Correspondence

Copper Intrauterine Devices and Tubal Infertility among Nulligravid Women

To the Editor: Hubacher and colleagues (Aug. 23 issue)[1] report that the use of copper intrauterine devices (IUDs) is not associated with an increased risk of tubal occlusion among nulligravid women. However, only 6 percent of the women in the study had used an IUD. Accordingly, the numbers used to test for an effect of the duration of IUD use, an extremely important aspect of the study, were even smaller. Only 44 women had used a copper IUD for more than one year, of whom only 8 had tubal occlusion. Nevertheless, the odds ratios for tubal occlusion show a moderate, nonsignificant trend of increasing risk with increasing duration of IUD use (up to 6 months, 0.8 [95 percent confidence interval, 0.4 to 1.8]; 7 to 12 months, 1.1 [95 percent confidence interval, 0.4 to 2.8]; and 13 months or more, 1.3 [95 percent confidence interval, 0.6 to 3.2]). The upper limits of these confidence intervals are consistent with a marked effect of longer duration of IUD use on tubal infertility.

We believe that the authors' conclusion that contemporary copper IUDs are safe is unwarranted. In a study of women using IUDs, mostly devices containing copper, we reported no deleterious effect on fertility of short-term use (up to 42 months) but strong evidence of such an effect after long-term use (78 months or more).[2] The study by Hubacher et al. cannot rule out an adverse effect of these devices and should be interpreted with caution.

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2. Doll H, Vessey M, Painter R. Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. BJOG 2001;108:304-14.

To the Editor: Hubacher and colleagues conclude that the previous use of a copper IUD is not associated with tubal occlusion, whereas chlamydia infection is. However, inserting a "safe" IUD into a woman with an active chlamydial infection can spread the infection to the upper genital tract, resulting in pelvic inflammatory disease. Hubacher et al. argue that an IUD is suitable for women who are not likely to be at risk for sexually transmitted diseases, but chlamydia is common and is often unrecognized. The problem is greater when an IUD is used for postcoital contraception and there is no opportunity for screening. In our opinion, there is no reason to pardon the IUD.

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The authors reply:

To the Editor: Vessey and Doll state that long-term use of copper IUDs may impair fertility. We disagree that our case–control study did not include enough long-term use of the IUD to show this putative effect. Vessey and Doll cite odds ratios based on data from the control group of infertile women; however, if their reasoning were applied to our second control group of primigravid women, they might have concluded that the longer a woman uses a copper IUD, the less likely she is to become infertile. With these women serving as controls, the odds ratios for tubal occlusion associated with IUD use of 6 months or less, 7 to 12 months, and 13 or more months were 1.4 (95 percent confidence interval, 0.6 to 3.6), 1.0 (95 percent confidence interval, 0.3 to 3.0), and 0.6 (95 percent confidence interval, 0.3 to

1.4), respectively. On the basis of the interpretation of our data and the research of others,[1,2] we stand by our conclusion that copper IUDs do not impair fertility.

Chlamydia is common and often goes unrecognized, as Verhoeven and colleagues state, but withholding the IUD is not the answer if a woman says she is in a mutually monogamous relationship and has no clinical signs or symptoms of genital tract infection. In Belgium,[3] the rates of cervical chlamydial infections in women who opted for an IUD were far lower than the rates in women who used oral contraceptives (presumably as a result of a combination of self-selection and careful screening). Perhaps, then, the fear with regard to chlamydia is misdirected. At the time of insertion of the IUD, bacteria can be pushed into the upper genital tract; though they require validation, clinical studies indicate that the rates of pelvic inflammatory disease, even in the presence of cervical infection, are within or below the reported ranges without IUD insertion.[4] Even when sexually transmitted diseases are more prevalent, the increased risk of pelvic inflammatory disease attributable to IUD insertion is estimated to be very low (about 1 in 667).[5] Blaming the IUD for problems that require a bacterial pathogen is misleading. We believe that decisions about contraception should be based on the best available evidence, rather than on clinical opinion. A growing body of literature indicates that IUD use is far safer than previously thought.

