

## Correspondence



## Arthroscopic Surgery for Osteoarthritis of the Knee

*To the Editor:* Although the study by Moseley et al. (July 11 issue)<sup>1</sup> was based on sound scientific principles and included a dramatic control (a sham operation), it was flawed because of the selection of patients. The study group comprised veterans, 75 years of age or younger, almost all of whom were men. This cohort of patients does not truly represent the general population. Osteoarthritis does not suddenly appear late in life, when increasing symptoms are accompanied by radiologic changes. Osteoarthritis is a degenerative process that starts with the earliest changes in the articular cartilage seen at arthroscopy and progresses to the secondary changes that can finally be identified by plain-film radiography.

Although I am in full agreement with the authors that arthroscopy is of little value in the more advanced stages of osteoarthritic degeneration, it is my experience that arthroscopic lavage and débridement can dramatically improve symptoms in the early stages of osteoarthritis and can do so for several years.

To cast doubt on all arthroscopic surgery for osteoarthritis, with the implication that it is worthless, does a disservice to the increasing number of people in our population who have early stages of arthritis and might deprive them of this treatment.

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1. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81-8.

*To the Editor:* No responsible orthopedic surgeon will claim that arthroscopic surgery is a help to all patients with arthritis of the knee. That would be untrue and inappropriate. It is just as inappropriate to state that arthroscopic surgery is useless in any case of arthritis of the knee. There is a subgroup of patients with arthritis of the knee that can be substantially helped with appropriate arthroscopic surgery. This point is alluded to in the editorial<sup>1</sup> that accompanies the report by Moseley et al.

The selection of patients is all important in arthroscopy of the knee in those with pain and early degenerative arthritis. Plain-film radiography during posterior–anterior flexion in a weight-bearing position may be the most important study in the evaluation of patients with knee pain. These evaluations were apparently not done in the group selected for the reported study. Minor alignment problems were apparently also disregarded. One could therefore predict, in advance of the study, the results that were obtained in a very elegant fashion.

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1. Felson DT, Buckwalter J. Débridement and lavage for osteoarthritis of the knee. *N Engl J Med* 2002;347:132-3.

*To the Editor:* Moseley et al. used the pain subscale of the Medical Outcomes Study 36-item Short-Form General Health Survey to determine the power of their study but then used the score on their own Knee-Specific Pain Scale as the primary end point. There was no link between the Knee-Specific Pain Scale as an outcome measure and the design of the study with respect to sample size. This instrument is a nonvalidated measurement and was “created for this study.” Though designed as a superiority trial, the study was converted into an equivalence trial. The authors defined post hoc equivalence bounds, or “minimal important differences,” which they “calculated on the basis of the trial data.”

To avoid data-dependent bias, equivalence bounds should be determined in advance.<sup>1,2</sup> Furthermore, it is well estab-

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**TABLE 1.** POWER TO DEMONSTRATE EQUIVALENCE.\*

PROCEDURE	INSTRUMENT				KSPS
	SF-36-P	SF-36-PF	AIMS2-P	AIMS2-WB	
	percent				
Lavage	53	17	14	35	70
Débridement	47	16	15	29	70

\*SF-36-P denotes the 2-item pain subscale and SF-36-PF the 10-item physical-function subscale of the Medical Outcomes Study 36-item Short-Form General Health Survey; AIMS2-P denotes the 4-item pain subscale and AIMS2-WB the 4-item walking-bending subscale of the Arthritis Impact Measurement Scales; and KSPS denotes the Knee-Specific Pain Scale.

lished that equivalence trials generally require greater power than superiority trials. Piaggio and Pinol<sup>3</sup> state, “The use of conventional superiority approach to design equivalence trials has led underpowered trials to show equivalence within clinical relevant margins.” Application of the standard power formula for equivalence studies<sup>4</sup> to the data presented by Moseley et al. reveals a power range of 14 to 70 percent for different variables (Table 1), with all the values in the range below accepted levels for claiming equivalence. Most of the values are so low that any conclusions about equivalence are meaningless. It is disturbing that the outcome with the greatest post hoc power was the one chosen as the primary end point, especially because it was created for the study and may have lacked validity as an outcome measure.

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1. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;313:36-9. [Erratum, *BMJ* 1996;313:550.]
2. Ebbutt AF, Frith L. Practical issues in equivalence trials. *Stat Med* 1998;17:1691-701.
3. Piaggio G, Pinol APY. Use of the equivalence approach in reproductive health clinical trials. *Stat Med* 2001;20:3571-7.
4. Fleiss JL. General design issues in efficacy, equivalency and superiority trials. *J Periodontal Res* 1992;27:306-13.

