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CONCEPT CLEARANCE

For

The Role of Environmental Agents in Cardiovascular Disease

Introduction

Cardiovascular disease is the primary cause of mortality in the industrialized world. According to the American Heart Association, over 950,000 people died of cardiovascular disease (CVD) in the United States in 1999. This represents a death rate of 350 per 100,000 people and accounts for 40% of all deaths. The major "traditional" risk factors for CVD include, race, age, lifestyle (such as smoking, physical inactivity, serum lipids, and diet) and family history. In addition to these "traditional" risk factors, clear links between CVD and environmental agent exposure(s) have now been established, but the mechanisms by which these agents cause or contribute to disease have not been well characterized.

Associations between CVD and inhaled particulate matter (PM) or other air pollutants, such as carbon monoxide and ozone, have been noted. The association between exposure to ambient particulate matter and CVD has been somewhat surprising but is nonetheless robust. Increases of 0.5 - 2.0% in premature CVD deaths per 10 mg/m³ of PM have been noted. Epidemiologic studies have also shown associations between exposure to PM and CVD morbidity (e.g., hospital admissions for CVD), as well as between PM and pathophysiologic changes that are associated with CVD, such as changes in heart rate variability (HRV) and blood parameters. PM exposure has also been shown, in experimental animal studies, to increase the severity of atherosclerosis. Polycyclic aromatic hydrocarbons (PAHs), such as benzo(a)pyrene, are components of outdoor air pollution, primarily from combustion of fossil fuels, as well as of indoor air, primarily from environmental tobacco smoke (ETS). PAHs have been shown to alter the redox environment in vascular walls, activating signaling pathways that can lead to proliferation of vascular smooth muscle cells. Similarly, cigarette smoke causes mitochondrial damage, which is associated with increased atherosclerosis. Certain aldehydes on the EPA's list of "Air Toxics" can present workplace as well as environmental exposure risks. Aldehydes, both exogenous and endogenous, can induce proliferation of vascular smooth muscle cells, one of the hallmarks of atherosclerosis. The mechanisms by which PM toxicity induces the CVD-related pathophysiological changes are not adequately known or understood. It has been suggested they might involve anomalous stimulation of the autonomic nervous

system, production of inflammatory mediators, generation of reactive oxygen species in the lung, and/or direct toxic effects on cardiovascular tissues.

Airway exposures to agents that are associated with CVD are not the only vector of exposure of consequence. It is known that exposure to arsenic (As) through occupational exposures or via drinking water is associated with increased CV morbidity, including a condition known as “blackfoot,” a peripheral vascular disease. Arsenic has been shown to cause oxidative stress in the vascular tissues of occupationally exposed workers. This is a condition associated with the development of atherosclerosis. Given that environmental arsenic exposure is a reality in the US as well as in other countries, the contribution of arsenic to CVD prevalence needs further study. In addition, *in vitro* experiments with arsenic hold the promise of further elucidating CVD-related cellular dysfunctions in endothelial and vascular smooth muscle cells.

There are, therefore, many avenues of research that have pointed to an important role for environmental agents in cardiovascular disease. However, a more focused effort to better understand this role in the adult is needed.

On August 6 and 7, 2002, a workshop entitled, “The Role of Environmental Agents in Cardiovascular Disease” was held in Durham, N.C. The workshop was sponsored by the NIEHS, EPA, NHLBI, the American Heart Association Council on Epidemiology and Prevention and Expert Panel on Population and Prevention Science, and St. Jude Medical, Inc. The participants identified numerous questions and research issues, which included:

- \$ What diseases of the cardiovascular system are associated with exposure to environmental agents?
- \$ What other factors might interact with environmental exposure to increase the risk of CVD?
- \$ By what mechanisms do environmental agents cause or contribute to CVD?
- \$ What factors make individuals more susceptible to the effects of environmental agents?