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GB Virus C and Mortality from HIV Infection

To the Editor: The reports of Xiang et al.[1] and Tillmann et al.[2] (Sept. 6 issue) further document that coinfection with the apparently nonpathogenic flavivirus GB virus C (GBV-C, or hepatitis G virus) prolongs survival in patients infected with the human immunodeficiency virus (HIV). As the accompanying editorial[3] emphasizes, there are no causal inferences to be drawn from these observations, and the suggestion that therapy with GBV-C might improve survival among HIV-infected patients is correctly labeled as "premature." Although viral cross-talk of this sort has been described in a number of other experimental systems,[4] there are other possible explanations for the "protective" effect. For example, a potent cytotoxic-T-lymphocyte response to one viral infection may reduce the level of cytotoxic-T-lymphocyte activity directed to infection by a second virus.[5] Persons who have a strong cytotoxic-T-lymphocyte response to HIV may have more difficulty mounting such a response to GBV-C and may thus be less likely to clear GBV-C infection. Tillmann et al. demonstrate no clear protective effect of exposure to GBV-C (as determined by a test for anti-E2 antibodies) but do demonstrate an obvious "protective" effect in those in whom GBV-C RNA was detected. Failure to clear active GBV-C infection may thus be an indirect marker of a particularly potent cytotoxic-T-lymphocyte response to HIV. This hypothesis, which can be readily tested, predicts that "therapeutic" coinfection with GBV-C would have no benefit for HIV-infected patients.

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To the Editor: We are concerned that the analysis of Xiang et al. may not have taken into account the changes that occurred in the management of HIV between 1988 and 2000. These changes have dramatically decreased mortality from HIV. On the basis of the data presented in the article by Xiang et al., we calculate that 27 of the 144 patients with GBV-C viremia (19 percent) enrolled in the study before 1990, as compared with 67 of the 218 patients without GBV-C viremia (31 percent, $P=0.005$). It is unclear how the investigators adjusted for this difference. The conclusion regarding improved survival may be confounded by the era of HIV therapy.

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To the Editor: In cases of coinfection with hepatitis C virus (HCV) and HIV, differences in the progression of HIV infection according to the HCV genotype have been reported.[1] Three studies of GBV-C and HIV — those of Yeo et al.,[2]

Xiang et al., and Tillmann et al. — included patients from the United States and Europe. However, data on GBV-C genotypes were not reported. An analysis of the association between coinfection with various GBV-C genotypes and the progression of HIV disease might help to explain the mechanism underlying the delayed development of AIDS in patients coinfected with HIV and GBV-C.

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The authors reply:

To the Editor: Macalalad and Snydman question whether changes in the management of HIV confounded our analysis, especially since there were fewer patients with GBV-C viremia than patients without GBV-C viremia enrolled before 1990. We do not believe that such confounding occurred, since we found no significant difference between the patients with and those without GBV-C viremia in terms of the proportion who began receiving care in the era before highly active antiretroviral therapy became available (84 percent vs. 89 percent, $P=0.20$). However, to address this issue, we stratified the patients according to the time of entry into the clinic and repeated the Cox proportional-hazards analysis with adjustment for the same prognostic variables. The association between GBV-C viremia and improved survival was significant for patients who began receiving care both before 1990 and after 1990. This relation held regardless of which year between 1990 and 1994 was chosen as the cutoff for stratification. We also conducted an analysis excluding the patients who began receiving care before 1990 and including only those whose care began between 1990 and 1996 to exclude any effect of highly active antiretroviral therapy. This analysis confirmed the association between GBV-C viremia and improved survival (adjusted relative risk of death for patients who were GBV-C–negative, 3.5 [95 percent confidence interval, 2.2 to 5.7]).

Takamatsu and colleagues question whether differences in GBV-C genotype might explain the underlying mechanism of delayed progression of HIV disease in persons coinfected with GBV-C. All of our GBV-C isolates tested to date with use of the method of Naito and Abe[1] were of genotype 2, reflecting the geographic origin of our patients. Given the low level of variation in amino acid sequences observed in different geographically and phylogenetically defined groups of viruses,[2] it seems unlikely that there are substantial biologic differences between genotypes that would explain the underlying mechanism of the association we observed.

Mosier and Chisari question whether GBV-C viremia is a marker of reduced GBV-C–specific cytotoxic-T-lymphocyte responses that occur as a result of a potent HIV-specific cytotoxic-T-lymphocyte response, which is ultimately the reason for the delayed progression of HIV disease. Our studies do not rule out the possibility of altered immunologic responses to HIV or GBV-C in coinfected persons, and differences in host cytokines and chemokines are probably involved in the varying rate of progression of HIV disease among infected persons. However, our in vitro model of coinfection demonstrated diminished HIV replication in the presence of GBV-C infection, strongly suggesting that GBV-C replication has an effect on HIV replication that is independent of cytotoxic-T-lymphocyte responses.

