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REPLY

The specific commission of our review, titled “The Year in Atherothrombosis,” was to highlight clinically relevant studies in the field published within the last year (1). The letter from Dr. Domínguez-Rodriguez and colleagues highlights the importance of the circadian rhythm in the presentation of acute coronary events, a concept established several years ago. The last citation of their letter quotes a study published in 2004, evaluating the light/dark cycle of cytokines and melatonin plasma levels in patients with acute myocardial infarction (AMI) (2). This single, observational, case-control study suggested an association between high levels of interleukin-6 and low levels of melatonin during the dark cycle in patients with AMI. The investigators should be congratulated for their effort. However, the study is not mechanistic, and does not prove causality. Furthermore, the clinical significance of their findings still remains to be elucidated. As a result, in our judgment the study may not meet the criteria to be included as a clinically relevant publication in atherothrombosis in the year 2004.

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Viruses and Other Environmental Factors as Possible Sources of Phenotypic Heterogeneity in Familial Dilated Cardiomyopathy

In their interesting and recent state-of-the-art study, Burkett and Hershberger (1) stated that “familial dilated cardiomyopathy (DCM) demonstrates incomplete penetrance, variable expression, and significant locus and allelic heterogeneity, making clinical and genetic diagnosis complex.” The statement clearly describes a key problem encountered during the genetic dissection of human DCM. This problem reaches beyond the fact that multiple genes may cause the DCM phenotype in humans and that further loci shall be revealed in the future. Even within a single DCM family or within a group of unrelated DCM patients harboring defects in the same gene, there is often very large and currently unexplained phenotypic heterogeneity. There are at least two possible sources for this heterogeneity.

First, unless representative healthy control populations are screened for a given mutation one cannot be sure that this mutation is capable of causing the phenotype without additional cofactors (modifier genes or environmental agents) being present. In other genetic disorders the screening of large control populations has been the indispensable basis for the discovery of such cofactors. For example, smoking was identified as an essential environmental factor for the development of lung disease in genetic α1-antitrypsin deficiency, initially assumed to cause the disease per se on a pure genetic basis. For most mutations associated with DCM we do not yet have frequency data representative of the general healthy population that can be compared with the rather small DCM patient cohorts from which the disease association is usually derived. The relative pathogenic contribution of the gene defect per se as compared to hitherto unknown cofactors is therefore uncertain.

Second, data on possible environmental agents are sparse in molecular genetic studies of familial DCM. Regarding such cofactors, we have recently detected cardiac viral infections in 165 (67.4%) of 245 cases in a molecular virological survey based on myocardial biopsies from a series of DCM patients (2), with a broad spectrum of virus species being involved. Cardiotropic viruses thus emerged as prevalent environmental factors that may possibly cause or influence the course of DCM. The high frequency of cardiotropic viruses detected in that DCM series makes it highly likely that cardiac viruses are also encountered in familial DCM. They may explain part of the large phenotypic heterogeneity mentioned by Burkett and Hershberger (1), but will go unnoticed unless cardiac biopsies are specifically investigated using molecular virological methods. A synopsis of the current data suggests that a comprehensive picture of the pathogenesis of familial DCM can only be obtained if both genetic and environmental factors are analyzed. Studies of this type may lead to the
identification of important new genome–environment interactions in DCM pathogenesis (3) and also have implications for the clinical management of DCM patients.

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REPLY

We appreciate the interest in our recent review (1) of the genetic basis of dilated cardiomyopathy from Drs. Poller, Schultheiss, and Kühl. We agree with the first point that the screening of healthy, unselected populations is always important to more fully understand genetic variation. We also agree with the general premise of the second point that understanding gene/environment interactions can be helpful, and at times essential, for understanding the pathogenesis and progression of genetic disease.

We also suggest that the first point of Drs Poller and colleagues (“... unless representative healthy populations are screened...”) may be even more important for their work (2) to ascertain any role of viruses in causing idiopathic dilated cardiomyopathy (IDC). In their study only myocardial samples from patients with IDC were examined for virus, but no myocardial samples from any control group (e.g., ischemic cardiomyopathy, or a “representative healthy population”) were reported. This raises the question of whether viruses, ubiquitous in all living organisms and perhaps equally so in control myocardium, are relevant for IDC.

Although it is likely that environmental influences affect penetrance and phenotype, it is also clear that a great deal of phenotypic variation can be attributed to epigenetic variation independent of environmental influence. Transcriptionally competent retrotransposons likely number in the thousands in mammalian genomes, and, for example, have been shown to cause the considerable phenotypic variation that is routinely observed in isogenic mouse strains (3). Understanding the genetic, epigenetic, and environmental factors that cause or modify human disease will require a great deal of careful effort supported by the most robust controls possible.

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Cardiovascular Manifestations of Carbon Monoxide Poisoning

We read with interest the report by Satran et al. (1) on the cardiovascular manifestations of carbon monoxide (CO) poisoning. In the Hospital Río Hortega of Valladolid (Spain), we followed CO poisonings prospectively for two years (2). The protocol included, among other parameters, carboxyhemoglobin (COHb) levels, electrocardiogram (ECG), creatine kinase (CK) and CK-MB. During the study period studied, 154 patients were included, of whom 20% (n = 31) presented sinusal tachycardia, 5% (n = 8) arrhythmias (mainly auricular fibrillation), and 4% (n = 6) ischemic changes, including one patient in whom cardiac catheterization was carried out without findings of coronary artery disease. Eight (7.2%) adult patients and 25.6% (n = 10) of patients under 10 years of age had elevated CK levels. Similarly, CK-MB levels were elevated in 1.8% (n = 2) of adults and in 12.7% (n = 5) of children (p < 0.01) (2). In our series, the percentage of patients with cardiovascular manifestations is inferior to that described by Satran et al. (1). We suggest that this is because our study population included all CO poisonings, of which 40% were mild (COHb <25%), whereas Satran et al. (1) included only moderate or severe poisonings. The fact that elevated CK and CK-MB levels occur more frequently in children than in adults suggests a greater toxicity or affinity of CO for the pediatric musculature, although this hypothesis remains to be verified.

Satran et al. (1) report that, in an unspecified number of patients, the etiology of the CO poisoning was fire exposure, and that eight patients died owing to burn injuries (1), but they make no reference to plasma lactate concentrations. Lactate is the principal marker of cyanide (CN) in the blood of patients who inhale fire smoke, and levels greater than 10 mmol/l suggest that, in these patients, CN plays a more important role than does CO (3,4). We suggest that a percentage of the myocardial ischemias described by Satran et al. (1) may be due to fire smoke inhalation syndrome and not solely to CO poisoning. Smoke from fires contains a mixture of gases, but of these it is CO and CN that provoke tissue hypoxia and may lead to death (5). Although the protagism of CO in the multifactorial hypoxia of fire smoke inhalation syndrome is well known, the role of CN is less so (4).