than transient extra heartbeats or skipped beats have been demonstrated in response in prior studies.

The innovative therapies of cardiac pacing and defibrillator therapy have provided lifesaving benefits to hundreds of thousands of patients in the 40 years since the first pacemaker was installed. In the final analysis, all such patients can and should be encouraged to lead normal lives and to act with prudence during exposure to societal sources of electromagnetic interference.

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1. Santucci PA, Haw J, Trohman RG, Pinski SL. Interference with an implantable defibrillator by an electronic antitheft-surveillance device. N Engl J Med 1998;339:1371-4.
2. Irnich W. Electromagnetic interference in current implantable devices. In: Vardas PE, ed. Cardiac arrhythmias, pacing & electrophysiology: the expert view. Dordrecht, the Netherlands: Kluwer Academic, 1998:427-36.
3. Madrid AH, Moro C, Martín J. Interference of the implantable defibrillators caused by slot machines. Pacing Clin Electrophysiol 1996;19:675. abstract.
4. Important information on anti-theft and metal detector systems and pacemakers, ICDs, and spinal-cord stimulators. Rockville, Md.: Center for Devices and Radiological Health, September 28, 1998. (Or see: http://www.fda.gov/cdrh/safety/easnote.html.)
5. McIvor ME, Sridhar S. Interactions between cardiac pacemakers and antishoplifting security systems. N Engl J Med 1998;339:1394-5.

To the Editor: We commend Santucci et al. for their discussion of the effects of electromagnetic interference on the activity of implantable cardioverter–defibrillators. However, we disagree with their assertion that clinical problems caused by electromagnetic interference with implantable defibrillators are rare and without life-threatening consequences. We are aware of cases in the literature and in our own experience in which electromagnetic interference in the perioperative environment has had potentially life-threatening ramifications.[1,2]

More than 500,000 patients in the United States have implantable cardioverter–defibrillators or pacer–cardioverter–defibrillators, and more than 40,000 are at risk for sudden death from malignant tachyarrhythmias. These devices are implanted in patients with severe, irreversible, structural heart disease with compromised myocardium. Many

of these patients who are highly dependent on the proper functioning of the devices are exposed to electromagnetic interference in the perioperative environment.

Santucci et al. correctly point out that electromagnetic interference is rarely life threatening in most settings, but in the highly electromagnetic-interference–contaminated perioperative environment, patients may be at serious risk. Perioperatively, the sources of electromagnetic interference include surgical electrocautery, extracorporeal shock-wave lithotripsy, nuclear magnetic resonance imaging, high-voltage electrical devices, and radiotherapy for nondiagnostic purposes. Electromagnetic interference "noise" may have several undesirable consequences: inappropriate therapy, since electromagnetic interference may be identified as arrhythmia, stimulating dangerous tachyarrhythmias; changes in programming, since electromagnetic interference may be misinterpreted, altering algorithms for detection and treatment; and damage to circuitry, leads, or electrodes, rendering the device inoperable and causing permanent myocardial damage.[3]

All U.S. manufacturers of implantable cardioverter–defibrillators and pacer–cardioverter–defibrillators recommend that the devices be disabled (that antitachycardia and other functions be suspended) at a pacemaker clinic or by a technician if patients are to be exposed to electromagnetic interference perioperatively. Positioning a strong magnet over the pulse generator will temporarily suspend the automatic-detection and therapeutic capabilities of the device. Other suggestions include keeping a grounding pad 15 cm from the site of electromagnetic interference, orienting external defibrillator pads away from the pulse generator,[4] avoiding diathermy in favor of bipolar cautery, careful monitoring of the pulse wave form and electrocardiogram, and remaining prepared to perform external conversion and cardiac resuscitation.[5]

Currently, despite the diversity and complexity of these devices, among the 10 U.S. manufacturers, there are no industry-wide guidelines for perioperative malfunction. To ensure the safety of patients, universal and practical solutions for perioperative management of implantable cardioverter–defibrillators and pacer–cardioverter–defibrillators should be developed by the appropriate clinical specialties in conjunction with the manufacturers.

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1. Gaba DM, Wyner J, Fish KJ. Anesthesia and the automatic implantable cardioverter/defibrillator. Anesthesiology 1985;62:786-92.
2. Important information on anti-theft and metal detector systems and pacemakers, ICDs, and spinal-cord stimulators. Rockville, Md.: Center for Devices and Radiological Health, September 28, 1998. (Or see: http://www.fda.gov/cdrh/safety/easnote.html.)
3. Atlee JL. Cardiac pacing and electroversion. In: Kaplan JA, ed. Cardiac anesthesia. 4th ed. Philadelphia: W.B. Saunders, 1998.
4. Mirowski M, Reid PR, Watkins L, Weisfeldt ML, Mower MM. Clinical treatment of life-threatening ventricular arrhythmias with the automatic implantable defibrillator. Am Heart J 1981;102:265-70.
5. Mehta Y, Swaminathan M, Juneja R, Saxena A, Trehan N, Atlee J. Noncardiac surgery and pacemaker cardioverter-defibrillator management. J Cardiothorac Vasc Anesth 1998;12:221-4.