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To the Editor: We agree with Mosier and Chisari that the reason for slower progression of disease in HIV-infected patients who also harbor GBV-C still needs to be identified. Although we favor the theory that GBV-C has a direct role in ameliorating HIV infection, we cannot rule out the possibility that GBV-C is only a marker of a factor that has yet to be identified. One such factor could be a potent cytotoxic-T-lymphocyte response against HIV associated with a weak cytotoxic-T-lymphocyte response against GBV-C, as suggested by Mosier and Chisari. In that case, however, one would expect to find more rapid progression among anti-E2–positive patients than among patients who had not been exposed to GBV-C. Furthermore, on the basis of the data indicating that HIV replication is reduced by coinfection with GBV-C in vitro, a direct interaction of the two viruses seems likely. Still, the cytotoxic-T-lymphocyte responses to HIV and GBV-C antigens must be investigated. Our ongoing work includes the analysis of immune responses.

Takamatsu et al. raise the issue of GBV-C genotypes, which we are also studying. The effect of coinfection with various HCV genotypes in HIV-positive patients is controversial.[1] Furthermore, none of the studies analyzing the relevance of the HCV genotype to the effect of coinfection on HIV have taken into account coinfection with GBV-C. Thus, these issues must be clarified in the light of new information on coinfection with GBV-C and HIV.

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Cardiac Rehabilitation

To the Editor: In his review, Ades (Sept. 20 issue)[1] describes the benefits of cardiac rehabilitation in patients with coronary heart disease. He notes the improvement that takes place with cardiac rehabilitation in a range of psychological factors and symptoms, including anxiety, emotional stress, lack of self-confidence, depression, social isolation, and patient-reported quality of life. Ades reports that when cardiac rehabilitation specifically includes psychosocial management, greater reductions in cardiac risk factors and morbidity and mortality are evident.

We have found in our clinical work in cardiac rehabilitation that coexisting psychiatric symptoms and disorders appear to play a critical part in influencing the psychosocial status of patients with coronary heart disease and the outcomes of cardiac rehabilitation. There is accumulating evidence of distinct pathophysiologic pathways associated with various psychiatric symptoms and disorders that have also been shown to be independent risk factors for coronary heart disease. We believe that the lack of critical evaluation of the psychological symptoms of patients with coronary heart disease, in terms of diagnosable psychiatric disorders with concomitant treatment algorithms, results in underdiagnosis and undertreatment of these psychiatric disorders.

We agree with Ades that psychosocial assessment of all patients with recently diagnosed coronary heart disease is needed, but we believe that the use of a standardized instrument that assesses the presence or absence of a wide range of psychiatric illnesses is a critical component of the evaluation of these patients. Only with a comprehensive assessment of psychiatric disorders will the full benefit of a multifactorial risk-reduction approach to the secondary prevention of coronary heart disease be realized.

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To the Editor: In his review of cardiac rehabilitation, Ades claims that "it has not been determined whether a cardiac-rehabilitation program that consists of exercise alone reduces mortality in current patient populations." A brief search of the *Cochrane Library* might have helped him. A recent systematic review of 34 trials of exercise-based cardiac rehabilitation, including 20 trials reported since 1990 and involving a total of 8440 patients, shows an overall reduction in mortality with this type of rehabilitation.[1] Ades's review is nonsystematic in its coverage and consequently runs the risk of biased assessment of the value of interventions. Systematic reviewing of the literature, particularly with the use of methods defined by the Cochrane Collaboration, has developed as a rational means to reduce the biases associated with traditional narrative reviews.[2] Evaluation of the effectiveness of treatment should always be guided by the best available evidence, starting with systematic reviews of large, well-conducted, randomized controlled trials.

