

scribed in this manner should be counseled about the risks and clinical presentation of these and other potential drug interactions.

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THE AUTHORS REPLY: Drs. Grönefeld and Hohnloser request information on antithrombotic treatment. In our study protocol, anticoagulation was not standardized but was left to the local practice of each center. Fifteen patients (7 percent) were treated with warfarin, and 38 (18 percent) with aspirin. During the follow-up period, no patient had a transient ischemic attack, stroke, or arterial embolism. However, we believe that the indications for antithrombotic therapy are not clearly defined in patients with transient, symptomatic episodes of atrial fibrillation that are treated with either the pill-in-the-pocket approach or long-term oral prophylaxis; this point deserves further investigation.

Drs. Konety and Olshansky underscore the lack of a control group. In many studies carried out in hospitalized patients, oral flecainide or propafenone has been shown to be superior to placebo in rapidly terminating atrial fibrillation of recent onset. In our opinion, further study to demonstrate this superiority was not indicated. We agree with Drs. Konety and Olshansky that the pill-in-the-pocket approach should be used only in selected patients. Current data show that flecainide and propafenone are safe in patients without heart disease or with only mild heart disease; thus, the exclusion criteria we used should be strictly adopted in clinical practice. We enrolled highly symptomatic patients with palpitations, who contacted the emergency room for almost all the arrhythmic episodes, as shown in Table 1 of our article. About one third of emergency

room visits were followed by hospitalization. Emergency room visits and hospitalizations often represent the most important concern for patients with recurrent atrial fibrillation. Not only did the pill-in-the-pocket approach make the arrhythmic episodes shorter, but it also dramatically reduced emergency room visits and hospitalizations. Although these patients were highly symptomatic with palpitations, we cannot rule out asymptomatic arrhythmic episodes in some of them. However, this would not represent a specific finding of the pill-in-the-pocket approach, since asymptomatic episodes have been observed during all antiarrhythmic treatments (long-term oral prophylaxis, catheter ablation, and pacemaker implantation).¹⁻³

Dr. Wittkowsky raises the problem of drug interactions. In particular, she refers to the interactions of propafenone with digitalis or warfarin. In our study, no patient was taking digitalis. The data on the interactions between propafenone and warfarin apply to long-term treatment with both drugs.⁴ Moreover, we are not aware of any clinical study reporting more hemorrhagic complications in patients receiving oral propafenone than in those receiving other antiarrhythmic agents.

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Vascular Events after Acute Infection or Vaccination

TO THE EDITOR: In their article about cardiovascular events after acute infections (Dec. 16 issue),¹ Smeeth et al. do not discuss alternative, time-

honored explanations for the occurrence of cardiovascular events within three days after acute infections. A reasonable explanation could be that fever

and the accompanying tachycardia trigger such events, not to mention the procoagulant effects an acute infection can have. The hypoxemia that accompanies a respiratory (but not urinary) infection can adversely affect vulnerable tissue, not to mention have procoagulant effects.² A less common phenomenon is a myocardial infarction masquerading as a respiratory infection. In one recent study, more than 40 percent of cases of myocardial infarction in women had the appearance of a respiratory infection.³ The widely held view about the role that inflammation plays in atherosclerosis and cardiovascular events has prevented recognition and discussion of the apparent paradox that common anti-inflammatory agents, such as corticosteroids and nonsteroidal antiinflammatory drugs (with the exception of aspirin), may actually increase, rather than decrease, adverse cardiovascular outcomes.^{4,5}

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TO THE EDITOR: Smeeth et al. found that persons with acute infections have an increased risk of cardiovascular and cerebrovascular events, whereas those who have been vaccinated do not. They conclude that this “lends strong support to the concept that systemic inflammation itself alters the probability of the occurrence of a vascular event.” We believe that this conclusion based on their data is flawed. Not discussed is the influence of acute infection on stress and on demand-induced ischemia. Acute infections, particularly those of the respiratory tract, may be associated with hemodynamic stresses that are not typically induced by vaccination. These hemodynamic stresses in high-risk older persons, such as those in the study by Smeeth et

al., who had an increased prevalence of coronary artery disease, may account for the increased rates of myocardial events noted in the study. Although evidence for a link between inflammation and vascular events is abundant, demand-induced ischemia due to acute hemodynamic stressors of a clinically significant degree may be a more straightforward explanation of the findings of this study.