The authors reply:

To the Editor: We agree with Dr. Harthorne that reports of inappropriate discharge of implantable cardioverter–defibrillators should not come as a surprise to anyone familiar with these devices. Although up to 20 percent of firings may be inappropriate, a very small percentage are caused by external electromagnetic interference. Clinically minor sequelae of electromagnetic interference in patients with pacemakers and implantable cardioverter–defibrillators have been described from a variety of sources. The intent of our report was to bring attention to the potential for such interactions to be serious and to alert patients, physicians, and the industry to the possibility of a severe interaction between implantable cardioverter–defibrillators and at least one type of electronic antitheft-surveillance unit. It was our impression that the potential seriousness of such interactions, although they are rare, was not known or widely anticipated and that patients were not routinely made aware of this phenomenon or informed of the simple method of prevention. Recently, Dr. Harthorne properly noted that no serious interactions had previously been documented between antishoplifting equipment and implantable cardioverter–defibrillators.[1]

Our recommendations were straightforward and in concordance with those of the FDA and American Heart Association. Specifically, the avoidance of prolonged exposure to antitheft equipment should minimize or eliminate problems. Since our report, several anecdotal reports of interactions between pacemakers and implantable cardioverter–defibrillators and antitheft equipment have been brought to our attention. Although it is not our intent to frighten patients unnecessarily, such interactions may not be as rare as previously thought, and we suspect they have been underreported. We believe that it is appropriate routinely to inform patients of the possibility of such an interaction and of the appropriate means to avoid it. This should be done in a reassuring manner, to avoid unnecessary psychological effects. It is only through a lack of awareness that more patients are likely to experience such events.

Dr. Barach and Mr. Baum correctly point out that electromagnetic interference in the hospital environment is a common cause of inappropriate functioning of pacemakers and implantable cardioverter–defibrillators. We have previously described common sources of electromagnetic interference in hospitals and the workplace.[2,3] It is therefore preoperative routine in most institutions to take precautions such as those described to avoid undesirable effects, which can certainly otherwise be life threatening. Electromagnetic interference is a rare cause of serious interference during routine daily life. Fortunately, most of these interactions can be prevented by appropriate awareness and planning.

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1. Harthorne JW. Theft deterrent systems: a threat for medical device recipients or an industry cat fight? Pacing Clin Electrophysiol 1998;21:1845-6.
2. Pinski SL, Trohman RG. Implantable cardioverter-defibrillators: implications for the nonelectrophysiologist. Ann Intern Med 1995;122:770-7.
3. *Idem.* More on patients with implantable cardioverter-defibrillators. Ann Intern Med 1995;123:893.

To the Editor: The myriad sources of electromagnetic radiation that can interfere with implanted medical devices have been recognized for quite some time.[1] Our interest in electronic article surveillance systems, or antishoplifting gates, dates to the experience of one of our patients, who had an inappropriate discharge of her implantable cardioverter–defibrillator while standing next to such a system in a store.[2] Our findings have since been confirmed.[3,4] The largest formal test of implantable cardioverter–defibrillators, whose results were presented to the FDA in September 1998, suggested that 1 in 50 patients will have an inappropriate firing of their implantable cardioverter–defibrillator when exposed to the field of an acoustomagnetic electronic article surveillance system. Whether a 2 percent incidence of inappropriate firings is clinically significant depends on one's point of view. There is no need to cause a panic among the 98 percent who will not be affected, but by educating patients not to linger in these fields, we can eliminate the problem altogether. Because such systems can be concealed behind walls or under flooring, we would also be in favor of advisory signs alerting patients not to linger in areas near these systems.

In our study of patients with implanted pacemakers,[5] virtually all interactions were confined to the strong, low-frequency, pulsed magnetic field generated by the acoustomagnetic type of system. Therefore, other types of systems may not need warning signs. We agree with Dr. Harthorne about the soundness of a "don't linger, don't lean" approach, since walking quickly through an acoustomagnetic electronic article surveillance gate (rather than pausing within or near the system) was associated with a large decrease in pacemaker interactions (from 96 percent to 16 percent). Most patients who are passing through such a system will not be actively using their pacing system at the time, so few will have symptoms, even if interactions occur. Others have a potential for interactions, some of which may cause symptoms. One type of pacemaker generator can even be reprogrammed by these systems, resulting in a faster base-line pacing rate.

It should now be accepted that interactions between such systems and implanted medical devices occur and are common in patients with pacemakers. What can be argued is whether enough patients are adversely affected to warrant concern. Our position is that the likelihood of clinical harm — even for the unlucky few who are at risk — can be virtually eliminated by proper education of patients.

