Stress & Hypertension

Examining the

Relation between

Psychological Stress and High Blood Pressure

Kevin T. Larkin

Current Perspectives in Psychology

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To my wife, Heather,
and daughters, Emily and Meredith,
and patients like Franklin

Contents

Series Foreword

Current Perspectives in Psychology presents the latest discoveries and developments across the spectrum of the psychological and behavioral sciences. The series explores such important topics as learning, intelligence, trauma, stress, brain development and behavior, anxiety, interpersonal relationships, education, child rearing, divorce and marital discord, and child, adolescent, and adult development. Each book focuses on critical advances in research, theory, methods, and applications and is designed to be accessible and informative to nonspecialists and specialists alike.

Essential hypertension is of epidemic proportions worldwide and is a key contributor to heart disease and stroke. The prevalence rates vary widely across cultures and groups (e.g., ethnic, socioeconomic strata) within a country. Stress plays a significant role in the development and exacerbation of hypertension. Both hypertension and stress are of interest in part because of their relation to a surprising array of areas of functioning including obesity, alcohol use, diabetes, physical activity and exercise, anxiety, work, and interpersonal relationships. This book provides an excellent review of the current status of research on both stress and hypertension, with excellent excursions into the other topics.

Hypertension encompasses intricate pathways involving biochemistry, genes and proteins, and brain and other organ regulation. Dr. Kevin Larkin has presented these complex topics in a way that is engaging and informative. This excellent style is continued throughout as he addresses the latest research findings and their nuances. This book reflects a balance of theory and research and attention to etiology, risk factors, treatment, and prevention. Also, there is an even weighting of biological and psychosocial influences. Gender, culture, and ethnic differences in hypertension are among the fascinating topics included in the book. In addition, practical and otherwise useful information is available (e.g., how to monitor one's own blood pressure, what devices not to use). We are very fortunate to have this book pre-

pared by a leading researcher who is in a position to provide an authoritative account of the problem of stress and hypertension and what can be done to mitigate their effects.

Alan E. Kazdin
Series Editor

Introduction

The Case of Franklin

Franklin is a forty-eight-year-old African American firefighter who was raised in a rural community in the midwestern United States. Although he has had high blood pressure for the past six years and has experienced a few job-related injuries, he has otherwise been healthy for most of his life. He lives in the same town in which he was raised. Both his parents, who live next door, have high blood pressure, and his father had a heart attack three years ago. He is very close to them, attending church with them and eating several meals with them weekly. Franklin is somewhat overweight, like his mother and father, but is in relatively decent physical shape, as evidenced by his ability to pass the regular physical examinations associated with his job as a firefighter. His diet is fairly typical in his community; although he has had some success in decreasing consumption of high-fat foods in an effort to lose weight over the past decade, his fiber intake is low. As his parents were on low-salt diets for years, Franklin easily adopted a low-salt diet. He does not drink alcohol or smoke.

The diagnosis of high blood pressure was first made following a medical evaluation associated with a brief medical leave in which Franklin was recovering from a job-related injury. He was on a call with the rescue squad during which he had attempted to free a child

from a burning vehicle without success. The child died despite Franklin's attempts to free him from the wreckage. Franklin received third-degree burns on his left arm and hand that required graft replacement. Although recovery from the burn was complete within eight weeks, his blood pressure was found to be elevated months after the incident, and his physician prescribed medication to lower it. Franklin filled the prescription but took the medication only if he encountered a particularly stressful period of time on the job or at home. He told his co-workers that he could tell when his blood pressure was elevated and that there was "no need to take it if I am feeling good."

Franklin's experience of diagnosis and treatment is far from unusual. Millions of Americans, and likely hundreds of millions of people worldwide, grapple with issues associated with the diagnosis and treatment of high blood pressure. Because elevated blood pressure is asymptomatic, many individuals don't take their condition seriously or follow through with the available medical treatment. Others agree to begin treatment but fail to maintain it after months or years. Often, patients fail to understand the chronic nature of high blood pressure and the associated risk for cardiovascular complications, thinking that it is only an episodic problem.

One could question whether Franklin, indeed, was adequately diagnosed with the condition. Perhaps his elevated arterial pressure was related to a stress response he was experiencing following the traumatic failed rescue attempt. Once he had begun to accept the inevitability of the loss of the child's life, his blood pressure might have returned to normal levels. Other questions arise regarding the causal events associated with the diagnosis. What role does Franklin's parental history of high blood pressure play in his current medical condition? What role might his difficulty maintaining normal weight play in leading to his high blood pressure? Were there other biologic or environmental parameters that should have been examined in evaluating the etiology of the elevated arterial pressures?

Even if one agrees that Franklin was appropriately diagnosed, there are additional unanswered questions regarding the treatment identified to lower his blood pressure. Why did the physician resort to prescribing a medication? What characteristics of Franklin's were considered when selecting an appropriate anti-hypertensive medication?

Were alternative non-pharmacologic interventions considered that might have resulted in reduced blood pressure? How was the effectiveness of the intervention monitored by the prescribing physician, and at what point should alterations have been made to the treatment plan?

The brief case description presented at the beginning of this chapter really does not give us enough information to answer these questions. In fact, we really do not even know whether Franklin has high blood pressure. Unfortunately, there are hundreds of thousands of patients like Franklin going about their daily lives not really having a comprehensive understanding of their diagnosis of high blood pressure and what role their behaviors may play in monitoring the problem and treating it. They are confused about the role of stress in causing high blood pressure and the belief that the only reason blood pressure is elevated is because they live stress-filled lives. Because of this confusion, they may opt to discontinue treatment during less stressful periods.

This book is written for health professionals who treat patients like Franklin and researchers with an interest in diagnosing and treating blood pressure problems. As with all medical problems, patients bear the ultimate responsibility for maintaining their health and making appropriate medical decisions, including decisions to acknowledge the diagnosis of elevated blood pressure, to treat the condition, or to prevent it altogether. Obviously, in order to make the best medical decisions, each patient needs to be fully informed regarding the variety of etiologic agents involved in the development of high blood pressure, the scientific support behind recommendations for various treatment options, and the risks, costs, and benefits of their decisions. In this regard, patients with high blood pressure and their families may also find this book helpful.

Why Focus upon Stress and Hypertension?

Among the numerous medical diseases, syndromes, and disorders that confront modern medicine, essential hypertension (high blood pressure) stands out as a disorder that is commonly associated with stress and living a stressful life. Even the term 'hypertension' suggests a close linkage of this disorder to stress and tension rather than its more accurate description of elevated arterial pressure within the circulatory sys-

tem. Although it is commonly believed that a strong causal link exists between stress and hypertension, just what kind of empirical evidence supports this assumption? Does living increasingly stress-filled lives or exposure to extremely stressful incidents, like the trauma Franklin confronted, result in elevated blood pressure? And, if so, why don't all firefighters exhibit high blood pressure? Can strategies to improve stress management effectively lower blood pressure? The primary purpose of this book is to address these questions by examining the body of empirical evidence testing the assumption that stress is associated with the onset and maintenance of essential hypertension.

Organization of the Book

The book is organized into three sections. In the first three chapters, relevant background information is provided regarding the condition of essential hypertension (Chapter 1), strategies for assessing blood pressure problems (Chapter 2), and current models of stress (Chapter 3). These chapters include an overview of the physiological mechanisms involved in regulating blood pressure and our body's stress responses, respectively. Although the reader will notice common physiological mechanisms described in these chapters, the description of essential hypertension focuses primarily upon the circulatory system and the description of stress focuses primarily on the nervous system. Attention is paid to both pertinent historical theoretical accounts and the latest empirical research conducted by behavioral scientists in these introductory chapters. Additionally, current methods of assessing blood pressure are discussed. Although most people are familiar with the standard method for measuring blood pressure using an occluding cuff, stethoscope, and a good set of ears, there are many other devices that can be used to measure blood pressure reliably. Most important, advances in ambulatory blood pressure measurement that have made blood pressure detection possible in locations and times that previously were not possible are covered in some detail.

In the next four chapters, theoretical and empirical work integrating the conditions of high blood pressure and stress will be introduced. In Chapter 4, evidence linking stress with incidence of essential hypertension is reviewed, providing the foundation for a comprehen-

sive model of stress and related factors involved in the etiology of essential hypertension. Mechanisms that explain how a psychological construct like stress can result in the physiological state of chronic elevated blood pressure are considered in Chapter 5, with a special emphasis upon acute physiological responses to stress. A considerable amount of attention is paid to examining evidence linking stress and hypertension through exaggerated cardiovascular reactions to stress. Finally, information presented in Chapters 6 and 7 illustrates the broad range of individual difference variables that have been suspected of being involved in the etiology of essential hypertension, including constitutional variables like gender and obesity, lifestyle factors like alcohol consumption, psychological parameters like inhibited anger expression, and social factors like a lack of social support.

The final section of the book focuses upon both pharmacologic and non-pharmacologic intervention strategies that have been used with hypertensive patients. Because the theme of this book is the integration of stress and hypertension, the analyses of these interventions focus on those that aim to lower blood pressure through lowering stress responses. The final chapter provides a summary of the major findings presented in the book and suggestions for research aimed at further clarifying the relation between stress and hypertension.

This book is aimed to provide the reader with a comprehensive overview of the literature addressing the complex relation between stress and hypertension. For behavioral researchers and scientists, I hope the content will stimulate new ideas worthy of investigation. For those who are patients or who know patients with essential hypertension, I hope the book will provide a greater understanding of the condition so that the best medical decisions regarding monitoring and treatment can be made. For the casual reader who might not want to read such a detailed presentation of empirical findings, particularly in the middle portion of the book, frequent summaries are included that present a thorough overview of the main findings of the individual studies presented earlier in each chapter.

1

Regulation of Blood Pressure

Blood has long been recognized as a vital body fluid. Prehistoric humans must have observed the spillage of blood that followed aggressive exchanges or accidents and quickly learned that loss of blood resulted in death. It is not surprising, then, that early physicians, including Hippocrates and Galen, placed a great deal of importance on defining blood as an essential bodily humor and that the examination of the pulse was described as the most important component of a correct medical diagnosis in *The Yellow Emperor's Classic of Internal Medicine,* which dates back to medical traditions in China around 2700 B.C. (for a recent translation, see Ni, 1995). Although modern medicine recognizes these early belief systems as being overly simplistic and often mystical in nature, the importance of the circulation of blood in sustaining life among virtually all vertebrate and invertebrate animals is a known scientific fact.

Our modern understanding of the human circulatory system is generally credited to William Harvey (1628/1941). Influenced by empirical study of the dissection of animals, he demonstrated that the circulation of blood worked like a hydraulic water-pumping system. In this regard, circulation of blood was conceptualized as a closed system containing blood that traverses a complex set of blood vessels to transport oxygen and nourishment to every type of cell in the body as well

as to remove cellular waste products. The heart worked like the pump in the hydraulic water-pumping system, orchestrating the rate of blood flow throughout the entire circulatory system. As in the hydraulic pumping system, pressure could be increased within the system to force the fluid (blood in this case) to flow in any direction, even against the force of gravity. What is called water pressure in a hydraulic water-pumping system is referred to as blood pressure in the circulatory system. Blood pressure clearly differs at various locations in that system. For example, blood pressure is much higher in the vessels through which it flows immediately after leaving the heart (arterial pressure) than in the vessels through which it flows as it reenters the heart (venous pressure). This difference in blood pressure is clearly evident when injuries result from severed arteries or veins. Most of the minor injuries individuals sustain throughout life involve severed veins close to the surface of the skin. In these types of injuries, blood oozes out, and blood flow can generally be stopped with gentle external pressure at the site of the wound, although it may take a few minutes. Arterial damage, in contrast, is a more dangerous situation; in this type of injury, blood ejects from the wound, pulsing with the beating of the heart. Failure to respond adequately to arterial injuries will quickly result in bleeding to death. The greater blood pressure within arteries versus veins is responsible for the rapid loss of huge amounts of blood with arterial injuries.

An organism can generate additional blood cells to release into circulation (increasing the density of circulating blood cells) or alter the resistance to the flow of blood by constricting or dilating blood vessels. Therefore, in contrast to the relatively stable water pressure that can be maintained in a hydraulic water-pumping system, blood pressure is constantly changing as the body creates and releases new blood cells and alters blood flow resistance. Additionally, because the heart does not pump blood continuously as a water pump does, blood pressure differs while the heart is pumping and while the heart is at rest. The higher arterial pressure observed during heart action (ejection of blood from the heart) is referred to as *systolic* blood pressure (SBP), and the lower arterial pressures that occur during rest just prior to the next heart beat (while blood refills the heart) is referred to as *diastolic* blood pressure (DBP). Obviously, the circulation of blood is much more

complicated than early physicians thought! Before addressing the relation between stress and hypertension, let's take a look at what we know about the structure and function of the various components of the circulatory system that affect blood pressure.

Physiology of the Circulatory System

It is likely that your blood pressure is different right now from what it was when you started reading this chapter. The difference may not be substantial, but due to the complexity of factors that affect blood pressure, it constantly changes in response to a number of physiological and environmental stimuli. For example, drinking a caffeinated or alcoholic beverage could influence your blood pressure while you read this page. Smoking a cigarette would have the same result. Your blood pressure will also differ if you are watching television while reading this page or if you are interacting with another person. Even the simple act of reading affects your blood pressure. In fact, given the constant adjustments in blood pressure that occur, we really should not refer to an individual's blood pressure as a stable medical parameter.

As depicted in Figure 1.1, blood pressure is jointly determined by the amount of blood ejected into circulation (cardiac output) and the forces of the circulatory system that impede blood flow (total peripheral resistance). Increases in either cardiac output or total peripheral resistance will result in increased blood pressure. Cardiac output, in turn, is determined by heart rate and stroke volume (amount of blood ejected from the heart with each stroke). Again, increases in either heart rate or stroke volume will increase cardiac output, and thus blood pressure. Total peripheral resistance is comprised of the degree of vasodilation and vasoconstriction that occurs in the various blood vessels that compose the entire peripheral circulation. All of these hemodynamic parameters (heart rate, stroke volume, cardiac output, total peripheral resistance) rarely operate in the same direction. Increased heart rate, for example, is often accompanied by a reduction in stroke volume, potentially resulting in no change in cardiac output or blood pressure at all. However, all physiologic or psychological states that affect blood pressure will do so by altering cardiac output, total peripheral resistance, or some combination of the two.

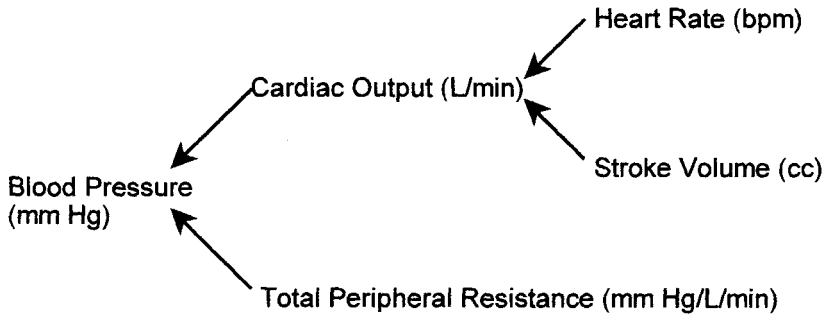

Figure 1.1. Hemodynamic parameters that affect blood pressure.

Several systems of the body directly influence blood flow through the body and the magnitude of blood pressure, including: (a) the metabolic demands of the local tissue and associated blood vessels, (b) the autonomic nervous system, (c) the neuroendocrine system, (d) the excretion of fluid by the kidney, and (e) an extensive feedback system that involves central nervous system activity. To illustrate these various interrelated systems, let's consider what happens to blood flow when a person engages in a bout of moderate exercise, like jogging on a treadmill, riding a bicycle, or taking a vigorous walk. Obviously, blood flow will need to increase to support the metabolic demands of the leg muscles, delivering more oxygen and nutrients while removing the waste by-products from the muscle cells of the legs. Unusually, although heart rate increases significantly during moderate exercise, very little change in diastolic blood pressure is typically observed (Kasprowicz et al., 1990). Therefore, during exercise, the body must engage in a variety of regulatory processes to maintain blood pressure in light of the increased cardiac activity. To provide an exhaustive overview of the physical, chemical, and neural elements involved in the regulation of blood pressure is clearly beyond the scope of this chapter and book. The following sections are meant to represent only an overview of the major systems involved in the regulation of blood pressure illustrated in Figure 1.2. The interested reader is referred to Kaplan (2002) for a more complete description of the physiological mechanisms that affect blood pressure regulation.

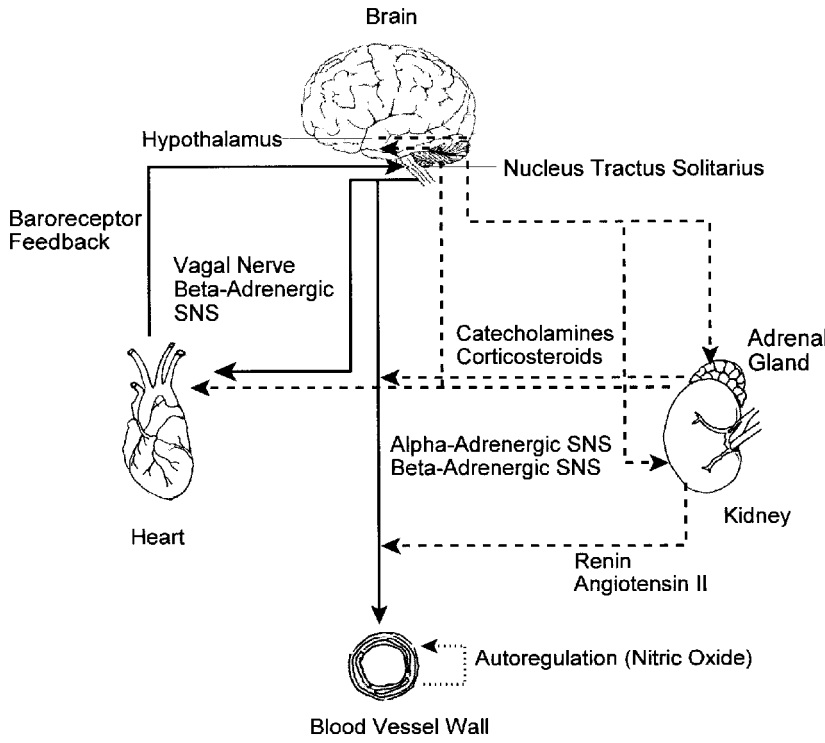

Figure 1.2. Major physiological systems involved in the regulation of blood pressure (dotted arrows represent local blood cell autoregulation; solid arrows represent neural influences; dashed arrows represent neuroendocrine influences; SNS = sympathetic nervous system).

Effects of Local Body Tissue on Blood Pressure

Because the oxygen and waste removal requirements of the muscle cells change in response to exercise, local body tissues (blood vessels that serve muscle cells) possess an intrinsic capability to regulate local blood flow. Through a process known as autoregulation, local blood vessels dilate or constrict in response to the prevailing blood pressure at that site in the vascular bed and the metabolic needs of the local cells to assure that appropriate blood flow is maintained. In this regard local factors in one part of the circulatory system can maintain blood flow under conditions of heightened blood pressure, while appropriate blood

flow can be maintained in other parts of the circulatory system under conditions of reduced blood pressure. What this suggests is that although blood flow is affected by signals from the nervous and neuroendocrine systems (described below), blood flow also can be regulated locally in the absence of these influences (see dotted arrow in Figure 1.2). Under conditions of exercise or physical exertion, blood flow increases to the striate muscles due to the increased metabolic demand of those tissues.

In recent years, increased attention has been paid to the identification of the mechanisms involved in the local regulation of blood flow. Nitric oxide, for example, has been isolated as a 'relaxing' factor that operates as a vasodilator released by local blood vessels in the circulatory system based upon the prevailing blood pressure at those sites (Palmer, Ferrige, and Moncada, 1987). As pressure increases are detected in local blood vessels, nitric oxide is released, causing the vessel to dilate and lower blood pressure. This action presumably explains how diastolic blood pressure remains relatively unaffected during cardiovascular activation that accompanies bouts of exercise. Unfortunately, circulating proteins, like C-reactive protein, that increase one's risk for atherosclerosis, appear to reduce quantities of nitric oxide, preventing adaptive blood pressure regulation at the local level (Ridker, 1998).

The Role of the Nervous System in Blood Pressure

Many fluctuations in blood flow occur as a result of alterations in signals the circulatory system receives from the nervous system. As depicted by the solid arrows in Figure 1.2, the brain communicates with various organs in the circulatory system through the autonomic nervous system. This system is comprised of two separate systems called the sympathetic nervous system and the parasympathetic nervous system. The former directs what is frequently called the 'fight-flight' response, and the latter directs what has been called the 'relaxation response.' Although initially it was thought that these two systems were interconnected (as sympathetic nervous system activity increases, parasympathetic activity decreases), it is now known that they can operate independently. In this regard, sympathetic and parasympathetic

influences can work simultaneously to affect the target organs in the body. The sympathetic nervous system employs two distinct neural systems that affect blood pressure, known as the alpha-adrenergic and beta-adrenergic systems. The alpha-adrenergic neurotransmitters and receptor systems affect blood vessels by causing them to constrict, whereas the beta-adrenergic system affects both the heart and the blood vessels. Beta-adrenergic activity leads to increased heart pumping action (increased heart rate) as well as vasodilation of blood vessels. This combination of neural influences represents an adaptive response, as the increased blood flow caused by the increase in heart rate needs more space in the vasculature in order for blood pressure to be properly regulated. The parasympathetic nervous system influences only the heart via the vagal nerve, which results in slowed heart rate. In sum, these components of the autonomic nervous system interact to regulate blood pressure with the aim of keeping it within adaptive limits. During the type of exercise described above, heart rate will increase accompanied by vasodilation of the blood vessels in the leg muscles mediated by the beta-adrenergic system. This response pattern permits increased delivery of oxygen to the leg muscles without a concomitant alteration in local diastolic blood pressure. At the same time, blood flow to the gastrointestinal system is likely reduced via vasoconstriction, as digestion is not an important use of the body's resources during a bout of exercise.

The Role of the Endocrine System in Blood Pressure

Blood pressure is also affected by various hormones of the neuroendocrine system, particularly norepinephrine (noradrenalin), epinephrine (adrenalin), and cortisol (see dashed lines in Figure 1.2). Stimulation of the sympathetic nervous system leads to the release of the catecholamines, epinephrine and norepinephrine, from the adrenal medulla and of the corticosteroid, cortisol, from the adrenal cortex. Unlike the immediate action of the autonomic nervous system described above, the neuroendocrine response is a little slower. In contrast to the direct neural pathways of the autonomic nervous system to the various elements of the circulatory system, the neuroendocrine response relies on the circulatory system itself to transport hormonal se-

cretions to various target organs and receptors. Norepinephrine generally results in increased vasoconstriction while epinephrine results in the dilation of vessels adjacent to muscle cells. Both epinephrine and norepinephrine increase heart rate. During a bout of exercise, epinephrine exerts a significant vasodilatory effect on the blood vessels associated with the skeletal muscles. Corticosteroids, including cortisol, also have an effect on blood pressure. Without the presence of cortisol, the influence of epinephrine and norepinephrine upon vascular responses is minimized (Drew and Leach, 1971). Therefore, cortisol facilitates the action of the catecholamines.

Renin, a humoral substance produced in the kidneys, also influences blood flow by converting angiotensin to angiotensin II, another vasoconstrictive hormone. Angiotensin II then signals the adrenal cortex to secrete aldosterone, which causes the body to retain sodium. Sodium retention causes the body to retain fluid, resulting in an increase in blood volume and thus increased blood pressure. There are numerous other hormones that affect blood pressure, operating as either vasoconstrictive or vasodilatory agents. The reader is referred to a full description of them in Kaplan (2002).

The Effect of the Kidney on Blood Pressure

The kidneys are organs that are ultimately responsible for the amount of fluid the body retains, and thus exert a significant effect on regulating blood volume and blood pressure. Increased blood pressure detected by the kidneys results in increased urinary excretion, and reductions in blood pressure result in lowered excretion rates, both regulating blood pressure by altering blood volume. During the bout of exercise, however, a portion of the blood volume is absorbed into muscle and skin cells and fluid excreted via sweat glands, rather than the kidneys alone regulating body fluid.

As stated above, the kidneys also affect blood pressure through release of renin. Essentially, when the kidneys detect a drop in blood pressure, renin is released, leading to increased vasoconstriction and sodium retention that elevate blood pressure to its previous level. This renin-angiotensin-aldosterone system, then, represents an important feedback system involved in blood pressure regulation.

The Central Nervous System Feedback System and Blood Pressure

The brain and circulatory system also make use of important feedback systems that assist in directing which elements of the neuroendocrine, renal, or autonomic nervous systems should be activated (see baroreceptor feedback system in Figure 1.2). Located along portions of the carotid artery and the aorta are several hundred pressure detectors called baroreceptors. These specialized cells operate like 'stretch' detectors that respond to alterations in blood pressure in the arteries and send neural signals to the brainstem to inform the brain which component of the autonomic nervous system should fire (Kezdi, 1977). For a properly functioning baroreceptor, increased blood pressure should lead to firing the parasympathetic nervous system and an immediate drop in heart rate. To the contrary, inadequate blood pressure should result in a signal to increase either heart rate or vasoconstriction via the sympathetic nervous system.

There are various elements of the central nervous system involved in this feedback system, including the brainstem, the hypothalamus, and other components of the limbic system. It is known that activation of baroreceptors results in activity in the upper medulla called the nucleus of tractus solitarius, which is a portion of the brain that regulates vagal tone (Lovallo, 1997). Stimulation of this group of neurons leads to increased parasympathetic activity, and deactivation results in labile blood pressure (DeJong et al., 1977). Blood pressure is also regulated by cortical mechanisms other than those in the brainstem. For example, stimulation of parts of the hypothalamus and other portions of the limbic system has been shown to result in blood pressure responses (Folkow and Van Euler, 1954; Gebber and Klevans, 1972).

In contrast to the relatively few mechanisms influencing water pressure in a hydraulic water-pumping system, it should be evident that a multitude of factors interact with one another to influence blood pressure. Not only do the factors outlined above contribute to an organism's current blood pressure, but they also influence one another (for example, the hypothalamus affects kidney function via the neuroendocrine system), and these interactive effects further complicate

the identification of mechanisms causing a specific elevation in blood pressure. Given the integrated system outlined, it is possible that no single mechanism is responsible for conditions of high blood pressure for every hypertensive patient. Perhaps different physiological mechanisms involved in the regulatory system result in dysfunctions in blood pressure regulation among different patients. Elevated blood pressure, then, may represent the final common pathway that results from a variety of underlying physiological disturbances.

Essential Hypertension

In a properly functioning circulatory system, the various components of the nervous, neuroendocrine, and renal systems operate together to maintain blood pressures at an adaptive level so that organisms can maintain blood flow to all essential body tissues in a variety of physical states, locations, and positions, including physical activity, changes in temperature and climate, and even standing on one's head. For some organisms, however, one (or more) of the various regulatory mechanisms outlined above no longer operates to maintain blood pressure in an adaptive range. In some cases, blood pressure is too low, leading to episodes of lightheadedness and fainting, particularly when one changes positions from sitting to standing. These are commonly referred to as syncopal or hypotensive episodes and are the result of the circulatory system's inadequacy in maintaining blood flow to the brain. In other cases, blood pressure is too high, and in extreme cases can lead to bleeding in weakened locations of the circulatory system, resulting in hemorrhagic stroke (bleeding into the cranium, which damages brain tissue) or the rupture of an aneurysm (a dilated blood vessel). High blood pressure is commonly referred to as hypertension, and takes two forms: primary or essential hypertension and secondary hypertension. In cases of secondary hypertension, there is an identified physiological abnormality causing the high blood pressure, such as kidney disease, endocrine disturbances like pheochromocytoma (adrenal tumor) or Cushing's syndrome, or a blockage of blood circulation that might occur with cardiovascular disease or stenosis (narrowing of the artery). It is also possible that regular ingestion of various exogenous substances, including amphetamines, oral contraceptives, and

licorice, will result in secondary hypertension. In most cases of hypertension, however, the exact cause of the elevated blood pressure is unknown; in these cases, the heightened blood pressure is called primary or essential hypertension.

Given the association of the word 'tension' with emotional states, it is interesting that the word 'hypertension' was selected to describe conditions of high blood pressure. The term 'hyper' comes from the Greek word 'huper,' which means over, above, or exceeding. The term 'tension' comes from the Latin word 'tensio,' which refers to the state of tenseness that accompanies stretching or extension. In this regard, the original use of the word 'hypertension' presumably referred to the exaggerated stretching of the blood vessels that accompanied the condition of high blood pressure. It is interesting that the common use of the word 'tension' to refer to emotional distress is derived from the same root Latin word. One might also wonder why the term 'essential' was used to describe hypertension with no known origin. According to Shapiro (1996), the term was initially chosen in the belief that the increase in blood pressure observed across the lifespan was 'essential' to maintaining blood flow in an aging circulatory system.

Stages of Hypertension

As physicians of the twentieth century began to employ newly developed measurement strategies for assessing blood pressure as part of patient evaluations, it became clear that interpretive parameters or guidelines were needed to determine risk for diseases associated with specific blood pressure values. Although truly elevated or remarkably low blood pressures were an obvious concern for physicians of the early twentieth century, there was no general agreement regarding when a specific blood pressure might place a given patient at risk for developing problems of blood circulation. The medical community needed to await the results of epidemiologic research conducted in the 1960s that clearly delineated the risk associated with various levels of blood pressure. Based upon these epidemiological findings, physicians adopted 160 mm Hg SBP and 100 mm Hg DBP as cut-off values for exhibiting increased risk for cardiovascular disease that warranted medical intervention, values that continue to be used today. Beginning in 1977, the

National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health regularly assembled groups of experts from their own laboratories as well as from a number of professional and voluntary organizations to review the body of evidence to date and make recommendations regarding the detection, evaluation, and treatment of high blood pressure. Each of these joint national committees (JNC) has disseminated the conclusions of its review to the scientific community and the public through a report, the most recent being released in December 2003 (Chobanian et al., 2003). It is well beyond the scope of this book to describe the various changes in recommendations that have occurred over the past several decades. Therefore, only the description of stages of hypertension from the most recent versions of the reports (JNC-6 and JNC-7) will be presented here (see Table 1.1).

As with preceding JNC reports, there were significant changes in the classification system from JNC-6 to JNC-7. Note that the upper two stages of hypertension severity in JNC-6 were combined in JNC-7, suggesting that the most recent data did not support separating these two levels of severity with respect to recommended interventions. The commonly used term 'borderline essential hypertension,' which had typically referred to mildly elevated blood pressures in the 140–160 mm Hg SBP or 90–95 mm Hg DBP range (Julius and Hannsson, 1983), has been subsumed into the categorization as Stage 1 hypertension in the most recent versions of the JNC diagnostic guidelines. Even more interesting is the fact that the two levels that JNC-6 labeled 'normal' and 'high normal' were renamed 'pre-hypertensive.' This is a significant change that has aroused considerable debate among researchers and clinicians who specialize in working with essential hypertensive patients. The use of the pre-hypertensive category was based on recent data showing that individuals in this category had a 90 percent greater risk of developing hypertension than persons with lower blood pressures (Vasan et al., 2002) and that risk for cardiovascular mortality among persons in this category increases for every 20 mm Hg above a SBP of 115 mm Hg or for every 10 mm Hg above a DBP of 75 mm Hg (Lewington et al., 2002). Mancia (2003) objected to the use of the term 'pre-hypertensive' on the basis that physicians do not diagnose normal patients as pre-diseased and that many so-called 'pre-hypertensive' patients may become unnecessarily worried about their

Table 1.1. Classification of Blood Pressure for Adults in JNC-6 and JNC-7

JNC-6 (1997)				*JNC-7 (2003)*			
Category	*SBP*		*DBP*	*Category*	*SBP*		*DBP*
Optimal	<120	and	<80				
Normal	<130	and	<85	Normal	<120	or	<80
High Normal	130–139	or	85–89	Pre-hypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99	Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	160–179	or	100–109	Stage 2 Hypertension	≥160	or	≥100
Stage 3 Hypertension	≥180	or	≥110				

Reprinted with permission from: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (1997). *Archives of Internal Medicine, 157,* 2413–2446 and A.V. Chobanian, G. L. Bakris, H. R. Black, W. C. Cushman, L. A. Green, J. L. Izzo Jr., et al. (2003), Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, *Hypertension, 42,* 1206–1252.

current health condition. He also claimed that the data supported intervention for patients in this group only if there was evidence of additional risk factors for cardiovascular disease. Mancia advocated the continued use of the JNC-6 classification system, which is more consistent with the classification system initially developed by the International Society of Hypertension (ISH) and the World Health Organization (WHO) and recently adopted in Europe (Guidelines Committee, 2003). There is, of course, continuing controversy regarding the specific criteria that physicians should apply in making diagnoses and developing effective intervention plans for their hypertensive and prehypertensive patients.

There has also been disagreement regarding whether elevations in systolic or diastolic blood pressures were associated with greater risk. For decades, physicians had focused primarily on diagnosing hypertension on the basis of casual DBP. However, findings from the Framingham Study have indicated that increased SBP may pose a greater health risk than increased DBP (Kannel, Gordon, and Schwartz, 1971; Lloyd-Jones et al., 1999). This is particularly important among older adults, who often exhibit what has been termed isolated systolic hyper-

tension. Among older adults, it has been documented that SBP continues to increase with aging, while DBP tends to plateau around the age of 60 (Franklin et al., 1997). Older adults with isolated systolic hypertension are characterized by SBPs in the hypertensive range accompanied by normal DBPs. Pulse pressure, calculated as the difference between SBP and DBP, is elevated among these patients, as is their risk for cardiovascular complications (Domanski et al., 1999; Psaty et al., 1992). According to the JNC-7 guidelines, DBP is a better predictor of cardiovascular risk until the age of 50, and SBP is a better predictor of cardiovascular risk thereafter.