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THE AUTHORS REPLY: Dr. Bursztyn raises the question of whether there might have been cases of misdiagnosis of myocardial infarction as respiratory infection. We did consider this important point. Our study identified an increase in the risk of myocardial infarction or stroke after a case of urinary tract infection or respiratory infection. We think it unlikely that myocardial infection was misdiagnosed as urinary tract infection or that either urinary tract infection or respiratory tract infection was misdiagnosed as stroke. Therefore, our conclusions that two different infectious processes increase the rate of cardiovascular events seem secure. As for the interesting question about associations between antiinflammatory drugs and event rates, it is unfortunate that the interpretation of the data are difficult because of confounding and the diversity of underlying disease states. Although we recognize that some drugs have detrimental effects, we are less certain than Dr. Bursztyn that, as a group, drugs that reduce inflammation are necessarily harmful in terms of cardiovascular events.

In our article, we list several possible mechanisms that might explain the association between acute infection and a short-term increase in cardiovascular risk. Drs. Sharifi and Mofrad suggest an additional one: that hemodynamic stresses may have played a part in mediating the effect. We agree with the correspondents that infection and systemic inflammation increase the heart rate and can alter hemodynamics and myocardial oxygen demand. Although it is conceivable that these acute changes may have contributed to the effect we observed, it seems less likely that they would have persisted dur-

ing the month or so in which we found an elevated risk after infection. Furthermore, although this alternative mechanism is plausible, we do not see how this alters our conclusion that our finding “lends strong support to the concept that systemic inflammation itself alters the probability of the occurrence of a vascular event.”

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Altered Nuclear Transfer

TO THE EDITOR: Altered nuclear transfer is a procedure that has been proposed as a morally acceptable means of procuring human embryonic stem cells.¹ In their Perspective article, Melton et al. (Dec. 30 issue)² appear to misunderstand, and therefore prematurely dismiss, the promising possibilities of this proposal.

The proposal for altered nuclear transfer, which was developed in wide consultation with leading scientists, moral philosophers, and religious authorities, represents a “third option” — a technological solution to the current moral impasse regarding the destruction of human embryos to obtain embryonic stem cells.

Using the techniques of somatic-cell nuclear transfer, but with the intentional alteration of the nucleus before transplantation, we could construct a biologic entity that, from its very inception, lacked the attributes and capacities of a human embryo. Studies with mice already provide evidence that we may be able to generate functional embryonic stem cells from a system that is not an organism but is biologically (and morally) more akin to tissue or cell culture. There is a natural precedent for entities that lack the characteristics of organisms, yet are capable of generating embryonic stem cells or their functional equivalent. Teratomas are germ-cell tumors that generate all three primary embryonic germ-layer cell types, as well as more advanced cells and tissues. Yet these chaotic, disorganized, and nonfunctional masses entirely lack the structural and dynamic character of an organism.

Most of the objections raised by Melton et al. are based on a mistaken identification of altered nuclear transfer with silencing of the gene *CDX2*, but — as was clearly stated in my presentation to the President’s Council on Bioethics — there are many potential approaches involving the alteration of genes that are necessary for early intercellular signaling, cell differentiation, or integrated patterning of de-

velopment.³ The exact gene or combination of genes will depend on the level of disorganization deemed essential to fulfill the moral criteria of this project.

Many Americans believe that a decent society should not build the foundations of its biomedical science on the intentional creation and destruction of human embryos. Such a view is consistent with the enduring traditions of our profession, encoded in the Hippocratic oath and extended in the 1948 Declaration of Geneva, which explicitly states, “I will maintain the utmost respect for human life, from the time of conception.” Altered nuclear transfer is not a “distraction” or a “diversion of resources” as stated by Melton et al., but a morally reasonable and technologically feasible proposal that honors the important human goods being defended by both sides of this difficult debate.

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THE AUTHORS REPLY: We did not misunderstand Hurlbut’s proposal. We focused on *CDX2* because this is the example that Hurlbut offered, but our point was more general. To repeat: “We see no basis for concluding that the action of *CDX2* (or indeed any other gene) represents a transition point at which a human embryo acquires moral status.”

Hurlbut now acknowledges that “the exact gene or combination of genes will depend on the level of