*To the Editor:* Moseley et al. note that about 13 percent of the patients in both the placebo and the intervention groups believed that their procedures were placebos. Do the authors have any data about these two subgroups? Did these patients have the same rate of relief of symptoms as the overall group, or did the mind-set of believing the procedure was a placebo influence the outcome?

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*To the Editor:* In a Sounding Board article accompanying the report by Moseley et al., Horng and Miller ask, “Is placebo surgery unethical?”<sup>1</sup> The Council on Ethical and Judicial Affairs of the American Medical Association, which I chair, has published an ethical opinion<sup>2</sup> that addresses the same question. The appropriateness of surgical placebo controls should be based on the following points. Surgical placebo controls should be used only when no other trial design will yield the requisite data; informed consent should receive particular attention, with disclosure of the risks of the operation and a description of the differences between the study groups in the trial; the use of surgical placebo controls is not justified when testing the effectiveness of an innovative surgical technique that represents a minor modification of existing procedures; surgical placebo controls may be justified when a new surgical procedure is developed to treat a condition for which no surgical procedure exists but must be weighed against the benefits, risks, and side effects of the current standard of care, including nonsurgical treatment; standard treatment must be offered as part of the study design, if it is efficacious and acceptable to the patient and if forgoing it would result in injury; when standard treatment is not fully efficacious or is unacceptable to the patient, surgical placebo controls may be used and standard treatment forgone if the informed-consent process includes adequate safeguards.<sup>3</sup>

The fact that 44 percent of the patients in the study by Moseley et al. declined to participate in this controlled trial of arthroscopic surgery speaks highly of the authors’ emphasis on informed consent.

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1. Horng S, Miller FG. Is placebo surgery unethical? *N Engl J Med* 2002;347:137-9.
2. Surgical “placebo” controls. In: Council on Ethical and Judicial Affairs. Code of medical ethics: current opinions with annotations: 2002–2003 edition. Chicago: American Medical Association, 2002:28-9.
3. Tenery R, Rakatansky H, Riddick FA Jr, et al. Surgical “placebo” controls. *Ann Surg* 2002;235:303-7.

The authors reply:

*To the Editor:* Jackson and Ewing and Ewing suggest that, although our results are valid in the patients we studied, there may be subgroups of patients — those with early stages of arthritis, those with normal alignment, and (as noted in the accompanying editorial) those with mechanical symptoms — in whom arthroscopy would be more efficacious. With regard to variation in outcomes related to the severity of arthritis or alignment, as measured by plain-film radiography during posterior-anterior flexion in a weight-bearing position: we have performed an extensive subgroup analysis that does not find differences to suggest any bias. Is this procedure effective in patients with mechanical symptoms? Of the 180 patients enrolled in this study, 172 had one or more mechanical symptoms.

Most of the patients in our study were men; however, as Felson and Buckwalter<sup>1</sup> state: “There is no reason to believe that the response to surgery would vary according to sex.”

We believe that the group of patients we studied is highly representative of the spectrum of patients in whom this procedure is currently being performed. As suggested by Jackson and Ewing and Ewing, these patients do have improvement after the procedure, but we showed that the benefit of arthroscopy is not greater than the benefit of the placebo effect. Given our results, we would argue the following: if someone questions whether arthroscopic surgery would be efficacious in a specific subpopulation of patients, then the ethical way to proceed would be to test the hypothesis by conducting a placebo-controlled trial in that specific subgroup.

When our study was designed, no psychometrically valid scale to assess knee pain was available. Thus, the Knee-Specific Pain Scale was developed for this study by a research team with two psychometricians. Subsequently, we have conducted rigorous psychometric testing that demonstrates that this scale has strong psychometric properties.<sup>2</sup> This study was designed as a superiority trial. However, when we failed to show that arthroscopy was superior to placebo, we did not assume equivalence; we statistically tested for equivalence.<sup>3,4</sup> As with all power calculations, the power approach to assessing the results of a negative trial addresses only the potential for the trial to detect certain differences (e.g., equivalence). However, the approach we used tested directly for equivalence. The analyses demonstrated equivalence; hence, concern about a priori power then becomes irrelevant.

Many of the outcomes in patients who guessed that they had undergone the placebo procedure were worse than those who guessed they had undergone one of the arthroscopic procedures.

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4. Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials* 1982;3:345-53.

*To the Editor:* The American Medical Association's ethical opinion on placebo surgery should encourage investigators to plan, and institutional review boards to approve, clinical trials of surgical procedures involving the use of placebo surgery when methodologically warranted and ethically justified.

