Response

Suspicions that oxygen was toxic had indeed led to its declining clinical use before the National Cooperative Study (NCS) randomized trial, but controversy was still widespread before 1956, and many clinicians were unpersuaded. The results of the trial gave convincing scientific evidence of the toxicity, and the subsequent textbook recommendations and media publicity helped contribute to a further decline in use of oxygen.

Toth claims that "later research failed to substantiate the 1956 trial", but he does not cite the research, and we are not aware of what it may have been. Toth correctly points out that deprivation of supplemental oxygen for premature infants may have led to increased mortality from other causes, but the main question that was addressed (and correctly answered) in the NCS trial was whether RLF was increased by administration of oxygen.

Toth argues that randomized controlled trials (RCTs) are expensive, time consuming, and may not always provide definitive results. We do not dispute his argument, but would point out that as long as clinicians, editors, and regulating agencies remain convinced that RCTs are the "gold standard" and the *only* acceptable source of convincing evidence, RCTs will continue to be demanded to settle therapeutic controversies.

We agree with Toth that it would be valuable to determine the true value of RCTs in settling disputes and affecting clinical practice. We also believe it would be valuable to develop less costly, alternative research methods that may, with suitable criteria [1–3], sometimes be equally or almost equally valid.

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REGIONAL VARIATION IN ISCHEMIC HEART DISEASE: A POSSIBLE MISSING RISK FACTOR?

In a recent issue, Garg *et al.* [1] investigated regional variations in the incidence of ischemic heart disease (IHD) in the U.S., and found an approximately 40% greater incidence of IHD in the non-western US, which could not be accounted for by adjustment for known cardiac risk factors. Although these results could have been influenced by methodologic problems, as noted by the authors, another possibility is that they reflect geographic variability in another coronary risk factor which was not accounted for in their study.

Recent intriguing epidemiologic information suggests that chronic *Chlamydia pneumoniae* infection may be an independent risk factor for coronary artery disease, and should be accounted for in future epidemiologic studies [2–4]. Furthermore, *C. pneumoniae* organisms have recently been demonstrated within coronary arterial fatty streaks and atheromatous plaques [5]. There is a significant interaction between *C. pneumoniae* infection and smoking, which raises the possibility that smoking may be associated with IHD in part via promotion of *C. pneumoniae* respiratory tract infection [6, 7].

C. pneumoniae infection is prevalent worldwide [8], and evidence suggests that it may be more endemic in younger age groups in areas of greater population density [9]. It is possible that chronic *C. pneumoniae* infection could be

responsible for some of the regional variation in the incidence of IHD noted by Garg *et al.* [1]. Further studies of the geographic variability of *C. pneumoniae* seroprevalence, and association with IHD, are important.

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Response

The relationship between *C. pneumoniae* infection and coronary artery disease has only recently been documented in the literature. It would be interesting to examine whether some of the regional variation in the incidence of ischemic heart disease was related to *C. pneumoniae*. Unfortunately, most of these cases are treated as outpatients and this data was not collected in this longitudinal study. Although this longitudinal study collected data on all hospitalizations, diagnosis of *C. pneumoniae* is not included in the 9th revision of ICD coding. Therefore, we are unable to examine this relationship because the data on hospitalization for *C. pneumoniae* was not available.

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