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1. Furman S, Parker B, Krauthamer J, Escher DJ. The influence of electromagnetic environment on the performance of artificial cardiac pacemaker. Ann Thorac Surg 1968;6:90-5.
2. McIvor ME. Environmental electromagnetic interference from electronic article surveillance devices: interactions with an ICD. Pacing Clin Electrophysiol 1995;18:2229-30.
3. Mathew P, Lewis C, Neglia J, Krol RB, Saksena S. Interaction between electronic article surveillance systems and implantable defibrillators: insights from a fourth generation ICD. Pacing Clin Electrophysiol 1997;20:2857-9.

4. Santucci PA, Haw J, Trohman RG, Pinski SL. Interference with an implantable defibrillator by an electronic antitheft-surveillance device. N Engl J Med 1998;339:1371-4.
5. McIvor ME, Reddinger J, Floden E, Sheppard RC. Study of Pacemaker and Implantable Cardioverter Defibrillator Triggering by Electronic Article Surveillance Devices (SPICED TEAS). Pacing Clin Electrophysiol 1998;21:1847-61.

Management of Acoustic Neuroma

To the Editor: Kondziolka et al. in their study (Nov. 12 issue)[1] and Pitts and Jackler in their accompanying editorial[2] miss two important issues concerning radiosurgery for acoustic neuromas. First, since the age of the patient is relevant to the decision about treatment, a more detailed analysis of age is required. We and a number of others recommend observation, not surgery, for patients over the age of 65 years with acoustic neuromas that are not causing distortion of the brain stem. Imaging is repeated as necessary, depending on the size of the tumor, and most of these older patients never require any intervention — either surgery or radiosurgery. In patients over 65 with acoustic neuromas, the issue is not whether radiosurgery is better than conventional surgery but whether any therapy is necessary. Second, the size of the tumor is very important. Kondziolka et al. do not give enough information about tumor size or about how the diameter of a tumor was determined, and no information correlating size and age was provided.

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1. Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. Long-term outcomes after radiosurgery for acoustic neuromas. N Engl J Med 1998;339:1426-33.
2. Pitts LH, Jackler RK. Treatment of acoustic neuromas. N Engl J Med 1998;339:1471-3.

To the Editor: Although there have been great strides in radiosurgery, Kondziolka et al. did not discuss how single-fraction gamma-knife radiosurgery (radiation delivered in one dose) compares with fractionated treatment. Historically, radiation has been given in divided doses to minimize damage to normal tissue.

Fractionated stereotactic radiosurgery gives excellent results, with the same dose used since the inception of this technique more than five years ago, for acoustic neuromas from 0.1 to 32 ml in volume and up to 5 cm in diameter, including those in patients with type 2 neurofibromatosis.[1-3] Despite the presence of large neuromas and type 2 neurofibromatosis, the preservation rate of the facial and trigeminal nerves in 142 patients was 100 percent, and 86 percent of the patients retained hearing. With fractionated radiosurgery, a noninvasive frame for the head obviates the need for skull pins, anesthesia, sedation, and hospitalization.[4]

In comparison, gamma-knife radiosurgery caused hearing loss in 49 percent of the patients in the study by Kondziolka et al., facial neuropathy in 21 percent, and damage to the trigeminal nerve in 27 percent. Thirty-one percent of previously employed patients who underwent gamma-knife radiosurgery became unemployed after the procedure. Kondziolka et al. report that 18 percent of their

patients underwent craniotomy followed by radiosurgery as primary treatment. This two-step strategy is associated with greater morbidity, but it makes subsequent single-fraction radiosurgery appear safer, since the patients will probably have surgically induced neurologic deficits, such as hearing loss and facial neuropathy, before radiosurgery.

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2. Lederman G, Wertheim S, Lowry J, et al. Acoustic neuromas treated by fractionated stereotactic radiotherapy. In: Kondziolka D, ed. Radiosurgery. Basel, Switzerland: Karger, 1998:25-30.
3. Rashid H, Lowry J, Wertheim S, et al. Improved results for acoustic neuroma treated with fractionated stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 1998;42:Suppl.
4. Gill SS, Thomas DG, Warrington AP, Brada M. Relocatable frame from stereotactic external beam radiotherapy. Int J Radiat Oncol Biol Phys 1991; 30:599-603.

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To the Editor: The article by Kondziolka et al. does little to define the place radiosurgery may have in the treatment of acoustic neuromas. The authors claim to have evaluated 162 consecutive patients prospectively over an extended period of time while frequently changing the criteria for entry into the study. However, only 38 patients were available for follow-up at seven to eight years. Have the authors forgotten that they reported treating no fewer than 134 patients with acoustic tumors between August 17, 1989, and June 1, 1991?[1] Where have all their patients gone? What they report on is not a group of consecutive patients but a highly selected sample from a much larger series.