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## Insect Repellents and Mosquito Bites

*To the Editor:* Fradin and Day's cage study (July 4 issue)<sup>1</sup> may be misleading. According to the Environmental Protection Agency (EPA), the only meaningful way to measure the efficacy of an insect repellent is to test it under realistic conditions. The EPA's FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) Scientific Advisory Panel, on which Dr. Day served, concluded that cage studies "are not a valid substitute for repellent field studies" and recommended that "only field studies be used to establish efficacy."<sup>2</sup> The DEET (*N,N*-diethyl-*m*-toluamide, now called *N,N*-diethyl-3-methylbenzamide) Issues Task Force also contends that "laboratory-derived data poorly predicts field data."<sup>3</sup> In addition, the study design used by Fradin and Day did not specify the amount of product applied by each subject. Such an omission makes it impossible to replicate the test and properly interpret the data. In contrast, the product containing IR3535 (ethyl butylacetylaminopropionate) that Fradin and Day tested has been subjected to well-controlled field studies. The results submitted to the EPA demonstrate a protection time for the product of up to three hours or more against mosquitoes. There are no safety concerns associated with the use of IR3535, which is not true of DEET. IR3535 can be formulated with sunscreen, and such combination products offer a twofold public health benefit.

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*Editor's note:* Dr. Teal is group vice-president and chief scientific officer, global research and development, Avon Products. Avon manufactures insect-repellent products for sale in the United States and overseas.

1. Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med* 2002;347:13-8.
2. Report of the FIFRA Scientific Advisory Panel Meeting, April 5-7, 2000, Arlington, Va. Washington, D.C.: Environmental Protection Agency, August 2000. (Accessed October 30, 2002, at <http://www.epa.gov/oscpmont/sap/2000/april/freportapril572000.pdf>)
3. Letter from Christopher Cathcart, president and chief operating officer for the DEET Issues Task Force of the Chemical Specialties Manufacturers Association, to the Office of Pesticide Programs. Washington, D.C.: Office of Pesticide Programs, Environmental Protection Agency, February 14, 2000.

*To the Editor:* The "arm-in-the-cage tests" employed by Drs. Fradin and Day have been used for over 50 years, but according to the Scientific Advisory Panel of the EPA, such tests should be used only for screening purposes, not for comparative purposes, nor to establish efficacy. According to the EPA, as per the Scientific Advisory Panel, field tests are the only method of determining the efficacy of a repellent.

In addition, the amount of material applied and the concentration used can account for significant differences in the results. One of the products tested was Skin-So-Soft Bath Oil, which is not a repellent.

Both the published information on DEET-based repellents and the information in the mass-media promotion state that

the repellents can be relied on to provide prolonged protection in environments where mosquito-borne diseases are a significant threat. This is a false assumption and has never been proved. These statements are also harmful, since laypeople are given a false sense of security, believing that if they use a DEET-based repellent, they will be totally protected from arthropod-borne pathogens. The Scientific Advisory Board of the EPA also agreed that no manufacturer of repellents could make such a statement of protection from mosquito-borne diseases.

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*Editor's note:* Drs. Gerberg and Novak served on the EPA's Scientific Advisory Panel on repellents.

*To the Editor:* As a physician and a resident of "bush" Alaska, I am a regular user of 95 percent DEET insect repellent and so are many of my associates. Drs. Fradin and Day failed to include in their study a repellent with a DEET concentration greater than 23.8 percent. What was the reason for this?

It would be useful to know whether the highest concentrations offer a significant benefit over those studied. Although the health risks of 95 percent DEET may be minimal, the risk of damage to plastic watches, pens, and camera bodies might be lessened with lower concentrations.

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*To the Editor:* Fradin and Day state, "Until a better repellent becomes available, DEET-based repellents remain the gold standard of protection under circumstances in which it is crucial to be protected against arthropod bites that might transmit disease." In their accompanying Perspective, Pollack and colleagues state, "concentrated DEET formulations ( $\geq 35$  percent) may be appropriate for those who are exposed for many hours to numerous black flies or mosquitoes or who work in tick-infested areas."<sup>1</sup> We agree that DEET is preferred for preventing bites from black flies or mosquitoes, but permethrin has been proved to be more effective for ticks.<sup>2-4</sup> The effect of permethrin is predominantly acaricidal rather than repellent.<sup>3,4</sup> Although it can be safely applied to the skin, permethrin remains effective longer when applied to clothing, netting, or tents and can withstand several washings.<sup>2-4</sup> In the U.S. military, the concurrent application of DEET repellent on the skin and permethrin on the battle dress uniform is officially known as the DOD (Department of Defense) Insect Repellent System. This combination provides the best-known protection against ar-

thropod bites and the transmission of arthropod-borne diseases to troops in the field.<sup>4</sup>

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1. Pollack RJ, Kiszewski AE, Spielman A. Repelling mosquitoes. *N Engl J Med* 2002;347:2-3.
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3. Brown M, Hebert AAA. Insect repellents: an overview. *J Am Acad Dermatol* 1997;36:243-9.
4. Young GD, Evans S. Safety and efficacy of DEET and permethrin in the prevention of arthropod attack. *Mil Med* 1998;163:324-30.