Regardless of the exact criteria used in JNC guidelines and the ongoing discussions regarding when to treat or not to treat elevated blood pressure, all agree that the higher one's blood pressure is, the more risk for cardiovascular disease and stroke increases. Blood pressure, after all, is a continuous variable that constantly adjusts to current physiological or environmental demands. It really may not be that important to quibble over whether a patient with a blood pressure of 138/88 mm Hg should be categorized as a pre-hypertensive patient or fall into the high normal category; rather, it may be more important to inform him or her where his or her blood pressure falls with regard to the normal distribution of blood pressure and what efforts he or she might put into place to reduce it. Modern medicine often has dichotomized continuous variables in an effort to develop decision rules that can be used to conform to a medical diagnosis and respond to a proscriptive treatment. As such, a hypertensive patient with a blood pressure of 140/90 mm Hg is often treated much more like a patient with a blood pressure of 158/99 mm Hg than a patient with a blood pressure of 138/88 mm Hg. Despite our inclination to dichotomize blood pressures into the various stages described above, it is probably best to remember that blood pressure is a continuous variable and that risk for cardiovascular disease increases as blood pressure increases.

Development of essential hypertension appears to progress through different stages characterized by distinct physiological profiles. Early hypertension, or what had previously been termed 'borderline' essential hypertension, is characterized by mildly elevated blood pressures that typically are quite variable and often do not show a chronic progression to more elevated blood pressures over time. Certainly, some

'borderline' essential hypertensive patients go on to develop sustained elevations in arterial pressure, but the majority do not (Julius, Weder, and Egan, 1983). Pathophysiologically, 'borderline' essential hypertensive patients have been shown to exhibit enhanced beta-adrenergic responsiveness, which leads to increased heart rate and increased blood volume ejected from the heart. These findings led to the characterization of this group of patients as neurogenic in origin and exhibiting 'hyperkinetic' circulation (Julius and Esler, 1975). It should be noted that not all 'borderline' essential hypertensives fit this profile, but the hyperkinetic state is much more likely to be observed among 'borderline' hypertensives than among patients with sustained elevated blood pressures. In contrast, sustained hypertensive patients tend to exhibit normal or decreased cardiac action accompanied by increased vascular resistance to blood flow. In brief, blood pressure elevations of 'borderline' essential hypertensive patients are more closely associated with increases in cardiac output, while blood pressure elevations of sustained hypertensive patients are more closely linked to increases in total peripheral resistance.

Although the differentiation between hypertension resulting from increased cardiac output (hyperkinetic hypertension) and hypertension resulting from altered vascular resistance has been observed consistently, it was unclear whether the two groups represented distinct categories of elevated blood pressure profiles or whether patients progressed from hyperkinetic hypertension to vascular-resistance hypertension as they aged. To examine this question, prospective data were needed in which hyperkinetic hypertensive patients were followed over time. Lund-Johansen (1991) conducted such a study in which a group of hyperkinetic hypertensive patients were followed over 20 years. At the beginning of the study, young hypertensive patients had higher blood pressures associated with higher cardiac outputs, but measures of total peripheral resistance comparable to normotensive volunteers. At 10- and 20-year follow-up assessments, the elevated blood pressures among hypertensive patients shifted from the original hyperkinetic hemodynamic profile to a profile characterized by low cardiac output and elevated total peripheral resistance. Interestingly, this progression from cardiac-related to vascular-related hypertension also occurred among hypertensive patients who had achieved good blood pressure control

with anti-hypertensive medication. The same transition from cardiac-related to vascular-related hypertension has been observed in experimental animal models of hypertension (Guyton, 1992).

The Prevalence and Demographics of Hypertension

Hypertension is not an equal opportunity disorder. That is, it affects persons with certain demographic characteristics more than persons without those characteristics. For example, there is a linear relation between blood pressure and age, and it is well known that hypertension proportionately affects persons of African ethnicity more than those of Caucasian ethnicity. Incidence of essential hypertension is actually slightly lower among Mexican Americans despite the increased prevalence of obesity and diabetes among them (Fields et al., 2004; Sorel, Ragland, and Syme, 1991).

As depicted in Figure 1.3, prevalence rates increase with age, but this change is affected by both sex and race. During early adulthood, males have higher rates of hypertension than females, particularly among African Americans. However, in middle adulthood, prevalence rates for female African Americans rise above male African American rates, while males continue to have higher prevalence than females among Caucasian Americans. Finally, in older adulthood, females of both races have higher prevalence rates than males. Regardless of sex or race, however, it is easy to conclude that a significant number of Americans, particularly older Americans, can be diagnosed with high blood pressure. In the United States nearly one out of every three adults has high blood pressure (Fields et al., 2004). Estimates of high blood pressure are even higher in some other industrialized countries. For example, in Germany, Finland, and Spain roughly 44 percent of the adult population can be diagnosed with hypertension (Wolf-Maier et al., 2003), and in Japan the estimated prevalence of high blood pressure is as high as 73 percent among older adults (Curb et al., 1996).

Regardless of prevalence differences pertaining to race or age, it is quite evident that hypertension is a very common medical problem. In fact, it is the most common primary diagnosis assigned during outpatient visits in the United States with over 35 million office visits to medical clinics annually (Cherry and Woodwell, 2002). Furthermore,

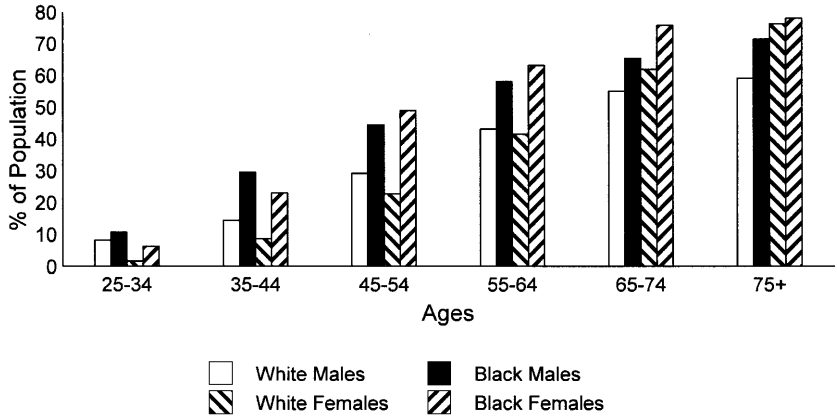

Figure 1.3. Prevalence of high blood pressure in Americans by age, sex, and race. Adapted from M. Wolz et al., Statement from the National High Blood Pressure Education Program: Prevalence of hypertension, *American Journal of Hypertension, 13,* pp. 103–104. Copyright © (2000), with permission from American Journal of Hypertension Ltd.

data from the National Health and Nutrition Examination Surveys (NHANES) have revealed that about 30 percent of hypertensive patients in the community were not aware they had high blood pressure, and were therefore not receiving treatment (Burt et al., 1995). Of those community-dwelling adults who were being treated, only about a third of them had achieved good control of their hypertension with treatment. Although some gradual improvement has been noted in identifying and treating hypertension over the past few decades, the condition still represents a significant medical problem for a large number of people.

It is generally acknowledged that there is a genetic component to the development of essential hypertension (Pickering and Sleight, 1977). Individuals with hypertensive parents possess a much higher risk for developing hypertension themselves than individuals of normotensive parentage (Paffenbarger, Thorne, and Wing, 1968; Zinner, Levy, and Kass, 1971). Transmission is considered polygenic, as there is no evidence that any single gene could regulate each of the interrelated systems that affect blood pressure. Although genetics certainly contributes to determining the risk for essential hypertension, it is clear that environmental factors also need to be considered when predicting

who will develop the disorder. To illustrate the interaction between genetic and environmental contributions, consider the classic work of Dahl, Heine, and Tassinari (1962), who demonstrated that elevations in blood pressure occurred among certain strains of rats only when exposed to conditions of salt loading. Despite the importance of hereditary factors, there are plenty of individuals who develop hypertension with no known genetic propensity for the disorder, as there are individuals who live out their lives with normal blood pressure despite having a strong family history of hypertension.

A few additional demographic or personal characteristics increase risk for developing hypertension, including concurrent diagnoses of diabetes mellitus, the presence of obesity, physical inactivity, and excessive use of sodium and alcohol (Page, 1983). The relative contribution for each of these characteristics is uncertain, however, because there is considerable overlap among them. For example, among the substantial number of obese patients who are diagnosed with diabetes, it is unclear whether the risk of hypertension is associated with the diabetic condition, obesity, or both diabetes and obesity.

Consequences of Hypertension

Hypertension is a known risk factor for cardiovascular and cerebrovascular diseases. The presence of hypertension raises the risk for coronary heart disease twofold, the risk of a stroke at least threefold, the risk of peripheral artery disease twofold, and the risk of congestive heart failure fourfold (Kannel, 1996). Elevated risk for both cardiovascular and cerebrovascular disease among persons with hypertension holds true for both men and women and after controlling for other major disease risk factors like smoking and high serum cholesterol (Pooling Project Research Group, 1978). Although it may be logical to conclude that the elevated risk for these diseases is from ruptured aneurysms or hemorrhagic events, the vast majority of these disease consequences are actually the result of the underlying physiological condition of atherosclerosis. Atherosclerosis involves the gradual depositing of plaque on the inner walls of blood vessels that results in a restricted (ischemic) or blocked (infarcted) blood flow. Obviously, if blood flow is blocked in the coronary arteries, a myocardial infarction (heart attack) occurs; if

blood flow is blocked in the cerebrovasculature, a stroke occurs. The process of atherosclerosis begins early in life, as our blood vessels are coated with fats (lipids) in our bloodstream. Over time, these fatty streaks harden and turn into plaques, particularly for those of us who regularly consume diets high in saturated fats. The presence of toxins in our bloodstream (for example, nicotine and carbon monoxide from smoking tobacco) or elevated arterial pressures appears to cause these plaques to crack, resulting in what might be called an intracellular injury. Additionally, the injury can promote a chronic inflammatory response that is mediated by immune system functioning (Schonbeck and Libby, 2004). As with other bodily injuries, the circulatory system responds by sending platelets to the site of the injury to clot it, preventing any loss of blood. The so-called scab, aggravated by the inflammatory response, extends from the internal cellular wall into the blood vessel, obstructing the normal flow of blood. If the injury recurs, more platelets are dispatched to the site, resulting in an even larger blockage of blood flow. In brief, then, it appears that high blood pressure promotes atherosclerosis and, indirectly, cardiovascular and cerebrovascular diseases, by causing regular injuries to the cellular lining of the blood vessels of the circulatory system. As one might imagine, these injuries are more likely to occur at locations where arterial pressure is highest and blood flow turbulence the greatest, like the coronary arteries, aorta, and bifurcation of the carotid arteries.

If this isn't bad enough, hypertension appears to have some other rather unpleasant consequences for the body's other organs. For example, chronic high blood pressure has been documented to have detrimental effects on the ventricles of the heart (particularly the left ventricle), the microvasculature of the kidneys, and the blood vessels in the retina. Because the effects of blood pressure upon these organs are so well known, they are termed the target organs, and damage to them is referred to as target organ (or end organ) damage.

In the hydraulic water-pumping system described earlier, continuous pump action at higher pressures results in greater wear on the pump itself than pumping at lower pressures. The same consequence occurs to the heart. Unlike a mechanical pump, the heart responds to the demand to circulate blood at a chronic elevated blood pressure level by becoming stronger and enlarged. Unfortunately, the increase

in muscle mass that results from this response, called left ventricular hypertrophy, places the heart at greater risk for malfunction (Kannel, Gordon, and Offutt, 1969). Presumably, left ventricular hypertrophy is associated with increased cardiovascular disease because the increased muscle mass infringes upon the volume of the left ventricle, resulting in lowered blood capacity of the ventricle associated with the greater oxygen requirements of the coronary arteries supplying the heart (Messerli and Aepfelbacher, 1995). Basically, this suggests that the enlarged heart uses more than its share of the body's blood resources, pumps less efficiently, and is placed at risk for myocardial infarction, congestive heart failure, or ventricular dysrhythmias (Messerli and Aepfelbacher, 1995). Physicians routinely test for left ventricular hypertrophy in patients with chronic problems with hypertension using electrocardiography or echocardiography, as the presence of left ventricular hypertrophy creates a substantially elevated risk for subsequent cardiovascular disease.

Chronic elevations in blood pressure also result in damage to the microvasculature of the kidney, in peripheral arteries, and in the retina. Damage to the blood vessels in the kidneys results in an increased secretion of albumen into the blood-stream, which can easily be detected through routine blood work. Although originally used for assessing kidney functioning among diabetic patients, measures of albumen have also been shown to be useful for determining the degree of target organ damage from hypertension (Cirillo et al., 1998).

In contrast to the indirect measurement strategies needed to detect vascular damage in the kidneys, vascular problems can be directly observed in the retina. The retina represents the only organ in the body in which blood vessels can be observed directly without removing surrounding tissue. The physician can examine optic fundi simply by looking into the patient's eye during a routine physical examination. Although this method provides a gross estimate of damage to the vasculature of the retina, recent technological advancements in retinal photography represent a more objective approach to examining this form of target organ damage (Olson et al., 2003). Like measures of left ventricular hypertrophy, assessment of vascular damage in both kidney and retina is highly correlated with blood pressure level (Cirillo et al., 1998; Perloff, Sokolow, and Cowan, 1991).

Chronic hypertension has also been shown to affect the elasticity of the vasculature itself (Franklin, 1995). As described earlier, the vessel wall of the artery constricts and dilates in response to alterations in blood flow in an effort to regulate blood pressure. As such, healthy artery walls are elastic. Aging, however, is associated with increased arterial stiffness, particularly in conjunction with elevated blood pressures (Franklin, 1995). With the advent of more sophisticated noninvasive methods for examining vessel responsiveness using ultrasound techniques, essential hypertension has been shown to be associated with lesser dilation of femoral arteries, indicating direct alterations in vascular elasticity (Trieber et al., 1997).

Finally, in addition to vascular changes, several subtle cognitive deficits have been associated with essential hypertension, including psychomotor response slowness (Light, 1975; Waldstein et al., 1996), poor visual recognition (Shapiro et al., 1982), and below average performance on tasks measuring attention, memory, and abstract reasoning (Franceschi et al., 1982; Wilkie and Eisdorfer, 1976). Although significant differences exist on these measures of cognitive processing between hypertensive and normotensive patients, they are typically small in magnitude, do not affect quality of life and work performance, and most likely go unnoticed by hypertensive patients and their family members. Nevertheless, recent research has shown that these cognitive deficits were associated with reduced blood flow to the right hemisphere of hypertensive's brains during working memory tasks (Jennings et al., 1998). Even though these cognitive deficits are associated with altered cerebral blood flow, these deficits appear to be reversible if stable blood pressure control is achieved with treatment (Miller et al., 1984), indicating that the cognitive deficits are likely to be the result of the elevated blood pressures of hypertensive patients.

Symptoms of Essential Hypertension

Many patients with essential hypertension report that they can determine when their blood pressure is elevated. Often, their perception of experiencing high blood pressure is accompanied by vague complaints of headache, fatigue, dizziness, sweating, a pounding heart, or nosebleeds (Berkow, 1982; Hoffman et al., 1973). The available data, how-

ever, refute these claims (Baumann and Leventhal, 1985; Brondolo et al., 1999; Kottke et al., 1979; Van Reek et al., 1982). No consistent relations have been observed among any particular symptom and the actual experience of high blood pressure, and when there appears to be a relation, it occurs for patients with both high and low blood pressure. Thus, in most cases, essential hypertension is best considered an asymptomatic disorder. In cases of chronic essential hypertension that have already resulted in target organ damage, some symptoms like headaches and visual disturbances do commonly occur, but are more likely the result of the damaged tissue than of the hypertension (Sandok and Whisnant, 1983).

Summary

Essential hypertension is a disorder that results from a disruption in the normal neural, cardiovascular, endocrine, and renal systems that regulate blood pressure. Due to the complexity of factors involved in blood pressure regulation, the exact cause of essential hypertension is unknown. Disruptions among local vascular feedback mechanisms, autonomic nervous system activity, endocrine secretions from the adrenal gland, renal function of the kidney, or baroreceptor feedback and related systems within the central nervous system all represent potential etiologic agents involved in essential hypertension.

As the most prevalent condition associated with physician office visits, essential hypertension represents a major public health problem confronting most industrialized nations. Diagnosis is made based upon existing consensus reports by groups like the Joint National Committee on Prevention, Evaluation, and Treatment of Blood Pressure or the International Society of Hypertension. While all clinical researchers agree that risk for cardiovascular disease and stroke increases with increased arterial pressures, there is often disagreement regarding at which level of measured blood pressure intervention is warranted. For example, the diagnosis of 'pre-hypertension' described in the JNC-7 represents a condition over which there is considerable controversy. Prevalence rates for hypertension increase with age, and the condition is more common among African American than Caucasian patients. Males are more likely to be diagnosed with hypertension than females

prior to menopause; however, afterward hypertension among women is diagnosed at higher rates than among men. Genetics plays a role in the etiology of hypertension, and it is commonly associated with obesity, diabetes, and physical inactivity.

Epidemiologically, high blood pressure is linked to increased risk for both cardiovascular disease and cerebrovascular disease. This link appears to be the result of damage to a number of organ systems caused by sustained high blood pressure, including the enlarging of the heart muscle, called left ventricular hypertrophy, and damage to the vasculature, as evidenced by damage to the retina, peripheral blood vessels, and the microcirculatory vessels in the kidney. Obviously, hypertensive individuals who have already sustained damage to these target organs are at greater risk for subsequent heart disease and stroke than hypertensives with no target organ damage.

Unfortunately, despite the serious physiological problems and diseases associated with hypertension, the condition often goes unnoticed and undiagnosed. Part of the problem, as evident in the case of Franklin described in the Introduction to this book, is that hypertension is asymptomatic. As in Franklin's case, the side effects of anti-hypertensive medications are often more noticeable to the patient than the condition itself, which creates complications in adhering to the treatment for this problematic medical condition.

2

Measurement of Blood Pressure

Diagnosis and monitoring of treatment of essential hypertension require the accurate repeated measurement of blood pressure. Although on the surface it may seem that measuring blood pressure is simple, many factors need to be considered when obtaining measures of blood pressure for purposes of diagnosing and monitoring essential hypertension. For example, arterial pressure differs depending upon the specific site of the arterial bed from which the measure is obtained; the closer the location is to the heart, the higher the blood pressure. Body position greatly affects blood pressure measurement, as does ingestion of a variety of substances, including alcohol, nicotine, caffeine, and a whole range of prescription and over-the-counter medications. To complicate matters further, blood pressure is a dynamic parameter, forever changing as the organism adapts to altering environmental contexts like noise level, temperature, and presence of interpersonal confrontation; therefore, a single blood pressure assessment will never really provide much useful information. In addition, although numerous manual and automated devices have been developed to measure blood pressures accurately, correspondence of blood pressure values among these devices is not always exact. Let's examine some of the primary methods employed to measure blood pressure.

Methods of Blood Pressure Measurement

Direct Intra-arterial Recording

The first method established for measuring blood pressure, intra-arterial recording, was discovered in 1733 when Hales inserted a thin glass tube into a horse's artery during a surgical procedure. The level of the blood rose and fell within the glass tube because of changes in arterial pressure associated with heart action. Experimentation with this method permitted Hales to directly observe changes in blood pressure by measuring the level of the blood in the glass tube. With continued experimentation, blood pressure gauges of this type became standardized so measures of blood pressure could be compared across time and situations as well as across species. Despite its impracticality due to problems associated with blood loss and potential infection, direct intra-arterial measures of blood pressure are still considered the 'gold standard' of measurement (Littler and Komsuoglu, 1989). Not only are these measures made directly from catheters positioned in the circulatory system, but they also permit continuous measures of blood pressure on a beat-by-beat basis. Thus, momentary fluctuations in blood pressure in response to various environmental stimuli can easily be detected. But despite the accuracy of intra-arterial methods, their impracticality for clinic use led to the reliance on pulse palpation (sensing variations in the pulse by touch) as a gross estimate of arterial pressure obtained during clinic visits in the 1800s.

Auscultatory Method

Due to the subjectivity associated with pulse palpation and general lack of correspondence between estimates obtained from pulse palpation and intra-arterial measures of blood pressure, considerable effort was focused upon developing an accurate noninvasive method (Cook and Briggs, 1903; Crenner, 1998). With the invention of the blood pressure cuff by Riva-Rocci in 1896, a new tool became available for determining blood pressures without insertion of a catheter. Still the primary method for determining blood pressure today, the occluding cuff is inflated around a limb (arm or leg) until blood flow is entirely blocked. Then, as the air pressure in the cuff is slowly released, audible

sounds from the arterial wall can be detected with a stethoscope as the pressure from the cuff drops below SBP and blood flow begins to resume. These audible sounds from the arterial bed eventually fade and disappear as the air pressure of the cuff drops below DBP and blood flow returns to normal in the limb. The onset of these sounds, called Korotkoff sounds after the Russian physician who studied them intensively (Korotkoff, 1905), coincides with SBP, as blood begins to flow into the occluded artery; the muffling (Phase IV) and disappearance (Phase V) of these sounds coincides with DBP. Riva-Rocci's invention, in brief, allowed the examiner to make inferences about an individual's blood pressure level by simply monitoring the air pressure in the occluding cuff that corresponded to the appearance and disappearance of Korotkoff sounds.

Traditionally, two types of air pressure gauges have been used in conjunction with occluding cuffs: mercury columns and aneroid manometers. Using the mercury column, an apparatus strangely reminiscent of the original glass tubes used by Hales (1733), involves observing the extent of direct displacement of mercury in a gauged column by air pressure in the occluding cuff. The examiner watches the mercury level decrease in the column as air is released from the cuff and records the values associated with the appearance and disappearance of Korotkoff sounds. The aneroid manometer involves a mechanical device in which air pressure in the cuff causes a display needle to move on a gauged dial. As with the mercury column, the examiner simply records the values from the gauge associated with the appearance and disappearance of Korotkoff sounds.

Studies comparing the auscultatory method of determining blood pressure, initially established by Riva-Rocci and Korotkoff, with intra-arterial measures have yielded very impressive correlations (Pickering and Blank, 1989). This led to gradually increased usage of the auscultatory method during the twentieth century, as physicians became trained in this newly validated method rather than relying on the older, less reliable practices of examining the radial pulses. Even during early tests of the auscultatory method in clinical setting, however, there was concern over the accuracy of the blood pressure determinations (Crenner, 1998). Indeed, the examiner must attend to several factors to make sure that standard measurement conditions are employed: an occluding

cuff of appropriate size, standard arm placement, positioning of the cuff at heart level, having the patient adopt a standard body posture, and assuring use of a calibrated manometer (Pickering et al., 2005). It is also important to obtain blood pressures during periods of silence; not only can the examiner hear the Korotkoff sounds better, but talking during blood pressure determinations has been associated with significantly increased blood pressures of the patient (Le Pailleur et al., 2001). Observer errors are also a source of inaccuracy; foremost among these is a digit preference for numbers ending in a 5 or 0 (Shapiro et al., 1996). These observer errors, however, can be minimized with the use of a random zero sphygmomanometer (Wright and Dore, 1970), a device gauged so that the actual zero point is unknown to the examiner. Additionally, determining DBP by detecting Phase IV Korotkoff sounds (muffling of the Korotkoff sound) typically results in poorer reliability than using Phase V DBP determinations; therefore, Phase V is more commonly used to demarcate DBP (Shapiro et al., 1996).

One strategy for eliminating observer error with the auscultatory method is to use an electronic device that both regulates cuff inflation and deflation and detects Korotkoff sounds using microphone arrays embedded within the occluding cuff. Indeed, a number of such devices are available for both clinical and research use (see Fowler et al., 1991). Because of concerns that many of these devices may not compare favorably with standard intra-arterial measures of blood pressure, the Association for the Advancement of Medical Instrumentation developed a set of standards to evaluate the reliability and validity of electronic blood pressure devices (White et al., 1993). In brief, these guidelines require an adequate number of blood pressure comparisons with either intra-arterial measures or the standard auscultatory method on persons with different arm sizes in a variety of postures (seated, supine, and standing). Blood pressure measures obtained from both the electronic device and standard comparison strategy need to be within ± 5 mm Hg in order for the device to be considered acceptable for making accurate determinations (Association for the Advancement of Medical Instrumentation, 1993). Additionally, clinicians or researchers who rely on using electronic auscultatory devices for measuring blood pressure should routinely calibrate their instruments with standard auscultatory methods.

Oscillometric Method

A second type of noninvasive blood pressure measurement strategy, the oscillometric method, also employs an occluding cuff. However, in contrast to the auscultatory method, which relies on detection of Korotkoff sounds, the oscillometric method operates by sensing the magnitude of oscillations caused by the blood as it begins to flow again into the limb. Typically, very faint blood flow oscillations begin to be detected as the air pressure in the cuff coincides with SBP. As air pressure is slowly released from the occluding cuff, the amplitude of these pulsatile oscillations increases to a point and then decreases as blood flow to the limb normalizes. Although the oscillation with the greatest amplitude has been shown to correspond reliably with mean arterial pressure (Mauck et al., 1980), determinations of SBP, which are associated with a marked increase in amplitude of oscillations, and DBP, which are associated with the point at which oscillations level off, are often less accurate when compared with auscultatory measures (Fowler et al., 1991). Therefore, while oscillometric methods tend to overestimate SBP and underestimate DBP (Maheswaran et al., 1988; Manolio et al., 1988), they can be useful for determining accurate estimates of mean arterial pressure.

Continuous Blood Pressure Monitoring Methods

Unfortunately, both auscultatory and oscillometric methods of blood pressure assessment are intermittent measures in that a single blood pressure determination can take almost an entire minute to obtain. Additionally, a brief rest period is recommended between measures of blood pressure that require use of an occluding cuff to allow circulation in the limb to return to normal. Therefore, if an investigator is interested in measuring immediate and short-lived alterations in blood pressure, intermittent blood pressure measures would not be a good choice. Two noninvasive approaches for measuring blood pressure continuously have been developed, pulse transit time (or pulse wave velocity) and the vascular unloading method.

Pulse Transit Time

Pulse transit time reflects the time it takes the pulse wave to travel from the heart to a site in the peripheral circulation, typically the finger or

earlobe. It is commonly assessed by measuring the duration of time (in ms) between the initiation of the cardiac contraction from the electrocardiogram (ECG) and the arrival of the pulse wave at the peripheral site, typically measured using photoplethysmography. Presumably, as arterial pressure increases, the pulse wave travels more quickly to the peripheral site (lower pulse transit time); conversely, as arterial pressure declines, pulse transit time lengthens (Gribbin, Steptoe, and Sleight, 1976). Although studies comparing changes in pulse transit time with blood pressure change have yielded significant inverse correlations, these correlations have been more commonly observed between measures of pulse transit time and SBP than between pulse transit time and DBP (Newlin, 1981; Obrist et al., 1979). Furthermore, researchers who employed measures of pulse transit time have disagreed as to whether the continuous temporal parameter actually represented an index of blood pressure, as there was considerable evidence suggesting it was more strongly linked to beta-adrenergic cardiac activity than to blood pressure (Newlin, 1981; Obrist et al., 1979). Because of these equivocal findings linking changes in pulse transit time to alterations in blood pressure, this method has not been recommended as a surrogate measure of blood pressure (Shapiro et al., 1996).

Vascular Unloading Method

The vascular unloading method, initially described by Peñaz (1973), involves obtaining estimates of blood pressure from a small pressurized cuff positioned over a finger in conjunction with a photoplethysmograph. One such apparatus, called the Finger Arterial Pressure System or FINAPRES™, monitors blood flow into the finger and provides continuous information to a mechanism that automatically adjusts air pressure in the cuff to maintain a stable partial blood flow through the artery in the finger. Blood flow oscillations are sensed by the encircling finger cuff and translated into beat-by-beat estimates of blood pressure. Although this device may become uncomfortable during extended measurement periods, it can be used to measure blood pressure continuously for a few hours, and the ambulatory version, which alternates blood pressure determinations between two integrated finger cuffs, has been used for periods as long as 24 hours (Imholz et al., 1993).

Naturally, whenever a new method for assessing blood pressure is

developed, it is important to validate it with established measurement strategies. In some studies of this type, blood pressure values obtained from the devices using the vascular unloading principle have been shown to compare favorably with intra-arterial measures of blood pressure (Imholz et al., 1990; Parati et al., 1989) as well as intermittent noninvasive measures (Dorlas et al., 1985; Pace and East, 1991). However, other studies have reported that indices of blood pressure from these devices either overestimated (Epstein et al., 1989; Kurki et al., 1989) or underestimated blood pressure (Imholz et al., 1988; van Egmond, Hasenbos, and Crul, 1985). It appears that some of this lack of correspondence between methods of blood pressure determination is unique to the vascular structure of individuals. With the device positioned at the recommended heart level, some individuals display estimates of blood pressure that are over 20 mm Hg higher than their corresponding oscillometric or auscultatory values, while others display estimates that are over 20 mm Hg lower (Larkin et al., 1995). Calibration of recordings by adjusting arm position above or below heart level improves correspondence between measures, but this effect appears to be only temporary (Larkin et al., 1995).

Regardless of whether the absolute measures of blood pressure obtained from devices employing the vascular unloading principle accurately portray an individual's resting blood pressure level, the continuous finger arterial recordings provide a reliable index of change in blood pressure in response to acute environmental stimuli (Parati et al., 1989). Therefore, perhaps the true utility of this instrument is to assist in providing accurate measures of acute blood pressure responses to stress, particularly responses to short-term stressors that may be missed if an intermittent noninvasive measurement is employed. In this usage, Gerin, Pieper, and Pickering (1993), indeed, demonstrated that the FINAPRES™-derived measures of blood pressure were more reliable than blood pressures obtained using an intermittent blood pressure measurement device.

Clinic Measurement of Blood Pressure

Although significant technological advances have permitted the development of several valid ways to measure blood pressure, most clinic de-

Table 2.1. Auscultatory Blood Pressures Measured during Franklin's Three Clinic Visits

First Clinic Visit	
10 min resting	152/100
15 min resting	158/108
20 min resting	160/104
Mean: First Visit	158/104
Second Clinic Visit	
10 min resting	140/98
15 min resting	148/108
20 min resting	132/94
Mean: Second Visit	140/100
Third Clinic Visit	
10 min resting	132/90
15 min resting	130/88
20 min resting	154/105
Mean: Third Visit	139/94
Mean: All Visits	145/99

Data collection supported by the American Heart Association, West Virginia Affiliate (Grant 93-7854S).

terminations of blood pressure are still made using the good old-fashioned auscultatory method. It is readily available in any medical setting and relatively inexpensive to maintain. Furthermore, medical professionals can be easily trained in the auscultatory method, making it a standard part of most clinic visits. When Franklin visited his physician's office, blood pressures were measured using the auscultatory method in conjunction with a mercury column. In order to increase confidence in diagnosis, Franklin's physician requested that he return to the clinic for two subsequent visits, approximately a week apart, to have his blood pressure measured again in the clinic by a trained health professional. The results of this blood pressure assessment are depicted in Table 2.1.

It is easy to see why Franklin's physician was concerned with his blood pressure readings. With only one exception (the second reading during the third visit), all of Franklin's blood pressure recordings were in the hypertensive range. Two features of these data are notable. First, although almost all readings were in the hypertensive range, Franklin's

blood pressures showed a decreasing trend across clinic visits until the final reading of the third visit, indicating that his blood pressure might be decreasing as he became accustomed to having it taken in the clinic. This is not surprising, as blood pressures are known to decrease with repeated measurement (Carey et al., 1976). Second, the final blood pressure recording of the third day was quite elevated in comparison to the earlier values obtained on the same day, warranting a closer inspection of clinic records to determine any source for this anomaly. The clinic nurse indicated in her chart note that Franklin was late for work on that day and became increasingly impatient to complete the blood pressure measurement session, leaving without rescheduling as soon as the final reading was obtained. Therefore, these data revealed not only that this patient met the diagnostic criteria for essential hypertension, but that his blood pressure level was responsive to stressful situations. Although Franklin's physician was justified in commencing treatment for his hypertensive condition given the magnitude of his elevated blood pressures, clinic records of this type yield information only about a patient's blood pressure while he or she is sitting quietly in the clinic. Presumably, these elevated arterial pressures would also be observed in environments outside of the clinic, including Franklin's home and work environments. In order to evaluate the truth behind this assumption, blood pressure measures needed to be acquired outside of the clinic with instruments that do not require clinic personnel for their operation.

Blood Pressure Monitoring during Daily Life

Two general strategies have been employed to obtain measures of blood pressure during daily life: home monitoring and ambulatory monitoring. Home monitoring typically involves training the patient (or a family member of the patient) to operate an occluding cuff properly to obtain auscultatory measures of blood pressure on a daily basis. In contrast, ambulatory monitoring typically employs an automated device that is programmed to measure blood pressure at periodic intervals over the course of a specified time period, typically 24 or 48 hours. Let's examine the costs and benefits associated with each of these approaches.