The outcome measure in the study was a change of ±2 mm in tumor size. The detection of such minute changes would tax the abilities of the most experienced radiologist working under optimal conditions. These tumors were measured by general radiologists at several hospitals with the use of various criteria. It seems highly implausible that these radiologists could measure tumors of irregular size, especially recurrent tumors in surgical defects, with the accuracy the study demanded. The authors failed to validate the interobserver reliability of tumor mensuration so critical to this study. The doses of radiation used throughout the study varied, and in some instances, even the wishes of the patient determined the amount of irradiation offered. Given such variation, the claims made by the authors about the effects of the dose on therapeutic efficacy are not well founded. The authors' description of the multivariate analyses does not include the statistical tests used or even which variables were studied. Unlike the authors of other quality-of-life studies in this area,[2] the authors failed to use a validated instrument to determine health status.

The article is less than forthcoming in addressing the hazards of stereotactic radiosurgery for acoustic tumors. In particular, the authors do not acknowledge the risk of cancer known to follow stereotactic radiosurgery. Of the five patients in the Copenhagen series, cancer developed in one after radiosurgery.[3] Finally, the authors would do well to remember that acoustic tumors may remain quiescent for years and that the rates of "control" attributed to radiosurgery may be no more than what would have happened had no treatment been given.

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1. Lunsford LD, Linskey ME, Flickinger JC. Stereotactic radiosurgery for acoustic nerve sheath tumors. In: Tos M, Thomsen J, eds. Acoustic neuroma. Amsterdam: Kugler, 1992:279-87.
2. Nikolopoulos TP, Johnson I, O'Donoghue GM. Quality of life after acoustic neuroma surgery. Laryngoscope 1998;108:1382-5.
3. Thomsen J, Tos M, Borgensen SE, Charabi B. Radiosurgery — a referring surgeon's experience. Presented at the European Skull Base Congress, London, 1997. abstract.

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The authors reply:

To the Editor: Dr. Broad notes the importance of the age of the patient in selecting a management strategy. As stated in our article, acoustic tumors in elderly patients are first managed conservatively with an evaluation of the volume of the tumor by serial imaging studies. Radiosurgery is recommended only when clinical progression or tumor growth has been documented.

The factor of tumor size is also important. As we stated, tumor size was determined by five separate measurements performed with the caliper technique, a method we have described previously.[1] Dr. O'Donoghue and colleagues also missed this statement in our paper. We do not know why they believe that "tumors were measured by general radiologists at several hospitals with the use of various criteria," since this was not stated in our article. All images were reviewed by our group with the use of the five separate measurements with calipers. O'Donoghue et al. also criticize our failure to use a "validated instrument to determine health status." Although we did not use their instrument, we chose to develop and use one that included neurologic function and potential complications specific to radiosurgery.

We agree with O'Donoghue et al. that some acoustic tumors can remain quiescent for years, although data on the natural history of acoustic neuroma indicate an average growth rate of 2 mm per year.[2] In our experience, more than 80 percent of acoustic neuromas followed with serial images show objective, measurable growth within five years. However, whether the effect of radiosurgery may be no different from that of no treatment is an argument that ended years ago.

We also clearly stated that this study was of a series of consecutive, unselected patients that included every patient whose acoustic neuroma was managed with radiosurgery at the University of Pittsburgh from August 1987 (when we began) through July 1992. This series allowed the maximal follow-up of all patients.

Finally, the purpose of our report was to define long-

term outcomes after radiosurgery, not after fractionated-radiation therapy. Lederman et al. believe that fractionated-radiation therapy may offer better tumor control or neurologic outcomes than gamma-knife radiosurgery. However, they provide no peer-reviewed comparative data.

The goal of the management of acoustic tumors, whether with observation, microsurgical resection, stereotactic radiosurgery, or some other emerging method, is to maintain lifelong function. Our systematic evaluation of an unselected, consecutive series of patients who underwent radiosurgery during our first 5 to 10 years of using this technique substantiates the value of stereotactic radiosurgery. Anecdotes and small series of patients aside, we await any comprehensive, long-term evaluation of other treatment strategies.

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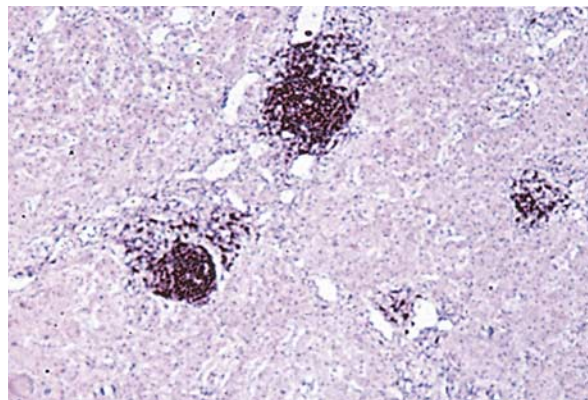University of Pittsburgh
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1. Linskey ME, Lunsford LD, Flickinger JC. Neuroimaging of acoustic nerve sheath tumors after stereotaxic radiosurgery. AJNR Am J Neuroradiol 1991;12:1165-75.
2. Bederson JB, von Ammon K, Wichmann WW, Yasargil MG. Conservative treatment of patients with acoustic tumors. Neurosurgery 1991;28:646-51.