*To the Editor:* Fradin and Day compared the efficacy of DEET and non-DEET insect repellents. It is unfortunate that they ignored a much better repellent — that is, 100 mg of vitamin B<sub>1</sub> (1000 times the vitamin dose). It is taken orally and is effective for many hours. (Pharmacokinetic studies are needed.) The repellent effect is attributed to a foul odor, undetected by humans, unless one smells the bottle. Biting insects, which are attracted by carbon dioxide, are repelled. Mosquitoes, deer flies, horse flies, and chiggers are repelled. It is not known whether arachnids are repelled, although deer ticks seem to be.

Not only is vitamin B<sub>1</sub> much less expensive than other repellents, but it also is nonwetting, is not oily, and is not rubbed off on clothes.

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*To the Editor:* A product not mentioned in Fradin and Day's article is Bayrepel, Bayer's trade name for a piperidine derivative that the company has developed. Bayer claims that the action of this product equals or exceeds that of DEET. (The company's Web site shows convincing evidence based on comparative testing against various arthropods.) Bayrepel is the active ingredient in their Autan line of insect-repellent products. Although this product may not be available in the United States (I suspect Fradin and Day would have tested it if it were), Autan products are widely used in Germany and Austria, probably throughout the European Union, and perhaps elsewhere in the world. It is good to know that a product commonly available to those of us outside the United States is effective.

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The authors reply:

*To the Editor:* Teal is correct that the recommendation of the EPA's Scientific Advisory Panel (in April 2000) was that

“only field studies be used to establish efficacy and subsequent registration”<sup>1</sup> of new repellents. Teal neglects to mention, however, that the panel also stated that cage studies “can be used to compare products.”<sup>1</sup> In our article, we explained the rationale for using the arm-in-cage method. It would have been impossible to conduct a valid comparative field study of this size, given the multiple environmental variables that affect biting rates. With West Nile virus now found throughout the United States, the ethics of requiring field trials may need to be examined by the EPA, which has not yet adopted the recommendations of the panel.

Our decision not to standardize the amount of repellent each subject applied was deliberate. We wanted our study to reflect real-life usage, and application quantities are not stated on repellent labels. In our experience, repellents are typically overapplied, not underapplied, so we are confident that our subjects applied sufficient quantities of repellent to make it possible to judge each one’s relative efficacy.

Gerberg and Novak properly emphasize that persons should not rely solely on insect repellents for the prevention of insect bites and insect-borne diseases. As we stated twice in our article, “Protection from arthropod bites is best achieved by avoiding infested habitats, wearing protective clothing, and using insect repellent.” We agree with Adams et al. that the combined use of the contact insecticide permethrin on clothing and DEET on the skin results in a formidable barrier, providing a level of protection against mosquito bites as high as 99.9 percent, even under conditions in which unprotected subjects received an average of 1188 bites per hour.<sup>2</sup>

Gerrish asks why we did not test products containing more than 23.8 percent DEET. Other than a few 95 percent DEET products, all DEET products on the U.S. market contain 40 percent DEET or less. DEET’s duration of action tends to plateau at concentrations higher than 50 percent, so relatively little additional benefit is afforded by 95 percent DEET. Given that we found a mean protection time of five hours for 23.8 percent DEET,<sup>3</sup> adequate protection can be achieved by using products with lower concentrations and reapplying the repellent as needed.

Like Harvey, we would like the convenience of having an effective oral arthropod repellent. Unfortunately, vitamin B<sub>1</sub> has been proved to be ineffective.<sup>4</sup>

Brownstone mentions a piperidine-based repellent, Bayer’s Bayrepel. This repellent has been available in Europe since 1998 and was registered with the EPA in 2000 but is not yet available in the United States. If it proves to provide protection against mosquito bites for two to eight hours (as stated in Bayer’s literature<sup>5</sup>), it may well provide repellent action similar to that of DEET.

We should have noted in our article that Dr. Day was an expert witness for S.C. Johnson, maker of OFF insect repellents, in April 2002. We apologize for the oversight.

