
Domain Introduction

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Imagine that a killer is loose and that not only is it the number one cause of death in the United States but also that it has been the number one killer every year since 1900, except one. Imagine that this killer stalks Americans over the course of many years, striking on average every 33 seconds and accounting for more deaths than the next seven leading causes of death combined! And imagine that social and behavioral factors are the major determinants of where this voracious killer strikes. It's not imaginary; it's true. The identity of this killer is cardiovascular disease (Wright, 1997).

Dealing with this killer is also financially ruinous. At the twilight of the twentieth century, there were approximately 60.2 million physician office visits and 4.5 million hospital emergency room visits with a principal diagnosis of cardiovascular disease (Slusarcick and McCaig, 2000). During approximately the same period, hospital expenses for cardiovascular problems totaled \$26.1 billion—or 33.3% of all hospitalization expenditures (Frankenfield, Marciniak, Drass, and Jencks, 1997). Persons with cardiovascular disease rank first among all disease categories in numbers of hospital discharges.

The National Heart, Lung, and Blood Institute was one of the first at the National Institutes of Health (NIH) to complement biological levels of analysis with social, psychological, and behavioral levels because the evidence for their contributions to the development and course of cardiovascular disease was undeniable. For instance, about one in five deaths from cardiovascular diseases is attributable to smoking. The risk of myocardial infarction is highest at lower levels of high-density lipoprotein (HDL) cholesterol levels and higher total cho-

lesterol levels, both of which are affected by diet and exercise (e.g., Day, 2001; Keil, 2000). Individuals who do not feel socially connected show larger age-related increases in blood pressure and are less likely to survive cardiovascular disease than are individuals who do feel socially connected (House, Landis, and Umberson, 1988; Seeman, 2000; Uchino, Cacioppo, and Kiecolt-Glaser, 1996). A sedentary lifestyle and emotional reactivity (e.g., hostility) have also been identified as major predictors of cardiovascular disease and death (e.g., Gump, Matthews, and Raikonen, 1999). Overweight (body mass index of 25–30) and obese (body mass index over 30) individuals also are at greater risk for cardiovascular disease (Melanson, McInis, Rippe, Blackburn, and Wilson, 2000). Overall, the relative risk of coronary heart disease associated with a sedentary lifestyle ranges from 1.5 to 2.4, an increase that is comparable to smoking, high blood pressure, or high blood cholesterol (e.g., Beilin, 1999).

Although social, psychological, and behavioral factors have been linked to cardiovascular disease, the mechanisms underlying these associations have received less attention. The chapters in Part I illustrate the important contributions of multilevel integrative analyses to the understanding of these basic mechanisms and to the delineation of the etiology of cardiovascular disease (Cacioppo, Berntson, Sheridan, and McClintock, 2000). Although the specific subject populations, methods, focus, and cardiovascular endpoint differ across these chapters, they share several features. First, each chapter represents a program of research that exemplifies scientific synergism, extending beyond the technical or scientific capacity of a single investigator. Each considers not only predisease pathways within the brain, genetic heritage, or cardiovascular system but also contextual (e.g., social, cognitive, behavioral) factors. Each also uses new and emerging methods and technologies that require multidisciplinary collaborations (e.g., biomedical engineers, cardiologists, biopsychologists, health psychologists). And each, in quite different ways, illustrates that cardiovascular regulation and dysregulation and, ultimately, the development and effective treatment of cardiovascular disease demands a consideration of social and behavioral, as well as physiological and genetic, levels of representation—levels that deal, for example, with individual differences, stress appraisal and reactivity, and social context.

Gary Berntson and John Cacioppo (chapter 1) review work on the heterarchical organization of the nervous system, with multiple but interactive levels of processing that may manifest differently as one moves from rostral (higher) to caudal (lower) levels of the central nervous system. For example, Berntson and colleagues used pharmacological manipulations in humans to map the range and topography of the neural control of the heart in response to both nonpsychological stressors (orthostasis) such as postural variation and psychosocial stressors such as active coping (e.g., mental arithmetic). The neural control of the heart's response to orthostasis is regulated primarily by mechanisms in the brain stem, whereas the neural control of the heart's response to active coping tasks involves more rostral (e.g., cortical) mechanisms. The neural control of the heart is communicated generally through the sympathetic (excitatory) and parasympathetic

(inhibitory) branches of the autonomic nervous system. Berntson and colleagues measured the sympathetic and parasympathetic contributions to cardiac responses based on autonomic blockade studies.

The traditional dogma is that sympathetic and parasympathetic innervations of the heart are reciprocally activated. This principle was evident in nomothetic (group) analyses for both the orthostatic and the active coping tasks. At the group level, both the orthostatic stressor and the psychosocial stressors yielded an essentially equivalent pattern of heart rate increase, with the underlying mechanism appearing to be sympathetic activation and parasympathetic withdrawal. Idiographic (individual difference) analyses revealed a different pattern, however. For the orthostatic (nonpsychological) stressor, the cardiac response reflected a relatively tight reciprocal central control of the autonomic branches, as suggested by the nomothetic analyses. But the cardiac response to psychosocial stressors showed considerable individual differences in the pattern of autonomic response and virtually no correlation between responses of the two branches of the autonomic nervous system. Furthermore, the idiosyncratic patterns of neural control were highly reliable across different psychological stressors, with some individuals showing primarily sympathetic activation, some showing reciprocal sympathetic activation and parasympathetic withdrawal, and others primarily parasympathetic withdrawal. These results suggest that cardiovascular regulation (and dysregulation) is more flexible and idiosyncratic as more central neurobehavioral mechanisms become involved. These studies also point to the need for more sophisticated conceptualizations of stress and cardiovascular disease, with a special emphasis on social and psychological characteristics that lead to risky patterns of sympathetic activation due to natural life demands.