Adrenal Lymphocytic Infiltration and Adrenocortical Tumors in a Patient with 21-Hydroxylase Deficiency
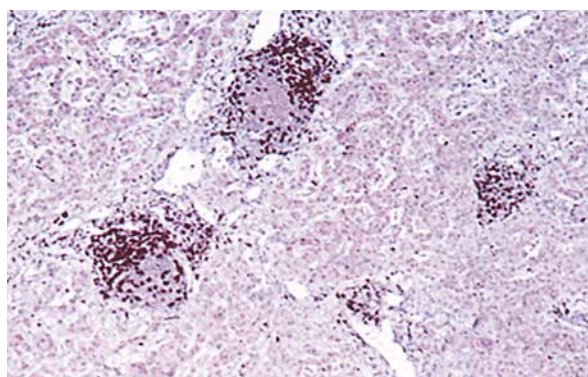
To the Editor: Congenital adrenal hyperplasia due to 21-hydroxylase deficiency results in deficient production of cortisol and aldosterone, chronic stimulation of the adrenal cortex by corticotropin, and overproduction of androgens. Cortisol-replacement therapy often fails to normalize corticotropin and androgen secretion, and high doses may be needed.[1] Adrenocortical tumors, including cancers, are rare in patients with 21-hydroxylase deficiency but have been reported in patients with large adrenal glands and presumably inadequate cortisol therapy.[2]

A 16-year-old girl with 21-hydroxylase deficiency was evaluated for hirsutism and primary amenorrhea. She had a muscular habitus, hyperpigmentation, and a low voice. Physical examination revealed a beard, cystic acne, and Tanner stage 2 breast development. While taking 25 mg of hydrocortisone and 0.5 mg of fludrocortisone daily, she had high serum corticotropin, 17-hydroxyprogesterone, and testosterone concentrations and high levels of plasma renin activity.
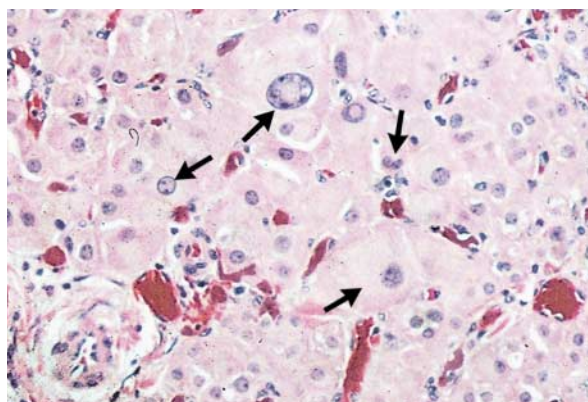
Because of persistent, severe symptoms, autonomy of adrenocortical steroidogenesis, and marked adrenal enlargement suggestive of tumor formation despite appropriate adjustments in therapy, informed consent was obtained for bilateral adrenalectomy, and the operation was performed without complications. Both adrenal glands weighed 52 g and had a nodular hyperplastic structure. Histologic and immunohistochemical analyses revealed massive lymphocytic infiltration with formation of lymphoid follicles (Fig. 1A and 1B) and diffuse sheets of adrenal cells with compact cytoplasm, an increased mitotic rate, atypical mitotic

Figure 1. Histologic Sections of the Adrenal Cortex of a Patient with Severe Congenital Adrenal Hyperplasia.

Nodular lymphocytic infiltrates resembling follicles of normal lymphoid tissue are apparent in Panels A and B (×50). B lymphocytes, immunostained brown with monoclonal antibodies to CD20 (L26, Dako), are seen mostly in the center of the follicles (Panel A), whereas T lymphocytes, immunostained brown with monoclonal antibodies to CD3, are seen in the periphery of the nodules, spreading into the adrenal tissue (Panel B). Bound antibodies were detected by the linked streptavidin–biotin–peroxidase method, and the enzyme reaction was visualized with 3-amino-ethylcarbazole. Panel C shows sheets of large cells with abundant compact cytoplasm, nuclear pleomorphism, and hyperchromasia (arrows), which were present throughout both adrenal glands (hematoxylin and eosin, ×400).

figures, and a high nuclear grade suggestive of adrenal carcinoma (Fig. 1C). There was no staining for major-histocompatibility-complex class II molecules, which is present in adrenal adenomas but not in carcinomas.[3] Subsequently, while receiving 20 mg of hydrocortisone and 0.5 mg of fludrocortisone daily, the patient had regular menses, an increase in breast size, resolution of acne, improvement of hirsutism and mood, and a decrease in muscle strength and salt wasting. Two years after surgery, there was no evidence of recurrence.