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5. Autan information. Leverkusen, Germany: Bayer AG, 2002. (Accessed October 30, 2002, at <http://www.autan.com/scientific-e.html>.)

## Hepatitis B e Antigen and the Risk of Hepatocellular Carcinoma

*To the Editor:* Yang et al. (July 18 issue)<sup>1</sup> report that the detection of hepatitis B e antigen (HBeAg) at a single point in time during the course of chronic hepatitis B predicts the development of hepatocellular carcinoma. As noted in the article and the accompanying editorial,<sup>2</sup> there are no hints of the direct involvement of HBeAg in the mutagenicity in the liver. On the other hand, HBeAg represents a surrogate marker of viral replication and necroinflammatory activity. The authors discuss both direct mechanisms of carcinogenicity (hepatitis B x antigen [HBxAg]–related effects) and indirect mechanisms of carcinogenicity (chronic hepatic inflammation as indicated by the monitoring of alanine aminotransferase levels). However, data on these primary markers are not reported by the authors, and this weakens the implications for clinical practice. If there is a significant difference in alanine aminotransferase levels between patients with hepatocellular carcinoma and patients without hepatocellular carcinoma, the alanine aminotransferase level represents a better and even less expensive marker. If this is not the case, as shown previously,<sup>3</sup> direct carcinogenic mechanisms should be monitored with a marker related directly to carcinogenicity (e.g., HBxAg) rather than with a surrogate marker.

Do the authors mean to imply that the sole detection of HBeAg serves as an indication for treatment to prevent hepatocellular carcinoma? We think that at present no clear change in the existing guidelines<sup>4</sup> for the evaluation and treatment of patients with hepatitis B virus (HBV) is warranted on the basis of the data presented by Yang et al.

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4. Lok ASF, McMahon BJ. Chronic hepatitis B. *Hepatology* 2001;34:1225-41.

The authors reply:

*To the Editor:* Geier et al. suggest that both HBxAg and the serum alanine aminotransferase level may be more appropriate than HBeAg as the primary markers for the prediction of the risk of hepatocellular carcinoma. Per their suggestion, we further analyzed the risk of hepatocellular carcinoma according to the serum alanine aminotransferase level and the presence or absence of seropositivity for HBsAg and HBeAg at the time of recruitment for our long-term follow-up study. The findings are shown in Table 1. In addition to seropositivity for HBsAg and HBeAg, an elevated serum alanine aminotransferase level (greater than or equal to 45 IU per liter) was also significantly associated with an increased risk of hepatocellular carcinoma. These three markers are independent risk factors for hepatocellular carcinoma. Men who were seropositive for HBsAg and HBeAg and who had an elevated serum alanine aminotransferase level were at highest risk for hepatocellular carcinoma (multivariate-adjusted relative risk, 109; 95 percent confidence interval, 51 to 233), as compared with those who were seronegative for HBsAg and HBeAg and who had a normal serum alanine aminotransferase level. A more interesting finding was that the adjusted relative risk for those who were seropositive for HBsAg and HBeAg and who had a normal serum alanine aminotransferase level was 61 (95 percent confidence interval, 34 to 112). Our findings provide strong evidence that HBeAg is an important marker, in addition to the serum alanine aminotransferase level, for the evaluation and treatment of patients with chronic HBV infection.

The HBxAg test is not performed routinely in most laboratories. We did not test for this marker in our study. However, an elevated rate of seropositivity for HBxAg has been found in patients with replicative markers of HBV (seropositivity for HBeAg, HBV DNA, or both), indicating that the expression of HBxAg is closely correlated with viral replica-

tion.<sup>1-3</sup> HBeAg is thus considered an appropriate surrogate marker for HBxAg.

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### Troponin T Levels and Acute Coronary Syndromes

*To the Editor:* In their article regarding the use of troponin T levels as prognostic factors in patients with renal dysfunction, Aviles et al. (June 27 issue)<sup>1</sup> conclude that these levels predict short-term prognosis “regardless of [the patient’s] level of creatinine clearance.” This statement should be amended.