Home Blood Pressure Monitoring

Home monitoring is one fairly inexpensive strategy for obtaining auscultatory measures of blood pressure out of the clinic. Obviously, this approach relies on having a patient who possesses the manual dexterity and sensory capabilities to acquire the skill of auscultation, adhere to the physician's instructions regarding frequency of recording, and report blood pressures honestly and accurately. For persons who are uncertain about their ability to acquire this skill, inexpensive devices that automatically inflate and deflate the occluding cuff and detect Korotkoff sounds may be used, although the accuracy of many of these instruments is questionable (Evans et al., 1989; O'Brien et al., 1990).

Validation of Home Blood Pressure Monitors

In an effort to evaluate the accuracy of automated instruments for the purposes of home blood pressure monitoring, the Consensus Conference on Self-Blood Pressure Measurement (White et al., 1999) recommended that these automated instruments be validated according to standards established by both the Association for the Advancement of Medical Instrumentation (1993) and the British Hypertension Society (O'Brien et al., 1993). In brief, these standards allow for discrepancies between blood pressures measured by an automated device and a valid reference device to average no more than ± 5 mm Hg and possess variabilities of no more than 8 mm Hg. Additionally, these standards emphasize training persons to operate the instrument properly and assuring the regular calibration of the device. Although the application of these standards to more recent versions of automated blood pressure recording instruments has held the industry accountable for manufacturing devices that measure accurate blood pressures (Yarows and Amerena, 1999; Yarows and Brook, 2000), some legitimate concern continues to be expressed that these devices still do not measure blood pressure accurately for many individuals (Gerin et al., 2002). For example, in one recent device validation study, Ploin et al. (2002) reported that the test device met the designated accuracy criteria, even though only slightly over half of the blood pressure determinations obtained from it met the ± 5 mm Hg criteria and approximately 10 percent of the SBP determinations exceeded a ± 15 mm Hg discrepancy

between methods. It would appear that at least for some hypertensive patients, automated devices developed for home use lack the degree of accuracy we have come to expect in medical devices.

In lieu of purchasing an automated device for home blood pressure monitoring, some individuals have turned to using public automated machines, now found in almost all drugstores. In general, this approach has been discouraged (Conway, 1986), because these devices are often not properly calibrated and maintained. Furthermore, taking one's blood pressure in a public place presents the individual with a whole new set of stimuli that are typically contraindicated in standardized instructions for obtaining accurate measures of blood pressure either in the clinic or at home.

Comparisons of Home and Clinic Blood Pressures

Ayman and Goldshine first reported comparisons between blood pressures measured in the clinic and at home in 1940. In this report, blood pressures of patients with essential hypertension were obtained through an extensive assessment in the clinic as well as from home blood pressures measured twice daily for several weeks. Thirty percent of the hypertensive patients exhibited home-derived measures of SBP that were more than 40 mm Hg lower than the clinic-derived measures, and 24 percent of the patients exhibited home-derived measures of DBP that were more than 20 mm Hg lower than clinic-derived DBPs. Across most patients, home-derived measures of blood pressure were substantially lower than clinic-derived measures. Research since that time has underscored the replicability of these findings (Bättig et al., 1989; Kleinert et al., 1984; Laughlin, Sherrard, and Fisher, 1980). In fact, this finding is so robust that some hypertension specialists have suggested establishing a lower blood pressure criterion for considering a diagnosis of essential hypertension (Thijs et al., 1998). Based upon a meta-analysis of 17 studies comparing home and clinic measures of blood pressure in well over 5400 persons, these authors reported that a clinic-derived SBP of 140 mm Hg corresponded to a home-derived SBP of 125 mm Hg, and that a clinic-derived DBP of 90 mm Hg corresponded to a home-derived DBP of 79 mm Hg. In a second analysis of pooled home blood pressures of over 4500 patients from an interna-

tional database, Thijs et al. (1999) found that at least 25 percent of hypertensive patients using clinic criteria had self-recorded blood pressures less than 135/85 mm Hg; this finding was particularly evident among patients who underwent fewer than three blood pressure measurements in defining their clinic SBP and DBP. Based upon the results of these two studies, Thijs et al. (1999) suggested that home blood pressure recordings that exceed 135/85 mm Hg should be considered hypertensive. This suggestion was endorsed by the task force comprised of international experts in blood pressure assessment at the Leuven Consensus Conference on Ambulatory Blood Pressure Monitoring in 1999 (White et al., 1999).

Although office blood pressures are typically higher than those recorded through home self-monitoring, this difference becomes much smaller among persons accustomed to the clinic environment (Welin, Svardsudd, and Tibblin, 1982). For example, Padfield et al. (1987) demonstrated a significant relation between home blood pressures and blood pressure measures obtained on the third clinic visit, a finding which was not apparent during the first two clinic visits. Therefore, if a slightly lower criterion for home blood pressure monitoring is adopted and the frequency of clinic visits increased, home monitoring can be a valuable tool for obtaining accurate assessments to evaluate and monitor treatment progress.

Prognostic Value of Home Blood Pressure Monitoring

Although it has been well established that elevated clinic-derived measures of blood pressure were associated with both target organ complications (like left ventricular hypertrophy) and increased risk for cardiovascular disease, the predictive relation between home blood pressures and target organ damage and risk for cardiovascular disease was unknown. However, because the physiological damage caused by elevated arterial pressures occurs continuously but gradually throughout daily life and not just during visits to the clinic, it was hypothesized that home measures would predict target organ pathology and associated risk for cardiovascular disease better than clinic-derived indices of blood pressure. Although not many studies have explored the relation between home monitoring and evidence of target organ damage or

subsequent risk for cardiovascular disease, of those that exist, measures of left ventricular hypertrophy were shown to be more strongly correlated with self-determined blood pressures than clinic-derived blood pressures (White et al., 1999). To provide further support for the prognostic utility of home monitoring, White et al. cited two recent prospective trials in which self-determined blood pressures were more strongly correlated with risk for cardiovascular diseases than clinic-derived blood pressure measures (Imai et al., 1996; Ohkubo et al., 1998b).

In summary, although home blood pressure monitoring serves as a helpful tool for following patients with essential hypertension as well as monitoring treatment effectiveness, it is less accurate in making the initial diagnosis of essential hypertension (Herpin et al., 2000). Additionally, if accurate home-derived measures of blood pressure can be obtained, they can differentiate patients with sustained elevated pressures from patients who exhibit elevated blood pressures only in the clinic (isolated clinic hypertensives or 'white coat' hypertensives), who presumably may be at lesser risk for target organ complications associated with hypertension. In this regard, home measures of blood pressure can be a useful proxy when ambulatory monitoring equipment is not available to confirm presence of isolated clinic hypertension (isolated clinic hypertension will be discussed in greater detail later in this chapter). There are several limitations to home measurement of blood pressure, as well, including the limited amount of prospective data linking various levels of home-determined blood pressures to associated risk for cardiovascular disease and limited information pertaining to the optimal schedule for self-monitoring of blood pressure (White et al., 1999).

Ambulatory Blood Pressure Monitoring

There are now over a dozen ambulatory blood pressure monitoring devices that meet the standards established by the Association for the Advancement of Medical Instrumentation (1993) and the British Hypertension Society (O'Brien et al., 1993; 2000). In contrast to the less expensive automated devices used for home monitoring, ambulatory monitors reveal what is truly happening regarding alterations in blood pressure during a patient's daily life. There is no need to stop daily ac-

tivities, take a quiet moment to sit down, attach the cuff properly, and take a few blood pressure recordings. With ambulatory monitors, all these functions are programmed into the instrument and they happen automatically. Data are stored digitally and downloaded into a computer for analysis when the patient returns the device to the clinic. Of course, patients are instructed to remove the device when bathing, swimming, or involved in any contact sports, but otherwise are free to do what they normally would do during any other day.

Initial bulky versions of ambulatory blood pressure monitors that employed the intra-arterial method of assessment were described by researchers in the 1960s (Bevan, Honour, and Stott, 1969; Richardson et al., 1964). These were some of the first studies to document the substantial variability of blood pressures among both hypertensive patients and normotensive controls during the day as well as during the night. As expected, blood pressures typically decrease during the nighttime for both hypertensives and normotensives. Since that time, significant technological advances have led to the development of a number of ambulatory blood pressure recording devices that are relatively compact, lightweight, noninvasive, quiet, and, most important, accurate (O'Brien et al., 2000). Typically, the device is attached and calibrated during a brief visit to the clinic and patients are instructed to go about their daily life for the subsequent 24 to 48 hours. Calibration with auscultatory readings is essential, as ambulatory blood pressure determinations have been reported to be affected by different constitutional characteristics including obesity, age, and arm circumference (Harshfield et al., 1989). Even with a properly positioned and calibrated cuff, situations are bound to occur in daily life in which unavoidable body movements or unusual arm positions will influence the accuracy of these determinations, like driving in heavy traffic or sleeping with an arm draped off the edge of the bed. Fortunately, all the ambulatory blood pressure monitors available for clinic or research use have automatic integrated programs for detecting potential sources of invalid measurement and marking these recordings as questionable.

Another very useful adjunctive assessment tool during periods of ambulatory monitoring involves asking the patient to record various contextual factors associated with each blood pressure determination

including state of wakefulness, body posture, mood ratings, activity level, and substance use. With this information in hand, clinicians can examine individual blood pressure measures at a later time to investigate patterns between contextual variables and blood pressure levels. Research employing measurements of these contextual factors, for example, has revealed, not surprisingly, that higher ambulatory blood pressures are likely to occur during periods involving emotional activation (Kamarck et al., 1998) and increased alertness (Shapiro, Jamner, and Goldstein, 1993). Additionally, because DBPs have been shown to be higher during cold versus warm seasons (Giaconi et al., 1989), evaluators should take average daily temperature into account when interpreting results from ambulatory blood pressure monitoring.

Let's examine the results of Franklin's ambulatory blood pressure monitoring (see Figure 2.1). During his late morning clinic appointment, an ambulatory blood pressure monitor was attached and calibrated with Franklin's resting clinic blood pressure. During the single 24-hour monitoring period, 44 valid recordings were made, reflecting considerable variability in his blood pressures over the course of a single day. The average ambulatory blood pressure was 145/88 mm Hg, suggesting that his ambulatory SBP was comparable to his clinic SBP, but his ambulatory DBP was somewhat lower (−11 mm Hg) than his clinic DBP. SBPs ranged from 98 to 184 mm Hg, and DBPs ranged from 55 to 113 mm Hg. Combining the ambulatory blood pressure profile depicted in Figure 2.1 with Franklin's diary of contextual factors revealed some additional and worthwhile data. First, two peaks in DBP occurred later in the afternoon. According to his diary, the first peak was associated with driving, and the second with a prolonged confrontation with a co-worker. Apparently, this confrontation started over the telephone around 4:30 pm, escalated into the need for a personal meeting, Franklin's driving to and from the meeting, and finally, his rehashing the entire event with his parents around 7:00 pm. This DBP peak was accompanied by a peak in SBP as well. Although Franklin's blood pressure dropped (dipped) when he went to bed, blood pressures gradually increased as the morning approached. The next morning's diary stated that he went on a three-mile walk at a rather brisk pace, which was evidenced by the increase in heart rate and SBP observed during the early morning hours. This example makes it

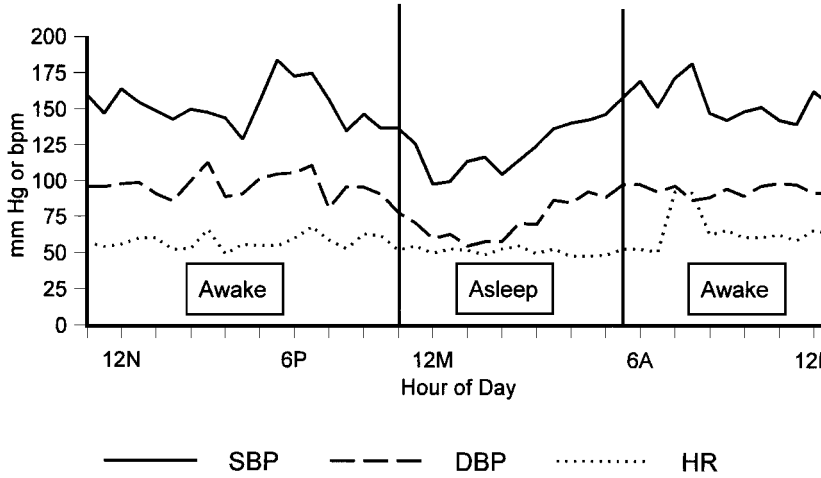

Figure 2.1. Franklin's ambulatory SBP, DBP, and HR during a 24-hour recording period. Data collection supported by the American Heart Association, West Virginia Affiliate (Grant 93-7854S).

easy to see the importance of gathering concurrent data on pertinent contextual factors to assist in interpreting the blood pressure variability observed during 24-hour monitoring periods. Otherwise we simply would not know what factors were associated with the blood pressure variation evident in this profile.

Accuracy of Ambulatory Blood Pressure Monitoring

Although ambulatory measurement devices compare favorably with auscultatory methods of blood pressure determination in the clinic, there are substantial differences in average blood pressures obtained during daily life and average blood pressures obtained in the clinic. Given the dynamic nature of blood pressure, it should not come as a surprise that resting blood pressures in the clinic may not correspond well with blood pressures obtained during an extended period of time comprised of daily activities at work and at home as well as several hours of sleep. Unusually, the nature of the differences between mean ambulatory and mean clinic blood pressure values often differs between hypertensive and normotensive patients. Among hypertensive patients, clinic-derived measures of blood pressure are typically a good

bit higher than average daily blood pressure readings (see Pickering and James, 1989); among normotensive controls, however, differences between clinic and ambulatory blood pressures are often minimal, and the opposite relation has even been reported; that is, ambulatory blood pressures were higher than clinic blood pressures (Cox et al., 1991). These findings are commonly associated with the speculation that groups of hypertensive patients often comprise a significant portion of isolated clinic hypertensive patients.

As with the lower reference values employed for evaluating home blood pressure measures, there has been considerable discussion regarding the appropriate cutoff criteria for considering a diagnosis of hypertension based upon ambulatory recordings. Since average ambulatory blood pressures are typically lower than clinic-derived measures of blood pressure (Pickering and James, 1989), it has been recommended that ambulatory blood pressures lower than 140/90 mm Hg still be considered within the hypertensive range. There have been a few different approaches as to how these ambulatory blood pressure diagnostic criteria should be established (see Pickering, 1999b). For example, one approach to this problem is to base these cutoff values upon a certain percentile of distributions of blood pressures of large samples of people. Adopting a 95th percentile criterion for 24-hour blood pressures across studies, however, yields different cutoff points. While the 95th percentile in a study by O'Brien et al. (1991) was reported to be 134/84 mm Hg, the same percentile from the PAMELA Study revealed criteria of 130/81 mm Hg (Mancia et al., 1995). In a more recent report, Rasmussen et al. (1998) found no differences between ambulatory and clinic measures on a large sample of Danish citizens; had they employed the 95th percentile criteria on the ambulatory blood pressure measurements, their cutoff for considering a diagnosis of essential hypertension would have been 156/90 mm Hg! Because such disparate criteria have been reported from study to study using this approach, it may not represent the optimal way of handling this issue.

Another strategy for establishing diagnostic criteria for ambulatory blood pressures is to aggregate findings across studies using meta-analytic procedures to arrive at uniform cutoff values. Staessen et al. (1991) conducted such a meta-analysis using data on more than 3400

people from 23 studies, revealing a criteria for probable hypertension at 139/87 mm Hg based upon the 95th percentile of the overall sample. Because the prevalence of hypertension is greater than 5 percent of the populations of industrialized countries, the general approach for both of the first two strategies for establishing appropriate criteria for elevated ambulatory blood pressure may miss categorizing many individuals with essential hypertension. Furthermore, as Pickering (1999b) points out, if hypertensive patients are not included in these studies in an effort to examine mean ambulatory blood pressures for a healthy population, findings regarding ambulatory blood pressures will underestimate the true population values.

Pickering (1999b) discussed a third strategy for defining normal ambulatory blood pressures involving the calculation of what has been called *blood pressure load.* Blood pressure load refers to the number of ambulatory blood pressure recordings for a given individual that fall above 140/90 mm Hg during the day and above 120/80 mm Hg at night. Individuals with sustained essential hypertension exhibit blood pressure loads of 100 percent, and normotensive individuals typically exhibit blood pressure loads of 0 percent. Blood pressure loads exceeding 40 percent have been shown to be related to target organ damage in hypertensive patients (White, Dey, and Schulman, 1989). Although this approach shifts the focus from population-based methods for determining risk for hypertension to methods based upon associations with target organ pathology, Pickering questions the arbitrary methods employed for choosing the specific criteria used in determining blood pressure load.

Finally, reference values for ambulatory monitoring could be established by examining the direct relation between ambulatory blood pressures and either measures of target organ pathology or prognosis for cardiovascular disease (Pickering, 1999b). For example, Ohkubo et al. (1998a) followed a rural cohort of over 1500 individuals for six years, during which 117 died. Ambulatory blood pressure monitoring was associated with increased mortality at both high and low levels; increased mortality associated with high ambulatory blood pressures was related to cardiovascular diseases, whereas increased mortality associated with low ambulatory blood pressures was related to other forms of mortality. Reference values of 134/79 mm Hg for ambulatory 24-hour blood

pressure recordings demarcated increased risk for cardiovascular mortality. In this strategy, the cutoff values were determined through association with actual risk for cardiovascular disease complications rather than the selection of a pre-designated percentile of the population.

In summary, there are numerous methods for determining the ambulatory blood pressure level derived from 24-hour recording at which diagnoses of hypertension and associated increased risk for cardiovascular disease should be considered. Acknowledging Pickering's (1999a) contention that blood pressure should be considered a continuous variable and that efforts at identifying cutoff points for demarcating the moment at which intervention is warranted may be misguided, there is general consensus across these various methods that mean 24-hour blood pressures associated with diagnoses of hypertension and increased risk for cardiovascular disease are lower than the established clinic-derived reference values. Although many investigators continue to disagree regarding the exact reference values to use in evaluating ambulatory blood pressures, current recommendations indicate that 24-hour ambulatory blood pressures that exceed 135/85 mm Hg should be considered elevated (O'Brien et al., 2000). Additionally, daytime ambulatory blood pressures that exceed 140/90 mm Hg or nighttime ambulatory blood pressures that exceed 125/75 mm Hg should be considered elevated (O'Brien et al., 2000).

Prognostic Value of Ambulatory Blood Pressures

With the advent of ambulatory blood pressure recording capability, many new empirical questions could be considered regarding the enhanced prediction of risk for cardiovascular disease associated with chronically elevated blood pressures. As with home blood pressures, it could be hypothesized that ambulatory blood pressure measures would predict target organ pathology and associated risk for cardiovascular disease better than clinic-derived indices of blood pressure. This is indeed the case. Almost all investigations that have compared clinic-derived and ambulatory measures of blood pressure with various indicators of target organ pathology (left ventricular hypertrophy, for example) have found ambulatory measures of blood pressure to predict target organ damage better than clinic-derived measures (see Appel and Stason, 1993; Mancia et al., 1996; Verdecchia et al., 1999; White,

1990; 1999). In a review of studies relating degree of target organ pathology with both ambulatory and clinic-derived measures of blood pressure, Verdecchia et al. reported mean correlations (weighted for sample size differences among studies) between left ventricular mass and ambulatory blood pressures to be .50 and .44 for SBP and DBP, respectively. The corresponding mean correlations between left ventricular mass and clinic blood pressures were .35 and .32 for SBP and DBP, respectively, showing quite clearly that ambulatory methods of blood pressure assessment were more closely linked with degree of target organ pathology than clinic methods. Furthermore, reductions in left ventricular hypertrophy associated with pharmacologic treatment of high blood pressure have been shown to be associated with reductions in ambulatory, but not clinic, blood pressure measurements (Mancia et al., 1997).

In addition to predicting target organ pathology better than clinic-derived measures of blood pressure, ambulatory measures of blood pressure have been shown to be better predictors of subsequent cardiovascular and cerebrovascular events (Clement et al., 2003; Perloff, Sokolow, and Cowan, 1983; Perloff et al., 1989). In a review of several prospective trials relating ambulatory blood pressures to actual cardiovascular disease endpoints, White (1999) reports a stronger relation between ambulatory blood pressure and cardiovascular and cerebrovascular disease endpoints than between clinic-derived measures of blood pressure and disease endpoints in "nearly every study performed during the past decade" (p. S20).

Although it is often assumed that the superiority of ambulatory over clinic blood pressure measures is related to the importance of stressors that patients encounter on a daily basis in determining the overall risk for target organ pathology, it is possible that these findings simply reflect the improved reliability of measurement that occurs with ambulatory methods due to the increased frequency of measurement. Kamarck and colleagues (2002) conducted a unique study to examine this alternative hypothesis. In this study, measures of carotid atherosclerosis were compared with blood pressures obtained in the clinic, during an ambulatory monitoring period, and during an extended clinic session of comparable length. Because the same number of measurements and the same blood pressure measurement instru-

mentation were used during both the extended clinic session and ambulatory monitoring periods, these measurement confounds could be controlled. Results of this study demonstrated the superiority of ambulatory over clinic measures in predicting carotid atherosclerosis, providing support for the initial hypothesis that predicting target organ pathology involves consideration of the daily lifestyles of hypertensive patients.

It is quite clear that ambulatory blood pressure measurements provide information regarding risk for cardiovascular disease that cannot be obtained from simply measuring blood pressures in the clinic (Pickering et al., 2005). Ambulatory methods of blood pressure assessment provide a broader assessment of blood pressure status during various phases of daily life including the night, when patients are presumably exhibiting true resting baseline blood pressure levels. Based upon observations that blood pressure declines during nighttime ambulatory recording, several investigators have given serious attention to examining the relation between this nocturnal decrease and risk for cardiovascular disease.

Nocturnal Dipping of Blood Pressure

One of the most obvious observations among early studies that employed ambulatory measures of blood pressure recording was the fact that blood pressure tended to decrease (or dip) during nighttime hours or the hours during which the patient was sleeping. In brief, blood pressure typically exhibits a circadian rhythm, with lowest values occurring at night among persons on a normal sleep-wake cycle. This was certainly no surprise, as comparable reductions in nighttime blood pressure were observed in hospitalized patients when intra-arterial recordings of blood pressure were being assessed. What became of interest to these investigators, however, was the considerable variability of the observed reduction in blood pressure that occurred during nighttime or periods of sleep. While many participants in these studies exhibited reductions in nocturnal blood pressure of 10 percent or more (dippers), about one third of them showed very little reduction at all (non-dippers; Verdecchia, Schillaci, and Porcellati, 1991). In contrast to dippers, research has shown that non-dippers exhibit higher left ventricular mass (Verdecchia et al., 1990), increased secretion of albu-

men (Bianchi et al., 1994), and increased incidence of stroke (Phillips et al., 2000) as well as cardiovascular disease (Ohkubo et al., 1997; Verdecchia et al., 1994). However, target organ pathology or risk for cardiovascular disease do not always differ in comparisons between dippers and non-dippers (Cuspidi et al., 1999; Roman et al., 1997), indicating that the association between dipper status and risk for cardiovascular disease may not be that robust. Furthermore, there is some evidence suggesting that extreme dipping (defined as a reduction in blood pressure during night greater than 20 percent) might also be associated with increased risk for cerebrovascular damage (Kario et al., 1996). Therefore, the association between the degree of dipping during nighttime and risk for cardiovascular or cerebrovascular disease may be curvilinear in nature. Certainly, additional prospective trials are needed to clarify the inconsistent findings in this body of literature.

Part of the reason for these conflicting findings has been thought to be related to the unreliability associated with measurement of dipping status. Simply put, a significant number of individuals who exhibit a given dipping status during an ambulatory blood pressure monitoring period fail to show that same status during a second monitoring period (Dimsdale and Herren, 1998; Manning et al., 2000). It is also possible that non-dipping is associated with increased disease risk only among a subgroup of individuals. For example, rates of non-dipping have been found to be greater among persons of African American ethnicity (Sherwood et al., 2001; Wilson, Sica, and Miller, 1999) or among persons who are sodium sensitive (Sica, 1999; Wilson et al., 1999), indicating that perhaps the increased risk associated with non-dipping may be uniquely linked to other constitutional differences of non-dippers.

Discrepant Clinic and Home/Ambulatory Blood Pressures

For the most part, measures of blood pressure obtained in the clinic and those obtained out of the clinic, either from home or ambulatory blood pressure recordings, are intercorrelated. That is to say, individuals who have elevated blood pressures in the clinic typically have higher blood pressures outside of the clinic. Conversely, individuals with nor-

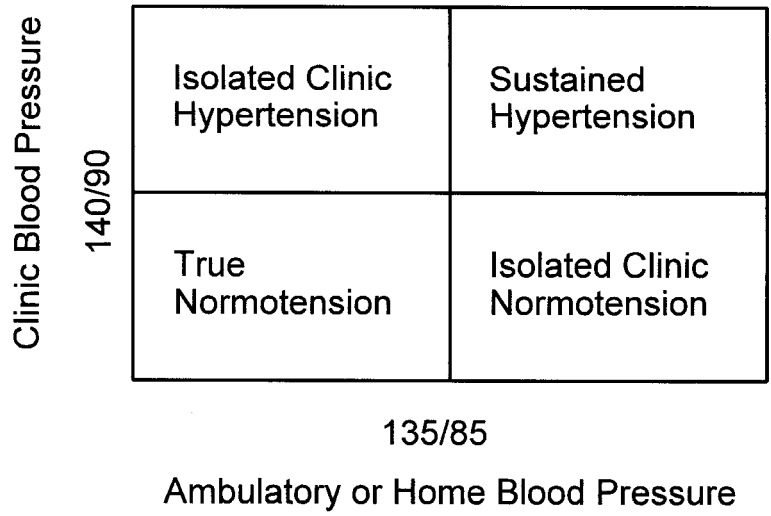

Figure 2.2. Categorization of hypertension, normotension, isolated clinic hypertension, and isolated clinic normotension from clinic and either home or ambulatory blood pressures. Adapted from Pickering et al. (1999), Task Force V: White coat hypertension, *Blood Pressure Monitoring, 4,* 333–341. Copyright © (1999), with permission from Lippincott, Williams, and Wilkins.

mal blood pressures in the clinic typically exhibit normal pressures during monitoring out of the clinic. There are, however, two categories of patients for whom this is not the case. Some patients have significantly greater blood pressures in the clinic than during daily life (see Figure 2.2). Although these patients have historically been referred to as 'white coat' hypertensive patients, based upon the premise that they were exhibiting a conditioned anxiety response to being evaluated by a medical professional wearing a white coat, a more descriptive term for this condition is isolated clinic hypertension. (Some patients indeed exhibit a 'white coat' effect without being hypertensive, as I will discuss in a moment.) In contrast, patients who exhibit elevated blood pressures throughout daily life, but normal blood pressures in the clinic, are referred to as isolated clinic normotensives. In both cases, one cannot rely solely upon clinic blood pressure determinations to evaluate patients regarding treatment decisions. Either home or ambulatory measures of blood pressure are needed to provide an accurate portrayal of the patient's current blood pressure status.

Before we discuss each of these conditions, it is important to acknowledge the importance of the considerations regarding appropriate reference values for both home and ambulatory blood pressures. If differential reference values are adopted, a patient with average clinic blood pressures of 144/92 mm Hg and average home blood pressures of 136/86 mm Hg would be diagnosed with essential hypertension using one set of criteria and with isolated clinic hypertension using another set of criteria. To complicate matters, not all research on patients with isolated clinic hypertension or isolated clinic normotension employs the same reference values for assigning patients to these categories. Keeping this limitation in mind, let's examine the literature regarding these two interesting clusters of patients.

Isolated Clinic Hypertension (White Coat Hypertension)

Isolated clinic hypertension presents a significant problem for physicians who rely on obtaining accurate clinic measures of blood pressure to render appropriate decisions regarding diagnosis and treatment. When nurses or physicians measure and record their elevated blood pressures in the clinic, these patients are often diagnosed and treated for essential hypertension as their elevated clinic arterial pressures are presumed to be representative of their daily arterial pressures. This may or may not be true. Certainly, patients with established essential hypertension sustain elevated pressures throughout daily life, suggesting strong correspondence between their clinic and non-clinic blood pressure measures. On the other hand, the correspondence between clinic and non-clinic blood pressures is quite poor for patients categorized as exhibiting isolated clinic hypertension. Unfortunately, isolated clinic hypertensive patients represent a significant proportion of adult patients identified in primary medical care settings as having high or borderline high blood pressure, with prevalence estimates ranging from 21 percent (Pickering et al., 1988) to 39 percent (Martínez et al., 1999). The prevalence rate of isolated clinic hypertension has been reported to be even higher (44 percent) among children (Hornsby et al., 1991). It is important to note that prevalence estimates of isolated clinic hypertension are somewhat lower in studies that employ multiple clinic visits than in studies that rely on a single clinic recording (Pearce et al.,

1992), again confirming the importance of taking blood pressure measures across multiple clinic visits prior to diagnosis. To further illustrate the importance of multiple clinic visits, Fogari et al. (1996) showed that the prevalence of isolated clinic hypertension in a sample of new hypertensive patients was quite different when calculated on the basis of a single clinic visit (25 percent isolated clinic hypertensive) or multiple clinic visits (14 percent isolated clinic hypertensive). Although multiple clinic blood pressure determinations are recommended to rule out isolated clinic hypertension, there is evidence to suggest that many isolated clinic hypertensives continue to exhibit elevated blood pressure recordings even after several clinic visits (Fogari et al., 1996; Pickering, 1999a).

Isolated clinic hypertension should be distinguished from what is called the 'white coat' effect. The white coat effect refers to the acute elevation in blood pressure in response to a clinic visit. In contrast to isolated clinic hypertension, the 'white coat' effect can be experienced by both normotensives and hypertensives alike. For example, a patient with normal daily blood pressures averaging 115/70 mm Hg might exhibit average blood pressures in the clinic of 125/80 mm Hg, a noticeable 'white coat' effect that does not compromise his or her categorization as a normotensive. Likewise, an essential hypertensive patient may have an average clinic blood pressure of 160/100 mm Hg and a mean daily blood pressure of 150/95 mm Hg, both within the hypertensive range yet exhibiting a noticeable 'white coat' effect. Because evidence linking the acute 'white coat' effect to risk for either essential hypertension or cardiovascular disease is lacking (Lantleme et al., 2000), the remainder of this section will focus on the etiology and risk associated with isolated clinic hypertension.

Isolated Clinic Hypertension as a Conditioned Response

One of the most promising hypotheses regarding the etiology of isolated clinic hypertension is that the observed cuff reaction among isolated clinic hypertensive patients represents a conditioned emotional response to blood pressure determinations (Pickering et al., 1990). In short, isolated clinic hypertensives exhibit a conditioned hypertensive response to the cues present during blood pressure determination such as the presence of a physician or the sight of the occluding cuff. This

would explain why blood pressure recordings decrease with repeated blood pressure determinations for a portion of patients with isolated clinic hypertension, reflecting a deconditioning or extinction effect. Some support for this hypothesis can be derived from a study by Rostrup et al. (1990) in which the casual blood pressures of a group of men increased from the first to the second clinic visit, but only when the men were led to believe their first recording was high. In addition, Mancia and colleagues (Mancia et al., 1983; Mancia et al., 1987) obtained continuous measures of blood pressure and heart rate using an intra-arterial recorder during multiple cuff blood pressure determinations by a physician in both hypertensive and normotensive patients. Their data showed immediate rises in both systolic (+27 mm Hg) and diastolic blood pressure (+15 mm Hg) as the physician approached the patient. Although the magnitude of this reaction declined with repeated measurements during the first visit, the full intensity of the reaction was observed again when the physician returned for a second visit. These findings parallel the magnitude and pattern of cardiovascular reactions typically observed in studies on phobic patients who are exposed to feared stimuli, lending some support to the conditioning hypothesis of isolated clinic hypertension.

The conditioning hypothesis proposed by Pickering and colleagues (1990) presumes that the conditioned response is related to an emotional reaction, perhaps involving the threat of negative evaluation, fear of interacting with authoritative medical personnel, or potentially learning that one has been diagnosed with a chronic medical condition. Congruent with this interpretation, it has long been suspected that isolated clinic hypertensive patients are more anxious than their hypertensive counterparts. However, existing studies have failed to support this hypothesis (Gerardi et al., 1985; Larkin et al., 1998b; Siegel, Blumenthal, and Divine, 1990). It must be noted though that only a few investigations have been conducted evaluating the relation between self-reported anxiety and isolated clinic hypertension. Those that have been conducted have typically used general measures of anxiety, rather than more specific measures of social and evaluative anxiety or fears of death and illness that may more accurately fit isolated clinic hypertensive patients. In a related area, it has also been hypothesized that isolated clinic hypertensives are more physiologically responsive to environmental chal-

lenges (including blood pressure determinations) than actual hypertensives or normal blood pressure controls. A few studies have examined this hypothesis, and findings have been largely negative, with Gerardi et al. (1985) finding partial support, but other studies failing to find reactivity differences between isolated clinic hypertensive and non-isolated clinic hypertensive patients during laboratory challenges (Cardillo et al., 1993; Larkin et al., 1998b; Lerman et al., 1989; Siegel et al., 1990; White et al., 1989). Although these findings appear to argue against the role of a conditioned emotional response in the etiology of isolated clinic hypertension, it is possible that hypertensive cuff reactions observed among isolated clinic hypertensive patients involve interoceptive conditioning, in which the conditioned blood pressure response is not emotionally mediated. We know, for example, that many autonomic functions (for example, salivation and eye blinks) can become conditioned to any number of external stimuli, and there is no reason to exclude blood pressure conditioning as another possibility. Therefore, the failure to demonstrate that isolated clinic hypertensive patients are either more anxious in clinical settings or more prone to reacting to stressful stimuli with blood pressure increases than patients with established hypertension is not sufficient for totally disregarding the conditioning hypothesis.