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Dr. Ades replies:

To the Editor: I agree with Bankier and Littman that psychosocial assessment is needed in all patients with recently diagnosed coronary heart disease. The cardiac-rehabilitation program is one obvious setting in which this should occur. Certain psychological characteristics, such as depression and social isolation, are associated with poor outcome and predictably improve with rehabilitation. Although treatment has not definitively been shown to decrease mortality from cardiac causes or overall mortality, an improvement in health-related quality of life with rehabilitation is predictable. Furthermore, depression or other psychological conditions often impede patients from taking preventive medications such as aspirin, beta-blockers, or lipid-lowering drugs or from following a nutritional or exercise program.

As suggested by Rees and Ebrahim, I read the very thorough Cochrane Review entitled "Exercise-Based Rehabilitation for Coronary Heart Disease."[1] Its focus is to compare the value of interventions consisting of exercise alone with comprehensive cardiac rehabilitation in terms of specific outcomes, such as overall mortality and mortality from cardiac causes. Most of the patients in this analysis did not receive exercise-only interventions. With regard to overall mortality, only three studies of exercise alone reported since 1990 (and involving 554 patients) are included in the review, and they are not assessed in a separate statistical analysis. According to the data in those studies, the mortality rate since 1990 in patients undergoing exercise alone is 8.1 percent, as compared with a mortality rate of 9.2 percent in controls; the difference is not significant ($P=0.64$).

In view of lower overall mortality rates among patients with coronary disease since the 1980s, even if contemporary exercise-only rehabilitation provides a roughly 25 percent reduction in mortality, the sample size required to demonstrate this benefit needs to be far greater. I concur with the comment in the Cochrane Review that "the incremental benefit of cardiac rehabilitation on mortality in a world where the majority of patients will receive thrombolysis,

aspirin, statins and increasingly ACE [angiotensin-converting–enzyme] inhibitors has not been studied adequately."[1] A lack of more recent data on exercise-only rehabilitation, however, should not interfere with the evolution of rehabilitation programs into "secondary prevention centers," which, in addition to guiding exercise programs, are actively involved in the measurement and treatment (by pharmacologic and lifestyle approaches) of risk factors such as hyperlipidemia and hypertension according to well-defined treatment goals.[2]

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Cephalosporin Allergy

To the Editor: We make the following observations about the review of cephalosporin allergy by Kelkar and Li (Sept. 13 issue).[1] First, anti-cephalosporin IgE antibody assays are available and are used by clinicians in Australasia. Second, specific haptenic determinants involved in hypersensitivity to cephalosporins have been identified.[2,3] Some of the cross-reactivity between cephalosporins and penicillin G results from the presence of IgE directed against a group as small as the methylene substituent linking the side chain to the rest of the penicillin molecule.[2] Cephalosporins exhibit greater heterogeneity of allergenic determinants than penicillin because of their extra side chain (R2) on the dihydrothiazine ring, and different fine structural recognition sites have been identified in patients who are allergic to cefaclor.[3,4] Our immunochemical studies have revealed a spectrum of allergenic determinants ranging in specificity from side-chain (R1 or R2) groups to compound determinants embracing one or both ring structures.[2-5]

TABLE 1. RESULTS OF RADIOIMMUNOASSAYS FOR THE DETECTION OF IgE AGAINST "-OYL" AND "-ANYL" CONJUGATES OF 12 DIFFERENT CEPHALOSPORINS AND PENICILLINS IN 1682 PATIENTS WITH POSSIBLE β-LACTAM ALLERGY.

DRUGS ELICITING A SPECIFIC IgE REACTION	NO. OF SERUM SAMPLES WITH A REACTION (%)
≥1 β-lactam antibiotic	433 (25.7)
≥1 Cephalosporin	397 (23.6)
≥1 Penicillin	248 (14.7)
≥1 Cephalosporin and 1 penicillin	212 (12.6)
Only ≥1 cephalosporins	185 (11.0)
Only ≥1 penicillins	36 (2.1)

Third, our extensive experience in clinical and laboratory testing suggests that cephalosporin allergy is much more common than penicillin allergy (Table 1).[5] We use radioimmunoassays to measure major determinants (penicilloyl and cephalosporoyl) and minor determinants (penicillanyl and cephalosporanyl) for up to six different penicillins and six different cephalosporins. The higher incidence of IgE antibodies against cephalosporins was not anticipated and most likely reflects both increased use of cephalosporins and greater parenteral exposure to these drugs.[5]