A major cause of our patient's adrenal findings was prolonged corticotropin stimulation. The lymphocytic infiltration of her adrenal glands may be a secondary finding; however, a local lymphocyte–adrenal-cell interaction might have contributed to her hyperandrogenism and adrenocortical growth and histologic signs of carcinoma. Cytokines produced by leukocytes increase adrenal steroid production independently of corticotropin.[4] Moreover, the growth of tumor cells may be potentiated by lymphocytes and cytokines, and aberrant expression of a cytokine receptor has been implicated in the formation of an adrenal adenoma.[5]

Bilateral adrenalectomy was a successful treatment for this patient and should be considered in patients with congenital adrenal hyperplasia with difficult-to-control hyperandrogenism and large nodular adrenal glands.

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1. Merke DP, Cutler GB Jr. New approaches to the treatment of congenital adrenal hyperplasia. JAMA 1997;277:1073-6.
2. Bauman A, Bauman CG. Virilizing adrenocortical carcinoma: development in a patient with salt-losing congenital adrenal hyperplasia. JAMA 1982;248:3140-1.
3. Marx C, Wolkersdorfer GW, Brown JW, Scherbaum WA, Bornstein SR. MHC class II expression — a new tool to assess dignity in adrenocortical tumours. J Clin Endocrinol Metab 1996;81:4488-91.
4. Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351-62.
5. Willenberg HS, Stratakis CA, Marx C, Ehrhart-Bornstein M, Chrousos GP, Bornstein SR. Aberrant interleukin-1 receptors in a cortisol-secreting adrenal adenoma causing Cushing's syndrome. N Engl J Med 1998;339:27-31.

Gentamicin Contaminated with Endotoxin

To the Editor: A succession of at least 57 moderate-to-severe endotoxin-like reactions has occurred in the western United States over an approximately six-month period. These reactions were associated with the administration of endotoxin-contaminated gentamicin for injection manufactured by Fujisawa USA.[1]

Endotoxin (a lipopolysaccharide) is a component of the cell wall of gram-negative bacteria and mediates many of the clinical features observed in gram-negative bacterial sepsis. These include fever, shaking chills, and cardiovascular symptoms, and in more severe cases include muscle proteolysis, uncontrolled intravascular coagulation, shock, and death. Endotoxin stimulates mononuclear cells to produce interleukin-1, tumor necrosis factor α, and possibly interleukin-6. These cytokines, when administered experimentally to humans, produce symptoms analogous to those elicited by endotoxin.[2]

The Food and Drug Administration (FDA) acknowledged the presence of endotoxin in Fujisawa's gentamicin early on. However, the concentration of endotoxin was within United States Pharmacopeia (USP) limits as long as the drug was administered as labeled (every 8 to 12 hours). Over the past decade, once-daily dosing of aminoglycoside antibiotics (such as gentamicin) has come into vogue. Considering the cost savings, potentially increased efficacy, and reduced toxicity associated with once-daily dosing,[3] it logically follows that this dosing schedule would become a preferred approach, though not approved by the FDA. Even though the endotoxin contamination of the gentamicin was below USP limits and thus below the FDA-enforceable limit of 1.7 endotoxin units per milligram, peak systemic endotoxin concentrations in these patients often surpassed the pyrogenic threshold of 5 endotoxin units per kilogram of body weight when gentamicin (5 to 7 mg per kilogram per day) was infused as a single dose,[1] and hence the deluge of reported adverse reactions.

Gentamicin has been a nonproprietary product for nearly 20 years. Therefore, pharmaceutical firms have no monetary impetus to petition for approval of once-daily dosing of gentamicin. If approval were granted, the USP would set a new upper limit for endotoxin in parenteral gentamicin preparations.

As an "off-label" use, once-daily dosing of aminoglycosides containing deleterious contaminants, such as endotoxin, presents formidable challenges for the FDA and for practitioners, as well as for patients. An interesting turn in an already twisted story relates to the FDA Modernization Act of 1997, according to which off-label uses of drugs may be promoted. This contrasts with the FDA's previously conservative position, forbidding pharmaceutical manufacturers from announcing nonapproved uses. This leaves us with the inevitable question: who is financially, ethically, and morally responsible for damage caused by endotoxin from gentamicin (or gentamicin misuse)? The FDA says that Fujisawa was acting within the law. Is the FDA acting within the law? Are we? Potential uses certainly outnumber the thousands of drugs that constitute the pharmaceutical armamentarium in the United States. Undoubtedly, these issues will arise again.