Isolated Clinic Hypertension and Target Organ Pathology

Although there exists some disagreement regarding the relative cardiac risk and subsequent treatment recommendations for individuals with confirmed isolated clinic hypertension, it has been suggested that this frequent condition may be partially responsible for the weak relation commonly observed between office blood pressure determinations and hypertensive target organ damage (Perloff et al., 1983). In other words, the reason that clinic-derived measures of blood pressure correlate poorly with indicators of target organ pathology is that samples of persons with elevated clinic blood pressures contain numerous individuals with isolated clinic hypertension, a condition thought to be relatively benign with regard to target organ pathology.

Although it seems obvious that persons with isolated clinic hypertension would exhibit less target organ pathology than persons with diagnosed essential hypertension, let's examine the evidence that has addressed this hypothesis. Over a dozen studies have assessed target or-

gan pathology among isolated clinic hypertensive patients and compared these values with both sustained hypertensive patients and normotensive controls (see Pickering, Coats, et al., 1999). From their review of this body of literature, Pickering et al. concluded that target organ pathology of isolated clinic hypertensive patients is invariably less than patients with established hypertension. However, the relation between target organ pathology of isolated clinic hypertensive patients when compared to normotensive controls is less clear. In about half the studies that have been conducted, target organ parameters from isolated clinic hypertensives closely resembled those of normotensive controls (for example, Cavallini et al., 1995; Pierdomenico et al., 1995); however, the remaining studies showed that target organ pathology among isolated clinic hypertension exceeded that of normotensive controls (for example, Kuwajima et al., 1994; Palantini et al., 1998). Findings from this latter group of studies were somewhat difficult to interpret because ambulatory blood pressures of the isolated clinic hypertensive patients were significantly higher than the normotensive controls, albeit in the normal range of blood pressure.

Mallion et al. (1999) also conducted a review of this body of literature and came to a similar conclusion; studies that found significant differences between isolated clinic hypertensive patients and normotensives tended to employ more liberal ambulatory blood pressure classification criteria for isolated clinic hypertensive patients. For example, in such studies, a patient with a mean clinic blood pressure of 140/90 mm Hg and a mean ambulatory blood pressure of 138/88 mm Hg could be classified as having isolated clinic hypertension. Given that the mean difference between these two assessments was only 2 mm Hg, it hardly seems to represent the type of discrepant blood pressure information typically seen in isolated clinic hypertension. Interestingly, in Mallion et al.'s review, studies adopting the recommended lower cutoffs for ambulatory blood pressures failed to show any difference between isolated clinic hypertension and normotension on a number of measures of target organ pathology.

In an effort to control for group blood pressure differences observed in previous studies, Muldoon et al. (2000) compared the degree of carotid artery atherosclerosis in isolated clinic hypertensives with both hypertensive patients matched on clinic blood pressures and nor-

motensive patients matched on ambulatory blood pressures. In contrast to the suggestions of Mallion et al. (1999), the same blood pressure criteria (140/90 mm Hg) was used for both clinic and ambulatory blood pressure measures in categorizing individuals into groups. After controlling for blood pressure, results revealed that the degree of carotid artery atherosclerosis was equivalent between isolated clinic hypertensive and essential hypertensive patients, and that both hypertensive groups exhibited greater pathology than normotensive controls. Therefore, these findings supported the hypothesis that isolated clinic hypertension was *not* a benign condition, at least as it pertained to carotid artery pathology.

Finally, Pickering et al. (1999) also examined studies that contrasted cardiovascular morbidity and mortality between isolated clinic hypertensive patients and patients with sustained hypertension. Although not a large number of studies have examined this relation, isolated clinic hypertension was associated with lesser risk for cardiovascular morbidity and mortality than essential hypertension.

In sum, isolated clinic hypertension appears to be associated with less risk for cardiovascular disease and hypertensive target organ pathology than essential hypertension. Among studies adopting the recommended lower cutoff criteria for home or ambulatory blood pressures (135/85 mm Hg), there are typically few differences observed between isolated clinic hypertensives and normotensives. In fact, Mallion et al. (1999) stated that as a result of adopting these lower reference values, isolated clinic hypertension became less prevalent and may no longer be considered a significant diagnostic problem. Nevertheless, there continue to be many patients who exhibit classic isolated blood pressure profiles, and they continue to create difficulties for establishing accurate diagnoses and making appropriate treatment decisions. Additionally, most of the studies that have explored the relation between isolated clinic hypertension and target organ pathology have focused upon measures of left ventricular functioning or kidney pathology. It is possible that isolated clinic hypertension may be associated with a specific type of target organ pathology, perhaps with the carotid artery as suggested by Muldoon et al. (2000). Although it is premature to derive this type of conclusion from the evidence of a single study, it is important to acknowledge that a variety of types of tar-

get organ pathology should be considered and examined before drawing any definitive conclusions regarding the pathological risks associated with isolated clinic hypertension.

Detecting Isolated Clinic Hypertension

Because patients with isolated clinic hypertension have presumably less risk for cardiovascular complications than essential hypertensive patients, there is a question about whether treatment is necessary in this group. Additionally, there have been some reports that anti-hypertensive treatments are less effective in decreasing blood pressures observed in isolated clinic hypertensive patients (Fitscha and Meisner, 1993; Pickering et al., 1994). Therefore, in order to make optimal treatment recommendations, it is important for the physician to distinguish isolated clinic hypertensive patients from those with established hypertension. Unfortunately, there are few guidelines that will assist a physician in making this distinction. For example, although it is known that more women than men exhibit isolated clinic hypertension (Myers and Reeves, 1995; Pickering et al., 1988), this information is not very useful for determining the appropriate diagnosis when examining a new hypertensive patient in the clinic. It has also been reported that isolated clinic hypertension is more frequent among nonsmokers, and among persons with low clinic DBP and low left ventricular mass (Verdecchia et al., 2001). Knowledge of these variables, too, provides the physician with very little guidance in establishing an appropriate diagnosis and treatment plan. Physicians are not going to dismiss a new patient as having isolated clinic hypertension and not offer treatment just because she is a nonsmoker. As stated above, there is also no evidence that obtaining measures of self-reported anxiety yields any helpful information to the physician regarding making this distinction (Gerardi et al., 1985; Siegel et al., 1990).

After examining the literature on isolated clinic hypertension, Verdecchia et al. (2003) derived the following list of factors that might cue a physician to consider the presence of isolated clinic hypertension and recommend ambulatory blood pressure monitoring: female gender, nonsmoking status, newly diagnosed hypertension, limited exposure to clinic settings, and low left ventricular mass. In an analysis of potential predictors of isolated clinic hypertension, Larkin et al.

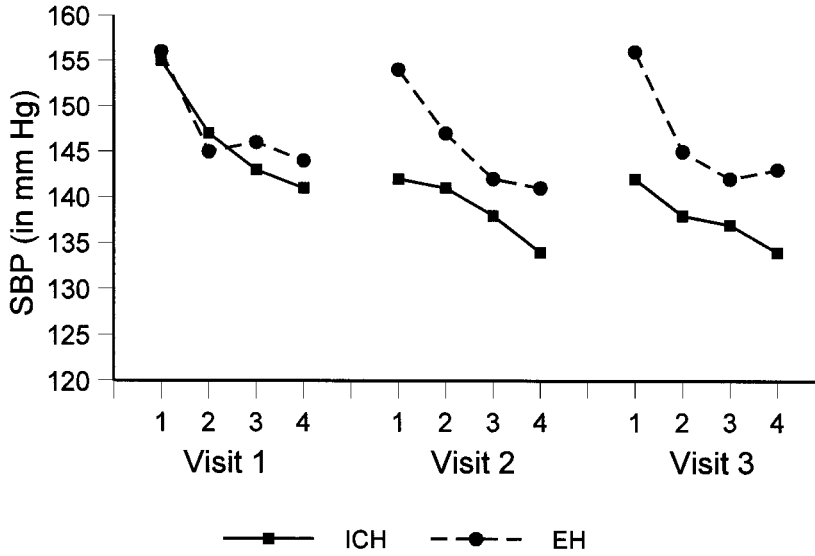

Figure 2.3. Clinic SBPs for isolated clinic hypertensive (ICH) and essential hypertensive (EH) patients. Blood pressure determinations for each of three clinic visits were made immediately upon arrival to the clinic and after 10, 15, and 20 minutes of quiet rest. Data collection supported by the American Heart Association, West Virginia Affiliate (Grant 93-7854S).

(1998b) confirmed that there is very little the physician can do during an initial clinic visit that can corroborate presence of isolated clinic hypertension. From a wide range of potential predictors of isolated clinic hypertension in this study, only two strategies were found to discriminate isolated clinic hypertension from sustained essential hypertension, home blood pressure monitoring and the degree of blood pressure habituation across clinic visits. Obviously, isolated clinic hypertensive patients reported lower blood pressures during a week of home blood pressure monitoring in comparison to the sustained hypertensive group. Regarding the degree of habituation across clinic visits, although SBPs of patients with isolated clinic hypertension were indistinguishable from essential hypertensive patients during the first visit to the clinic, they tended to habituate during subsequent visits as the patients grew accustomed to the clinic environment (see Figure 2.3). A comparable effect, however, was not observed for DBP.

Isolated Clinic Normotension

A few investigators have now observed a condition in which normal blood pressures in the clinic are accompanied by elevated measures during daily life, a condition termed isolated clinic normotension. A variety of other names have been associated with this condition, including isolated home hypertension (Bobrie et al., 2001), 'white coat' normotension (Prattichizzo and Galetta, 1996), reverse 'white coat' hypertension (Wing et al., 2002), or masked hypertension (Pickering et al., 2002). For our purposes, let's refer to the condition as isolated clinic normotension to be consistent with the terminology used to describe isolated clinic hypertensive patients.

Prior to the advent of reliable ambulatory technologies, physicians were unaware that isolated clinic normotension existed. It was simply assumed that patients who had normal blood pressure values in the clinic also maintained these normal values during daily life. This assumption, however, turned out to be incorrect. Although the existence of isolated clinic normotension was acknowledged in some earlier work with ambulatory instrumentation (Hoegholm et al., 1992), the prevalence of these individuals was unknown until relatively recently. Results now from several studies have confirmed that isolated clinic normotension is very common, with prevalence estimates ranging from 10 to 45 percent among patients with normal clinic blood pressures (Bobrie et al., 2001; Donner-Banzhoff et al., 1998; Larkin, Schauss, and Elnicki, 1998a; Segre et al., 2003; Selenta, Hogan, and Linden, 2000; Wing et al., 2002). Although the exact prevalence of isolated clinic normotension in the general population is yet unknown, there is clear evidence that it occurs frequently and that hypertension is presumably undetected in these individuals.

Isolated Clinic Normotension and Target Organ Pathology

Assuming that patients with isolated clinic normotension exhibit elevated blood pressures during most of their daily life (except when in the clinic of course!), it could be hypothesized that patients with these blood pressure profiles possess the same target organ pathology and elevated risk for cardiovascular disease as individuals with untreated essential hy-

pertension. Although a lot of data have not been gathered to test this hypothesis, the evidence that exists shows that isolated clinic normotensive patients indeed exhibit the same target organ pathology as patients with sustained essential hypertension (Liu et al., 1999; Sega et al., 2001). Liu et al. (1999) reported comparable indices of left ventricular hypertrophy and carotid artery atherosclerosis as well as numerous blood assays (glucose level, cholesterol level, creatinine concentration) between isolated clinic normotensive and essential hypertensive patients. Both hypertensive groups exhibited a greater incidence of left ventricular hypertrophy, plaque development in the carotid arteries, and increased levels of serum glucose and cholesterol than normotensive controls, lending support to the hypothesis that isolated clinic normotension is associated with increased risk for cardiovascular disease consequences. By using data from the PAMELA Study, Sega et al. (2001) confirmed that isolated clinic normotension is not a benign condition. As in the aforementioned findings reported by Liu et al., isolated clinic normotensive patients exhibited greater left ventricular hypertrophy than persons with normal blood pressures in all settings. Although not many studies have examined target organ pathology in isolated clinic normotension, and no studies have yet examined the relation between actual cardiovascular disease endpoints in isolated clinic normotension, the current evidence indicates that individuals with this unique blood pressure profile exhibit risk for cardiovascular complications comparable to untreated essential hypertensive patients. In a sense, that is what they are.

Etiology of Isolated Clinic Normotension

Due to the relative recency of this body of literature, not much is known about the cause of isolated clinic normotension. On the one hand, it could be hypothesized that isolated clinic normotension is associated with an increased frequency of situations during daily life that are related to increased blood pressure (for example, increased smoking, physical activity, and stress); on the other hand, it is possible that isolated clinic normotensive patients adopt self-relaxing strategies during clinic visits that result in lower-than-actual clinic blood pressure determinations. At present, there is more evidence to support the former hypothesis. For example, isolated clinic normotensives have been shown to exhibit poorer daily health habits than either essential hypertensive patients or normotensive controls. Several studies, for example,

have found that isolated clinic normotensives were more likely to be past or current smokers than normotensives (Larkin et al., 1998a; Liu et al., 1999; Selenta et al., 2000; Wing et al., 2002). Two studies have shown that isolated clinic normotensives are more likely to be men rather than women as well as persons who consume alcohol (Larkin et al., 1998a; Selenta et al., 2000). Although no differences between isolated clinic normotensives and either hypertensive patients or normal blood pressure controls have emerged on measures of stress (Donner-Banzhoff et al., 1998), there is some indication that isolated clinic normotensives sleep less and engage in more physical activity during ambulatory monitoring periods than comparison groups (Larkin et al., 1998a). One gets the picture that daily lives of isolated clinic normotensive patients are packed with work and home activities and that these patients may lack adaptive coping skills to deal with the number of activities in their lives. As such, they tend to adopt less adaptive coping strategies like smoking or drinking alcohol to deal with their daily emotional duress. At the current time, there is no evidence to suggest that isolated clinic normotensive patients adopt self-relaxing or self-soothing strategies while in the clinic; indeed, if they possessed such strategies, one would suspect they would use them outside of the clinic during their daily lives, which apparently they do not do. Regardless of the specific behaviors involved in the etiology of isolated clinic normotension, the existence and pathology of the condition provide an important reason for considering broader applications of ambulatory blood pressure measurement. In fact, the most recent American Heart Association recommendations for measuring blood pressure advocates a more prominent role for ambulatory blood pressure monitoring in diagnosing cases of essential hypertension (Pickering et al., 2005).

Measurement of Hemodynamic Functioning

As outlined in Figure 1.1, blood pressure is jointly determined by cardiac output and total peripheral resistance. To answer several types of empirical questions relating to blood pressure, it is necessary to obtain corresponding measures of cardiac output or total peripheral resistance, the so-called parameters of hemodynamic functioning. Unfortunately, hemodynamic parameters are not convenient to measure. The primary strategy for measuring cardiac output involves insertion

of catheters into locations proximal to the heart so that dye can be injected into the right atrium of the heart and then detected as it is ejected from the left ventricle over a period of time. Obviously, this procedure is not easily conducted in clinical practice, nor can it be used for large-scale epidemiologic trials. Because total peripheral resistance reflects resistance to blood flow throughout the entire body, there is no known procedure for measuring it directly; however, it can be measured indirectly by dividing mean arterial pressure by cardiac output. Although it may appear that reliable measures of cardiac output and total peripheral resistance are too cumbersome to be of any use, impedance cardiography has enabled clinical researchers to obtain measures of hemodynamic functioning with minimal hassle.

Impedance Cardiography

Impedance cardiography is a noninvasive assessment strategy that can be used to estimate stroke volume and cardiac output (Mohapatru, 1981). Basically, the process involves transmitting a small constant electrical current through the thorax from the neck to the abdomen using a series of electrodes that encircle the body. Resistance to this electrical current is influenced by the volume of blood being ejected during each cardiac cycle. When a large amount of blood is ejected into the circulatory system, resistance to the electrical current temporarily decreases, as blood is a good conductor of electricity. The impedance cardiograph then detects these alterations in electrical resistance, and through a formula initially proposed by Kubicek et al. (1966), the measure of resistance can be converted into an index of stroke volume and consequently cardiac output. There are several advantages to using impedance cardiography for obtaining estimates of hemodynamic functioning. In addition to its obvious advantage of being noninvasive, measures of stroke volume are obtained continuously, so that immediate acute responses to various environmental stimuli (stressors) can be determined. Furthermore, the impedance method permits concurrent assessment of other measures of interest, including indices of cardiac contractility and systolic time intervals, like pre-ejection period, that have proven useful in assessing autonomic nervous system influences upon the heart.

Several dozen studies have compared measures of stroke volume and cardiac output obtained via impedance cardiography with mea-

sures of these same parameters by means of a variety of invasive strategies (see Fuller, 1992; Mohapatru, 1981). Correlations between impedance-derived and invasive estimates of these hemodynamic parameters are typically very high, with the vast majority above .80, providing evidence that both are measuring the same hemodynamic process. But although the two are highly intercorrelated, there is evidence that impedance cardiography tends to overestimate stroke volume consistently, occasionally more than 10 percent, leading to its infrequent adoption and use in hospital settings where more precise measures of hemodynamic functioning are needed (Sherwood, 1993). Because investigations of the transition from early-stage elevated blood pressure associated with increased cardiac output to sustained high blood pressures maintained by increased total peripheral resistance rely upon accurate measurement of absolute levels of hemodynamic functioning, they have typically used invasive methods of assessing hemodynamic functioning (for example, Lund-Johansen, 1991). However, despite these limitations associated with impedance cardiography–derived absolute levels of stroke volume and cardiac output, it is generally recognized that relative changes in stroke volume and cardiac output can be determined quite accurately using the impedance cardiograph (Sherwood et al., 1990). Therefore, impedance cardiography has been shown to be very useful in determining the hemodynamic processes that are responsible for specific increases or decreases in blood pressure in response to environmental events. To extend its usefulness beyond the scope of the clinic or laboratory setting, an ambulatory version of the impedance cardiograph has been devised and validated to assist researchers in determining the hemodynamic foundations associated with blood pressure elevations that occur during daily life (Nakonezny et al., 2001).

Summary

Methods of blood pressure assessment have come a long way from the days when Hales (1733) developed the invasive glass tube gauges for measuring blood pressure directly. Most clinics in medical settings rely on the auscultatory method for measuring blood pressure because it is noninvasive, inexpensive, and accurate. Although sophisticated automated devices have been developed and validated using either auscul-

tatory or oscillometric methods, they are typically more useful in research laboratories or in hospitals where frequent, regular measures of blood pressure are needed. Likewise, continuous measures of blood pressure using the vascular unloading principle or measures of hemodynamic functioning using impedance cardiography are more likely to be used in research laboratories rather than clinic settings. In both cases, although the methods represent reliable ways for determining relative change in important cardiovascular parameters, their ability to derive accurate absolute measures of those parameters is lacking.

It is well known that clinic measures of blood pressure do not often correspond well with measures of blood pressure obtained outside the clinic. To obtain accurate measures of blood pressure during daily life, either home blood pressure recording or ambulatory methods of blood pressure assessment must be employed. Both home and ambulatory methods typically yield values lower than those observed in the clinic. Furthermore, because they provide a more comprehensive evaluation of a person's daily blood pressure profile, they are better predictors of hypertensive target organ pathology and risk for subsequent cardiovascular disease than clinic-derived measures.

Two clusters of patients exhibit considerable disagreement between blood pressure values obtained in the clinic and those obtained during daily life: isolated clinic hypertensives and isolated clinic normotensives. Isolated clinic hypertensives, who exhibit hypertensive blood pressure readings in the clinic but normal readings during daily life, typically have a lesser risk for target organ pathology and subsequent cardiovascular disease than essential hypertensive patients. Conversely, isolated clinic normotensives, who exhibit elevated blood pressures in their daily life but normal values in the clinic, typically exhibit an elevated risk for target organ pathology. In other words, isolated clinic hypertensives tend to resemble normotensives, and isolated clinic normotensives tend to resemble untreated hypertensive patients. Because these two clusters of patients represent a substantial portion of patients seen in medical clinics, it could be argued that an accurate portrayal of blood pressure status necessarily involves obtaining multiple measures of blood pressure obtained both in the clinic and during daily life. With this type of assessment strategy, more reliable estimates of our constantly fluctuating blood pressures can be assuredly obtained.

3

Models of Stress

Like many other psychological constructs (for example, personality or intelligence), the construct of 'stress' lacks a uniformly accepted definition. Literally, the term was borrowed from physics, in which it referred to a force or mechanical pressure that resulted in strain upon a particular structure. For example, a professional diver creates stress on a diving board in his or her approach to it; the flexibility of the diving board in response to the stress of his or her action represents strain. In this usage, stress leads to strain, with stress serving as a stimulus and strain as the response. This logic, however, has not been consistently followed in the translation of the term 'stress' from physics to psychology. Statements like "you are stressing me out" or "my job is causing me a lot of stress," seem to use the term 'stress' as a response rather than a stimulus.

For purposes of clarity, it is probably best to differentiate between the use of the term 'stress' to refer to an environmental stimulus and its use to refer to the body's response to that stimulus. Let's call stimuli related to stress *stressors,* and the body's response to stress the *stress response.* Given this distinction, events like job stress, traffic jams, interpersonal conflict, being pestered by telemarketers, and daily hassles represent stressors, while autonomic nervous system arousal, insomnia, worry and anxiety, and social withdrawal represent stress re-

Table 3.1. Affective, Behavioral, Cognitive, and Physiological Stress Responses

Affective	*Behavioral*	*Cognitive*	*Physiological*
Anxiety	Escape/Avoidance	Worry	Autonomic Arousal
Depression	Substance Use/Abuse	Catastrophic Thinking	Neuroendocrine Activation
Anger	Social Withdrawal	Poor Concentration	Muscle Tension
Guilt	Over/Under Eating	Selective Attention	Hyperventilation
Fear	Irritability Aggression Inactivity	Thought Blocking Rumination Hopelessness	Compromised Immune Function

sponses. Although it has been helpful to distinguish stressors as either physical (change in temperature, posture, or physical activity) or psychological (threat to self-esteem or safety) in nature (Lovallo, 1997), the body's response to them is often quite similar.

Conceptually, it is useful to differentiate stress responses into physiological, cognitive, affective, and behavioral (see Table 3.1). Physiological responses include the various components of the fight-flight response system of the autonomic nervous system outlined in Chapter 1 in addition to muscle tension, a manifestation of the somatic nervous system. In a synchronized response to a particular stressor, pupils dilate, blood flow is redistributed to the muscles and brain, heart rate increases, respiration rate increases, and the neuroendocrine system releases catecholamines and cortisol into the bloodstream (see Table 3.2). Neuroendocrine responses lead to a compromised immunologic status, leaving the body less able to resist infection by bacteria, viruses, and fungi (Lovallo, 1997). Cognitive stress responses include increased worry, maladaptive catastrophic thinking, and rumination, coupled with decreased concentration and information processing (blocked thoughts). Depression, anxiety, and anger constitute some affective stress responses, and social withdrawal, behavioral avoidance, substance use and abuse, irritability, and aggression are possible behavioral stress responses. It is generally recognized that these various response

Table 3.2. Effects of the Autonomic Nervous System

Sympathetic Nervous System ("fight-flight" response)	*Target Organ*	*Parasympathetic Nervous System ("relaxation" response)*
Dilation	Pupils of the eye	Constriction
Thick	Saliva	Thin
Increased rate	Heart	Decreased rate
Dilation	Bronchi in the lungs	Constriction
Decreased digestion	Stomach and intestines	Increased digestion
Glucose secretion	Liver	No effect
Epinephrine secretion	Adrenal gland	No effect
Relaxation	Bladder	Contraction
Constriction (skin, abdomen); Dilation (muscles)	Blood vessels	No effect
Increased activity	Skin sweat glands	No effect
Ejaculation/orgasm	Genitals	Erection/lubrication

systems are interrelated in some way so that increases in one response system affect responses in the three remaining systems.

It is also important to differentiate short-term, or acute, stress responses, from longer-term, or chronic, stress responses. A single stress-filled encounter is extremely unlikely to result in an enduring medical problem like a peptic ulcer, asthma, or cardiovascular disease. As has been widely reported, however, there are recognized associations between life stressors and a variety of chronic medical disease endpoints, including cancer (Anderson, 2002), coronary heart disease (Rozanski, Blumenthal, and Kaplan, 1999), diabetes mellitus (Cox and Gonder-Frederick, 1991), gastrointestinal disturbances (Duffy et al., 1991; Levenstein, 2002), and skin diseases (House et al., 1979), among others (Caplan et al., 1975; Cobb and Rose, 1973). Because these chronic health problems develop over periods of time as long as years or even decades and the physiological changes that occur during this period occur gradually, it is generally believed that these chronic stress responses evolve from acute stress responses that occur either too frequently or at too great an intensity. In other words, chronic stress re-

sponses could be prevented if acute stress responses to environmental stressors never happened in the first place.

The exact mechanism involved in the transition from acute to chronic stress responses is a matter of debate. While some investigators have focused on the causal relations among acute physiological responses and chronic diseases (McEwen and Stellar, 1993), others have highlighted the direct link between various acute behavioral stress responses (for example, smoking or substance use) and chronic diseases (Cohen and Rodriquez, 1995). In the case of cardiovascular disease, for example, exaggerated acute physiological responses (Krantz and Manuck, 1984), acute behavioral responses like smoking and leading a sedentary life (Paffenbarger et al., 1986), and the acute affective response of depression (Rozanski et al., 1999) have all been implicated as factors contributing to the development of atherosclerosis. It is evident in relations like these that multiple causal factors are likely to be involved in explaining how acute stress responses lead to specific chronic stress responses. Several theories regarding the mechanisms responsible for mediating the relation between a psychological construct like stress and actual physiological tissue damage have been examined and have received some empirical support.

Theories of Stress

There are several theoretical positions devised for examining and understanding stress and stress-related disorders. Brantley and Thomason (1995) categorized them into three groups: response theories, stimulus theories, and interaction (or transaction) theories. Given the distinction made earlier between stress as a stimulus and as a response, this system serves as a useful way to present the various theories and associated research.

Response Theories and Research

Because chronic stress responses involve actual physiological changes to body systems and organs, a good bit of attention has been paid to acute physiological stress responses and how they might possibly lead to subsequent chronic stress responses (McEwen and Stellar, 1993).

Historically, both Walter Cannon (1929) and Hans Selye (1956) provided the foundation for the current interest in this physiological process.

The Work of Walter Cannon

Cannon was a physiologist at Harvard University who was the first to use the term 'homeostasis.' According to Cannon (1929), the body possesses an internal mechanism to maintain stable bodily functioning or equilibrium. As the environment presents the organism with various challenges, the body must respond to each new situation by adjusting various physiological systems to compensate for the resources being taxed. A classic example of this type of compensation involves fluid regulation. When an organism ingests a large amount of water, the kidney releases more waste fluid into the bladder for eventual disposal in an effort to maintain bodily equilibrium. Many of the feedback mechanisms that regulate blood pressure presented in Chapter 1 share similar characteristics with bodily systems that maintain homeostasis. According to Cannon (1935), failure of the body to respond to environmental challenges by maintaining bodily homeostasis results in damage to target organs and eventually death. Translating his work with physical challenges associated with eating, drinking, and physical activity into those of a psychological nature, Cannon hypothesized that common homeostatic mechanisms were involved. Accordingly, if an organism's response to threat involves significant sympathetic nervous system arousal so that respiration and heart rate increase significantly, the body's compensatory response should involve either reducing sympathetic nervous system activity or increasing parasympathetic nervous system counter-activity. If the compensatory response is inadequate, tissue damage can result, placing the organism at a greater risk for subsequent medical problems associated with the damaged tissue. In brief, the concept of homeostasis introduced by Cannon has proved to be very valuable in explaining how acute physiological stress responses to threats of survival lead toward chronic stress responses.

The Work of Hans Selye

Selye (1956) was the first investigator to use the term 'stress' to describe the problems associated with homeostasis identified by Cannon de-

cades earlier. Although he borrowed the term from physics, he used it to describe the effects on the organism rather than the environmental stressors he examined in his empirical work. According to Selye, the 'stress' response of the organism represented a common set of generalized physiological responses that were experienced by all organisms exposed to a variety of environmental challenges like temperature change or exposure to noise. From his perspective, the stress response was nonspecific; that is, the type of stressor experienced did not affect the pattern of response. In other words, a wide variety of stressors elicited an identical or general stress response. He termed this nonspecific response the General Adaptation Syndrome, which consisted of three stages: Alarm Reaction, Resistance, and Exhaustion. Selye reasoned that the first stage, Alarm Reaction, involved the classic 'fight-flight' response described above. As a result, the body's physiological system dropped below optimal functioning. As the body attempted to compensate for the physiological reactions observed in the Alarm Reaction stage, the organism entered the Resistance stage. Physiological compensatory systems began working at peak capacity to resist the challenges the entire system was confronting, and according to Selye, actually raised the body's resistance to stress above homeostatic levels. However, because this response consumed so much energy, a body could not sustain it forever. Once energy had been depleted, the organism entered the stage of Exhaustion. In this stage, resistance to environmental stressors broke down and the body became susceptible to tissue damage and perhaps even death. In Selye's terminology, the Alarm Reaction Stage was comparable to the acute stress response described above and the Exhaustion Stage was comparable to a chronic stress response.

The Work of Bruce McEwen

More recently, the historic works of Cannon and Selye that have attempted to explain how acute physiological stress responses evolved into chronic stress responses have been revisited by Bruce McEwen and colleagues (McEwen and Stellar, 1993; McEwen, 1998) at Rockefeller University. In contrast to the state of physiological equilibrium of homeostasis essential for survival that Cannon discussed, McEwen used the term 'allostasis,' referring to the body's ability to adapt to a

changing environment in situations that did not challenge survival. From his perspective, an organism that maintained a perfectly stable physiological equilibrium during a stressful encounter (a nonresponse) might be just as problematic as an organism that exhibited an exaggerated physiological response. Allostasis referred to the body's ability to adjust to a 'new steady state' in response to the environmental challenge (McEwen and Stellar, 1993). To clarify the distinction between homeostasis and allostasis, consider two physiological parameters: body temperature and heart rate. For an organism to survive in a changing environment, there exists a very narrow window of acceptable body temperatures. Even though the temperature of the environment can change 50 degrees over the course of a single day, body temperature remains constant. Deviations from a normal temperature are met with a range of symptoms (sweating, chills) that occur as part of our body's attempt to regain homeostasis. For body temperature, homeostasis is a very important mechanism of survival. Now, let's consider heart rate. In contrast to body temperature, our body can tolerate a wide range of heart rates. When we are asleep, our heart rate drops to basal levels. When we are awake, heart rates increase substantially, and when we are engaged in aerobic exercise, heart rates climb even higher. Rather than maintaining stability in the face of a changing environment, as body temperature does, heart rate adjusts to a changing environment to optimize functioning. In this case, the ability of the body to adjust to aerobic exercise by resetting heart rate at a higher level is called allostasis, not homeostasis. McEwen argues that most acute stress responses represent challenges to the body's allostasis, not challenges to its homeostasis.

According to the work of McEwen and colleagues, 'allostatic load' is a term that refers to the price the body pays for being challenged repeatedly by a variety of environmental stressors. Increased allostatic load, or what McEwen and Wingfield (2003) called 'allostatic overload,' occurs with increased frequency of exposure to stressors, increased intensities of these stressors, or decreased efficiency in coordinating the onset and termination of the physiological response. McEwen (1998) outlined four distinct types of allostatic overload (see Figure 3.1). In the first type, the organism is exposed to multiple environmental stressors during a short period of time. For example, imag-

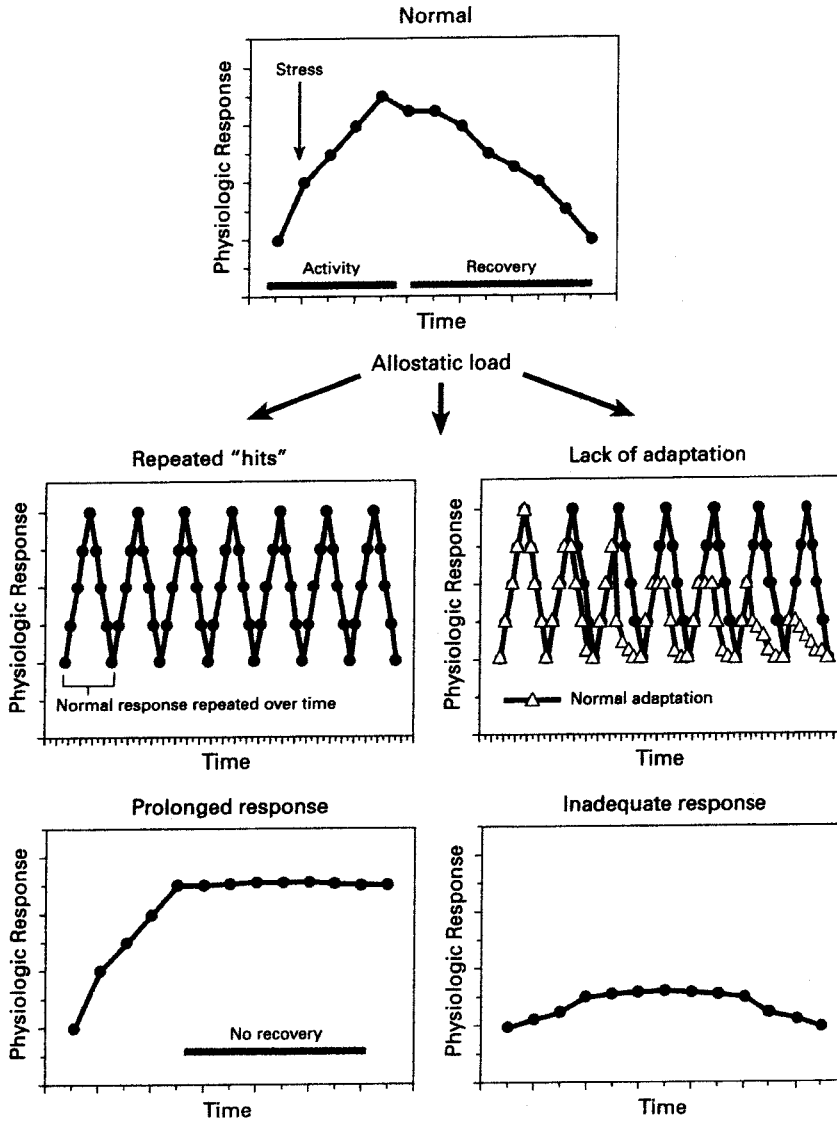

Figure 3.1. The various types of allostatic overload. Reprinted from B. S. McEwen (1998), Protective and damaging effects of stress mediators, *The New England Journal of Medicine, 338,* 171–179. Copyright © 1998 Massachusetts Medical Society. All rights reserved.

ine chasing a pesky salesperson off your front porch, running to get the phone only to realize it is a telemarketer, then finding your three-year-old coloring on the kitchen wall with permanent markers, and the family dog urinating on the floor. In a case like this, the physiological response associated with the first stressor was just starting to lessen when the second stressor hit, and likewise, recovery from the second stressor was interrupted by the onset of the third stressor. In this type of allostatic overload, the problem is associated with the frequency of the stressors encountered.

