fied latent TB among untreated anergic HIV-infected individuals may be lower than that of the general population, because many would have already developed active TB related to a previous latent infection. I suspect that many practitioners do not ordinarily prescribe isoniazid in this context, although they may occasionally find good reason to do so (for example, a particularly high likelihood of previous exposure, without documentation of specific contacts).

I agree that my statement that the 2-month rifampin–pyrazinamide regimen is "clearly contraindicated for anyone with underlying liver disease or with isoniazid-related hepatotoxicity" was too strong.[8] This reflected considerable concern about recent reports of liver toxicity,[9] perhaps related to suboptimal patient selection and supervision, as noted by Houston and colleagues. The key point is that rifampin–pyrazinamide should not ordinarily be prescribed for latent TB when there is substantial risk of hepatotoxicity, except with expert supervision and close monitoring.

I would be particularly hesitant to use this regimen where there is evidence of active ongoing liver disease (as opposed to positive viral serologies or a history of alcohol use). Pyrazinamide is the most likely culprit when liver toxicity does occur.[10,11] Hence the 4-month rifampin regimen provides a reasonable "short-course" alternative to isoniazid, where feasible.

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Myocardial infarction in South Asians

In their discussion on risk factors and myocardial infarction in South Asians[1] Milan Gupta and colleagues omit some important issues. Lipoprotein (a) and homocysteine levels, reported higher in South Asians[2] and with multiplicative risk, may partly explain their excess cardiovascular disease (CVD).[3] Although not measured in this study, these factors warrant discussion because of risk amplification of conventional risk factors, which has implications for care.

Excess premature CVD (men < 55 years, women < 65 years), a crucial feature of CVD in South Asians, with implications for screening, prevention and treatment, also merits discussion. Recognized across the South Asian diaspora,[3] this was previously reported in South Asian men and women admitted with acute myocardial infarctions to a Toronto hospital from 1990–95.[4,5] The expected 10-year delay in onset of heart disease in women was reduced for South Asian women to a mean of 4.2 years (median 2.0 years). Premature CVD should thus probably be specifically examined and reported in studies on South Asia.

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[Four of the authors respond:]

We thank Vivian Rambihar for taking an interest in our study[1] and recognize his important contribution to the field of heart disease in South Asian Canadians. Although we agree that novel risk factors such as lipoprotein (a) (Lp[a]) and homocysteine may be implicated in the excess cardiovascular disease noted in South Asian Canadians, this was not the focus of our study. Regarding implications for care, pharmacologic intervention for elevated Lp[a] and/or homocysteine has not yet been shown to affect outcomes. Because our study was a matched case–control comparison, we are unable to comment on the prevalence of premature cardiovascular disease in our study population. However, we have shown in a related study[2] that South Asian Canadians undergoing coronary angiography are significantly younger than patients of European origin. In that study, South Asian Canadians had more severe angiographic disease in each coronary artery, despite

being younger and having fewer traditional coronary risk factors.

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Placebo tribulations

Charles Weijer's[1] recent indictment of the Canadian research review process is unsupported. On the basis of the meagre information given, it is impossible to determine whether the protocol in question violates the *Tri-Council Policy Statement* (TCPS).[2] That guideline enunciates a strong presumption against placebo use when "standard therapies" are available. It does not state an exceptionless rule, and, indeed, the policy discusses some of the exceptions. Demonstrating that the protocol violates the TCPS statement is crucial to Weijer's accusation that Canadian researchers, research ethics boards (REBs), universities and federal funding agencies are shirking their responsibilities.

Health Canada cannot dictate decisions on particular cases to REBs, but nothing is wrong with it promulgating general policy on research ethics. The passage Weijer quotes contains nothing but statements of general principles. Not a single one of them is objectionable, idiosyncratic or even at odds with the TCPS statement. I know of no national or international guideline that specifies that the judicious use of placebo controls in clinical trials is unethical. (There is, of course, great controversy over what counts as a judicious use.) Benjamin Freedman agreed with the TCPS that REBs should reject trials with inconclusive designs.[3]

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In his commentary, Charles Weijer poses interesting and challenging questions regarding placebo-controlled clinical drug trials.[1] However, it is unfortunate that he chooses to make negative and unsubstantiated assertions about for-profit research ethics boards (REBs), lumping them all together.

He states that the failures of university teaching hospital REBs are attributed to "lack of clarity … regarding the need for adherence to the *Tri-Council Policy Statement*" while for-profit REBs are assailed because of "obvious conflicts of interest doing ethics reviews." Why is the latter an "obvious" conflict of interest? Getting paid for work does not necessarily compromise judgement.

We would suggest that the members of most for-profit REBs are guided, or should be, by the same ethical standards as are the members of university teaching hospital REBs. For example, the members of the latter are subject to the same conflicts of interest because university teaching hospitals receive "overhead" funds whenever a study is done at that institution. Moreover, the voting members of university teaching hospital REBs regularly review studies submitted by their colleagues and thus potentially have more conflicts of interest than do the members of for-profit REBs. Our institutional review board (IRB) is totally independent, without a research arm, and is well positioned to pass judgement on the merits of a particular study. We are completely independent of outside pressures and able to consider the safety of the patient foremost, providing the study has scientific merit.

We would like to point out that our IRB rejected an unethical study involving an angiotensin-converting enzyme (ACE) inhibitor versus an angiotensin-II blocker versus placebo in diabetics with proteinurea, although 7 Canadian university teaching hospital boards approved it. Only 1 university teaching hospital REB rejected it. What's even more worrisome is that this particular study had been running for more than 2 years before it was sent to us, and each of the approving university teaching hospital REBs had extended the approval. None shut it down despite incontrovertible evidence of the ACE inhibitor's nephroprotective effect during the continuing review period.

We also restricted approval of a study with a new thrombolytic agent to 3 months due to safety concerns, although a university teaching hospital REB approved it for 1 year. Why did we restrict it? Because we knew of an exsanguinating hemorrhage with the study compound that occurred at the hospital REB's sister hospital. The bleeding could not be stopped, and the case was discussed during the university's cardiology department rounds. Despite this occurrence, the REB apparently did not review their approval or require changes to the consent form, despite information from their own investigators that the study drug might cause life-threatening bleeding.

How do we know about the hospital REBs' decisions? Because in each instance we were told by the sponsor or the principal coordinating investigator when we refused to approve these studies that "you are the only one to refuse!"

In several other cases, we have rejected unethical studies that other REBs have not (see the complete letter at www.cmaj.ca).

Weijer should also consider the well-publicized ethical problems at presti-