On November 30, 1998, Fujisawa voluntarily withdrew all unexpired 40-mg-per-milliliter preparations of parenteral gentamicin, as a gesture of good faith. This was not an FDA-forced recall, since no current laws or regulations had been violated. It is noteworthy that Fujisawa recently sold the injectable-drug division that manufactured gentamicin.

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1. Endotoxin-like reactions associated with intravenous gentamicin — California, 1998. MMWR Morb Mortal Wkly Rep 1998;47:877-80.
2. Isselbacher KJ, Martin JB, Braunwald E, Fauci AS, Wilson JD, Kasper DL, eds. Harrison's principles of internal medicine. 13th ed. New York: McGraw-Hill, 1994.
3. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 1997;24:796-809.

Case 35-1998: Use of Lithium to Prevent Corticosteroid-Induced Mania

To the Editor: I was surprised to read that a physician caring for the patient described in Case 35-1998 (Nov. 19 issue)[1] administered lithium to prevent corticosteroid-induced manic symptoms. No reference was given for this intervention, and lithium itself can cause central nervous system side effects. Several reviews of the central nervous system side effects of corticosteroids mention the possible value of the prophylactic administration of lithium.[2-4] These reviews all cite the same study,[5] an interesting report on the effects of lithium in a cohort of patients treated with corticotropin for multiple sclerosis. In this study, lithium-treated patients were compared with a historical control group of patients who had similar medical problems and treatment. The lithium-treated patients had no severe psychiatric symptoms. One definite and one possible case of lithium intoxication occurred. The investigators also noted substantial variation in lithium levels and used a twice-weekly monitoring program to achieve control. Fourteen percent of the historical control patients had psychological side effects severe enough to require termination of corticosteroid therapy or intervention with antipsychotic drugs.

That study, by Falk et al.,[5] suggests possible benefits and risks of the lithium intervention. However, the nature of the study, which used historical controls rather than random allocation of patients, limits the value of the observations. The authors were appropriately careful in their recommendations concerning their findings. They comment that lithium "prophylaxis" might be warranted for patients who have previously had adverse effects during treatment with corticosteroids, but they did not recommend routine prophylaxis for any patient group.

Thus, the literature does not appear to support routine lithium therapy "in anticipation of the development of manic symptoms."[1] Patients who become manic during corticosteroid therapy should be treated for mania if corticosteroid therapy must be continued. The use of lithium might be considered for patients who have previously had mood disorders while taking corticosteroids.

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1. Case Records of the Massachusetts General Hospital (Case 35-1998). N Engl J Med 1998;339:1534-41.
2. Brown ES, Suppes T. Mood symptoms during corticosteroid therapy: a review. Harv Rev Psychiatry 1998;5:239-46.
3. Long TD, Kathol RG. Critical review of data supporting affective disorder caused by nonpsychotropic medication. Ann Clin Psychiatry 1993;5:259-70.
4. Peet M, Peters S. Drug-induced mania. Drug Safety 1995;12:146-53.
5. Falk WE, Mahnke MW, Poskanzer DC. Lithium prophylaxis of corticotropin-induced psychosis. JAMA 1979;241:1011-2.

Hallux Rigidus and Atrophy of Calf Muscles

To the Editor: Unilateral calf swelling is abnormal and a cardinal manifestation of deep-vein thrombosis. The finding of asymmetry of the circumference of the two calves may lead to an extensive and occasionally invasive workup to rule out this potential cause of pulmonary embolism.

A 52-year-old woman who was being evaluated for nonspecific arthralgias noted that a recently purchased pair of knee-high boots was loose on one leg. Physical examination revealed a 2-cm difference in calf circumference at a point 15 cm below the insertion of patella, with no other abnormalities except for unilateral hallux rigidus on the smaller side. Hallux rigidus is a term used to describe restricted dorsiflexion of the metatarsophalangeal joint of the great toe related to dorsal osteophytes that restrict motion. These osteophytes are easily palpable on physical examination and may develop as a result of osteoarthritis or as a reaction to prior inflammatory arthritis. When symptomatic, hallux rigidus produces pain in the metatarsophalangeal joint that is related to activity. It was hypothesized that lack of dorsiflexion in the great toe led to atrophy of the gastrocnemius in the affected leg and the appearance of calf swelling in the unaffected leg.

To test this hypothesis, more than 1000 consecutive patients in a general rheumatology practice were examined during the next year for the presence of unilateral hallux rigidus, as determined by a finding of passive dorsiflexion of the first metatarsophalangeal joint of less than 30 degrees on one side and of more than 60 degrees on the unaffected side. Seventeen patients met this criterion. Each had between 1 and 2.5 cm of atrophy in the affected calf at a point 15 cm below the insertion of the patellar tendon. In none was great-toe pain the primary symptom at presentation. Twenty-five control patients were examined by the same technique, and none had a difference in circumference between the two sides of more than 0.5 cm.