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To the Editor: Kelkar and Li recommend avoiding cephalosporin use in patients with a history of penicillin allergy and more specifically in patients who have a positive skin test for allergy to penicillin. This strategy is not supported by the data from the studies they cite. On the basis of their Table 3, the authors could also have argued, inappropriately, that the skin test itself reduces the risk of a reaction to cephalosporin by 86 percent, from 4 in 34 (11.8 percent) to 8 in 486 (1.6 percent, $P<0.001$). They have partially misrepresented the data from Shepherd and Burton,[1] who really reported four adverse reactions, not zero, in the 159 patients with a negative skin test. If one uses these data to recalculate the reported rates of adverse reactions to cephalosporins in the groups with positive and negative skin tests (6 of 135 and 6 of 351, respectively) one finds no significant difference ($P=0.08$). However, the disparate qualities of the data cited in Table 3 make combining these data and their combined analysis invalid.

The authors' statement that "these prospective studies are too small to evaluate accurately the value of skin testing in patients with a history of allergy to penicillin" is also not supported by the data they present. In the single largest study that has been conducted to explore this question,[2] one reaction occurred in a group of 62 patients with positive skin tests for penicillin allergy who were exposed to parenteral cephalosporins. The 95 percent confidence interval for this proportion, 0.016, was 0.004 to 0.085. Finally, there are no data to support the authors' recommendation

that penicillin skin tests be performed in persons with a history of adverse reaction only to cephalosporins.[3,4]

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2. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204-15.
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To the Editor: Penicillin G has progressively been replaced by other β-lactam antibiotics, in terms of both prescribing habits and the induction of allergic reactions[1,2]; as a result, skin testing with antigenic determinants of penicillin G is no longer sufficient for evaluating patients for allergy to β-lactams, and other determinants, such as those of amoxicillin or cephalosporins, must be used instead.[1-3] The assumption that anaphylaxis from cephalosporins is rare is based on insufficient evidence from individual case studies. Anaphylaxis from β-lactams has become more common[2] and is accompanied by a reduced rate of positive skin tests for major determinants of penicillin G and an increased rate of positive tests for minor determinants of other β-lactams, including cephalosporins.[2,3] The degree of cross-reactivity among cephalosporins is not necessarily greater than that between penicillins and cephalosporins. It depends on the similarities in the chemical structures (nuclear or side-chain) that are recognized by specific IgE antibodies or sensitized T cells. For example, the cross-reactivity between cephadroxil and amoxicillin is greater than that between cephadroxil and another unrelated side-chain cephalosporin.[4]

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The authors reply:

To the Editor: Dr. Macy points out that the risk of a systemic reaction to cephalosporin is low (1 in 62 in one study), even among patients with a positive skin test for allergy to penicillin.[1] However, deaths caused by anaphylaxis from cephalosporins do occur, and they seem to occur more frequently among patients with a history of penicillin allergy.[2] Dr. Macy cites a potential rate of systemic reactions of up to 8.5 percent. We suggest the clinical circumstances of each case should determine whether or not this level of risk can be accepted. A careful review of the medical literature indicates that there is insufficient evidence on which to base a recommendation for a universally applicable strategy. We offer skin testing for penicillin allergy as one strategy, particularly for patients who have a high likelihood of cephalosporin allergy and a history of a serious reaction to penicillin.

Dr. Macy implies that we recommend penicillin skin tests for patients with a history of cephalosporin allergy. The cross-reactivity of penicillin and cephalosporins suggests that penicillin should be administered with caution in patients with a history of a systemic reaction to cephalosporins. Penicillin skin tests can be helpful in this clinical situation.

Drs. Baumgart and Baldo and Dr. Mayorga and colleagues state that cephalosporin allergy is common and provide data or references on tests for IgE antibodies or skin tests for allergy to cephalosporins. Sensitization to cephalosporins and drug reactions caused by hypersensitivity to cephalosporins may be increasing. There is a distinction between sensitization, as revealed by IgE antibody tests or skin tests, and clinical drug allergy.

Baumgart and Baldo and Mayorga et al. offer helpful details of the immunochemistry of β-lactam antibiotics. Study of haptenic determinants of β-lactam antibiotics may lead to the development of anti-cephalosporin IgE antibody assays and reagents for skin tests for immediate-hypersensitivity reactions that can find a place in routine clinical practice. However, the sensitivity and specificity of such tests do not provide sufficient support for clinical decisions. Anaphylaxis from β-lactam antibiotics is a life-threatening event.

