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## 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 cholesterol

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 hierarchical 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  $\beta$ -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 hierarchical relationships. Even in the absence of an atherosclerosis-inducing diet, disruption of social connections increased the formation of coronary disease (in the form of endothelial lesions). This result was eliminated by  $\beta$ -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 help 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.

### Postscript

The dominant metaphor for the scientific study of the human mind during the latter half of the twentieth century has been the computer — a solitary device with massive information processing capacities. So powerful was the grip of this metaphor on the field that the first published reference to the term “soci

neuroscience" in 1992 required an accompanying explanation of why the term was not an oxymoron (Cacioppo and Berntson, 1992). Computers today are massively interconnected devices with capacities that extend far beyond the resident hardware and software of a solitary computer. It has become apparent that the tele-receptors (e.g., eyes, ears) of the human brain have provided wireless broadband interconnectivity to humans for millennia. Just as computers today have capacities and processes that are transduced through but extend far beyond the hardware of a single computer, the human brain has evolved to promote social and cultural capacities and processes that are transduced through but that extend far beyond a solitary brain. To understand the full capacity of humans—and the full range of pathogenic stimuli contributing to human disease—one needs to appreciate not only the memory and computational power of the brain but also its capacity and predilection for representing, understanding, and connecting with other individuals.

Indeed, humans are irrepressibly social, and their connections with one another extend beyond time and space. These effects are evident in the updates by Light, Girdler, and Hinderliter (Chapter 3), who have built on their earlier collaboration to investigate the salubrious effects of social contacts that extend beyond the presence of significant others. In studies of loving spouses and loving mothers and infants, Light and colleagues have found that meaningful social connections buffer the effects of stress even when the other is absent, that these effects are not only palpable but are large and replicable, and that specific, neurohormonal mechanisms are responsible for these effects. Rigorous scientific advances have come forth so quickly, it seems inconceivable that fewer than 20 years ago one had to justify the scientific validity of social neuroscience.

Berntson and Cacioppo (Chapter 2) have extended their studies of the effects of social isolation on mind, brain, neuroendocrine activity, genetics, and health in a population-based longitudinal study of middle-aged and older adults from the Chicago metropolitan area. The size and interdisciplinary breadth of their collaboration have increased as the nature and complexity of the questions that were asked and the methods that were incorporated stretched their collective expertise. Where measures of the internal workings of the brain and body in the recent past required invasive procedures, often limited a short time ago to patient and animal studies, imaging procedures are now safe and available to study predisease processes in normal, waking individuals. Where a decade ago, single gene transcripts were assayed with difficulty, assays for tens of thousands of gene transcripts are now readily available. Using functional magnetic resonance imaging, Berntson, Cacioppo, and colleagues recently found that the ventral striatum, an area associated with reward, is down-regulated in people lacking meaningful social connections when viewing pleasant pictures involving people. This finding provides a mechanistic explanation for the stress buffering effects enjoyed by individuals who have satisfying social connections but not by individuals who feel socially isolated. In the early 1990s, Williams, Kaplan, Manuck and colleagues found that disrupted social environments were associated with endothelial dysfunction in cynomolgus

monkeys (Williams, Kaplan, and Manuck, 1993). Thirty-six monkeys were given an atherogenic diet for 36 months in one of three experimental conditions: (1) "stable" social environment group, (2) "early stress" group characterized by unstable social environment in the first half of the study followed by stable social environment in the second half, and (3) "late stress" group characterized by stable social environment in the first half of the study followed by unstable social environment in the second half. Among monkeys in the "late stress" group, vasodilation to acetylcholine was decreased compared to the stable group, indicating a decrease in endothelial function. In recent work, Kaplan and Manuck (Chapter 4) have found greater endothelial dysfunction in subordinate than dominant female animals, and this effect did not depend on diet. Their results indicate that social stressors may have a greater effect on endothelial function in female animals, rather than on changes in plasma lipid profiles. The association between mental stress and endothelial function has also been observed in humans, and underscores the importance of the social environment as a pathogenic agent.

Finally, biological systems are particularly prone to variation, and to bridge the gap between psychological phenomena and their underlying biological substrata such variation can be regarded as important data in its own right (Kosslyn et al., 2002). All three collaborative teams featured here combine nomothetic and idiographic factors to identify the transduction pathways through which the social world promotes or protects against cardiovascular disease.

In sum, the scientific teams whose work was highlighted in the first edition have continued their collaborations and in each case their work has grown more interdisciplinary. Multidisciplinary research is characterized by the aggregation of the work of different experts—i.e., by investigators coming together with their different expertises to solve problems, and then returning, largely unchanged by the collaboration, to their own disciplines. Interdisciplinary research, by contrast, is characterized by synergies among experts that can transform. Interdisciplinary scientific research can be riskier than multidisciplinary research because multidisciplinary research requires only that one share an established procedure with an investigator in another field. Interdisciplinary research, however, often requires innovation at the conceptual and operational levels of research. The success of interdisciplinary efforts rest on interactions among group members—it is a group product rather than the simple sum of its individual products. Accordingly, interdisciplinary teams are more subject to failure than solitary and multidisciplinary scientific efforts. But with this higher risk also comes the potential for higher payoffs in the form of innovation and comprehensiveness.

Although obstacles remain, there is an increasing dominance of interdisciplinary teams in the production of scientific knowledge, and an increasing impact of scientific discoveries that reflect the work of teams relative to individuals (e.g., Wuchty, Jones, and Uzzi, 2007). The contextual conditions that have fostered the current momentum are manifold. The twentieth century saw a growth and maturation of psychological science and relevant disciplines to the point that they now

provide a solid base from which to launch successful interdisciplinary expeditions. Advances in mathematical tools for dealing with large and complex data structures have helped the psychological sciences bridge to other disciplines. At the same time, the development of new and powerful methods and measurement tools promoted productive interdisciplinary research across the neurosciences, cognitive sciences, behavioral sciences, and social sciences. As the postscripts to this new edition testify and as detailed analyses have verified (e.g., Wuchty, Jones, and Uzzi, 2007), the landscape of science is changing and the notion of the solitary genius advancing knowledge is being replaced by teams of scientists asking big questions that are no longer constrained by traditional disciplinary boundaries. The recent abandonment of the metaphor of the solitary computer in favor of the metaphor of the internet with its massively interconnected computers may be as applicable to the scientific enterprise as to the mind.

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