In the second form of allostatic overload, repeated stressors elicit responses that fail to habituate. Consider an example in which you are dealing with five consecutive irate customers who are demanding their money back for a defective product that you sold them. Normally, one's physiological response to this series of encounters would decrease, or habituate, with each subsequent encounter. When the body fails to exhibit the normal habituation response, this type of allostatic overload occurs.

A third form of allostatic overload involves delayed physiological recovery from a given environmental stressor. In this case, the frequency or magnitude of the physiological response may be entirely normal; however, it is the length of time that the response is sustained that leads to allostatic overload. For example, imagine having an argument with a family member and experiencing some physiological arousal associated with the argument. Rather than the arousal gradually declining after the argument, in this type of allostatic overload the physiological recovery is delayed and the arousal is still apparent hours or days later.

The final form of allostatic overload involves an inadequate physiological response. In this case, the organism encounters a stressful circumstance or environmental change, but the physiological response is either very weak or entirely absent. Imagine walking through the woods and encountering a black bear, only to find that your body's fight-flight response failed to occur and therefore did not provide the necessary energy and altered blood flow to run away from the threat.

According to McEwen and Stellar (1993), allostatic overload, whatever its source, is the mechanism through which acute physiological responses result in permanent tissue damage. Research using ani-

mals documents not only changes in peripheral tissues associated with increased allostatic load, but also altered functioning in the cerebral cortex (McEwen, 1998). This altered brain functioning has included atrophy of dendrites on neurons, suppression of neurogenesis (creation and proliferation of new neurons), and permanent loss of pyramidal neurons. Obviously, McEwen and other contemporary stress researchers have extended the theories and empirical work of Cannon and Selye to further our understanding of how stress results in actual tissue damage in the brain and peripheral body systems.

Selye's (1956) General Adaptation Syndrome described above is a classic representation of a theoretical perspective that focuses upon stress as a response. In fact, Selye went so far as to state that the nature of the stimulus was irrelevant to the stress response. To support his view, he subjected animals to a wide variety of experimental conditions that elicited very similar physiologic stress responses including temperature change, pain stimulation, and exposure to infection. Likewise, although acknowledging the importance of the stress stimulus in their theoretical models, McEwen and colleagues have also focused on the physiological stress response, paying less attention to the type or nature of the eliciting stimulus (McEwen and Stellar, 1993; McEwen, 1998). Although response theories have contributed greatly to our understanding of the physiological response systems that mediate the relation between environmental stressors and chronic stress responses, they have typically neglected a detailed exploration of types of environmental stressors and how they might influence the disease process.

Stimulus Theories and Research

Remaining consistent with the usage of the term 'stress' described in physics, some investigators have focused on stress as a stimulus. Most notable among researchers employing this approach were Holmes and Rahe (1967). These investigators devised a list of major life events known as the Social Readjustment Rating Scale. Intuitively selecting 'death of a spouse' as the barometer of the most stressful life event, this instrument consisted of 43 items measuring distinct life changes that were self-reported over a specified period of time, typically one year. Each item was assigned what Holmes and Rahe called a Life Change

Unit score based upon the item's relative severity with reference to 'death of a spouse.' Research employing the Social Readjustment Rating Scale has demonstrated an association between the number of significant stressful life events and incidence of a number of psychological disorders and medical diseases (Brown and Harris, 1989; Horowitz et al., 1977).

Elliott and Eisendorfer (1982), also focusing on stimulus characteristics, differentiated the various types of stressors that provoked challenges to bodily homeostasis. For example, they believed that acute or limited stressors, like a single surgery, elicited quite different stress responses than chronic stressors like job strain. Chronic stressors could also be categorized as enduring or intermittent. Being married to a nonsupportive spouse would be enduring, but having a sexual dysfunction would presumably be intermittent. Finally, they also discussed what were called 'stressor sequences.' Stressor sequences represented prolonged stressors that contained multiple and often different types of challenges to the individual. Divorce, for example, typically involved a prolonged sequence of stressful life events that presented different sorts of challenges to the individuals as they occurred (for example, separation, learning your spouse is getting remarried, working out child custody arrangements, loneliness, loss of joint friends, etc.). According to these stimulus theories, the distinct types of stimuli led to unique and predictable patterns of stress responses.

Other researchers have focused more on daily stressors than the major life events that were proposed by Holmes and Rahe (1967). These daily stressors or 'hassles' have included events like arguments with co-workers, dealing with traffic congestion, and receiving irritating phone calls. Some research has found that the effect of these daily hassles on health outcomes is more problematic than the effect of major life events on health outcomes (Brantley and Jones, 1993; Delongis et al., 1982).

Although research examining stress as a stimulus using self-report checklists has provided valuable evidence linking stress to various disease endpoints, many problems have been identified with this methodology. Foremost among these is the limited content of items contained in these inventories, the confounding of items on stress and health questionnaires, the questionable methods employed for assign-

ing weights in scaling life events, and the generally low reliability and validity of the instruments themselves (Zimmerman, 1983). In an effort to deal with the problems associated with self-report inventories typically employed in this type of research, some investigators have adopted alternate methods of assessing stressors that people encounter on a daily basis. For example, Wethington, Brown, and Kessler (1995) suggest that personal interview strategies for assessing stress do a better job of capturing unique stressful situations that influence individuals than standardized checklists. The constellation of unique family dynamics, financial strain, and spiritual struggles that accompany a patient encountering a transplant procedure, for example, represents a stressful situation that is not easily captured on a self-report checklist. In this situation, it is clear that an interview assessment strategy may capture the degree of stress more richly. Interview-based strategies of assessment are much more labor intensive, however, and unlikely to be used in large epidemiologic trials. Additionally, Lepore (1995b) recommends the use of observational assessment methods or securing information from significant other informants to complement either self-report or interview-based methods of assessing stressors. Basically, the more consistent the information obtained from multiple sources, the greater confidence researchers can have in their assessment of stress.

Interaction (Transactional) Theories and Research

Although some theoretical perspectives have focused on stress as a stimulus and others have focused on stress as a response, most modern conceptualizations of stress can be considered interactive or transactional in nature. Transactional theories incorporate the importance of both stressors and stress responses in explaining the linkage between stress and illness or disease. Additionally, transactional theories of stress suggest that stress responses can serve as new stressors that elicit more intense stress responses. For example, if an individual responds to interpersonal conflict (a stressor) by drinking alcohol and smoking cigarettes (an acute behavioral stress response), these behavioral responses may become new stressors that warrant additional stress responses. Thus transactional theories of stress incorporate components of stress stimuli and responses that operate upon one another in a cyclic fash-

ion. In addition, interaction or transactional theories emphasize the relation between the individual and the environment, something rarely discussed by purely stimulus or response theorists. Transactional theorists recognize that a great deal of variability exists regarding the magnitude of acute stress responses to seemingly comparable stimuli. As such, they have looked to individual difference factors to help explain these common observations.

Lazurus and Folkman (1984) proposed a transactional theory of stress that has received considerable attention over the years. According to their perspective, it was not the initial stressor per se that was critical in linking stress to disease, but the individual's response to the stressor that determined whether a cyclic stress reaction developed. Focusing upon the acute cognitive stress response system, Lazurus suggested that three types of cognitive appraisal occurred in determining the magnitude of the stress reaction: primary appraisal, secondary appraisal, and reappraisal. Primary appraisal focused upon the degree to which a person detected a stressor as being harmful (leading to potential injury or illness), threatening (causing anxiety, fear, or damage to self-esteem), or challenging (leading to potential gain or growth). According to Lazurus, individuals determined whether a stimulus was irrelevant, benign-positive, or stressful; only stimuli appraised as stressful elicited ongoing stress responses. Imagine, for example, brushing one's leg against something furry while hiking. It might be appraised as irrelevant if it was moss, benign-positive if it was a baby rabbit, or stressful if it was a rabid skunk!

Primary appraisal was conceptualized as being accompanied by secondary appraisal, which focused upon a person's determination of his or her resources to cope with the stressor perceived during primary appraisal. Most individuals clearly possess the resources to cope with brushing up against moss or a furry baby rabbit; however, many would question what to do when encountering a rabid skunk. Finally, the process of reappraisal involved any change in the primary appraisal as a result of the assessment of coping resources that occurred during secondary appraisal.

Not all transactional perspectives rely on cognitive appraisal. Jay Weiss, for example, conducted seminal laboratory examinations of the stimulus characteristics of predictability and control on stress re-

sponses in rats (1970; 1971a; 1971b). Weiss devised a set of sophisticated experiments demonstrating that rats that were provided with both control and predictability over a stressful stimulus exhibited reliably smaller stress responses and lesser tissue damage than yoked control animals without control or predictability (Weiss, 1970; 1971a; 1971b). Therefore, controllability and predictability represented contextual components of the laboratory experiment that were shown to determine the magnitude of the stress response evoked by the stressor.

Weiss's influential work on the importance of control and predictability of the stimulus affecting an organism's stress response provided the empirical foundation for a transactional theory of stress commonly referred to as the Defense-Defeat Model of Stress (Henry and Stephens, 1977). According to these authors, there are two distinct stress responses: the defense reaction and the defeat reaction (see Figure 3.2). As this perspective employed attention to both stimulus and response characteristics, it represented another good example of an interactive or transactional perspective on stress.

As depicted in Figure 3.2, the controllability of the stimulus was clearly related to the type of cortical response that occurred. In a situation that provoked a threat to an organism, the fight-flight response was triggered, resulting in the *defense reaction* characterized by fleeing or displaying aggression. In contrast, if the situation resulted in a loss of control by the organism, the *defeat reaction* occurred, characterized by limited activity and subordination. These two systems clearly were differentiated behaviorally as well as physiologically. Not only were they associated with distinct observable behavioral differences, they also involved different brain mechanisms, different neurotransmitter systems, and different peripheral manifestations of the response in the peripheral nervous system.

Individual Differences in Stress Responses

Regardless of whether researchers approach their field of study from a stimulus, response, or transactional perspective, there is a general recognition that individual differences exist in how individuals respond to stressful situations (Lazarus and Folkman, 1984; McEwen,

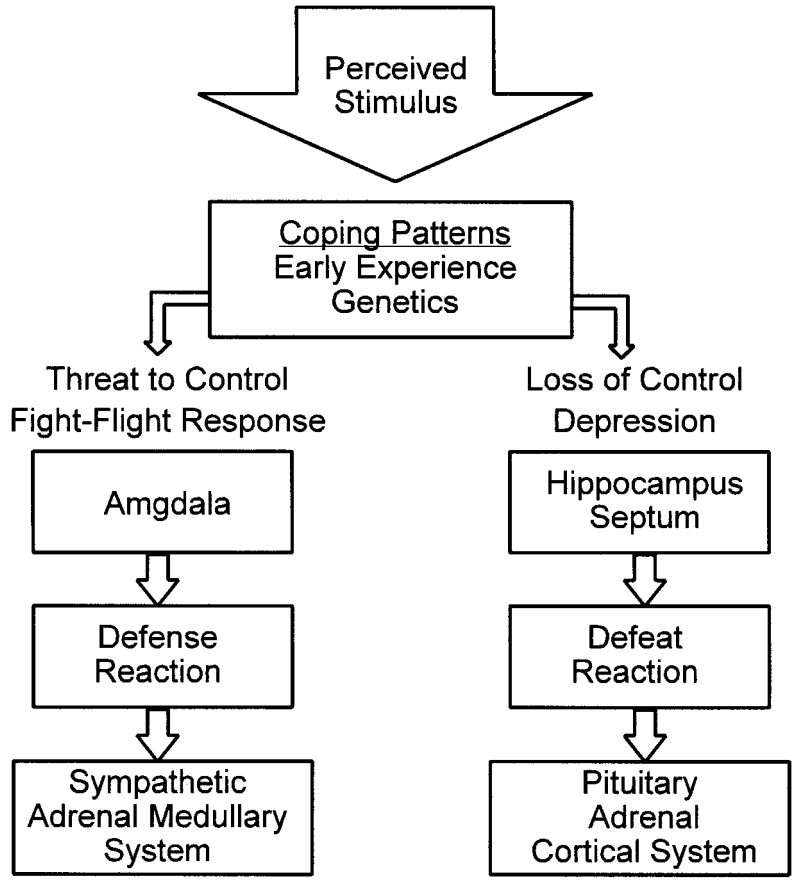

Figure 3.2. The defense and defeat reactions. Adapted from J. P. Henry, P. M. Stephens, and D. L. Ely (1986), Psychosocial hypertension and the defence and defeat reaction, *Journal of Hypertension, 4,* 687–697. Copyright © (1986), with permission from Lippincott, Williams, and Wilkins.

1998). A striking example of this appeared on television during Hurricane Andrew in which the high winds leveled two neighbors' homes with no loss of life. A news reporter interviewed the middle-aged fathers from both families who were standing in front of slabs of concrete that were once their respective Palm Beach houses. One man was crying profusely, exclaiming that he had lost everything he had worked for all his life, while the other calmly expressed his thanks that every-

Table 3.3. Selected Individual Difference Variables Related to Stress

Variable	*Selected Citations*
Demographic and Historic Developmental Variables	
Age	Palmer, Ziegler, and Lake (1978)
Gender	Saab (1989)
Ethnicity	Anderson, McNeilly, and Myers (1992)
Genetic Predisposition	Hewitt and Turner (1995)
History of Trauma or Abuse	McEwen (1998)
Personal Medical History	Corse, Cantwell, and Manuck (1982)
Modifiable Psychophysiological Variables	
Coping Skills	Lazurus and Folkman (1984)
Attitudes and Behavior Patterns	Smith (1992)
Spirituality and Religious Beliefs	Thoreson, Harris, and Oman (2001)
Physical Fitness	Seraganian (1993)
Modifiable Social Variables	
Acculturation	Brown and James (2000)
Social Support	Greenwood et al. (1996)
Socioeconomic and Educational Status	Steptoe et al. (2003)
Leisure Time Activities	Gump and Matthews (2000)

one in his family was safe, even the dog. Clearly, the stressor was identical for these two men, but their responses, at least the responses that were captured by the camera, were quite different. Observations like these lead one to consider individual difference variables that might affect the intensity or pattern of the acute stress response, and theoretically alter risk for subsequent disease processes. Some individual difference variables that have been examined regarding their association with stress responses are listed in Table 3.3.

For presentation purposes, the individual difference variables that have been examined in the literature have been grouped into three categories: demographic or historic developmental factors that are presumably unchangeable, psychological variables that could be modified through existing behavioral interventions, and social variables that could be modified by changing one's environmental context. Although a comprehensive analysis of each individual difference variable will not be attempted, representative references are provided.

Demographic and Historic Developmental Factors

Stress reactions have been shown to be influenced by a number of individual difference variables over which one has very little control. For example, our age, genetic constellation, developmental and medical history, and in most cases gender are variables we have no direct control over. By this time next year, we will all be one year older and still composed of the same constellation of genes that we possess today. Although we may not be able to influence these variables, many of these factors have been shown to influence the magnitude and patterning of physiological stress responses observed under conditions in which we are exposed to standard environmental stressors. For example, it has been shown that neuroendocrine and blood pressure responses to stress increase with age (Palmer, Ziegler, and Lake, 1978), males typically exhibit greater blood pressure reactions to standardized stressors than females (Allen et al., 1993; Saab, 1989), and black participants exhibit greater blood pressure responses to stress presentations than white counterparts (Anderson, McNeilly, and Myers, 1992). In addition to genetic factors contributing to susceptibility to disease through behavioral responses and risk factors like alcoholism and smoking, the magnitude of physiological responses to standardized stressors administered in laboratory settings has been shown to possess a heritable component (Hewitt and Turner, 1995). Accordingly, patterns of physiological responsivity to stress among first-degree relatives tend to be more alike than among unrelated persons. Finally, both significant developmental (McEwen, 1998) and medical events (Corse et al., 1982) have been shown to affect physiological response patterns to behaviorally elicited stress.

Modifiable Psychological Variables

In addition to the several demographic or developmental factors that influence the magnitude and patterning of the acute physiological stress response, numerous psychological variables have been shown to affect stress responses that are presumably learned throughout life and therefore more amenable to change. Foremost among these variables is a group of behaviors that might best be referred to as coping skills. We all

know people who seem to possess the ability to cope with life's most challenging stressors (like becoming quadriplegic or losing the family home in a hurricane) without apparent distress; we also know others who experience extreme distress if they are five minutes late for an appointment. Clearly, these individuals differ regarding the sorts of coping skills they have learned throughout life. Lazurus and Folkman (1984) used the term 'coping' to refer to the cognitive and behavioral efforts that a person made to manage the specific stressors that were appraised as taxing or exceeding their resources. They categorized these groups of skills into two types: emotion-focused coping and problem-focused coping. *Problem-focused coping* involves cognitive and behavioral efforts on the part of the person to deal directly with the source of the stress. For example, a person with considerable job-related stress might generate strategies to become more efficient on the job or make suggestions to the employer regarding steps to make the company operate more smoothly. Quitting the job and finding a better position would also be an example of problem-focused coping. *Emotion-focused coping,* in contrast, is aimed at regulating the individual's emotional stress response. Using emotion-focused coping to deal with job stress might involve learning how to mediate or engage in positive self-talk to reduce the negative effects related to the acute stress response associated with the job. In general, problem-focused coping works better when an individual has some control over the situation and emotion-focused coping may be preferred when the situation cannot be controlled. For example, if you were diagnosed with heart disease and informed that your quitting smoking and eating a low-fat diet would greatly assist in treating your condition, developing a problem-focused plan to do so would definitely be in your best interest. In contrast, if you were diagnosed with a rare chronic viral condition for which there is no known treatment and your actions would not influence the outcome, emotion-focused coping might prove more beneficial in regulating your stress response.

In contrast to persons with few coping skills, persons with excellent problem-focused and emotion-focused coping skills are likely to exhibit less severe acute stress reactions, and by so doing will experience lesser risk for stress-related disease outcomes (Lazurus and Folkman, 1984). Even persons with adequate skills in both areas, however, need to know when best to use them. Integrating the findings from the

literature on styles of coping with the Defense-Defeat Reaction Model presented above, one could speculate that problem-focused coping might be preferred for situations eliciting a defense reaction and emotion-focused coping might be preferred for situations eliciting defeat reactions. Although this hypothesis makes intuitive sense, empirical support is needed before final conclusions can be drawn.

Several attitudes and behavior patterns have also been shown to influence the magnitude and pattern of the physiological stress response. For example, persons who exhibit high scores on measures of cynical hostility or the Type A behavior pattern have been shown to exhibit significantly greater physiological stress reactions and risk for stress-related illnesses than their respective low-hostile or Type B counterparts (Harbin, 1989; Smith, 1992). Like coping skills, these 'personality' variables are presumably learned throughout life as individuals interact with their environments and are thus amenable to change, provided the individual is adequately motivated and provided efficacious interventions to alter these behavioral features. Interestingly, these behavioral parameters appear to evoke a greater physiological stress reaction only when the stressor chosen involves confrontation, anger recall, or harassment by an experimenter (Harbin, 1989; Smith, 1992). Therefore, high-hostile and Type A persons are not uniformly more reactive than low-hostile or Type B persons during all types of stressors; rather, their exaggerated responses appear to occur only when the stressors they encounter elicit anger.

In recent years, an increasing number of studies have examined the relation between spirituality and health outcomes (Thoreson, Harris, and Oman, 2001). The vast majority of these studies have shown that being religious or spiritual is associated with positive health benefits. One common behavior associated with spirituality, forgiveness for transgressions or betrayal, has been examined with respect to physiological stress responses and found to be associated with smaller stress responses (Witvliet, Ludwig, and VanderLaan, 2001).

Modifiable Social Variables

A number of social parameters have also been identified that influence the nature of the stressor–stress response association. Most notably

among these variables is the influence of one's social network and the support an individual receives from it. Strong social support networks are associated with lesser risk for a wide variety of chronic diseases, including cardiovascular disease and cancer (Uchino et al., 1996). The onset of chronic diseases, at times resulting in fatal outcomes, is quite prevalent following the loss of significant sources of social support, like the loss of a spouse. In order to examine the role of this type of stress–stress response relation, several investigators have taken these questions into the laboratory. Laboratory investigations of social support have demonstrated that the magnitude of an acute stress response can be significantly reduced by simply having a supportive friend present during the stress presentation (Kamarck, Annunziato, and Amateau, 1995; Uchino, Cacioppo, and Kiecolt-Glaser, 1996). In several of these laboratory demonstrations, the magnitude of the cardiovascular response to the stressor is approximately half that of those exposed to the stressor alone (Kamarck et al., 1995). Therefore, social support results in attenuated acute stress responses as well as more positive long-term health outcomes.

Several other social variables have been associated with the magnitude and patterning of both acute stress responses and risk for disease. For example, it has been well established that risk for cardiovascular disease is increased among Western countries and persons from Eastern cultures who have acculturated to Western countries (Brown and James, 2000). Likewise, persons of lower socioeconomic status have been shown to exhibit greater stress responses than those with higher socioeconomic status (Steptoe et al., 2003). Finally, even a relatively simple social behavior, like taking one's annual vacation, has been shown to affect chronic stress responses positively (Gump and Matthews, 2000). In sum, there are a number of modifiable social parameters that affect both acute stress responses and overall risk for disease.

There are certainly additional factors that influence the magnitude and pattern of both acute and chronic stress responses. For purposes of this book, however, only a few examples with a significant amount of empirical support were selected. Future empirical investigations will certainly reveal new parameters that influence known stressor–stress response associations.

A Comprehensive Model of Stress

The empirical and theoretical work presented in this chapter demonstrates that a number of stages are needed in creating a comprehensive model of stress that can be used to address the primary questions posed in the Introduction to this book. Certainly, the important distinction between stressors and stress responses needs to be incorporated into such a model, as does acknowledgment that individual factors influence the magnitude and patterning of stress responses. Further, in order to integrate the important facets from the literature on the stress–health relation, it is clear that an interactive or transactional model would be necessary.

Diathesis–stress models have been useful in discussing the interaction of environmental and genetic factors in several forms of psychiatric disorders (for example, Zubin and Ludwig, 1983). In this terminology, an individual possesses a vulnerability or diathesis that places him or her at increased risk for developing a specific psychiatric disorder. This vulnerability could be either genetic or environmental; regardless of origin, it places an individual at increased risk for the disorder. Not all persons with the vulnerability, however, develop the psychiatric diagnosis. Only those exposed to specific environmental conditions or stressors experience the full range of symptoms required to make the clinical diagnosis.

The vulnerability model serves as the foundation for the comprehensive model of stress outlined in Figure 3.3. In this model, individual difference factors serve as the vulnerability factor that interacts with environmental stressors to direct the magnitude and type of acute stress response observed. To return momentarily to the two men whose homes were lost in Hurricane Andrew, this model can be used to explain their differential stress responses. Although the environmental stressor was identical for both of them, one man was clearly better equipped to handle the nature of the stressor than the other. While we may not be able to determine, from the brief news report seen on television, what specific individual difference factor was responsible for the difference in observed responses, it is clear that these two men were different regarding their vulnerability to stress.

The fundamental progression from stressor to acute stress re-

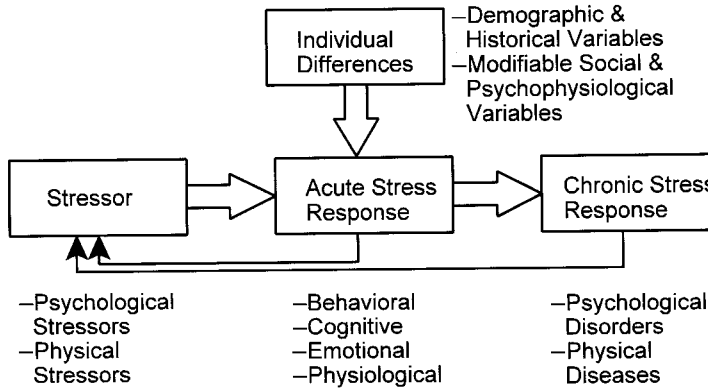

Figure 3.3. A comprehensive model of stress.

sponse to chronic stress response depicted in this comprehensive model of stress is consistent with all existing models of stress. Obviously, some previous models go into much more detail regarding specific components of this one (McEwen, 1998; Selye, 1956) and, as such, these previous models can usefully be integrated into this broader model of stress. The comprehensive model clearly recognizes the transactional nature of both the acute and chronic stress responses as evidenced by the inclusion of bidirectional arrows. Although specific stress responses may not have caused the initial environmental stressor, they can become additional stressors themselves. For example, Franklin's father, who suffered a heart attack three years ago, now exhibits health-related worries and concerns (acute cognitive stress reactions) that were not evident prior to the heart attack and his diagnosis of cardiovascular disease. As such, the experience of having a heart attack adds one more stressor to his life. In this regard, chronic stress conditions serve as the foundation for subsequent acute stress responses, and consequently, the magnitude of acute stress reactions is influenced by these chronic stress conditions.

A central role is assigned in this model of stress to individual difference variables, both inherited and acquired, that influence the nature of the acute stress response to specific environmental stressors. It is generally believed that as the magnitude of the environmental stressor and the vulnerability to stress increase, the more complicated and in-

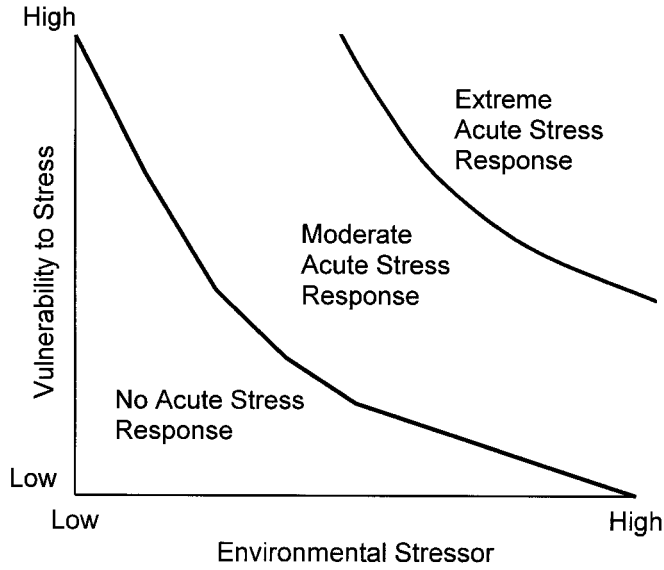

Figure 3.4. Relation between environmental stress and vulnerability factors in predicting the magnitude of acute physiological responses to stress.

tense acute stress response is observed. Imagine that we could systematically rank environmental stressors as well as overall individual vulnerability to stress quantitatively. In this regard, our rankings of environmental stressors would probably rate having an argument with an employer higher than being five minutes late to a nonessential meeting, but considerably lower than experiencing a concentration camp confinement. Likewise, our measure of vulnerability factors would probably rate a person with newly learned coping skills higher in vulnerability to stress than a person equipped with a vast array of stress coping skills. An individual with no coping skills at all would likely be rated higher than both others on our global measure of vulnerability to stress. Assuming some amount of linearity of these conceptually derived variables, they would be expected to interact with one another to determine the intensity of the observed acute stress response. As seen in Figure 3.4, highly vulnerable individuals under extreme environmental stress would exhibit the most intense stress reactions. Individuals high in vulnerability but under minimal environmental stress and

individuals low in vulnerability but under heightened environmental stress would exhibit moderate stress reactions. Finally, individuals with low vulnerability to stress who are under conditions of minimal environmental stress would demonstrate minor acute stress reactions, if any at all.

Summary

Considerable attention has been paid to the examination of behavioral or psychological factors related to medical disease outcomes. Borrowing the term 'stress' from the field of physics, psychological researchers have distinguished environmental stimuli, known as stressors, from stress responses. Stress responses have included the affective, cognitive, behavioral, and physiological alterations that occur immediately in response to the eliciting stimuli, as well as the more chronic stress responses that consist of psychological disorders and physical diseases.

Researchers examining the influence of stress upon health can be categorized into three groups: those that have focused on stress as a response, those that have focused on stress as a stimulus, and those that have adopted transactional or interaction models incorporating both stimulus and response components. Among investigators focusing upon stress as a response, greater attention has been paid to the physiological stress response of the organism and how it translates into physical manifestations of disease. Researchers who have focused upon stress as a stimulus have typically investigated different categories of stimuli (psychological stressors, physical stressors), determining the relation between specific stressors and disease outcomes. Finally, those investigators employing transactional perspectives have focused upon the bidirectional influences between environmental stressors and resulting stress response patterns.

Stress researchers have long acknowledged that two organisms exposed to the same environmental stressor typically exhibit differential stress responses. These observations have led to a greater examination of individual difference variables that may influence the relation between the stress stimulus and the stress response. Several individual difference variables have been identified and examined, including demographic and historical developmental variables, modifi-

able psychophysiological variables, and modifiable social variables. In brief, many individual difference variables must be considered when attempting to predict the magnitude of stress response to a given stimulus.

Common themes among existing theoretical perspectives permit the development of a comprehensive model of stress. Although not as detailed as some previous models, this broad model contains elements of the stressor–stress response relation that have uniform agreement among current stress researchers. In particular, a diathesis–stress approach is taken in the conceptual model proposed, in that individual differences play a central role through an accumulated parameter called vulnerability to stress. Both vulnerability to stress and environmental stressors are proposed to interact in influencing the magnitude and patterning of the acute stress response. To refer again to the case of Franklin, very little attention was paid to the current life stressors he was experiencing at the time of diagnosis. He had just experienced a very traumatic rescue attempt, and his father had experienced a heart attack a few years previously. Although both of these environmental stressors could have influenced measures of blood pressure, they were not given much attention during his medical evaluation. As such, it was unclear whether his increase in blood pressure represented a chronic condition that warranted treatment or whether the increased blood pressure was part of an acute stress response that might dissipate with time. In cases such as Franklin's, it is often difficult to disentangle the various genetic and environmental factors contributing to elevated arterial pressures.

4

Stress and Essential Hypertension

Now that the foundations for both essential hypertension and stress have been established, we can begin to address the primary question of the book, namely, what is the relation between a psychophysiological construct like stress and the physical manifestation of essential hypertension? It has probably become apparent that many of the bodily organs, systems, and mechanisms responsible for regulating arterial pressure are the same organs, systems, and mechanisms that have served usefully in explaining how environmental stress leads to physical disease. These include the branches of the autonomic nervous system, hormone and steroid release from the neuroendocrine system, and various brain regions like the hypothalamus, brain stem, and limbic system. All in all, there is a great deal of overlap between the physiological mechanisms described in Chapter 1 and Chapter 3; thus there is good reason to consider that an association exists between stress and hypertension.

In examining the evidence for the relation between stress and hypertension, the model of stress depicted in Figure 3.3 can be applied specifically to the condition of essential hypertension. An application of this model to essential hypertension, shown in Figure 4.1, serves as the foundation for research presented in this chapter and the three

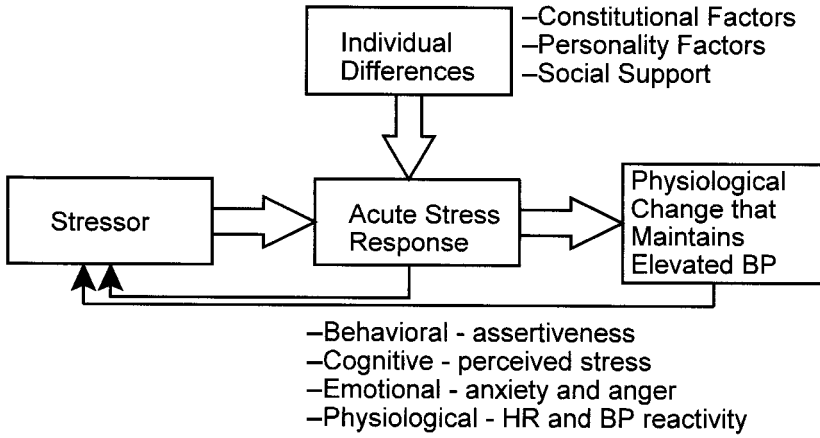

Figure 4.1. The comprehensive model of stress as it applies to essential hypertension.

chapters that follow. In this chapter, we will consider research supporting a link between environmental stressors and essential hypertension. In Chapter 5, we will examine research supporting various elements of the acute stress response that may mediate the relation between environmental stressors and essential hypertension, most importantly the physiological responses of heart rate and blood pressure reactivity to stress. Then, in Chapters 6 and 7, we will examine individual difference variables that influence the magnitude and patterning of the acute stress response that presumably leads to the development of essential hypertension.