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Case 29-2001: Oncogenic Hypophosphatemic Osteomalacia

To the Editor: Several important issues were overlooked in the Case Record of the 14-year-old boy with oncogenic hypophosphatemic osteomalacia (Sept. 20 issue).[1] Terek

was correct in stating that oncogenic hypophosphatemic osteomalacia has many similarities to X-linked hypophosphatemia. However, the onset of hypophosphatemia is not delayed in X-linked hypophosphatemia. Terek did not consider a diagnosis of autosomal dominant hypophosphatemic rickets, which has incomplete penetrance and a variable age of onset.[2] Therefore, an affected child's parent may carry a mutation for autosomal dominant hypophosphatemic rickets that is nonpenetrant, and the child may have delayed phosphate wasting. It is important to note that weakness, fatigue, and fracture are prominent features in patients with autosomal dominant hypophosphatemic rickets who present with delayed onset of disease and that these patients are clinically indistinguishable from patients with oncogenic hypophosphatemic osteomalacia.

Recent work regarding fibroblast growth factor 23 should also have been addressed. Missense mutations in the gene encoding fibroblast growth factor 23 cause autosomal dominant hypophosphatemic rickets.[3] In addition, fibroblast growth factor 23 is highly expressed by tumors causing oncogenic hypophosphatemic osteomalacia.[4] Fibroblast growth factor 23 is therefore a strong candidate for "phosphatonin," the factor implicated as a cause of the phosphate wasting in patients with oncogenic hypophosphatemic osteomalacia. The mutations that cause autosomal dominant hypophosphatemic rickets stabilize fibroblast growth factor 23, potentially elevating its concentration in serum and leading to renal phosphate wasting.[5] Because fibroblast growth factor 23 is produced in tumors causing oncogenic hypophosphatemic osteomalacia at high levels, the same net result as in autosomal dominant hypophosphatemic rickets — elevated serum concentrations of the factor — would be present in oncogenic hypophosphatemic osteomalacia, albeit by a different mechanism. In conclusion, a diagnosis of autosomal dominant hypophosphatemic rickets should be considered in patients with late-onset hypophosphatemia, especially in the light of the implications for genetic testing and counseling.

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Dr. Terek replies:

To the Editor: White and colleagues are correct to point out that one cause of delayed-onset vitamin D–resistant rickets is autosomal dominant hypophosphatemic rickets. However, the importance of ruling out the presence of a tumor cannot be overstated. In this case, the tumor was malignant and required multidisciplinary treatment, which not only cured the tumor but also reversed the metabolic derangements associated with vitamin D–resistant rickets.

Identification of fibroblast growth factor 23 as phosphatonin is an exciting advance in our understanding of the pathophysiology of vitamin D–resistant rickets. The publication of these findings postdated the clinicopathological conference at which I discussed the case.

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The Ethics of Placebo-Controlled Trials

To the Editor: Emanuel and Miller (Sept. 20 issue)[1] characterize the current debate about placebo-controlled trials as a debate between two orthodoxies: placebo orthodoxy and active-control orthodoxy. We used the term "placebo orthodoxy" to describe the widely held but incorrect view that the use of a placebo control is always better than the use of an active control.[2,3] Labeling our position "active-control orthodoxy" wrongly suggests that we believe that "if an effective therapy exists, the use of a placebo should be prohibited" in all cases.[1] We do, however, represent a clinical-equipoise orthodoxy in believing that therapeutic interventions in research must be consistent with physicians' duty of care to patients.[4] Mounting a trial requires genuine disagreement among expert practitioners as to the preferred treatment.[4] If expert clinicians hold, as we believe they do, that not treating baldness or headaches is consistent with competent medical practice, then a placebo control is permissible. No competent clinician believes that withholding treatment from a severely depressed or schizophrenic patient is acceptable, and hence placebo-controlled trials in such cases are unethical.[5]

Emanuel and Miller assert, but neither argue nor prove, that the use of placebo controls and not active controls are required for scientific validity.[1] They further claim that the requirement of scientific validity provides ethical justification for the use of placebo, thus leaving no room for the limitation of harm in trials. By claiming different moral standards for clinical research and clinical care, they can no longer answer the fundamental question in clinical research: When is it ethically acceptable for physicians to suggest that their patients enroll in a trial?[4] This question is answered by clinical equipoise, making the protection of patients a cost of the ability to perform trials at all.