NIEHS maintains an active program in environmentally related cardiovascular disease. Many of the studies describing the association between PM and CVD were funded by prior activities of the NIEHS, as were the studies on the effects of PAHs and ETS on vascular smooth muscle cells. NIEHS previously released two Program Announcements related to CVD linkages resulting from prenatal exposures: “Environmentally Induced Cardiovascular Malformations” (PA-02-093) and “The Fetal Basis of Adult Disease: Role of the Environment” (PAR-02-105). However, given the importance of CVD as a public health concern, the growing evidence that exposure of adolescents and adults to various ambient environmental agents plays a role in subsequent CVD prevalence, and the recommendations from the above-mentioned workshop, it appears timely and highly warranted to focus additional research efforts on specifically identifying environmental cardiovascular toxicants and elucidating their toxicity mechanisms. Recent, rapid advances in the fields of cellular biology (e.g., cell signaling and signal transduction) and

molecular biology technology, including genomics and proteomics, now greatly increase the likelihood of significant advancements in the field. Multidisciplinary approaches to complex questions like these are generally more successful, some environmental health science and cardiovascular researchers have successfully bridged the gap between multiple disciplines to develop innovative approaches to the study of environmentally induced CVD. Therefore, enhanced multidisciplinary research collaboration is now seen as vital to the success of contemporary research efforts.

Research Goals and Scope

The purpose of this initiative is to support innovative, multidisciplinary research to identify environmental agents that cause or exacerbate cardiovascular disease, to elucidate mechanisms of cardiovascular toxicity by these agents, and to identify susceptibility factors, such as genetics and pre-existing disease. The major focus of the initiative will be the identification and evaluation of the mechanisms of environmentally induced adult CVD. The initiative is also designed to expand the number of researchers working in the area of environmentally related cardiovascular disease, by encouraging cardiovascular researchers to apply the newest tools and models to the problem of environmentally related CVD. Collaborative, multidisciplinary approaches are seen as the best way to address gaps in knowledge in this area. Cardiovascular researchers have developed models and technologies that could prove invaluable in the study of the cardiovascular effects of environmental agents. Therefore, collaborations between environmental health science researchers and cardiovascular researchers or cardiologists would be required for the R01 grant applications responsive to this initiative.

The initiative will encourage basic (*in vitro and in vivo*) research, as well as controlled human exposure studies and small clinical studies (but not large-scale population-based or epidemiological studies) using state-of-the-art technologies, such as proteomics/genomics/systems biology and the use of transgenic and gene-targeted mutant animal models. As it is clear that certain populations and individuals are more susceptible to the effects of certain environmental agents, studies using animal and /or human exposure models to consider the role of such factors as genetic predisposition, race, age, gender (including the influence of hormones), pre-existing disease (e.g., lung disease, or diabetes), diet, socioeconomic status, and obesity will be encouraged.

Proposals will be expected to directly address the role of environmental agents in specific cardiovascular diseases or disease processes, such as atherosclerosis, cardiac hypertrophy, heart failure, sudden cardiac death, stroke, arrhythmias, hypertension, and cardiomyopathy. Examples of environmental agents of interest include air pollutants (such as particulate matter or gases like carbon monoxide or ozone), metals, aldehydes, PAHs, and xenoestrogens (e.g., bisphenol). If the agent is a complex mixture, such as PM, efforts to characterize the agent and identify the important components will be encouraged. Examples of potential mechanisms might include changes in cell signaling (including apoptosis) and signal transduction, inflammatory processes (e.g., inflammatory

mediators, cytokines, adhesion molecules), changes in gene expression, oxidative stress (e.g., the roles of reactive oxygen and nitrogen species, enzymes such as NAD(P)H oxidase and the cyclooxygenases, and antioxidants), electrophysiological changes (such as heart rate variability), and changes in blood components. Proposals would be encouraged to study organs and tissues from all levels of the cardiovascular system, including cardiac (e.g., myocardium and the conducting system) and vascular tissue, including the large vessels, coronary arteries, peripheral vasculature, microcirculation, various vascular beds (e.g., kidney glomeruli), and blood (e.g., leukocytes and plasma proteins and lipids). Within these tissues, cellular functions of specific interest would include endothelial cell functions, ion channel function and contractility in cardiomyocytes and vascular smooth muscle cells (VSMCs), and leukocyte function as it relates to CVD (e.g., macrophages in atherosclerotic plaques).

It is anticipated that this initiative will involve collaboration with the NHLBI and/or the Environmental Protection Agency.