The model linking stress with essential hypertension shown in Figure 4.1 is quite similar to several existing models (for example, see Beilin, 1997, Jorgensen et al., 1996, and Pickering, 1997), in that all recognize that the relation between stress and essential hypertension is not simple or direct. There are multiple intervening variables that need to be measured and tested regarding their roles in the stress–hypertension relation. Because of the numerous organ systems involved in blood pressure regulation, it is quite likely that multiple etiologic pathways exist that lead to the onset of essential hypertension, and the search for *the* single cause of the medical condition is misguided. The present model recognizes the potential multiple pathways to essential hypertension as

well as the variety of intervening variables that influence disease onset. Additionally, this model, as well as previous models, recognizes the bidirectional relation among many intervening variables. For example, in the model presented in Figure 4.1, both the acute stress response and physiological changes that maintain elevated blood pressure result from stress in addition to contributing to the level of stress an individual experiences. Jorgensen et al. (1996) proposed a more complicated synergistic model suggesting that individual difference personality variables were linked bidirectionally to all other components of the model, including stressors, acute stress responses, and the physiological changes that maintain elevated blood pressure. Although these synergistic relations may indeed exist, the model presented in Figure 4.1 provides a useful structure for organizing the results from empirical research presented in the next several chapters. Regardless of the exact directionality of the proposed linkages in these various models, all models highlight the importance of individual difference variables in determining who will or who will not develop essential hypertension. Before we consider the research examining the role of various intervening variables in explaining the onset of hypertension, however, it is important to examine evidence for the fundamental stress–hypertension relation.

Research Linking Stress and Essential Hypertension

Since the 1900s, a variety of studies have been conducted to examine the relation between stress and essential hypertension. Although it is beyond the scope of this book to review each of these in detail, representative studies that have explored this association will be presented. These can be categorized into several different types: studies of major life event stressors, studies of job stress and strain, studies contrasting prevalence of hypertension in cultural regions characterized by differential levels of stress, and animal research linking stress and hypertension.

Major Life Events and Blood Pressure

Studies of the first type have typically examined the relation between stress and hypertension by measuring exposure to significant life stressors and concurrent blood pressures. Presumably, if a relation exists be-

tween these two variables, one would expect strong positive correlations between measures of life stress and blood pressure. For example, individuals living in the community around Three Mile Island were compared with individuals living in a control region of Frederick, Maryland, during the years following the industrial accident at Three Mile Island in 1979 during which a threat of radioactive exposure occurred in that community (Baum, 1990). Results of blood pressure measurement data during the decade following the accident revealed that inhabitants of the area surrounding Three Mile Island experienced significantly higher SBPs and DBPs than inhabitants of the control community. Peak blood pressure increases were observed during the first year following the accident, only among inhabitants around Three Mile Island. Comparable elevations in blood pressure among elderly Japanese residents were reported during the first few weeks following the Hanshin-Awaji earthquake. However, these elevations were transient, returning to normal levels approximately one month after the event (Kario et al., 2001). Likewise, witnesses of a deadly explosion in Texas in the 1940s (Ruskin, Beard, and Schaffer, 1948) and bombings of Leningrad during World War II (Miasnikov, 1961) exhibited elevated blood pressures for various durations of time following exposure to these life-threatening events. Recently, comparable blood pressure elevations were observed in a man residing in New York City who witnessed the tragedy of September 11, 2001, in which thousands were killed in the terrorist attacks on the World Trade Center towers (Lipsky, Pickering, and Gerin, 2002). In this case, the man's average SBP increased 24 mm Hg and his average DBP increased 12 mm Hg in the week following the attacks, returning to normal levels the following week.

Imprisonment is also a significant stressful major life event, particularly among those housed in dormitory-style settings. Dormitory housing, in contrast to incarceration in single cells, involves more interaction with other inmates, many of whom may be antagonistic. D'Atri and Ostfeld (1975) contrasted blood pressures of prisoners housed in single cells and those housed in dormitories and found a significantly higher SBP among prisoners housed in dormitories. Prisoners who moved from dormitory housing to single cells exhibited reductions in blood pressure, while those who were moved from single cells to dormitories exhibited increases (D'Atri et al., 1981).

Some stressful life events are more chronic in nature. For example, the amount of stress experienced in an individual's residential neighborhood is endured on a daily basis, often for periods of years or even decades. Some neighborhoods are characterized by stable single family dwellings, good school systems, and low crime rates, while others are much less stable and have higher crime rates. To examine the effects of living in stressful residential neighborhoods on blood pressure, Harburg et al. (1973) contrasted blood pressures among black and white adults in various neighborhood areas in Detroit characterized as either high or low stress according to various domains like home ownership and crime rate. Young black males living in high stress neighborhoods exhibited higher blood pressures than those living in low stress areas. Similar relations between blood pressure and stressful living environments have been reported among pregnant women living in areas prone to terrorist attacks (Rofé and Goldberg, 1983).

Lal, Ahuja, and Madhukar (1982) compared a group of hypertensive patients with age-matched controls on a measure of significant events over the lifespan. Both male and female hypertensive patients reported significantly greater frequencies of distressing life events, in particular, bereavements, injuries, illnesses, and other health-related stressors. Comparable associations between elevated blood pressure and life events have been reported among samples of borderline essential hypertensive patients (Linden and Feuerstein, 1983; Myers and Miles, 1981). More recently, Larkin et al. (2004) reported a similar increased frequency of daily stressors among hypertensive patients over a one-week prospective recording period. In contrast to normotensives, who indicated an average of 53 stressful events over the course of the week, hypertensives reported an average of 86 such events. Interestingly, the intensity ratings of these daily stressors were not consistently different between groups, suggesting that hypertension was more closely associated with the quantity of stressors encountered rather than the perceived stressfulness of them.

There is also some evidence linking exposure to stressful life events to alterations in the circadian blood pressure cycle (Ituarte et al., 1999; Wilson et al., 2002). In both of these investigations, exposure to life stress or violence was associated with the lack of blood pressure deceleration at night (non-dipping). It appears that individuals experi-

encing more stress in their lives are less able to 'wind down' in the evenings in preparation for sleep and to experience the normal reductions in blood pressure than less stressed individuals.

Research examining a number of different life event stressors has generally shown that increased environmental stress is associated with higher blood pressures. However, this is not always the case, as inverse relations between stressful life events and blood pressure have also been reported (Melamed et al., 1997; Suter et al., 1997; Theorell et al., 1986). Because most of the studies examining the link between life stress and blood pressure were conducted on community-dwelling or incarcerated samples with presumably normal ranges of blood pressures, it is unknown whether the observed increased blood pressures resulted in higher rates of diagnosed essential hypertension. Because of the continuous nature of blood pressure measurement, however, the importance of these contradictory findings should not be overlooked.

Nyklíček, Vingerhoets, and Van Heck (1996) point out two factors that should be carefully considered when interpreting findings relating stressful life events to essential hypertension: patients' awareness of the diagnosis of essential hypertension and whether they had received treatment for the condition. Regarding the former, there is evidence that hypertensive patients who are aware of their diagnosis are more likely to report increased symptoms of stress in their lives than patients who have yet to learn they have high blood pressure (Irvine et al., 1989; Zonderman, Leu, and Costa, 1986). Regarding the latter, hypertensive patients undergoing treatment have been more likely to report increased symptoms of stress than untreated hypertensive patients (Goldberg, Comstock, and Graves, 1980; Tibblin and Lindstrom, 1972), unless the treatment successfully lowered blood pressure to normal ranges (Soghikian et al., 1981). Therefore, studies examining ratings of stressful life events among hypertensive patients should be cautiously evaluated when employing samples of patients aware of their diagnostic status.

Job Stress and Strain and Blood Pressure

An extensive amount of research has been conducted in work settings exploring the relation between blood pressure and either job stress or job strain (see Pickering, 1997, for a review). Many of the studies ex-

ploring the relation between job stress and hypertension have been based upon the Job Strain Model proposed by Karasek and colleagues (Karasek, 1979; Karasek et al., 1981). According to this perspective, job strain is influenced jointly by the psychological demands of the job *and* the degree to which the employee controls or makes decisions regarding work outcome. Jobs that involve considerable psychological demands on the worker accompanied by very little control are characterized as having high job strain (Karasek, 1979). Interestingly, Karasek chose to use the term 'strain' to refer to these stimulus characteristics of an individual's job. To remain true to the original usage of stress and strain in physics, Selye (1956) should have probably used the term 'strain' to discuss the physiological response components to stress and Karasek should have probably used the term 'stress' to refer to the stimulus characteristics of the job. Regardless of his choice of terms, Karasek hypothesized that workers in positions with high job strain would be expected to exhibit higher rates of a variety of stress-related diseases including coronary heart disease and essential hypertension. Let's examine the evidence for this perspective.

Studies Relating Job Stress/Strain to Prevalence of Hypertension

Several studies examining the relations between job stress and hypertension have focused on comparing prevalence rates of diagnoses of hypertension among various jobs categorized as being more or less stressful. In these studies, a participant's blood pressures are typically measured during a medical examination or diagnosis is confirmed through a review of the participant's medical records. Although many of these studies employ standardized measures of job strain, à la Karasek (1979), others rely on less objective methods for defining job stress. For example, Cobb and Rose (1973) conducted one of the earlier studies examining the relation between job stress associated with being an air traffic controller and hypertension. In this study, the investigators chose to examine what they considered a single high-stress position, that of air traffic controller, based upon the knowledge that persons in this occupational category experience grave consequences for any mistake that might be made. They compared the air traffic controllers with a group of second-class airmen, who were judged to experience considerably less stress on the job. Not only did they report that

the prevalence of hypertension was higher among air traffic controllers than second-class airmen, but also that the rates of hypertension increased among air traffic controllers in proportion to the density of air traffic at their work location. Associations between a stressful job environment and increased rate of hypertension have been observed in many other samples as well, including blue-collar factory workers (Matthews et al., 1987), pregnant women with high-status jobs (Landsbergis and Hatch, 1996), transit vehicle operators (Ragland et al., 1997), and workers in electrical factories (Kawakami, Haratini, and Araki, 1998).

Pieper, LaCroix, and Karasek (1989) conducted an extensive analysis of the relation between job stress and cardiovascular risk factors, including hypertension, using data from five major investigations, including the Western Collaborative Group Study, the Exercise Heart Study, the National Health Examination Survey, and both the first and second reports of the National Health and Nutrition Examination Surveys. As in the Karasek (1979) model, job stress was conceptualized as involving both psychologic demands on the worker and job control. Psychologic demands were based upon ratings of working hard and fast, confronting conflicting demands, and not having enough time to complete job-related assignments. Job decision latitude (or job control) was defined by participants' responses to questions regarding their ability to learn new skills on the job, have a variety of work assignments, and be involved in decision-making on the job. Although there was no association between job decision latitude and DBP, there was a relation observed between job decision latitude and SBP in three of the five data bases. In these large-scale data sets, higher job decision latitude (greater job control) was associated with lower SBP. Unusually, higher psychologic demands of the job were associated with increased SBP in only one data base, but inversely correlated with both SBP and DBP in the Western Collaborative Group Study. In other words, excessive work with conflicting demands was unexpectedly associated with lower blood pressure in the Western Collaborative Group Study sample. Although these findings may be attributed to the uniqueness of the executive men that comprised the Western Collaborative Study group, the general lack of evidence for a relation between job demands and blood pressure among the other

large-scale samples suggested that job control may be a more important predictor of blood pressure status than job demands.

Using Karasek's (1979) job strain measure, Schnall et al. (1990) found that hypertensive urban employees were almost three times more likely to have high job strain than normotensive employees. Further, hypertensive patients with high job strain exhibited greater left ventricular hypertrophy (hypertensive target organ damage) than hypertensive patients with low job strain. Not only was a strong association between job strain and hypertension reported among patients with high job strain, but also evidence of actual tissue damage to the heart. In a similar study, Cesana et al. (2003) recently examined the relation between job strain measured using Karasek's categorization system and clinic measures of blood pressure and found that high job strain was linked to increased SBP in men; there was no effect for DBP however, nor did the findings extend to women. In direct contrast to these findings, Alfredsson et al. (2002) found job strain to be associated with an increased prevalence of hypertension among women, but not men. Finally, Markovitz et al. (2004) reported that increased job strain during an eight-year data collection period was predictive of onset of essential hypertension. In this study, persons who changed from low-strain to high-strain jobs exhibited a higher incidence of high blood pressure, even more than persons who had high-strain jobs throughout the entire period.

Not all studies that have examined the relation between job stress or job strain and prevalence of hypertension have revealed significant associations. Albright et al. (1992) found an inverse relation between job stress and prevalence of hypertension among bus drivers, and Tarumi, Hagihara, and Morimoto (1993) found a similar inverse relation among white-collar workers in Japan. Employment, even in stressful jobs, has also been shown to be inversely associated with levels of blood pressure in women (Rose et al., 1999; Weidner et al., 1997). In a few other reports, no association between job stress and hypertension was reported among female nurses (Riese et al., 2000) or within a community of African American men and women (Curtis et al., 1997).

To further complicate these mixed findings, several researchers have found that the linkage between job stress or job strain and high blood pressure is affected by individual difference variables. For exam-

ple, Chesney et al. (1981) found the expected association between both worker autonomy and peer support and lower blood pressure, but only among workers with a Type A behavior pattern. Likewise, job dissatisfaction has been shown to be associated with hypertension, but only among men who suppress anger (Cottington et al., 1986). In a more recent investigation, although no direct relation was observed between work-related stress and blood pressure among government tax office workers, there was support for an indirect association between stress and blood pressure that was explained by coping strategies (Lindquist, Beilin, and Knuiman, 1997). Specifically, persons who engaged in less adaptive coping, which included those who drank alcohol, engaged in binge eating, and were physically inactive, responded to stress with increased blood pressures. Comparable relations between stress and blood pressure were not observed among workers who exhibited more adaptive means of coping with stress. The empirical work to date makes it quite clear that the association between job stress or strain and hypertensive status, as measured by either clinic records or clinic measures of blood pressure, is not a simple and straightforward one.

Studies Relating Job Stress/Strain to Ambulatory Measures of Blood Pressure

With the advent of ambulatory blood pressure monitoring technology, there was considerable interest in extending the understanding of the relation between job stress/strain and blood pressure by measuring blood pressure while the worker was actually on the job. As described in Chapter 2, measures of blood pressure obtained in the clinic may either overestimate or underestimate actual daily blood pressures; thus, ambulatory measures of blood pressure are thought to provide a more accurate depiction of a patient's daily blood pressure profile. In one of the earlier studies to use ambulatory blood pressure monitoring on the job, Theorell et al. (1991) reported that job strain, as defined by Karasek's classification model (1979), was associated with higher DBPs among borderline hypertensive men both at work and at night (during sleep). No relation, however, was observed between job strain and SBP.

Based upon observations that hypertensive patients from several work sites in New York City were more likely to have positions with high job strain than normal blood pressure controls, the Cornell Work

Site Blood Pressure Study, devised as a prospective study of the relation between job strain and hypertension, began in 1985. Ambulatory measures of blood pressure from participants in this large-scale study revealed that job strain was associated with a 6.8 mm Hg increase in daily SBP and a 2.8 mm Hg in daily DBP (Schnall et al., 1992). As in the study by Theorell and colleagues, the observed blood pressure differences associated with job strain were also evident at home and during periods of sleep. Three-year follow-up data confirmed the chronic nature of this association (Schnall et al., 1998). Workers who were in high job strain positions maintained higher ambulatory blood pressures after three years than those in low job strain positions. Interestingly, ambulatory blood pressures decreased among workers who reported high-strain jobs during the initial evaluation and low-strain jobs three years later. The opposite effect, however, was not observed among workers who initially reported having a position with low job strain and reported a high-strain job at follow-up. The authors speculated that perhaps a period longer than three years was needed for individuals who recently assumed a high-strain job to develop hypertension. To support this hypothesis, a subsequent analysis was conducted on lifetime job history and blood pressure status at the follow-up visit. Results confirmed that workers who spent the majority of their working life in high job strain positions, defined as having a high 'cumulative burden' of job strain, evidenced significant blood pressure elevations in contrast to those workers who spent fewer years in such positions (Landsbergis et al., 2003a). Recent empirical work has confirmed the associations between job strain and ambulatory blood pressures among workers in other industrialized countries (Cesana et al., 1996; Melamed et al., 1998).

In a comprehensive study addressing the relation between job strain, as assessed using the Karasek model, on nurses, Fox, Dwyer, and Ganster (1993) obtained measures of both subjective job strain (from nurse self-reports) and objective job demands (from ratings of patient load, number of deaths witnessed, and percentage of patient contact as determined by nursing supervisor ratings). Although subjective measures of job strain were related to SBP and cortisol measured at work and both SBP and DBP at home, the univariate correlations between measures of job stress and blood pressure were higher for objective

than subjective measures. These findings suggest that self-reported ratings of perceived job stress by women may be influenced by factors that may obscure actual associations between workload and blood pressure status factors (for example, the tendency to underreport symptoms of stress).

Like studies relating job stress/strain to hypertension or office blood pressure measures, findings from research linking job stress/strain to ambulatory measures of blood pressure have revealed that numerous individual factors appear to influence the relation. Even the data from the Cornell Work Site Study showed that alcohol use interacted with high-strain jobs to raise SBP, but had no effect on SBPs among workers in low-strain jobs (Schnall et al., 1992). Furthermore, in another report from the Cornell group, associations between job strain and ambulatory blood pressures were stronger among workers with low socioeconomic status; the relation between job strain and blood pressure was much smaller among workers with higher socioeconomic status (Landsbergis et al., 2003b).

In several studies, the relation between job strain and blood pressure status typically observed among men was not seen for women (Light, Turner, and Hinderliter, 1992; Schnall et al., 1992); however, in one study a significant relation between job stress and SBP was observed among women, but not men (Blumenthal, Thyrum, and Siegel, 1995). Finally, one study reported no relation between job strain and blood pressure among samples of both men and women (Matthews et al., 2000). It has been suggested that one reason that many studies fail to detect a relation between job strain and blood pressure among women pertains to the restricted range in job strain that exists among jobs typically held by women. Many jobs held by a significant portion of women are categorized as being high in strain, including those of elementary school teachers, secretaries, and nurses. Gallo et al. (2004) recently reported that women in these lower-status occupations indeed exhibited higher SBP and HR during ambulatory monitoring than women in higher-status occupations.

It has also been hypothesized that the stress women experience is more likely due to their combined family and work responsibilities, rather than purely work-related job stress. To explore this hypothesis, Brisson et al. (1999) conducted a study relating job strain among

white-collar women and ambulatory blood pressures. They found that among women with college degrees, the highest ambulatory blood pressures were observed in those with both high job strain and significant family responsibilities. James, Schlussel, and Pickering (1993) also examined job stress and ambulatory blood pressures in working women categorized into those who reported a more stressful work than home environment and those who reported a more stressful home than work environment. In this study, ambulatory SBP was higher at work among work-stressed women than home-stressed women. Furthermore, the increased SBPs were associated with a greater increase in sympathetic nervous system activity during daily life, as measured by change in catecholamine secretion. Finally, in a study comparing ambulatory blood pressures of men and women, Marco et al. (2000) found higher blood pressures among men during workdays versus non-workdays, but a different pattern among women. Women without children exhibited the same pattern as men; women with children, however, exhibited comparable blood pressures at home and at work or even higher blood pressures at home. The findings from these studies suggest that research examining relations between job stress and hypertension in samples of women needs to develop better ways of including measures of family job responsibilities as well as job responsibilities at work settings.

Additionally, the relation between job stress and ambulatory measures of blood pressure has been shown to be influenced by occupational status (Blumenthal et al., 1995; Light et al., 1995), marital status (Blumenthal et al., 1995), high-effort coping or John Henryism (Light et al., 1995), social support (Steptoe, 2000), and anger expression style and defensiveness (Shapiro et al., 1993). For example, Light et al. found that women with high-status occupations *and* traits of high-effort coping (the perception that achievement can be attained through hard work and personal effort) exhibited higher DBPs during the workday than women with lower job status or without high-effort coping traits. Furthermore, the relation between job stress and hypertension is less likely to be observed among participants who are married or who have strong positive social support networks (Blumenthal et al., 1995; Steptoe, 2000).

Marital Stress and Blood Pressure

Familiar with the convincing evidence linking job strain with ambulatory measures of blood pressure, several investigators began to employ ambulatory blood pressure measures to examine another type of stress commonly encountered in life—marital stress (Baker et al., 1999; 2000; Carels et al., 2000). Like studies of job strain and ambulatory blood pressures, these studies have uncovered comparable associations between marital stress and both ambulatory blood pressures and left ventricular hypertrophy. Extending this work into the domain of the marital relationship makes it appear that perhaps the observed associations between job strain and blood pressure may not be unique to the work environment.

Summary

One thing becomes quite apparent when one examines the studies that have explored the relation between job stress or job strain and essential hypertension: the association is not a simple one. It is quite evident that there is no direct linear relation between job stress and measures of blood pressure. Among studies that have examined the relation between job stress and hypertension by using standard methods for establishing a diagnosis of hypertension (clinic measures, chart reviews), no consistent association has been observed. Among studies employing ambulatory measures of blood pressure, the relation between job stress and elevated blood pressure has been observed fairly consistently. However, it is sometimes unclear whether the elevated blood pressures observed in these studies constitute a diagnosis of essential hypertension or simply elevated normal blood pressures. Both literatures have revealed a substantial number of variables that appear to influence the relation between job stress and hypertension, including gender, the presence of social support, occupational status, socioeconomic status, marital status, presence of coexistent family responsibilities, alcohol use, and other coping strategies. Clearly, not all persons employed in high-strain jobs exhibit elevated blood pressures. In some reports, persons employed in high-strain jobs actually exhibited lower blood pressures (Albright et al., 1992; Tarumi et al., 1993; Weidner et al., 1997).

There are also inconsistent findings regarding the particular mea-

surement of blood pressure that is related to job stress. Some studies report a relation between job stress and SBP, but not DBP (Blumenthal et al., 1995), and others report a relation between job stress and DBP, but not SBP (Light et al., 1995). Although most studies using ambulatory blood pressure measurements found an association with job strain when examining blood pressures measured during work hours, inconsistent findings emerge when they examined blood pressures measured at home or during sleep. Some studies report associations between job stress and blood pressure at night (Schnall et al., 1992; Theorell et al., 1991) whereas other studies fail to detect this association (Sega et al., 1998; Steptoe et al., 2003). These findings suggest that although job stress and strain may be related to elevated ambulatory arterial pressures, the relation may operate through different mechanisms among different samples of workers.

Cultural Influences on Stress and Blood Pressure

Researchers have long been interested in the relation various cultures exert upon measures of blood pressure. It is well known, for example, that average blood pressures among inhabitants of industrialized nations are higher than those of inhabitants of cultures predominantly consisting of agricultural and hunter-gatherer societies (Waldron et al., 1982). In fact, in some empirical reports, inhabitants of nonindustrialized countries were shown to exhibit stable blood pressures throughout life, in contrast to the gradual increases in blood pressure typically observed with aging in industrialized countries (Harper, Crews, and Wood, 1994; Marmot, 1984). This gradient of increased blood pressures associated with degree of industrialization is evident even when controlling for average age and body mass index of inhabitants. Within given cultures, there is evidence that blood pressure is inversely related to socioeconomic status, with persons of lower status exhibiting the highest blood pressures (Luepker et al., 1993; Steptoe et al., 2003). The association between blood pressure and socioeconomic status is particularly strong among women (Colhoun, Hemingway, and Poulter, 1998).

Timio et al. (1988) reported a widely cited study of Italian nuns in a cloistered convent compared with a control group. Although there

were no differences in blood pressure between the two study groups at the beginning of the study, after 20 years, blood pressures in the control group were 30 mm Hg higher than the blood pressures of the nuns. Because this difference could not be explained by other factors including change in body weight or dietary changes, the authors attributed the difference to the relatively stress-free life among the cloistered nuns.

Several studies have also examined blood pressures among persons who migrate from one culture to another (Cassel, 1974; Poulter et al., 1990; Truswell et al., 1972). Specifically, the most interesting data come from studies where individuals migrate from relatively stress-free cultures into more stressful cultures (acculturation). For example, Kaminer and Lutz (1960) measured the blood pressures of bushmen of Kalahari and showed that blood pressure did not increase with age. However, bushmen who abandoned the nomadic tradition and became laborers in more agricultural cultures exhibited increased blood pressures (Truswell et al., 1972). In a similar study, Poulter et al. (1990) followed rural Kenyans who migrated to Nairobi versus controls who stayed in their home villages. Migration was associated with an increase in blood pressure within the first few months that persisted during two years following migration. It is unknown, however, whether alterations in blood pressure observed during acculturation were more closely associated with the psychological stress of migration or the altered dietary and related lifestyle habits that occurred with migration.

Brown and James (2000) conducted a study using ambulatory blood pressure measures from immigrant Filipino American nurses and nurses' aides living in the United States. They reported that although no relation was observed between job strain and blood pressure, there was a significant association between length of time since immigration and diastolic blood pressure at night. Nurses who had been in the United States the longest had the highest nighttime blood pressures. These increases in blood pressure associated with acculturation were accompanied by increased norepinephrine levels both in work and home settings, suggesting that these findings were more closely linked to stress than changes in dietary practices, physical activity, or access to health care. Comparable observations of increased blood pressures among persons who migrate to more industrialized

countries have been reported among inhabitants from a number of regions, including people from the Amazon (Fleming-Moran and Coimbra, 1990), Mexican Americans (Espino and Maldonado, 1990; Hovey, 2000), Korean Americans (Kim et al., 2000), and Asian immigrants in Canada (Kaplan et al., 2002).

In a series of investigations done in Mexico, Brazil, and in a southern community of black Americans, Dressler and colleagues (1987a; 1987b; 1990) have provided support for the contention that sociocultural factors other than acculturation to a new country can influence blood pressure. Foremost among these factors is something that Dressler calls 'lifestyle incongruity.' Lifestyle incongruity refers to the degree to which an individual attempts to maintain a lifestyle beyond his or her economic means. Individuals of any socioeconomic strata may experience lifestyle incongruity, but it is more likely to affect those from lower socioeconomic classes who often lack the financial resources to provide adequate housing, health care, and food for their families. Across all of these communities, lifestyle incongruity was associated with higher blood pressures (Dressler et al., 1987a; 1987b; 1990).

Dressler (1999) theorized that the observed changes in blood pressure that accompanied both acculturation and socioeconomic class differences were related to the degree to which a society is modernized. Modernization, according to Dressler, refers to the consumer lifestyle and acquisition of material items that pervade Western countries. It is generally accompanied by the existence of wage labor, a focus on formal education and training, and individualistic values (as opposed to collectivistic or group values). The majority of studies that have compared modernized communities with rural communities based upon subsistence economies have found higher blood pressures among the modernized communities (Dressler, 1999), lending support to this hypothesis. For example, Dressler, Grell, and Viteri (1995) reported blood pressure data from inhabitants of the outskirts of a town in Jamaica that consisted of both residents who chose to live there to escape city living and residents of a traditional farming community. Congruent with Dressler's hypothesis, blood pressures were significantly higher among the upwardly mobile inhabitants of the community than the lower-class peasants. This study is important in that

modernization or lifestyle incongruity appeared to affect blood pressure of this upwardly mobile group to the point that the typical inverse relation between blood pressure and socioeconomic status was reversed.

Using data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, Vargas, Ingram, and Gillum (2000) reported an inverse relation between educational attainment and incidence of high blood pressure. In this national survey, a higher risk of hypertension was associated with low educational attainment (not completing high school or attending college), even after adjusting for other standard risk factors. Using the same data set, Waitzman and Smith (1994) found a comparable association between risk for hypertension and occupational class. Both persons from lower occupational classes and persons who were raised in higher occupational classes but ended up in lower occupational classes were shown to have a higher risk for hypertension than persons from higher occupational classes. In a ten-year follow-up study of the influence of socioeconomic factors and blood pressure status, Matthews et al. (2002) found that the risk for essential hypertension was predicted by an index of difficulty paying for life's basic needs. This association was still significant after controlling for standard risk factors for high blood pressure like body mass index, gender, age, race, and initial blood pressure.

Like the relation between job strain and hypertension, the effect of socioeconomic factors upon hypertension has been shown to be influenced by several individual difference variables. For example, Bindon et al. (1997) found the typical relation between lifestyle incongruity and blood pressure among male American Samoans, but the opposite relation among female American Samoans. In this case, females with higher lifestyle incongruity actually exhibited lower blood pressures than females lower in lifestyle incongruity, and this relation was affected by whether both spouses worked outside of the home. In another study, James et al. (1992) reported that the blood pressure gradient typically observed across levels of socioeconomic status was found only among adults scoring high on a scale of John Henryism in a sample of blacks in Pitt County, North Carolina. The John Henryism Scale assessed the perception that achievement could be attained through hard work and personal effort. Of participants with high

scores on the scale of John Henryism, 29 percent in the lowest socioeconomic class, 26 percent in the middle socioeconomic class, and 20 percent in the high economic class exhibited hypertension. Among participants scoring low in John Henryism, there was no association between socioeconomic status and blood pressure. Finally, Ford and Cooper (1991) found that the relation between risk for hypertension and low educational attainment after controlling for standard risk factors for hypertension was significant only among white women, not among white men or black men and women.

In summary, several socioeconomic factors have been shown to influence blood pressure status and the prevalence of essential hypertension. In this regard, it is generally accepted that persons of lower socioeconomic status exhibit higher blood pressures and rates of hypertension, although these relations can be influenced by lifestyle incongruity or modernization. Furthermore, it seems that other factors, like gender and style of coping (like John Henryism), have been shown to affect the relation between socioeconomic factors and blood pressure status. It is likely that other variables may also influence this relation, but they have yet to be tested and identified.

Animal Research Linking Stress to Hypertension

Ethically, experimental studies on the effect of intensive prolonged stress upon levels of blood pressure cannot be conducted on humans. Recognizing the unpleasant impact of chronic stress and potential health consequences, we simply cannot expose humans to experimental stress conditions voluntarily. As seen above, life events commonly occur that present humans with stressful situations to which they will respond, but we do not purposefully expose humans to natural stressors like tornados, hurricanes, and floods, nor do we expose them intentionally to manmade disasters like Three Mile Island and the World Trade Center collapse. However, when these events unfortunately occur, we can learn a great deal regarding the human stress response by measuring various aspects of acute and chronic stress responses among individuals exposed to them.

Experimental studies using animals (usually rats or mice) can be conducted to examine directly the relation between exposure to stress

and the chronic stress responses that are observed, including hypertension. Much of the work on developing our current understanding of stress that was presented in Chapter 3 was learned through such animal models. In this regard, several different stressors have been employed to determine whether exposure to stress results in chronic heightened blood pressures in rats or mice, including exposure to noisy, vibrating environments (Smookler and Buckley, 1969), electric shock (Shapiro and Melhado, 1958), and a variety of operant conditioning procedures (Brady, Findley, and Harris, 1971; Forsyth, 1969; Herd et al., 1969). In general, the operant conditioning paradigms have been more successful in elevating blood pressure than the other procedures (Lawler, Cox, and Hubbard, 1986). However, the observed increases rarely persisted following the duration of the experimental manipulations and when chronic elevations in blood pressure were observed, they occurred only among some animals. Based upon the inconsistent findings from these early attempts to devise an experimental animal model of hypertension, research on four primary animal species has been employed to improve our understanding of the relation between stress and hypertension: socially crowded mice (Henry, Stephens, and Santisteban, 1975), spontaneously hypertensive rats (Yamori et al., 1969), salt-sensitive rats (Friedman and Dahl, 1975), and borderline hypertensive rats (Lawler et al., 1981).

Research on Social Crowding in Mice

An experimental paradigm was developed and tested by Henry and colleagues (1967; 1975) in which mice raised in isolation were exposed to a crowded living environment. In the apparatus that was developed for purposes of these experiments, all mice shared a common feeding area that was accessible by tiny passages in which only one mouse could travel at a time. Mice that were initially raised in a social environment readily established a dominance hierarchy, and subordinate mice yielded to dominant mice in gaining access to the food chamber. In contrast, mice raised in isolation had no previous exposure to dominance hierarchies; thus, these animals were exposed to frequent confrontations and aggressive exchanges with more dominant mice when introduced to the socially crowded environment. SBPs of these previously isolated mice increased during weeks of living in this 'crowded' living arrangement, but returned to normal a few months after being

removed from it. However, if mice were exposed to living in the crowded environment for longer periods of six to nine months, blood pressures remained elevated even upon their being returned to isolated living quarters (Henry et al., 1975). Subsequent work with various genetic strains of rats exposed to six months of living in comparable stressful conditions has replicated this work, but only among certain genetic strains. Creating unstable living arrangements by periodically mixing males from different groups has also led to substantial increases in blood pressure among aggressive strains of rats, but has had virtually no effect on blood pressure among more placid strains (Henry et al., 1993). Findings from these studies support the hypothesis that the etiology of hypertension in animals involves an interaction between genetic composition and degree of environmental stress.