Kathy Light, Susan Girdler, and Alan Hinderliter (chapter 3) have similarly focused on cardiovascular reactivity, but they have examined its relationship to hypertension and predisease indicators of hypertension (such as left ventricular mass). They report, for instance, that the magnitude of blood pressure responses during laboratory stressors and natural life demands were stronger predictors of left ventricular mass index and relative vascular wall thickness than was either clinical blood pressure or baseline blood pressure. These and related studies by Light and colleagues indicated that cardiovascular responses to the demands of everyday life add prognostic information to that obtained from clinical blood pressure levels. Consistent with the work of Berntson and his colleagues, such identification of the social and psychological processes responsible for high reactivity (e.g., cognitive appraisal processes) will further advance our understanding of the etiology and prevention of cardiovascular disease.

As a significant example of such studies, Light and colleagues have shown that the risk of hypertension varies with family history, but family history per se does not doom one to life with hypertension. To test whether stress reactivity to the demands of everyday life would increase the risk of later blood pressure elevation in those individuals with a genetic susceptibility to develop hypertension, Light et al. conducted a 10-year follow-up study of young men. The results

revealed that men with a positive family history of hypertension had a twofold increase in risk of elevated blood pressure over 10 years than had men with a negative family history. However, men with a positive family history who also were in the top quartile in cardiovascular reactivity (as measured 10 years earlier) had a sevenfold increase in risk. In addition, in the high reactors, high exposure to stress fostered increases in blood pressure at the follow-up visit. This research not only suggests substantial plasticity in the relationship between genetic factors and the development of cardiovascular disease but also attributes a major role to social and psychological influences on cardiovascular function.

In a series of studies in cynomolgus monkeys, Jay Kaplan and Stephen Manuck (chapter 4) demonstrate that social disruptions and instability promote coronary atherogenesis, a form of cardiovascular disease. Animals that exhibited a heightened cardiac reactivity to stress were found to develop the most extensive coronary lesions. But β -adrenergic blockade, which eliminates the effects of sympathetic activation, diminished the behavioral exacerbation of atherosclerosis. This result points to sympathetic activation as a major contributor to coronary atherogenesis.

To study the effects of a stressful social environment, social groups were repeatedly reorganized in the Kaplan and Manuck studies. Macaque males responded antagonistically to the presence of strangers and reasserted their hierarchic relationships. Even in the absence of an atherosclerosis-inducing diet, disruptions of social connections increased the formation of coronary disease (in the form of endothelial lesions). This result was eliminated by β -adrenergic blockade, again implicating sympathetic activation as a major contributor to coronary disease, at least in males. The story for Macaque females is somewhat different but helps explain the differential susceptibility of males and females to atherosclerosis before menopause and then the similarities after menopause.

Given that all of these pioneering programs of research have had to overcome funding issues that typically hinder interdisciplinary research, the authors address both the obstacles to such research they encountered and the means by which they overcame them. We hope that their stories—the trials and tribulations, as well as successes—will offer some guidance and encouragement to others who are contemplating multilevel integrative research so that we might better understand, prevent, and ameliorate the effects of what has been the leading killer in the United States for more than a century.

REFERENCES

- Beilin, L. J. (1999). Lifestyle and hypertension: An overview. *Clinical and Experimental Hypertension*, 21, 749–762.
- Cacioppo, J. T., Berntson, G. G., Sheridan, J. F., and McClintock, M. K. (2000). Multi-level integrative analyses of human behavior: The complementing nature of social and biological approaches. *Psychological Bulletin*, 126, 829–843.
- Day, D. (2001). Population-based screening with the coronary heart disease risk factor calculator. *Advances in Therapy*, 18, 21–32.

- Frankenfield, D. L., Marciniak, T. A., Drass, J. A., and Jencks, S. (1997). Quality improvement activity directed at the national level: Examples from the health care financing administration. *Quality Management in Health Care*, 5, 12-18.
- Gump, B. B., Matthews, K. A., and Raikkonen, K. (1999). Modeling relationships among socioeconomic status, hostility, cardiovascular reactivity, and left ventricular mass in African American and White children. *Health Psychology*, 18, 140-150.
- House, J. S., Landis, K. R., and Umberson, D. (1988). Social relationships and health. *Science*, 241, 540-545.
- Keil, U. (2000). Coronary artery disease: The role of lipids, hypertension and smoking. *Basic Research in Cardiology*, 95 Suppl 1, I52-158.
- Melanson, K. J., McInnis, K. J., Rippe, J. M., Blackburn, G., and Wilson, P. F. (2000). Obesity and cardiovascular disease risk: Research update. *Cardiology in Review*, 9, 202-207.
- Seeman, T. E. (2000). Health promoting effects of friends and family on health outcomes in older adults. *American Journal of Health Promotion*, 14, 362-370.
- Slusarcick, A. L., and McCaig, L. F. (2000). National hospital ambulatory medical care survey: 1998 outpatient department summary. *Advance Data*, 317, 1-23.
- Uchino, B. N., Cacioppo, J. T., and Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin*, 119, 488-531.
- Wright, R. O. (1997). *Life and Death in the United States: Statistics on Life Expectancies, Diseases and Death Rates for the Twentieth Century*. New York: McFarland.
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