The current Kidney Disease Outcomes Quality Initiative defines chronic kidney disease by a glomerular filtration rate of less than 60 ml per minute — a definition that encompasses an estimated 7.6 million patients in the United States.<sup>2</sup> An increasing proportion of these patients have a glomerular filtration rate of less than 30 ml per minute, for which care by a nephrologist and preparation for dialysis are recommended. Cardiovascular disease becomes increasingly prev-

**TABLE 1.** ADJUSTED RELATIVE RISK OF HEPATOCELLULAR CARCINOMA ACCORDING TO THE RESULTS OF HBV ANTIGEN TESTS AND SERUM ALANINE AMINOTRANSFERASE (ALT) LEVEL.\*

HBsAg/HBeAg/ALT	PERSON-YR OF FOLLOW-UP	NO. OF MEN	NO. OF CASES OF HEPATOCELLULAR CARCINOMA	ADJUSTED RELATIVE RISK (95% CI)†
Negative/negative/normal	71,105	9129	23	1.0
Negative/negative/elevated	2,711	354	6	5.4 (2.2–13.8)‡
Positive/negative/normal	14,477	1867	42	10.3 (6.2–17.2)‡
Positive/negative/elevated	884	117	8	29.3 (12.9–66.4)‡
Positive/positive/normal	2,204	297	22	61.3 (33.5–112.4)‡
Positive/positive/elevated	514	70	10	109.0 (51.1–232.5)‡

\*Data on alanine aminotransferase were not available for 59 men. A serum alanine aminotransferase level greater than or equal to 45 IU per liter was considered to be elevated. HBsAg denotes hepatitis B surface antigen, HBeAg hepatitis B e antigen, and CI confidence interval.

†The analysis was adjusted for age, the presence or absence of antibodies against hepatitis C virus, cigarette-smoking status, and use or nonuse of alcohol. P for trend <0.001.

‡P<0.001.

alent as the glomerular filtration rate decreases; patients with end-stage renal disease have a rate of death from cardiovascular causes of 50 percent.<sup>3</sup> In the study by Aviles et al., patients in the lowest quartile for creatinine clearance with a normal troponin T level (Table 2 of the article) still had a risk of death that was twice as high as that of patients in the highest quartile of creatinine clearance with an abnormal troponin T level. Thus, in a population with a high probability of cardiac events before testing, such as the population studied in the Global Use of Strategies to Open Occluded Coronary Arteries IV trial, a low glomerular filtration rate alone, independent of the troponin T level, should serve as an indication for aggressive treatment. On the other hand, in patients with a low glomerular filtration rate, a negative troponin T test cannot be used to predict a favorable prognosis. Troponin T measurements in this population therefore predict events well but are not useful for ruling out the possibility of death from cardiac causes in the short term.

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The authors reply:

*To the Editor:* We agree with Dr. Hentschel that renal dysfunction is an independent predictor of poor short-term outcome among patients with suspected acute coronary syndromes, and indeed our data confirm that fact. Our concern regarding the prognostic value of troponin was not whether an elevated troponin level would predict a good prognosis in patients with renal dysfunction, but rather whether such an elevation would predict an even worse prognosis than would otherwise be the case.

Dr. Hentschel states that among patients with a suspected acute coronary syndrome, a low glomerular filtration rate alone should be an indication for aggressive treatment, since it predicts a poor outcome. Data from randomized trials clearly show that among patients with an elevated troponin level, aggressive treatment is likely to lead to a reduction in the rate of major clinical events.<sup>1,2</sup> Similar evidence from randomized trials regarding the use of renal function alone to dictate the treatment strategy does not yet exist.

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## Poison Ivy

*To the Editor:* In his contribution regarding poison ivy in the Images in Clinical Medicine section (July 4 issue),<sup>1</sup> Dr. Parkinson correctly points out that contact dermatitis from the plant can occur at any time of the year. However, in the interest of total accuracy, the allergenic oleoresin is “uroshiol,” not “uroshiol” as printed.

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1. Parkinson G. The many faces of poison ivy. *N Engl J Med* 2002;347: 35.

*To the Editor:* We would like to call attention to the commonly perpetuated inaccuracy, which comes down to us from Linnaeus himself, in referring to poison ivy as “*Rhus radicans*.” Nearly 50 years have passed since poison ivy and its immediate relatives were shown to represent a distinct developmental lineage from the genus *rhus*, albeit still within the family Anacardiaceae. It is a daunting task to keep abreast of changes in botanical nomenclature; however, the time has arrived for physicians to recognize this botanical advancement and to use the preferred generic name, *Toxicodendron*.

Compelling evidence emerged in the 1950s and 1960s supporting the separation of *rhus*, with mostly benign plants, from poison ivy and related allergenic plants. In 1971, Gillis convincingly called for placing these allergenic species in the genus *Toxicodendron*.<sup>1</sup> The name *Toxicodendron*, meaning “poisonous plant,” originated with Tournefort, who preceded Linnaeus. Thus, it by no means represents new terminology. In addition to allergenicity, the evidence supporting division rests on many observable botanical features.<sup>2</sup> Therefore, separation is not merely semantic, but vital to proper field recognition and avoidance strategies. Moreover, the traditional means of recognition based solely on leaf morphology is unreliable, since *Toxicodendron* leaflets vary markedly according to both season and geographic area.