Research on Spontaneously Hypertensive Rats

Researchers in Japan were the first to selectively breed Wistar rats to create a new strain with a high propensity for developing hypertension very early in life, appropriately termed spontaneously hypertensive rats (SHR; Okamoto and Aoki, 1963). In an early study contrasting SHRs with Wistar-Kyoto (WKY) control rats, Yamori et al. (1969) showed that blood pressures of the SHRs were substantially higher than the WKY control animals after being exposed to several hours of stressful stimuli for several weeks. However, as Lawler et al. (1986) point out, it is difficult to determine any long-term effects of stress on SHRs as their blood pressures typically rise spontaneously within the first four to six weeks of life. By ten weeks of age, SHRs exhibit blood pressures in the hypertensive range with or without exposure to stress.

To explore the interaction between social stress and genetic factors further, Hallbäck (1975) compared SHR and WKY rats raised either in social living conditions or in isolation. Higher blood pressures were observed among SHRs living in social environments than among those in isolation; in contrast, no differences in blood pressures were observed between the two living environments for WKY rats.

Research on Dahl Salt-Sensitive Rats

About the same time that the SHR strain was being developed in Japan, Dahl and associates (1962) were developing another genetic strain

of rats that differed with regard to their blood pressure sensitivity to salt. The Dahl salt-sensitive (DS) rats exhibited normal blood pressures, but if fed diets high in sodium, they would develop hypertension. The corresponding Dahl salt-resistant (DR) rats maintained normal blood pressures on either high or normal sodium diets. Studies examining salt-sensitive strains of rats exposed to experimental stress inductions for several hours per day revealed that the DS rats exposed to stress exhibited increased SBP within the hypertensive range in contrast to DS rats not exposed to stress (Friedman and Dahl, 1975; Friedman and Iwai, 1976). DR rats, in contrast, did not become hypertensive in either experimental condition. Unfortunately, like the SHRs described above, DS rats develop hypertension with or without exposure to stress. The group exposed to stress, however, developed hypertension faster.

Research on Borderline Hypertensive Rats

Trying to overcome some of the difficulties in establishing an animal model of hypertension in which relations with stress could be examined carefully before hypertension became chronically elevated regardless of the level of stress, Lawler et al. (1986) described the development of a new genetic strain based upon the human condition of borderline hypertension. Appropriately, they named this strain of rats, created by cross-breeding SHR and WKY strains, borderline hypertensive rats (BHR). In contrast to the SHR and DS strains, the BHR strain exhibited a less drastic progression to sustained elevated arterial pressures, making it amenable to investigations of the relation between chronic stress and the etiology of essential hypertension. Early investigations aimed at addressing this question yielded some very compelling results. Indeed, BHR males exposed to a shock conditioning paradigm exhibited substantial increases in SBP in comparison to control BHR males who were placed in the same conditioning apparatus but not shocked (Lawler et al., 1981). Furthermore, these elevated SBPs persisted for ten weeks following completion of stress exposure. In a replication and extension of this initial work, Lawler et al. (1984) demonstrated that these effects were unique to the BHR strain, as WKY control rats did not develop hypertension.

Building upon the earlier work of Dahl and colleagues (1962),

Sanders, Cox, and Lawler (1985) examined the effect of sodium sensitivity in the BHR. Congruent with expectations, they found that BHRs on a high sodium diet exhibited significantly higher SBP than BHRs on normal sodium diets, a difference not observed among the WKY control rats. However, in efforts to replicate their findings relating stress and hypertension, results have been less convincing (Gelsema et al., 1994; Lawler et al., 1993).

In summary, animal research exploring the relation between stress and hypertension has revealed quite convincingly that exposure to environmental stress is associated with increased blood pressure. However, the duration of stress-induced elevations in blood pressure is questionable. In some studies, as with findings on humans exposed to natural and manmade life events, blood pressures of animals returned to pre-experimental levels once exposure to stress had ceased. When extended durations of heightened SBP were observed, it typically occurred in organisms that possessed some type of genetic susceptibility for developing hypertension. Therefore, animal research supports the contention that both hereditary and environmental factors are involved in explaining the association between stress and hypertension.

Theories Linking Stress and Essential Hypertension

Based upon the accumulated evidence linking stress with essential hypertension presented in this chapter, several investigators began to consider how a psychological construct like stress, which presumably involved neural activation of the brain, came to be associated with the condition of essential hypertension that occurred in the circulatory system. One place to start is to examine the shared regulatory systems and circuitry described in Chapters 1 and 3 that involve both the nervous and circulatory systems (for example, the autonomic nervous system and the neuroendocrine system). It seems likely that these mechanisms would be excellent candidates for explaining the connection between stress and hypertension. In fact, it is quite clear that several organ systems and regulatory feedback loops depicted in Figure 1.2 involve the integration of brain substrates and components of the circulatory system. Dysfunctions originating from each of these organ systems and associated feedback loops have been postulated to play a

role in the linkage between stress and essential hypertension. Let's consider some of the theoretical positions that have been devised to explain how stress may be causally linked to onset of hypertension. Keep in mind that the various positions presented here are theoretical in nature, and that no definitive answer to this question has been revealed.

Volume Dysregulation

Let's start by examining the potential role of the kidney in explaining the stress–hypertension association. According to Guyton (1977), a major proponent of this theoretical perspective, the overretention of sodium and fluid and failure to direct an appropriate release of urine by the kidneys leads to an elevation of the renal threshold. The body then becomes overperfused with fluids and cardiac output increases, resulting in an elevated blood pressure. As a result of the increase in cardiac output and blood pressure, sodium transport across cell membranes becomes impaired. Consequently, over relatively short periods of time, vascular cells lose their natural ability to respond to local alterations in blood pressure through an autoregulatory process, displaying increased vascular resistance to blood flow and chronically elevated blood pressure. Although the etiologic role of the kidney in essential hypertension has been clearly documented by Guyton (1977), it is apparent that volume dysregulation may not occur in all cases of hypertension. For example, Julius et al. (1971) found no evidence of increased blood volume in a sample of borderline essential hypertensive patients.

In Guyton's view, neural systems play only a minor role in the maintenance of high blood pressure; kidney dysregulation and the associated autoregulatory vascular changes lead to hypertension with or without neural involvement. However, it is well known that kidney function is influenced by neural activity. As depicted in Figure 1.2, the hypothalamus directs the release of hormones from the pituitary gland that are involved in body fluid regulation controlled by the kidney, which in turn influences vascular elasticity. It is known, for example, that exposure to acute stress can result in prolonged sodium retention (Light et al., 1983) as well as altered intracellular sodium transport (Ambrosioni et al., 1982), in particular among persons who may ex-

hibit sodium sensitivity. Therefore, considering the neural connections between the brain and the kidney, the volume dysregulation theory of hypertension can be extended to provide some clues into how stress might lead to problems with blood pressure regulation.

Renin Dysregulation

Expressing a related theoretical perspective, Laragh (1983) hypothesized that the stress–hypertension relation can also be explained by kidney function. Although he concurred that for some hypertensive patients, sodium retention leads to increases in blood pressure through expanded blood volume, as Guyton (1977) suggested, he proposed a second route to establishing high blood pressure. Rather than a dysregulation of fluid retention and blood volume, Laragh (1983) argued that this second pathway involved a dysregulation of the renin-angiotensin-aldosterone system. According to this theoretical perspective, plasma renin activity, which normally decreases in response to elevated blood pressure, remains elevated in some hypertensive patients as a result of an overactive sympathetic nervous system. Support for the existence of this subgroup of essential hypertensive patients was confirmed by Esler et al. (1977), who found that blood pressure normalized among high-renin hypertensives when the autonomic nervous system was blocked. Laragh recognized that a high renin profile was not apparent in all cases of essential hypertension, as high plasma renin levels are typically associated with lower DBP in older hypertensive patients whose blood pressures are more likely to be elevated due to increases in peripheral resistance (Thomas et al., 1976). In agreement with Guyton (1977), then, Laragh hypothesized that volume dysregulation was responsible for elevated blood pressures observed among normal or low-renin hypertensives.

Vascular Hypertrophy

Although one could conclude from the positions espoused by Guyton (1977) and Laragh (1983) that two subtypes of essential hypertension exist, namely, volume dependent and high-renin subtypes, another theoretical perspective has focused directly on vascular factors (Folkow,

1983). Avoiding kidney function entirely, Folkow theorized that hypertension resulted primarily from blood vessel hypertrophy caused by repeated cardiac output responses to acute environmental stressors. In a sense, the vascular change occurred in an effort to protect the capillaries downstream by limiting the elevated arterial pressure–laden blood flow. These enlarged blood vessels infringe into the lumen of the artery interfering with normal blood flow, leading to increased blood flow resistance and arterial pressure. Furthermore, vessels exposed to chronic elevations in blood pressure have been shown to exhibit a reduction in external diameter, through a process known as vascular remodeling, leading to even greater vascular blood flow resistance (Heistad, Lopez, and Baumbach, 1991). Complementing this position, Obrist (1981) hypothesized that blood vessel hypertrophy occurred when blood vessels responded to the overperfusion of oxygen that occurred with repeated cardiac output responses to stress. As such, these elevated cardiac output responses, which were presumably mediated by beta-adrenergic activation, resulted in vessel hypertrophy and an associated increase in total peripheral resistance. More recently, reduced production of nitric oxide in the vessel wall has been shown to be associated with this type of vascular alteration, which further contributes to the establishment of heightened vascular resistance and elevated blood pressures (Gibbons, 1998). As vessel hypertrophy is established, blood pressure responses to stress, once mediated by increased cardiac output, become chronically elevated due to increased vascular resistance, perpetuating the hypertensive condition. As with the volume and renin dysregulation theories, there is strong evidence that these vascular structural changes occur in cases of human hypertension as well as in animal models (Folkow, 1983).

Autonomic Dysregulation

Rather than focusing on components of kidney function or vascular changes in the circulatory system in explaining the stress–hypertension association, Julius and Esler (1975) theorized that essential hypertension is caused by a nervous system dysregulation, involving both the central nervous system and branches of the autonomic nervous system. According to their theory, enhanced nervous system activation

stimulates the circulatory system, much like the fight-flight (defense) response characterized in Chapter 3, resulting in elevated arterial pressures. In support of their position, they showed that the elevated blood pressures of borderline essential hypertensive patients were related to increased autonomic nervous system activity. As stated in Chapter 1, these mild hypertensive patients who exhibited elevated blood pressures associated with autonomic dysregulation have been categorized as having 'hyperkinetic' hypertension, a profile characterized by increased cardiac output rather than increased peripheral resistance, increased indices of sympathetic nervous system activation, and elevated resting heart rate (Anderson et al., 1989; Julius and Esler, 1975). This subtype of hypertensive patients also exhibits characteristic behavioral problems expressing anger and coping with stress and conflict (Julius, Weder, and Egan, 1983).

Julius et al. (1983) recognized that not all hypertensive patients exhibited this 'hyperkinetic' profile, and that even among those who did, many underwent a transition from this hyperkinetic form of hypertension to a non-hyperkinetic form of established hypertension characterized by increased vascular resistance. Borrowing from the perspective of Folkow (1983), Julius (1991) initially hypothesized that this transition occurred as blood vessels became hypertrophic in response to the extreme cardiac reactions that occurred during the hyperkinetic state. More recently, Julius and Majahalme (2000) have also implicated a reduction in beta-adrenergic responsiveness and hyperinsulinemia as agents that affect the transition from hyperkinetic hypertension to sustained hypertension. Although the exact mechanisms responsible for this transition remain to be elucidated, this theoretical perspective strongly implicates the nervous system rather than the kidney as the culprit in the etiology of essential hypertension.

Dysregulation of Baroreflex Threshold and Sensitivity

It has also been postulated that another component of the blood pressure regulation system that bridges the gap between the circulatory and nervous systems, the baroreceptor, plays a role in the relation between exposure to stress and the development of essential hypertension (Ferarrio and Takishita, 1983). It is well known that carotid baroreceptors

reset to new blood pressure thresholds after being exposed to different levels of blood pressure (Pickering and Sleight, 1977). Therefore, if an individual is exposed to an environmental stressor that results in an acute elevated blood pressure response, the baroreceptors will reset to maintain this new, elevated level. In this regard, although baroreceptor involvement in the etiology of hypertension is uncertain, baroreceptor function is clearly implicated in maintaining elevated blood pressures.

In addition to baroreceptors' capability to establish new thresholds, blood pressure regulation can also be disrupted by limited baroreceptor sensitivity. Variability in baroreceptor sensitivity exists, with some individuals having baroreceptors that are highly sensitive to blood pressure changes and others with less sensitive baroreceptors. Presumably, baroreceptor insensitivity is associated with less optimal blood pressure control. Indeed, patients with essential hypertension have been shown to have less sensitive baroreceptor function than persons with normal blood pressure (Gribbon et al., 1971). Furthermore, less sensitive baroreceptors have been reported among offspring of hypertensive patients (Parmer, Cervenka, and Stone, 1992), indicating that baroreceptor insensitivity may precede development of high blood pressure.

Interestingly, the amygdala, a part of the limbic system involved in the acute stress response, is also involved in regulating baroreceptor activity (Stock et al., 1988). Further evidence of cortical regulation of baroreceptor activity stems from research that has shown that exposure to mental stress results in a dampening of baroreceptor sensitivity (Ditto and France, 1990; Steptoe and Sawada, 1989), suggesting that exposure to stress is associated with alterations in this important blood pressure regulatory mechanism. According to this theory, then, exposure to stress leads to less responsive baroreceptors that are less capable of detecting blood pressure changes, and consequently fail to respond adequately by directing the appropriate parasympathetic responses. This failed feedback system effectively permits the blood pressure threshold of the circulatory system to reset at an elevated level. Although dysfunctions of the baroreceptor reflex are inherent among hypertensive patients, most research has shown that decreased baroreceptor sensitivity is a consequence of high blood pressure rather than a cause (Dustan, 1983; Sokolow and McIlroy, 1981). Dysfunctions in this

system could be responsible, however, for the maintenance of elevated blood pressures once developed.

Baroreceptor Reinforcement Model

Using a somewhat different approach, Dworkin (1991) also focused on baroreceptor functioning in establishing the baroreceptor reinforcement model of stress and hypertension. In contrast to many of the other theoretical perspectives, Dworkin's theoretical model of hypertension was based upon animal models of instrumental learning. A quick reminder of the principles of instrumental conditioning: behaviors that are followed by reinforcement are maintained for extended durations, whereas behaviors not accompanied by reinforcement extinguish and are not retained in an individual's behavioral repertoire. Extrapolating from work on instrumental conditioning, Dworkin postulated that involuntary physiological responses of an organism were subject to the same learning principles as the voluntary responses typically employed in studies of instrumental conditioning. According to his perspective, elevated blood pressure could be maintained, even if associated with distal negative effects on health, if a short-term response was followed by positive reinforcement. His dilemma, of course, was to identify a component of the short-term blood pressure response that was associated with reinforcement. Just what could be reinforcing about exhibiting acute blood pressure responses to aversive environmental stimuli? Dworkin's consideration of this question directed him to consider baroreceptor activity. Indeed, baroreceptor activation results in a range of physiological effects, many of which are associated with naturally occurring reinforcement, including sensory inhibition (removal of aversiveness), decreased pain and anxiety, and sleep. Accordingly, then, exposure to stress that results in escalations in blood pressure triggers the baroreceptor reflex, which in turn elicits a chain of cortical alterations that promote adaptive calming responses. In accordance with the principles of reinforcement, then, elevated blood pressures, particularly in response to environmental stress, are learned and maintained by the organism due to their frequent association with the reinforcing properties of baroreceptor activation.

Evidence to support the baroreceptor reinforcement theory largely

stems from studies examining pain tolerance of hypertensive and normotensive participants. For example, Elbert et al. (1988) compared hypertensive and normotensive patients' tolerance of pain during baroreceptor stimulation. Only the hypertensive patients exhibited a greater tolerance for pain during baroreceptor stimulation, suggesting that their baroreceptors had been conditioned to reduce pain during exposure to a painful stimulus. In a subsequent study, the extent of pain reduction that occurred with baroreceptor stimulation was shown to predict blood pressures almost two years later, particularly among persons reporting high amounts of stress (Elbert et al., 1994). In other words, blood pressures during the study period increased the most among persons who reported stressful lives and experienced reductions in pain sensitivity with baroreceptor stimulation. Although the baroreceptor reinforcement theory has not been as widely accepted as some of the other theoretical positions, it represents an important step in integrating psychological and physiological factors in explaining how stress may be causally related to high blood pressure.

Insulin Resistance

In recent years, essential hypertension, in conjunction with several other physiological parameters (glucose intolerance, upper-body obesity, elevated triglycerides), has been shown to be related to insulin resistance. The combination of these variables has been called the *insulin resistance syndrome* or *Syndrome X* (Reaven, 1988). Insulin resistance is commonly cited as a causal agent for Type II diabetes. In contrast to Type I diabetes, which is characterized by the body's lack of insulin production, normal or even enhanced amounts of insulin are typically available in Type II diabetes; the insulin receptors, however, are insensitive to insulin. It is generally thought that insulin resistance represents an adaptive bodily response to prevent additional weight gain that accompanies unhealthy lifestyles and dietary practices. Under conditions of extreme insulin resistance, an overabundance of sugars and lipids remains in the bloodstream rather than being absorbed into body tissue. According to this theory, the same underlying process is responsible for onset of both essential hypertension and Type II diabetes.

Insulin resistance (impaired insulin sensitivity) has been shown

to be associated with several pathological processes of blood pressure regulation, including increased sodium and fluid retention, vascular hypertrophy, and increased sympathetic nervous system activity (Hjermann, 1992; O'Hare, 1988), variables already hypothesized to be involved in explaining the stress–hypertension link. Regarding the relation between insulin resistance and the sympathetic nervous system, the fight-flight response involves increased glucose utilization by the brain; consequently, it has been hypothesized that peripheral insulin resistance increases in an adaptive maneuver to preserve glucose for use by the brain (Julius, 1995). Importantly, for purposes of the current discussion, both elevated SBP and DBP are associated with hyperinsulinemia (Denker and Pollock, 1992). Additionally, impaired insulin sensitivity has been detected among normotensive offspring of hypertensive patients, suggesting that insulin dysfunction precedes the development of hypertension (Endre et al., 1994). As with the high-renin and volume dependent types of hypertension, not all hypertensive patients exhibit hyperinsulinemia or increased insulin resistance. Reaven (2003) estimates that only about half of patients diagnosed with hypertension exhibit insulin-related dysfunctions. In sum, although it is clear that hyperinsulinemia is related to the onset of some cases of hypertension, it is unknown through which mechanism (fluid retention, vascular hypertrophy, and enhanced nervous system activity) it exerts its effect on blood pressure regulation.

Hypertension as an Inflammatory Disease

Based upon recent evidence linking inflammatory processes in the circulatory system to the onset of cardiovascular disease (Ridker, 1998), hypotheses that essential hypertension either may be caused by the same inflammatory process or may foster the development of the inflammatory process were considered. Indeed, hypertension has been shown to be associated with increased levels of C-reactive protein, a marker of chronic inflammation within the cardiovascular system (Saito et al., 2003; Schillaci et al., 2003). Therefore, increased arterial pressures are associated with increased levels of inflammation within the cardiovascular system. To evaluate the classic chicken-or-the-egg question, Sesso et al. (2003) conducted a seven-year prospective trial

examining whether levels of C-reactive protein predicted onset of hypertension. Controlling for traditional risk factors for coronary artery disease, they found that elevated C-reactive protein markers of inflammation were significantly related to increased risk for hypertension, even among participants with low-risk profiles at the beginning of the trial. Although not a lot is known regarding how inflammation leads to hypertension or how stress might interact with cardiovascular system inflammation, it appears that inflammation of the vascular system is involved in the etiology of hypertension.

The Mosaic Theory

Naturally, with the existence of so many theoretical perspectives, one would hope that, as empirical evidence accumulated, one theory would receive the bulk of support as support for remaining theories waned. Unfortunately, that is not the case. There is empirical evidence to support each of the mechanisms theorized to mediate the link between stress and hypertension. In an effort to make sense of this state of affairs, many investigators have returned to a systems perspective reminiscent of what was originally termed the 'mosaic' theory of hypertension proposed by Page in 1967. According to this perspective, no individual physiological mechanism explains all cases of essential hypertension by itself, and each hypothesized physiological component represents a different piece of the mosaic of causes. In this regard, the vasculature, kidneys, sympathetic nervous system, baroreceptors, renin-angiotensin-aldosterone system, and insulin resistance interact with one another in sometimes complex ways to cause elevated blood pressure levels.

Recognizing that essential hypertension is a chronic medical condition that may progress through various stages, some of these theoretical perspectives have focused primarily on isolated stages of the condition. For example, research conducted on high renin (Laragh, 1983) and on hyperkinetic hypertensive subgroups (Julius, 1991) both do a better job of explaining early stages of hypertension than some of the other perspectives. Conversely, Folkow's (1983) description of the role of vascular hypertrophy does a better job of explaining the later stages of sustained hypertension. Furthermore, some factors appear more promising in explaining how stress causes elevated arterial pres-

sures (renin dysregulation, autonomic dysregulation), and others do a better job of explaining how elevated blood pressures are maintained once they have been developed (vascular hypertrophy, baroreceptor insensitivity). In summary, each of the proposed theories explains an important piece of the mosaic as we attempt to figure out how a psychological construct like stress can result in elevated arterial pressures.

Summary

Stress has long been associated with the condition of essential hypertension. However, the relation between stress and hypertension is probably not direct, but rather involves various intervening variables depicted in Figure 4.1. Considerable empirical work has examined the relation between environmental stress and the etiology of essential hypertension, including research on stressful life events, job stress, comparisons of blood pressure across cultures, and research using rats and mice with experimentally induced high blood pressures. Findings from research on the relation of stressful life events and hypertension are mixed, with some demonstrating elevations in blood pressure following traumatic or chronic stressful events (Baum, 1999; Kario et al., 2001) and others showing no relation (Melamed et al., 1997; Suter et al., 1997). Among studies supporting a relation between stressful life events and hypertension, it is unclear whether these alterations in blood pressure persist for long durations following an event.

Research examining the relation between job stress or the more objectively defined job strain (Karasek, 1979) and essential hypertension have also been mixed. Studies employing the more traditional clinic-based measures of blood pressure have not been nearly as convincing as those studies that have employed ambulatory measures. These studies using ambulatory monitoring of blood pressure have not only shown differences in workday blood pressures between workers in high- and low-strain jobs, but also differences in nighttime or sleep measures of blood pressure. Furthermore, these findings have been more consistently observed among working men; however, examinations of job strain that also include marital and family stressors have found comparable associations among women.

Cultural factors, including socioeconomic status, have consis-

tently been shown to affect blood pressure. Inhabitants of more industrialized cultures typically exhibit higher blood pressures than those from traditional hunter-gatherer societies. Persons from lower socioeconomic status families have higher blood pressures than those in middle- and upper-class families. Furthermore, inhabitants of more traditional cultures who migrate to more westernized cultures exhibit increases in blood pressure almost as soon as they arrive.

Finally, several experimental animal models have been devised to explore the relation between environmental stress and hypertension. In these studies, various groups of rats or mice are bred to create new genetic strains that have propensities for developing hypertension (spontaneously hypertensive rats; Dahl-salt sensitive rats) or borderline hypertension (borderline hypertensive rats). Exposure to stress among these animals has resulted in a much more rapid acceleration of the development of hypertension than happens in animals not exposed to stress. A unique set of experiments by Henry and colleagues compared mice exposed to stressful crowded living arrangements with those in low-stress environments. Comparable to the genetically programmed hypertensive rats, mice exposed to stressful environments exhibited much higher blood pressures than control mice, and this effect was accentuated among mice reared in isolation.

Several theoretical perspectives have been developed to explain how a psychological construct like stress can cause essential hypertension. The primary culprit in these theories has included the kidneys, renin-angiotensin-aldosterone activity, vascular hypertrophy, the autonomic nervous system, baroreceptor sensitivity and associated reinforcing effects, and insulin resistance. As each theory has brought important empirical support to the table, each has a role in explaining the stress–hypertension relation. From a developmental perspective, it is likely that some theoretical perspectives do a better job of explaining the early phases of hypertension and other perspectives do a better job of explaining later stages of the condition.

Across all of the research domains presented in this chapter, there is very little evidence that a direct relation exists between environmental stress and hypertension. Very simply, not all persons exposed to stress develop hypertension, leading us to the conclusion that there are other significant factors that influence the stress–hypertension rela-

tion. We will examine these in the next three chapters. Before we do, however, let us return to our patient, Franklin. Although we do not know a lot about his life and work history, we are aware that he worked as a firefighter, which could be categorized as a high-strain job. Certainly, firefighting involves significant psychological demands upon the worker, as firefighters are often the first to arrive at accident scenes that involve death and dismemberment. Also, because firefighters cannot predict what might happen during their work shifts, they lack control over whether they will be called upon to put out a fire, rescue victims of an accident, or respond to a series of false alarms. Franklin clearly worked in a high-strain job. We also know that he experienced a significant life event as he witnessed the death of a young child that he worked desperately to free from a crashed automobile. To what extent these factors led to the development of Franklin's problem with high blood pressure is unknown. It is entirely possible that Franklin had high blood pressure or was predisposed to it prior to accepting his job as a firefighter or responding to the call in which the child died. Given the state of the literature at this point, we would be hard-pressed to conclude that the stress associated with his job and this stressful life event caused his blood pressure problem. However, if we knew that Franklin's blood pressure was normal before he began working as a firefighter, we could hypothesize that stress associated with his work, in particular, the recent incident associated with his attempts to rescue the child who died, provided an environmental trigger for the physiological alterations that resulted in his elevated arterial pressure.

5

Acute Stress Responses

How Do Environmental Stressors Lead to Essential Hypertension?

Although stress is clearly implicated in the etiology of essential hypertension, it is not easy to explain how a characteristic of a job, like degree of psychologic demand or job control, or exposure to an earthquake results in the physiologic tissue damage (like vascular hypertrophy) or altered regulatory system functioning (like baroreceptor insensitivity) observed in chronic hypertension. Just how can a characteristic of an environmental stimulus lead to these physiologic changes? Several of the theoretical perspectives that were highlighted in Chapter 4 hypothesized that the intensity, pattern, and duration of the acute blood pressure response to stress are important to consider when addressing this question (Folkow, 1983; Julius and Esler, 1975; Laragh, 1983). It is not surprising, then, that the comprehensive model of the stress–hypertension relation depicted in Figure 4.1 places the acute stress response in between stress and physiological change associated with essential hypertension. As its position in the model indicates, exposure to environmental stressors leads to onset of essential hypertension via the acute stress response. Individuals who respond to stress with minimal acute stress responses, according to this model, exhibit

no increased risk for development of a stress-induced hypertensive condition. This is not to say that these individuals could not possibly develop hypertension, but if they are diagnosed with high blood pressure, this model would predict that the onset of their hypertensive condition may be associated with risk factors other than stress (for example, obesity or a high-salt diet).

Borrowing heavily from the works of Selye (1956) and McEwen (1998), one can logically conclude that the relation between features of environmental stress and pathological conditions that lead to chronically elevated blood pressure is mediated by the patterning and magnitude of the acute stress response. Although both Selye and McEwen focused on the acute physiological stress response, this idea can be extended to include other components of the acute stress response (cognitive, affective, or behavioral). For example, it is possible that persons who respond to environmental stress with intensely hostile emotions (affective reactions) or increased alcohol and caffeine use (behavioral reactions) may increase their risk for developing essential hypertension through these channels. However, because the majority of theoretical and empirical work that has examined mechanisms involved in explaining the stress–hypertension association has focused on acute physiological responses, this chapter is heavily weighted in this area.

The investigation of acute stress responses associated with essential hypertension has employed both case–control and prospective methods. Case–control studies involve measurement of parameters associated with the acute stress response in samples carefully selected on the basis of hypertensive status. Responses of hypertensive patients (cases) are compared with those of non-hypertensive controls to stressful stimuli either presented in the laboratory or during daily life. Although these types of studies can be conducted fairly quickly due to the high prevalence of essential hypertension and the relative ease of locating samples of hypertensive patients, the causal nature of their findings can always be challenged. After all, if significant differences in acute stress responses were observed between hypertensive and normotensive patients, one could always conclude that the observed response differences were a consequence of essential hypertension rather than an etiologic factor. For example, if hypertensive patients were

shown to exhibit heightened blood pressure responses to stress in comparison to normotensive controls, it would still be unknown whether the exaggerated reactivity leads to onset of hypertension or whether the physiologic changes associated with essential hypertension lead to the expression of exaggerated blood pressure responses to stress.

In order to clarify the direction of relations observed in case–control studies, the more time-consuming prospective designs are essential. In contrast to case–control methodology, prospective designs involve measuring acute stress responses hypothesized to be associated with the onset of hypertension during an initial time point and then conducting follow-up visits with the same patients years later to assess change in blood pressure status. With this methodology, acute stress responses can be measured before onset of hypertension, and should significant relations between them and subsequent blood pressure status be observed, the findings make a much more convincing causal statement. The majority of studies reported in this chapter have employed case–control methods, which suggests that definitive causal conclusions regarding these variables are limited. However, with some parameters (for example, cardiovascular response to stress), prospective evidence has emerged.

The Acute Affective Stress Response

Affective variables associated with the stress–hypertension relation include an array of acute emotional responses to environmental stressors. Although positive emotions like happiness or joy could serve as potential acute affective stress responses associated with hypertension, research in this area has typically focused on emotions that constitute negative affect, mainly anxiety and anger. In this regard, not all emotions have received equal attention.

In order to examine more closely the role of acute anxiety or anger responses in connection with the stress–hypertension relation, it is more important to measure short-term affective states that occur in response to situational or environmental stressors than the more enduring anxiety and anger traits. In Spielberger, Gorsuch, and Lushene's (1970) terminology, acute stress responses are best assessed using measures of state affect (responding how anxious or angry you feel right

now), and the more enduring characteristics of affect resembling personality dimensions are best assessed using trait measures (responding how anxious or angry you are typically). Although there is generally a moderate degree of correspondence between state and trait measures of anxiety or anger, individuals reporting high trait scores may or may not respond to a designated situation with elevated state affective responses. Likewise, individuals reporting low trait scores could exhibit substantial state reactions if they were exposed to a situation that was perceived as threatening.

For purposes of this chapter, we will examine only research that has employed measures of state anxiety or state anger in response to standard environmental stressors or during daily life. Studies employing trait measures of anxiety or anger in relation to measures of blood pressure or hypertension belong more appropriately in Chapter 7, where individual differences on psychological parameters that affect the relation between stress and hypertension are presented. Although this may seem like a confusing way to present these findings, there has been considerable disagreement regarding the relation between measures of affect and hypertension, with some reviewers concluding that certain measures of affect are important predictors of hypertension (Markovitz, Jonas, and Davidson, 2001) and others claiming that this conclusion may be premature (Rosenman, 1991). Because the acute stress response represents something quite different from enduring individual difference variables, presenting findings separately for state and trait measures of affect is congruent with the model of the stress–hypertension relation and may help clarify where sources of disagreement exist in the literature.

Support for distinguishing between state and trait measures of affective response to stress can be derived from a study by Porter, Stone, and Schwartz (1999) in which both state and trait measures of anger expression were obtained on a sample of young adults during a one-week ambulatory monitoring period. Results revealed that there was not a strong association between how participants reported they typically expressed anger (trait anger expression) and how they actually expressed anger during the ambulatory monitoring period. In contrast, several situational variables affected actual expression of anger during monitoring, including the target of the anger, the type of relationship

that existed between the target person and the study participant, the difference in perceived power between the target person and study participant, whether they were in a public location, and whether the target person was present. Based upon findings from this investigation, the authors recommended that future research examining associations between affective and health-related variables consider distinguishing between measures of trait and state affect.

State Anxiety

Almost everybody has experienced anxiety at some time in life, including persons with high blood pressure as well as those with normal blood pressure. Imagine the various sensations you experience if you are asked by a teacher to report to the class the basic conclusions from an article you were supposed to have read but did not. This experience of anxiety is comprised of a number of cognitive manifestations, including catastrophic thinking, anticipation of danger, and sensing doom, accompanied by a full array of physiological symptoms associated with sympathetic and somatic nervous system arousal, including increased heart rate, sweating, shortness of breath, muscle tension, and disturbances of the gastrointestinal system. The discomfort associated with the experience of these cognitive and somatic symptoms of anxiety often leads to behavioral escape or avoidance responses (for example, "I feel ill and need to go home"). Although anxiety is a normal emotion to experience in situations like this, when the experience of anxiety becomes too frequent or too intense and begins to interfere with daily functioning, diagnoses with a range of anxiety disorders can be made, including panic disorder, generalized anxiety disorder, and obsessive compulsive disorder. Although there have been reports of increased blood pressure among patients with anxiety disorders (Fontaine and Boisvert, 1982; White and Baker, 1987), the incidence of essential hypertension among anxiety disorder patients is no different from the population at large (Chapman et al., 1990). Because acute anxiety responses to stress are not typically measured in these reports, these studies provide very little information regarding the role of anxiety reactions in the etiology of essential hypertension.

To focus on state anxiety, if individuals who respond to environ-

mental stress with increased acute anxiety responses go on to develop high blood pressure, anxiety may be considered a component of the acute stress response that warrants further examination in understanding etiologic factors of hypertension. Let's consider the evidence for this association among both normotensive and hypertensive patient samples.