Unilateral hallux rigidus is a common condition that can produce atrophy of the calf musculature in the affected leg, creating the appearance of swelling in the other leg. It should be considered along with a ruptured Baker's cyst as one of the rheumatologic conditions that may be manifested as the syndrome of "pseudophlebitis."[1]

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1. Katz RS, Zizic TM, Arnold WP, Stevens MB. The pseudothrombophlebitis syndrome. Medicine (Baltimore) 1977;56:151-64.

Large Hepatic Hematoma and Intraabdominal Hemorrhage Associated with Abuse of Anabolic Steroids

To the Editor: Hepatocellular neoplasms, peliosis hepatis, and hepatic necrosis have been reported to be complications of long-term therapy with androgenic anabolic steroids.[1] We report a case of a large subcapsular hepatic hematoma and subsequent intraabdominal hemorrhage associated with the abuse of anabolic steroids by a bodybuilder.

A 24-year-old man was admitted to the hospital with right-upper-quadrant pain, mild tachycardia, hypertension, and oliguria. The patient reported a 23-month history of polydrug abuse to enhance the results of his bodybuilding exercises. He had been taking mesterolone (50 mg) daily and nandrolone (400 mg), clomiphene (50 mg), and chorionic gonadotropin (1250 IU) weekly. The patient reported no history of abdominal trauma. The serum aspartate
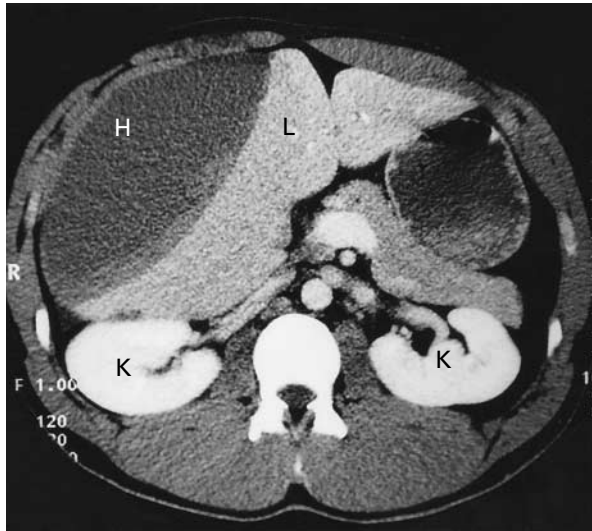
Figure 1. Abdominal Spiral Computed Tomography with Contrast Enhancement in a Patient with Hepatic Hematoma.

A large hypodense mass can be seen in the right hepatic lobe, with a size of 20 by 8 cm and a craniocaudal distance of 19 cm. H denotes subcapsular hematoma, L liver, and K kidney. (Image courtesy of W. Lotz, M.D., Bad Oldesloe, Germany.)

aminotransferase level was 295 U per liter, and the serum alanine aminotransferase level was 927 U per liter, with normal levels of total bilirubin, alkaline phosphatase, and γ-glutamyltransferase. Abdominal computed tomography (Fig. 1) showed a large subcapsular hematoma of the right liver lobe measuring 20 by 8 by 19 cm. The patient's condition was stabilized, and he was observed in the intensive

care unit. An abdominal sonogram showed more than 1.5 liters of free fluid in the abdominal cavity, and rapid surgical exploration was necessary. The macroscopic appearance of the affected hepatic region and the histologic results of the biopsies showed extensive hepatic necrosis with no atypical or malignant cells.

Coronary artery disease,[2] thromboembolic complications,[3] and intraabdominal bleeding caused by benign liver tumors[4] are known complications of long-term abuse of anabolic and contraceptive steroids. This case adds hepatic subcapsular hematoma to the list.

A recent survey of commercial health clubs in northern Germany reported that the average dose of nandrolone is 308 mg per week per consumer.[5] The maximal dose for nandrolone should not exceed 50 mg per month, so the patient had taken more than 30 times the upper therapeutic dosage over a period of 23 months.

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1. Ishak KG. Hepatic lesions caused by anabolic and contraceptive steroids. Semin Liver Dis 1981;1:116-28.
2. Mewis C, Spyridopoulos I, Kuhlkamp V, Seipel L. Manifestation of severe coronary heart disease after anabolic drug abuse. Clin Cardiol 1996;19:153-5.
3. Palfi S, Ungurean A, Vecsei L. Basilar artery occlusion associated with anabolic steroid abuse in a 17-year-old bodybuilder. Eur Neurol 1997;37:190-1.
4. Bein NN, Goldsmith HS. Recurrent massive haemorrhage from benign hepatic tumors secondary to oral contraceptives. Br J Surg 1977;64:433-5.
5. Boos C, Wulff P, Kujath P, Bruch HP. Medikamentenmißbrauch beim Freizeitsportler im Fitneßbereich. Dt Ärztebl 1998;95:A-953–A-957.

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