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Dr. Parkinson replies:

*To the Editor:* I appreciate the updates on nomenclature. To paraphrase Juliet, "A rhus by any other name would itch as much."

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### Chronic Urticaria and Angioedema

*To the Editor:* In his letter to the editor, Kaplan (July 18 issue)<sup>1</sup> suggests that cetirizine is one of the active ingredients of hydroxyzine. It is not, although their chemical structures are similar.

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1. Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002; 347:222.

Dr. Kaplan replies:

*To the Editor:* My statement regarding the relation of cetirizine to hydroxyzine warrants clarification. Cetirizine is the active metabolite (not ingredient) of hydroxyzine, and as such, cetirizine is responsible for much of the histamine H<sub>1</sub>-receptor blockade associated with the use of hydroxyzine, even though hydroxyzine has H<sub>1</sub>-receptor-binding activity in vitro.

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### Can Ticks Be Vectors for Hepatitis C Virus?

*To the Editor:* We describe a case of acute *Babesia microti* infection temporally associated with hepatitis C virus (HCV) seroconversion in a blood donor in Connecticut. Blood donated on July 9, 1999, tested negative for all markers of infectious diseases for which donated blood is routinely screened. However, as part of a study, this donation and a follow-up specimen from August 6, 1999, tested positive for antibodies against *B. microti*, and the follow-up specimens subsequently tested positive for *B. microti* by nested polymerase chain reaction (PCR).

The donor, a resident of southeastern Connecticut, worked as a medical technologist. In September 1999 she

noted having fatigue, appetite loss, abdominal cramps, and dark urine. She reported that she had not engaged in activities associated with a high risk of blood-borne infections and that she had not had occupational exposure to blood. A specimen obtained on September 20, 1999, by her employer was reported to be negative for hepatitis B surface antigen, antibodies to the core antigen of hepatitis B virus, and antibodies against both hepatitis A virus and HCV. The serum alanine aminotransferase concentration was 850 U per liter, and it normalized several weeks later. Her symptoms resolved over the course of the next several weeks. The donor had an intact spleen.

Routine testing of a subsequent blood donation in December 1999 revealed infection with HCV as shown by positive test results for anti-HCV antibodies and HCV RNA. The donated blood unit was destroyed, and further donation was deferred. A serum specimen from August 1999 that had been obtained for the *B. microti* study was positive for HCV RNA as well as positive for *B. microti* on PCR. In February 2000 the donor's blood tested negative for HCV RNA but remained positive for anti-HCV antibodies. Additional serologic tests for *B. microti* performed by an outside laboratory (Imugen, Norwood, Mass.) on the samples from July and August 1999 confirmed IgG reactivity on immunofluorescence assay and revealed both IgG and IgM reactivity on Western blotting in both samples. IgG reactivity was stronger in the August sample than in the July sample, but IgM reactivity was stronger in the July sample than in the August sample. Laboratory results are summarized in Table 1.

The *B. microti* serologic pattern observed in the donor is most consistent with acquisition of infection in early June, a month before the donation in July. The time window from the acquisition of HCV infection to the detection of HCV viremia on nucleic acid amplification testing has not been precisely determined (Dodd RY: personal communication). However, the appearance of HCV viremia between the July 9 and August 6 samples is compatible with the acquisition of HCV infection in early June as well.

Several scenarios could account for this temporal association. Most directly, exposure to *B. microti* through a tick bite could have coincided with a parenteral or sexual exposure to HCV. Although the prevalence of *B. microti* infection detectable by PCR among Connecticut blood donors is approximately 1 in 1800,<sup>1</sup> the rate of seroconversion for HCV antibody among repeated blood donors in the United States is only 1.889 new infections per 100,000 person-years.<sup>2</sup> Thus, simultaneous discovery of these two independent infective events in an established blood donor would be highly unusual.