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The authors reply:

To the Editor: Central to research ethics is the distinction between clinical care and clinical research.[1-3] Weijer and Glass muddle this distinction by claiming that "therapeutic interventions in research must be consistent with physicians' duty of care to patients." The goal of all clinical research is to improve health care by testing scientific hypotheses, not by providing personalized care. The fundamental duty of clinical investigators is to avoid exploiting research participants.[3,4] This is not ethically equivalent to a physician's therapeutic duty to provide optimal care to patients. Without an understanding of this difference, it would never be ethical for investigators to perform research procedures on patient volunteers, such as blood sampling, lumbar punctures, positron-emission tomographic scanning, and biopsies, which pose some risks without offering compensating personal benefits.

In our article we describe criteria for the ethical justification of placebo-controlled trials according to which they should be ruled out if research participants would be exposed to risks of substantial harm, including severe discomfort. These criteria are consistent with the responsibility to avoid exploiting research participants. Consequently, Weijer and Glass's claim that our position leaves "no room for the limitation of harm in trials" seems puzzling.

Finally, reflecting their conflation of clinical care and clinical research, Weijer and Glass assert that "the fundamental question in clinical research" is, "When is it ethically acceptable for physicians to suggest that their patients enroll in a trial?" They surely are mistaken. This is a secondary question. It presupposes a satisfactory answer to the prior question: When is it ethically justifiable to conduct a randomized clinical trial? We provide clear guidance on this question when the trial includes a placebo control.

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Cesium-Induced Torsades de Pointes

To the Editor: Up to 50 percent of patients with cancer seek help in the form of alternative medicine.[1] Such therapies may include cesium chloride, a blocker of the inward-rectifying potassium channel that is used in animal models to study the long-QT syndrome and torsades de pointes.[2] We report a documented case of cesium-induced toxicity.

A 62-year-old man presented with recurrent syncope. The patient had no history of cardiovascular disease, syncope, or palpitations and no family history of sudden death. Previously, the patient had had normal echocardiographic and laboratory data. The patient underwent a naturopathic treatment consisting of 2000 mg of cesium chloride four times a day intravenously for two weeks for prostate cancer. During treatment, he had his first episode of syncope. He continued to take 1000-mg tablets of cesium chloride three times a day. (The capsules were examined and were shown to contain cesium chloride.) Two months later, the patient was hospitalized because of recurrent syncope. The electrocardiogram showed a prolonged QT interval (approximately 700 msec) and ventricular ectopic beats arising from the terminal part of the T wave (Fig. 1A). Runs of torsades de pointes tachycardia were recorded on telemetry (Fig. 1B). The serum potassium level was 2.8 mEq per liter. Analysis of a blood sample revealed a plasma cesium level of 830 μmol per liter (reference range, 0.0045 to 0.0105) and an erythrocyte cesium level of 3460 μmol per liter (reference range, 0.0188 to 0.0564). The patient was treated with intravenous magnesium and potassium. The QT interval remained prolonged and ventricular premature beats persisted after normalization of the serum potassium level. The patient agreed to stop taking cesium chloride. After six months of follow-up, the patient had not had any further episode of syncope and the corrected QTc interval had returned to normal.

In a series of 50 patients treated with oral cesium chloride for cancer, side effects such as nausea and diarrhea were described, but not arrhythmia.[3] In a recent case report of syncope and polymorphic ventricular tachycardia in a patient who was taking various naturopathic substances, cesium was thought to be the cause of the abnormalities.[4] In the present case, cesium-induced toxicity was documented. Hypokalemia may also have contributed to the arrhythmia, but ventricular arrhythmia and prolongation of the QT interval persisted after the normalization of the serum potassium level. This report underscores the importance of clinical caution in the use of naturopathic medicinal therapies.