There are two other possibilities: coincidental acquisition of *B. microti* and HCV from occupational exposure (although occupational acquisition of *B. microti* has not been reported) or acquisition of both *B. microti* and HCV from a dually infected tick. Ingestion of host blood by ticks permits efficient transmission of pathogens to the host. The competence of *Ixodes scapularis* as a vector for HCV has not been established clinically or experimentally. However, several reports demonstrate transmission of other flaviviridae by ticks.<sup>3,4</sup>

This case suggests the possibility of HCV transmission by a tick vector. Additional epidemiologic investigation of the

TABLE 1. LABORATORY RESULTS.\*

TEST	RESULTS				
	JULY 1999 BLOOD DONATION	AUGUST 1999	SEPTEMBER 1999	DECEMBER 1999 BLOOD DONATION	FEBRUARY 2000
IgG antibody to <i>B. microti</i> on IFA					
Initial	1:512	1:512			
Repeated	≥1:1024	≥1:1024			
Antibody to <i>B. microti</i> on Western blotting					
IgG	Positive	Positive			
IgM	Positive	Positive			
<i>B. microti</i> DNA	Not performed	Reactive on retrospective testing (frozen at -70°C, tested 1 yr later)			
Anti-HCV antibody	Nonreactive on ELISA	Not performed	Nonreactive	Reactive on ELISA; positive on confirmatory RIBA	Reactive on ELISA; positive on confirmatory RIBA
HCV RNA	Nonreactive	Reactive on retrospective testing (690,000 copies/ml) (frozen at -70°C, tested 1 yr later)	Not performed	Reactive	Nonreactive
Serum alanine aminotransferase (U/liter)	21	Not performed	850	115	22

\*Results for initial immunofluorescence assays (IFAs) for IgG antibody to *Babesia microti* and for tests for *B. microti* DNA were interpreted in accordance with Cable et al.<sup>1</sup> Repeated IFAs and Western blotting for IgG and IgM antibodies to *B. microti* were performed by Imugen (Norwood, Mass.). The enzyme-linked immunosorbent assay (ELISA) used in July 1999, December 1999, and February 2000 to detect anti-hepatitis C virus (HCV) antibody was Ortho 3.0 (Ortho Diagnostics); confirmatory testing was performed with a recombinant immunoblot assay (RIBA; HCV 3.0 Strip Immunoblot Assay [Chiron]); testing in September 1999 was performed at an outside laboratory. Testing for HCV RNA in July 1999, December 1999, and February 2000 was performed with a transcription-mediated amplification assay (Chiron); retrospective testing on the sample obtained in August 1999 used a validated proprietary polymerase-chain-reaction method (National Genetics Institute, Los Angeles).

*I. scapularis* tick for the presence of the HCV virus is warranted.

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## An Unusual, Nonhealing Ulcer on the Forearm

*To the Editor:* A 32-year-old woman presented to the emergency department because of a large and painful ulcer over the ulnar aspect of her left forearm. She said it had been present for more than a year but had become increasingly

painful during the previous few weeks. On further questioning, she admitted to using it to inject heroin. The border of this chronic ulcer was very vascular, and injections into it produced nearly the same effect as the intravenous route.

The ulcer shown in Figure 1 was approximately 5 cm by 9 cm with a relatively clean surface and prominent vascular granulation tissue along the border. There were rings of scar tissue around it. Radiographs of the ulna (Fig. 2) showed a marked periosteal reaction, with changes consistent with a diagnosis of osteomyelitis. Cultures of the wound surface recovered methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and skin bacteria. The patient had a good response to methadone and intravenous antibiotics during 11 days in the hospital, but she did not return for follow-up after discharge.

This "shooter's patch" is an example of a nonhealing ulcer with an unusual cause. Diagnosis requires knowledge of the history of injection-drug use. Patients may describe these wounds as having mysterious origins and as very painful, as part of a quest to obtain more narcotics. Staphylococci are the dominant pathogens, but many organisms may be recovered.<sup>1</sup> Biopsies show chronic inflammation with talc or fibrous material. Osteomyelitis is not uncommon with injection-drug use and may involve organisms from the flora of the mouth.<sup>2,3</sup>

The location of the wound in this case was a particularly convenient one, on the back of the left forearm. It provided the patient with easy, visible access to her vascular system, without forcing her to rely on scarred veins or to leave injection marks. The ulcer could be concealed easily with a



**Figure 1.** Nonhealing Ulcer over the Ulnar Aspect of the Left Forearm of an Injection-Drug User.

long-sleeve dress or shirt. Shooter's patches have also been observed on the thighs and sometimes on the lower legs. They may start with an injury or with an injection abscess, and they vary in size depending on the duration and frequency of drug use.

Treatment should first address the opioid dependence. Antibiotic therapy should be instituted on the basis of cultures of deep aspirates or biopsy specimens, since swabs of the surface material may not reveal the true pathogens. With local care and patience, the wounds may slowly be epithelialized and close. A surgical approach may sometimes be required and should include removal of the scar tissue and for-



**Figure 2.** Radiograph of the Forearm Showing a Marked Periosteal Reaction and Osteomyelitis of the Ulna.

eign material embedded in the ulcer. An unusual ulcer such as this patient had is a clue to the patient's larger, life-threatening problem.

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