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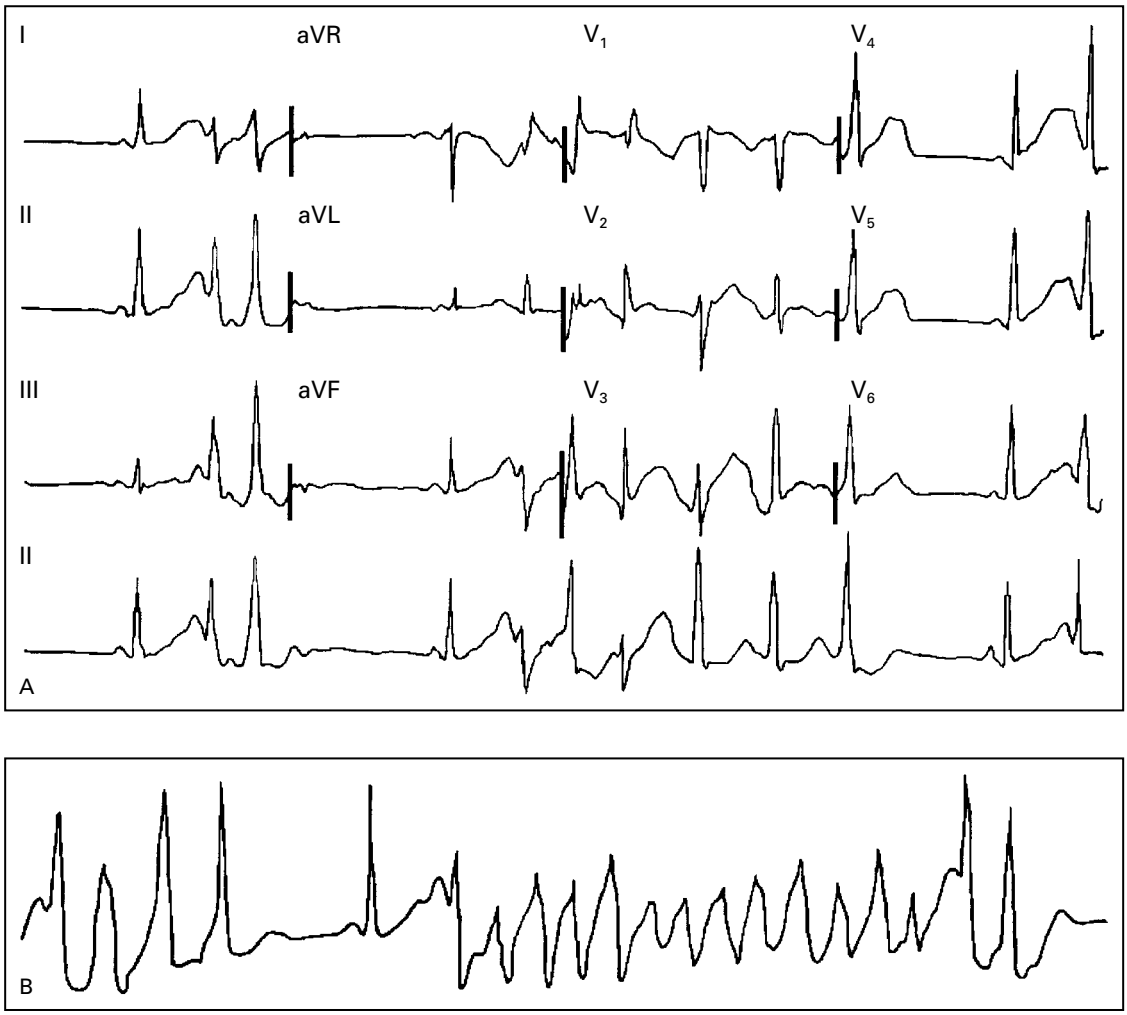

Figure 1. Electrocardiographic Findings in a Patient Who Was Receiving Long-Term Oral Cesium Therapy.

Panel A shows a standard 12-lead echocardiographic tracing obtained at admission after the patient's third episode of syncope. The QT interval of 680 msec is interrupted by frequent ventricular ectopic beats, all of which occur at the end of repolarization. Ventricular ectopy interrupts a prolonged and bizarre-shaped TU complex of cardiac repolarization. Panel B shows all of the typical features of torsades de pointes, with a short–long–short initiating sequence generated by a 1080-msec compensatory pause after a run of ventricular premature beats, followed by a sinus beat and then by the first beat of a self-terminating polymorphic ventricular tachycardia that starts at the end of a TU complex of repolarization. The plasma and erythrocyte cesium levels were approximately 60,000 times as high as the normal value at the time these tracings were obtained. The paper speed was 25 mm per second.

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