Acute Anxiety Responses and Blood Pressure among Normotensives

Although correspondence between measures of state anxiety and blood pressure does not reflect a perfect correlation, these variables do tend to correlate in a small but positive way when applied in laboratory stress manipulations. For example, Turner, Beidel, and Larkin (1986) reported increases in both state anxiety and blood pressure in response to a social conversation task as well as an impromptu speech among both socially anxious and nonsocially anxious normotensive participants. There are countless additional studies like this in the assessment literature pertaining to anxiety disorders that show that indices of both state anxiety and blood pressure increase when exposed to fear-evoking stimuli, although correlations between response channels are often minimal or moderate at best (see Lang, 1978). Given the conclusions of these studies, it is generally accepted that exposure to fearful stimuli results in increases in both blood pressure and measures of state anxiety.

In two studies that measured state anxiety during high school health courses in which blood pressure determinations were made, state anxiety during blood pressure measurement was shown to correlate with both SBP and DBP among young black males, but only with SBP among white males (Johnson et al., 1987b) and black females, but not white females (Johnson, Schork, and Spielberger, 1987a). Most of these correlations, however, failed to achieve significance when controlling for traditional risk factors for essential hypertension like family history of essential hypertension, weight, and sodium intake. Therefore, while young adults, particularly young black adults, who express heightened state anxiety during blood pressure measurement sessions exhibited higher blood pressures than less anxious young adults, the association was explained by a number of other variables.

In summary, among persons with normal blood pressures, there is evidence indicating that conditions that arouse state anxiety also re-

sult in increased blood pressures (Lang, 1978). However, among studies that measure acute anxiety responses to stress among normotensives, there is no evidence that these acute state anxiety and blood pressure responses lead to sustained elevations in blood pressure. In fact, quite the contrary, the blood pressure elevations observed among these studies are typically temporary and return to normal shortly following the stressful encounter. In order to demonstrate a relation between acute state anxiety responses and the etiology of essential hypertension, case–control studies using hypertensive patients need to be examined.

Acute Anxiety Responses and Blood Pressure among Hypertensives

With the knowledge that exposure to stressful stimuli results in increased state anxiety as well as blood pressures in non-hypertensive samples, several researchers began to test whether the magnitude of this observed increase in state anxiety was accentuated among samples of essential hypertensive patients or persons at risk for sustained hypertension, including borderline essential hypertensive patients. In accord with the hypothesis that the increased blood pressures observed in the clinic among isolated clinic ('white coat') hypertensive patients is related to anxiety surrounding the clinic visit, these patient groups have also been examined with respect to their acute anxiety responses to stress.

Comparable to findings using normotensives, measures of state anxiety during clinic visits of essential hypertensive patients have been shown to be related to blood pressure (Jeter, Bush, and Porter, 1988; McGrady and Higgins, 1990). Jeter et al. found that SBPs declined over multiple blood pressure determinations during a single clinic visit for both hypertensives and normotensives, and that these reductions in SBP were correlated with reductions in state anxiety. McGrady and Higgins reported that hypertensive patients, as determined by initial clinic measures of blood pressure, who exhibited reductions in blood pressure during weekly clinic visits over a period of six weeks (isolated clinic hypertensives) had higher measures of state anxiety during the initial clinic visit than patients with sustained levels of high blood pressure over the six weeks. These findings suggest that state anxiety may influence measurement of blood pressure in the clinic, obscuring accu-

rate diagnoses. Other studies contrasting patients with isolated clinic hypertension and patients with persistent hypertension on measures of state anxiety, however, have failed to detect any difference in state anxiety between these two groups (Larkin et al., 1998b; Siegel, Blumenthal, and Divine, 1990).

Additionally, in another study, exposure to a standard mental arithmetic stressor yielded a significant correlation between state anxiety and SBP response, but not DBP response, among a group of essential hypertensive patients (Aivazyan et al., 1988). Therefore, essential hypertensive patients appear to exhibit the same associations between state anxiety and blood pressure responses seen among normotensives when undergoing clinic blood pressure measurements or while being exposed to mental stress. However, because few of these studies employed a normotensive control group for purposes of comparison, little can be said regarding the potential role of state anxiety in the stress–hypertension relation. If indeed the acute state anxiety response to stress is involved in onset of hypertension, it is important to demonstrate that the magnitude of state anxiety responses to stress is much greater among hypertensive patients than normal blood pressure controls.

In a study examining performance of hypertensive and normotensive patients on a variety of tests of memory and information processing, Blumenthal et al. (1993) found that hypertensive patients exhibited higher scores on a measure of state anxiety than normotensives. Crane (1982), likewise, found higher scores on state anxiety among hypertensive patients than normotensive counterparts. Other studies, in contrast, found no difference between hypertensive and normotensive volunteers using the same measure of state anxiety (Larkin and Zayfert, 2004; Russell, 1983). To complicate matters further, some studies have reported greater state anxiety responses among normotensive volunteers than their hypertensive counterparts (Nyklíček, Vingerhoets, and Van Heck, 2001; Steptoe, Melville, and Ross, 1982).

Some studies have examined state anxiety among samples of borderline essential hypertensive patients (James et al., 1986; Perini et al., 1990). If stronger associations between state anxiety and blood pressure could be demonstrated among these patients than persons with

normal blood pressures, an argument could be made that the linkage existed before onset of essential hypertension and may therefore be involved in its etiology. James et al. found a strong correlation between state anxiety and DBP during an ambulatory blood pressure recording period that was most dramatic among borderline hypertensive patients with labile blood pressures. Perini et al. contrasted a group of borderline hypertensive patients with a group of normotensives without a parental history of hypertension. Borderline hypertensive patients exhibited higher state anxiety responses to a standardized presentation of mental and physical stressors than the normotensive controls.

In summary, evidence examining the magnitude of the acute state anxiety response among hypertensive patients as well as borderline hypertensive patients has been mixed. Furthermore, data from patients with diagnosable anxiety disorders, who clearly exhibit elevated acute anxiety responses to feared stimuli on a regular basis, do not reflect an increased incidence of chronic hypertension (Chapman et al., 1990). Therefore, there is little evidence at this point in time supporting the hypothesis that hypertensive patients regularly exhibit elevated acute anxiety responses (state anxiety) to stress in comparison to normotensives.

State Anger

Anger represents another measure of negative affect that is quite different from anxiety, but could also be involved in the stress–hypertension relation. Although both anxiety and anger involve activation of the sympathetic and somatic nervous systems, the cognitive and behavioral responses typically seen to anger-evoking incidents can be easily differentiated from those observed for anxiety. Anger typically involves an appraisal of intentional threat or goal blockage from an environmental encounter or situation. Although the perceived threat could be aimed at one's physical well-being (physical altercation following a traffic mishap), it is also possible to experience anger in response to perceived threats to social status, self-esteem, and psychological well-being (being the target of a racial slur). In this regard, persons can experience comparably intense anger responses to being criticized in public and being threatened with bodily harm. Behaviorally, the expe-

rience of anger can lead to avoidance and withdrawal like the experience of anxiety; however, the experience of anger is much more likely to lead to overt expressions of anger and related aggressive behaviors than the experience of anxiety. As with anxiety, much of the research linking anger with essential hypertension has focused on the temperamental characteristics of anger rather than state anger reactions. Temperamental characteristics of anger will be examined more closely in Chapter 7, and acute anger responses to stressful encounters (state anger) will be examined here.

Acute Anger Responses and Blood Pressure among Normotensives

As in research on acute anxiety responses and blood pressure among normotensives, there is convincing evidence that exposure to certain stressors (harassment, goal blockage, criticism) evokes both substantial state anger and blood pressure responses among individuals regardless of their hypertensive status (Dimsdale, Stern, and Dillon, 1988; Larkin, Semenchuk, et al., 1998). As an example, imagine being asked to complete a serial subtraction task (counting backwards by sevens from a three-digit number provided to you by an experimenter) and to work as quickly and as accurately as you can. As you are just getting into the groove of completing the task, you are interrupted, informed you are going to have to work faster, and told to start over. If this happens repeatedly during task presentations, and the nature of the harassment escalates, it is not difficult to imagine that your ratings of both state anger and blood pressure would increase.

Johnson et al. (1987a; 1987b) obtained measures of state anger on their sample of black and white high school students described above. As with measures of state anxiety, they found correlations between state anger and both SBP and DBP among black males, but not white males (Johnson et al., 1987b), and with DBP among black females (Johnson et al., 1987a). Also, as in their findings on state anxiety, associations were less impressive when traditional risk factors for hypertension were controlled in the analysis.

Again resembling research results on anxiety among normotensives, alterations in state anger and blood pressure in response to harassment or induced conflict are short-lived. Within minutes after par-

ticipants completed the task, their blood pressures typically return to normal, and evidence that repeated elevations in state anger responses to environmental stress leads to essential hypertension is lacking. While these sorts of studies link stress-elicited state anger responses to acute blood pressure responses, research employing these sorts of tasks with samples of hypertensive and borderline hypertensive patients is important to consider when examining whether the acute anger response is involved in the stress–hypertension relation. If one operates from this hypothesis, essential hypertensive patients (or those at risk for establishing hypertension) would be expected to exhibit greater state anger responses to stress than normal blood pressure comparison patients. Let's examine the evidence for this expected outcome.

Acute Anger Responses and Blood Pressure among Hypertensives

Evidence supporting state anger response differences between hypertensives and normotensives is not all that convincing. While a few studies have shown higher scores on measures of state anger among hypertensives than normotensives (Crane, 1982; Johnson, 1989b), others have found no differences between these groups (DeShields, 1985; Russell, 1983). Schneider et al. (1986) examined what they called state anger reaction scores of a group of isolated clinic borderline hypertensive patients and a group of borderline hypertensive patients whose blood pressures remained elevated both in the clinic and during home recordings. State anger reaction referred to the intensity of anger that was experienced in response to either "time pressure" or situations involving potential for negative evaluation. Their findings revealed that, in comparison to the isolated clinic hypertensive patients, the group with sustained blood pressure elevations exhibited higher scores on state anger reaction, but not state, or trait, anger scores in response to stressful daily situations. Additionally, clinic SBPs correlated significantly with measures of state anger, indicating that borderline hypertensives with the highest blood pressures exhibited the highest scores on state anger.

Schachter (1957) conducted a study in which hypertensive and normotensive participants were exposed to laboratory manipulations of emotions of fear and anger. Rather than relying on state anger ratings during relatively benign periods of time (resting periods), he ex-

posed these participants to (a) a fear condition in which the laboratory equipment presumably was electrically malfunctioning, placing the participant in danger; and (b) an anger condition in which the experimenter directly harassed the participant. Schachter reported that hypertensive patients exhibited somewhat higher ratings of expressions of fear and anger than the normotensive control participants, but that these differences were not statistically significant.

We must interpret these findings carefully, though, as there has not been a substantial number of studies conducted to address the role of state anger in the stress–hypertension relation, and among those that have been conducted, this question was of secondary importance. Given the evidence that does exist, however, the hypothesis that hypertensive patients exhibit greater state anger responses to stress in contrast to normotensive controls has very little support.

Summary of Measures of State Affect as Mediators of the Stress–Hypertension Relation

Measures of state affect, both anger and anxiety, often are confounded by the novelty of the experimental situation. If differences in state affect are detected between hypertensive and normotensive participants, it is unknown whether the changes in affect are occurring in response to stressful stimuli used in the study or whether they represent study participants' responses to the novelty of the experimental situation. Certainly, if you volunteered for a study and found yourself in a strange laboratory environment for the first time, there is a possibility that even basal levels of state affect measured upon arrival to the laboratory would not reflect the levels of state affect that you were experiencing earlier in the day. Therefore, to truly examine acute state affective responses to standard laboratory stressors, it becomes crucial to calculate the difference between measures of affect obtained during a rest period and those obtained immediately following stress presentation. This change score then reflects the magnitude of the acute emotional response to a given laboratory stressor. Studies that rely on a single measure of state affect following a stress presentation are much more difficult to interpret. In this regard, data from many of the stud-

ies reviewed above do not reflect the sort of data needed to address whether hypertensive and normotensive patients exhibit differential acute affective responses to stress.

Although all studies of this type have measured state affect via self-report questionnaires, it is important to remember that state affect can be assessed using a variety of measurement strategies, including coding of facial affect as well as analysis of physiological response patterns (Lang, 1978). Perhaps the failure to uncover differential acute affective responses between hypertensive and normotensive samples is related to the sole reliance on the self-report mode of assessment. It will be up to future research to determine whether differences in acute affective responses of hypertensives and normotensives can be detected when a broader array of assessment strategies is employed.

It is also important to consider that emotional states like anxiety and anger represent a conglomeration of cognitive, physiological, and behavioral response domains. Anxiety involves physiological arousal, certain cognitive manifestations, and typically behavioral avoidance responses. Anger also contains physiological arousal, accompanied by a different set of cognitive and behavioral responses. As noted by Lang (1978), the magnitudes of responses across these domains are only weakly correlated, suggesting that they are measuring unique attributes of the affective response. As a more recent illustration of this finding, Feldman et al. (1999) analyzed the relation between measures of negative emotional reactivity (anxiety, anger, and stress) and cardiovascular reactivity to mental stress tasks from nine different studies. Their results revealed that only 2 to 12 percent of the variance of cardiovascular reactivity was explained by measures of negative affective responding, suggesting only a small correspondence between these two response domains. Because affective responses represent an amalgamation of the remaining acute stress responses (behavioral, cognitive, and physiological responses), perhaps the failure to detect consistent findings relating acute affective responses to stress with essential hypertension is not that surprising. It might be more important to examine each of these remaining components individually to determine their unique roles as potential mechanisms that explain how psychological stress leads to essential hypertension.

The Acute Behavioral Stress Response

There are several behaviors known to be associated with essential hypertension, including eating a diet high in sodium (Law, 1997), excessive use of alcohol (Puddey, Beilin, and Rakic, 1997), sedentary lifestyle (Blair et al., 1984), using diet pills containing phenylpropanolamine (Lake et al., 1989), and even consuming significant amounts of licorice (Sigurjonsdottir et al., 2001). If hypertensive patients respond to stress with any of these or other acute behavioral responses more than normotensives, then these behaviors may be important in understanding how environmental stressors lead to hypertension. Alternatively, other investigations have focused on specific behavioral responses of hypertensive patients during stressful interpersonal encounters (Baer et al., 1980; Morrison, Manuck, and Bellack, 1985). If individuals who employed these acute behavioral responses to interpersonal stress progressed to chronic hypertensive states, and those who chose more adaptive behavioral responses to interpersonal stress did not, it could be argued that these behavioral responses play an influential role in the relation between stress and hypertension. Although these represent plausible hypotheses, very little empirical work has examined the roles of these behavioral variables in explaining how stress causes essential hypertension. In this section, empirical work on both behavioral lifestyle factors and interpersonal behaviors that may be potential mechanisms through which stress leads to hypertension will be considered.

Lifestyle Factors

Although a number of lifestyle factors are associated with risk for essential hypertension (sedentary lifestyle, excessive alcohol consumption, high-sodium diet; Kaplan, 2002), in order to consider these factors in explaining how stress leads to hypertension, it is important to demonstrate that individuals who respond to environmental stress by engaging in these lifestyle factors are more likely to develop essential hypertension than individuals who respond to stress using more adaptive strategies. Unfortunately, studies of this type are not routinely reported in the literature. Although we recognize that these lifestyle factors are associated with an increased risk for essential hypertension, the

available evidence suggests that this increased risk might be independent of exposure to stress. For example, many people who consume high-sodium diets, drink alcohol, and exercise infrequently may maintain these behaviors during periods of stress as well as during periods of relaxation. In fact, if one observes behaviors during vacations, it is quite common to see increased consumption of alcohol, poorly regulated diets, and increased sedentary behaviors during these periods when stress is presumably quite low. Only a few studies have examined these lifestyle behaviors as potential mechanisms through which stress leads to hypertension.

In a study of normotensive government workers, the role of behavioral lifestyle factors in explaining the relation between job strain and resting blood pressure levels was examined (Lindquist, Beilin, and Knuiman, 1997). Although no relation between job strain and blood pressure was observed, several lifestyle factors were related to blood pressure level, including consumption of alcohol and unhealthy food items. Using stepwise multiple regression analyses, the study showed lifestyle factors of smoking, alcohol consumption, exercise, and dietary habits to be better predictors of DBP among men than other psychosocial variables (stress and coping). Comparable findings, however, were not observed for women. On the basis of these findings, Beilin, Puddey, and Burke (1999) proposed a theoretical model of the stress–hypertension relation congruent with Figure 4.1, which depicted lifestyle factors (acute behavioral responses to stress) as mediators for the association between stress and essential hypertension. However, because the relation between stress and hypertension was not observed in their study, it is unclear whether their data actually supported the full model.

It is of interest that one lifestyle habit, alcohol use, has emerged as a factor that influenced the job strain–hypertension relation (Schnall et al., 1992). In this study, alcohol intake was not associated with blood pressure among workers in low-strain jobs. In contrast, workers in high-strain jobs exhibited higher blood pressures, but only if they consumed alcohol regularly. In this study, job strain did not lead to increased alcohol use; rather, it was the combination of job strain and alcohol use that best predicted blood pressure status. Although this finding does not establish alcohol use as a mechanism that explains

how stress leads to essential hypertension, it clearly supports further examination of alcohol use as a potentially important behavioral response variable.

In summary, although many lifestyle factors are associated with risk for high blood pressure, there is currently very little evidence that persons who respond to stress by increasing their sodium and alcohol intake and decreasing physical activity are more likely to develop hypertension than persons with more adaptive behavioral responses. These targeted lifestyle factors appear to exert more of a direct effect on blood pressure, rather than through mediation of the stress–hypertension link. In other words, there is currently no evidence that individuals who go on to develop hypertension drink more alcohol, consume more sodium, or become less physically active during periods of stress than individuals predestined to have normal blood pressures.

Interpersonal Behaviors

Some research investigating acute behavioral responses of hypertensive patients has focused directly on behaviors observed during interactions with other people. If hypertensive patients resort to different acute behavioral responses to stressful interpersonal encounters than normal blood pressure controls, then perhaps these behavioral differences might help to explain how stress leads to hypertension. From this perspective, life stress leads to the onset of essential hypertension, but only if the acute stress response contains the maladaptive behavioral strategy. Although any number of interpersonal behaviors could be examined with respect to this approach, almost all studies exploring differences in interpersonal behaviors between hypertensive and normotensive persons have focused on the array of behaviors evoked in response to confrontation.

Early investigations of behavioral responses to confrontation provided some support for the hypothesis that hypertensive patients exhibited behavioral deficits when exposed to interpersonal conflict (Harris et al., 1953; Kalis et al., 1957; 1961). Harris et al. used two interpersonal scenes known to elicit emotional reactions among the college-aged women in their study (a dress for a dance was not ready at the dry cleaners; asking the dean of the college to postpone an examination).

Students were observed and rated by two independent observers using a series of adjectives. Women with elevated blood pressures in the borderline hypertension range (termed pre-hypertensives) were more likely than normotensive women to be described as lacking emotional control (unstable and excitable), self-centered, and moody. In contrast, normotensives were more likely to be described as being likable, cooperative, even-tempered, and poised than pre-hypertensives. Self-ratings made by study participants confirmed the differences detected by the observers, indicating that hypertensive patients were well aware of their interpersonal inadequacies. Observer ratings on a group of these women who were contacted several years later (in their mid-20s) revealed that pre-hypertensive women were still rated as being more tense, hostile, and judgmental than normotensive controls, and that these problems resulted in increased interpersonal conflict and stress in their lives (Kalis et al., 1961).

Kalis et al. (1957) conducted a similar study comparing hypertensive women with a control group of working women with normal blood pressure. In this study, the content of the interpersonal scenes was modified to be more appropriate for community-dwelling women (dealing with a friend who has not paid back a loan; talking with an unsympathetic neighbor about joining an exclusive club). Hypertensive women exhibited greater increases in both SBP and DBP during the conflict scenarios. Regarding behavioral reactions, hypertensives were generally rated as being less persistent, more submissive, and more likely to suppress anger than the normotensive women. Interestingly, hypertensives were also rated as being more hostile than normotensives during the role-play in which their goal was to impress their neighbor regarding access to the exclusive club, behavior that would certainly not be adaptive in this situation. Arguments of normotensive controls were rated as being more effective and better organized than those of the hypertensive patients. Other early studies examining behavioral responses also reported less dominance and less assertiveness and more submissive interpersonal behaviors among essential hypertensive patients (Hamilton, 1942) and college males with elevated, but not hypertensive, blood pressures (Harburg et al., 1964).

Keane et al. (1982) contrasted a group of essential hypertensive patients with a group of normal blood pressure controls as well as a

group of patients with other chronic medical conditions on their behavioral responses to a series of interpersonal role-plays. Although deficits in assertive behaviors were detected among hypertensive patients, they were also observed among patients in the chronic illness control group, suggesting that the assertiveness deficits were not specific to the condition of essential hypertension. Morrison, Manuck, and Bellack (1985) also used role-plays to examine assertiveness in hypertensive patients. In contrast to the previous work that found uniform deficits in assertiveness among hypertensives, they identified two subgroups of patients that could be characterized by their pulse pressure response to the role-plays. As in previous research, one group was characterized by assertiveness deficits and reductions in pulse pressure reactivity to the scenarios. The other group, in contrast, was characterized by increased hostile and aggressive behaviors, higher pulse pressure responses, and lesser social competence. Findings from Larkin and Zayfert (2004) confirm that different subgroups of essential hypertensive patients exist that can be distinguished both on measures of assertiveness and on pulse pressure reactivity to anger-arousing scenes. It appears that nonassertive hypertensives are likely to respond to conflict with blood pressure reactions associated with an increased DBP response, possibly reflecting increases in total peripheral resistance, while hostile-aggressive hypertensives respond to conflict with greater SBP responses, possibly reflecting increases in cardiac output.

Delamater et al. (1989) contrasted a group of hypertensive patients with normal blood pressure controls during role-play scenes as well as a naturalistic encounter in which the experimenter made an unreasonable request of the patient (to complete extra forms for an additional 20 minutes at the end of the experiment). Among all behaviors that were coded, only two showed a significant difference between hypertensives and normotensives. Hypertensives made fewer request statements during role-plays and used more appreciative statements during the naturalistic encounter than normotensives. Greater cardiovascular reactivity to negative interactions was significantly correlated with enhanced ratings of interpersonal effectiveness, indicating that lower assertiveness was associated with lower, not higher, blood pressures.

Several studies have also examined specific behavioral responses observed during social confrontation encounters. Baer et al. (1980), for

example, compared specific behaviors among hypertensive fathers during family conflict discussions with their wives and children. In contrast to normotensive fathers, hypertensive fathers exhibited more negative nonverbal behavior (gaze aversion) during these staged family discussions. Lack of eye contact in conflict-laden situations is associated with less assertive skill, a desire to distance oneself from the source of the conflict, and a reduction in opportunities for conflict resolution. Comparable differences in gaze aversion were detected in three samples of both white and black hypertensive and normotensive patients and their families (Baer et al., 1983), essentially replicating the initial findings. More recently, duration of eye contact during role-play conflict scenarios with nonyielding confederates was also shown to be shorter among hypertensive patients than normotensive controls (Larkin and Zayfert, 2004). In this study, differences in duration of eye contact were observed only during anger-eliciting role-plays, not neutral interactions. Hypertensive patients have also been shown to engage in lesser self-disclosure behaviors during interviews regarding a variety of personal topics than normal blood pressure controls (Handkins and Munz, 1978).

Ewart et al. (1991) examined specific behavioral responses of both male and female hypertensive patients while they engaged in a problem-solving discussion with their spouse. No control participants were included in this study as its purpose was to explore relations between blood pressure and behavioral responses to the discussion task among hypertensives. A different pattern of findings was uncovered for men and women patients. For hypertensive women, blood pressures increased during portions of the discussion in which they made hostile remarks, in contrast to neutral and supportive remarks. For hypertensive men, there was no association between the nature of the remarks and blood pressure reactions; however, men's blood pressure elevations were directly associated with speech rate. Therefore, it appears that different behavioral responses during an interpersonal discussion task are associated with blood pressure reactions for hypertensive men and women.

In summary, there is some convincing evidence that patients with essential hypertension exhibit less socially competent behaviors than normal blood pressure controls, particularly during situations in-

volving conflict and confrontation. These deficits appear to occur in the area of social behaviors typically referred to as assertive behaviors. In brief, assertiveness involves the genuine expression of feelings and desires stated in a way that minimizes negative emotional responses from others. Assertiveness does not always involve the assertive expression of anger; however, studies that have contrasted essential hypertensive patients with normotensive controls have tended to use anger-eliciting stimuli. Additional research is needed to determine whether comparable deficits in assertive behaviors exist among hypertensives when they are asked to express feelings of joy or tenderness.

Among specific behavioral deficits, it appears that essential hypertensive patients are more likely than controls to adopt conflict-avoidant nonverbal behaviors, particularly gaze aversion. Additionally, there is evidence that hypertensives reveal less emotionally laden information than normotensives during interactions with others. While not all stressors encountered in life are interpersonal in nature, it seems that hypertensive patients are less equipped to respond to those that are with optimal acute behavioral responses, particularly in the area of eye contact. It is entirely plausible that hypertensives adopt gaze aversion strategies for dealing with stress to minimize the emotional and physiological arousal anticipated to occur during conflict. Unfortunately, avoidance of eye contact may also prevent hypertensives from receiving any benefit associated with intimate interpersonal interactions, if they are shown to limit eye contact in these sorts of interactions as well. Because there is no prospective evidence linking these behavioral deficits to subsequent diagnoses of essential hypertension, conclusions regarding the causality of these differences in acute behavioral stress responses cannot be made.

The Acute Cognitive Stress Response

In comparison to the literature that has examined potential affective and behavioral factors that might help explain how stress leads to hypertension, fewer studies have considered acute cognitive stress response variables. It is possible that researchers are reluctant to examine cognitive variables due to the inherent difficulty in accessing reliable measures of cognitive activity. In general, there are two methods for

measuring acute cognitive responses to stress, retrospective recall of thoughts and think-aloud procedures. The former involves requesting individuals to report thought content associated with a given stressful situation after the stress has dissipated, and the latter involves training respondents to state their thoughts aloud into a recorder for later scoring during the given stressful situation. Both possess obvious problems. Retrospective reports of cognitive activity are contaminated by problems of inaccurate and selective recall. While some thoughts are going to be lost because they were not properly coded into memory, others are selectively recalled, often based upon the participant's perception of task performance or situation outcome. For example, if a participant who was engaged in a serial subtraction task performed poorly, retrospective reports of his or her thoughts that occurred during the task may yield an overestimate of self-deprecating thoughts. One advantage of the think-aloud procedure is that cognitive responses are gathered prospectively; however, because virtually nobody responds to stress naturally by stating aloud the content of his or her thoughts, generalization of findings from think-aloud studies to real-life stressful encounters is quite limited. Heiden, Larkin, and Knowlton (1991), for example, conducted a study in which distracting self-statements made during a cold pressor task (forearm submerged in a bucket of ice water) were associated with reduced DBP responses to the task. Although data from this study revealed an association between certain types of self-statements and blood pressure responses to laboratory challenges, it says very little about the sustained elevated blood pressures observed in essential hypertension.

Perception of Emotion-Laden Content

It is possible to examine acute cognitive responses from an information-processing perspective. From this point of view, cognitive processing involves perception of stimuli, attentional factors, coding and storage in memory, recollection of stored information, and selection of appropriate response alternatives. It is possible that persons at risk for developing hypertension exhibit differential cognitive responding at some point in the information-processing model. For example, Shapiro (1961) reported significant differences between hypertensives and

normotensives who were exposed to conditions of fear, anger, and frustration. Interestingly, despite the harassment experienced by participants in this study, hypertensive patients rated the experimenter as more 'friendly' than normotensives, indicating that either hypertensive patients perceived the experimental situation as less noxious than normotensives or they were glossing over the negative interactions they had just experienced.

To examine this question further, Sapira et al. (1971) exposed a group of hypertensive patients and normotensive controls to videotape segments of two doctor–patient interactions, one characterized as a 'rude' doctor and the other as a 'warm' doctor. Hypertensive patients exhibited greater blood pressure and heart rate responses to the filmed segments than the normal blood pressure controls. But in contrast to the normotensives, who were able to detect differences between the rude and warm doctors, the hypertensive patients reported observing no differences between the two doctors. Sapira et al. argued that hypertensive patients perceived information differently from normotensives, particularly information pertaining to conflict and confrontation. Because they reported no detectable differences between rude and warm doctors, the hypertensive patients would have had no conscious reason to evaluate the rude doctor negatively, and perhaps effectively avoided potential conflict or confrontation that might have occurred if they acknowledged the patient was being treated poorly. As such, hypertensives were shown to process information differently from their normotensive counterparts.

Linden and Feuerstein (1983) examined responses of hypertensive and normotensive patients during both high-distress and low-distress role-play scenarios. Although they observed no overt behavioral differences between groups, hypertensive patients showed greater SBP reactions during the role-play scenarios than normal blood pressure controls. The fact that the physiological reactions of untreated hypertensive patients were elevated without corresponding increases in self-reported distress during the interactions lends credence to the hypothesis that hypertension is associated with a 'repressive–defensive cognitive style.' In other words, although hypertensive patients experienced more arousal during the interactions, they denied feeling any more distressed than the normotensive controls.

In yet another early study comparing cognitive reactions of hypertensive and normotensive patients, Weiner, Singer, and Reiser (1962) found that hypertensives responded to the presentation of Thematic Apperception Test cards with avoidance of emotional content more than normotensive volunteers or patients with peptic ulcers. Although hypertensives actively resisted efforts from the test examiner to consider the emotional content of the stimuli, when they were forced to explore the emotional content, increased blood pressure responses were observed. In a study comparing hypertensive and normotensive patients, Handkins and Munz (1978) found that self-reported ratings of stress varied directly with the level of intimacy of the personal topic being discussed among normotensives. However, no relation between ratings of stress and levels of intimacy regarding the topic were observed among hypertensives, suggesting that hypertensives 'denied' emotional content of the topic as well as concealed emotion-laden topics from the interviewer. Congruent with other studies examining how hypertensives react to stress cognitively, these findings suggest that hypertensives resist efforts to report emotion-laden material, perhaps recognizing that should they engage the emotional content, they will exhibit maladaptive increases in blood pressure.

In a study that explored the correspondence between hypertensive status and coping with the experience and expression of the emotions during an interview (Knox et al., 1988), normotensives were shown to express sorrow to others more frequently than hypertensives, and their expressions of sorrow were qualitatively better at attaining instrumental support from others. Additionally, normotensives reported experiencing joy more often than hypertensives. These findings also support the hypothesis that hypertensive patients engage in emotional content much less than normotensives.

Although studies that have explored the cognitive responses of essential hypertensive patients have used a variety of different methodologies, there is a consistent finding that high blood pressure is related to a reluctance to acknowledge the aversive or negative elements of a social interaction or the experience of an emotional state. As such, hypertensives, in contrast to normotensives, appear to screen out emotion-laden experiences. Conceptually, this protective cognitive style may serve the function of preventing exaggerated physiological re-

sponses to stress that would be sure to occur if the situation was appraised as threatening. Because no prospective studies have examined this tendency, however, no definitive conclusions can be drawn regarding the causality of this association. It is entirely possible, and quite likely, that these cognitive response differences between hypertensive and normotensive patients are a consequence of hypertension rather than being involved etiologically.

Perception of Pain

It has been well established that pain is a subjective experience that can be influenced by psychological and situational factors (Melzack and Wall, 1965). Remarkable stories of athletes who suffer severe injuries during sporting events and continue to engage in the sporting activity without pain attest to this fact. Pain ratings in response to a given pain stimulus are obviously subjective in nature, and the more objective measures of pain tolerance or pain endurance are also influenced by subjective pain appraisals.

Although one might wonder what hypertension could possibly have to do with the experience of pain, there is actually a fairly consistent body of evidence demonstrating that essential hypertensive patients or persons with elevated blood pressures, in contrast to normotensive controls, have significantly greater pain tolerance and lower ratings of pain (Bruehl, Carlson, and McCubbin, 1992; Sheps et al., 1992; Zamir and Shuber, 1980). These findings have been very consistent across a range of pain-inducing stimuli, including electrical stimulation of tooth pulp (Zamir and Shuber, 1980), thermal pain (Sheps et al., 1992), and finger pressure pain (Bruehl et al., 1992). Comparable associations have also been observed between pain perception and ambulatory measures of blood pressure (Guasti et al., 1995; 1999).

Although most of the studies examining the relation between perception of pain and blood pressure status have used case–control methods, a recent study (Campbell et al., 2002) used a prospective design to determine whether ratings of pain tolerance predicted blood pressure at a later time. In this study, young males were exposed to a painful finger pressure stimulus and contacted five years later to obtain measures of blood pressure. Pain tolerance ratings significantly pre-

dicted blood pressure status five years later, even after controlling for parental history of blood pressure, initial blood pressure, and body mass index. Although no other longitudinal studies testing this relation have yet been reported, the evidence linking perception of pain and increased blood pressure is quite strong.

As mentioned in Chapter 4, findings examining the specific pathophysiology of perception of pain have shown that the observed differences in pain thresholds between hypertensive and normotensive patients are at least partially regulated by baroreceptor function (Elbert et al., 1988; 1994). In addition, this body of literature has provided support for Dworkin's (1991) hypothesis that elevated blood pressures are learned via reinforcement associated with decreased pain sensitivity stemming from baroreceptor stimulation.

Summary of Cognitive Measures as Mediators of the Stress–Hypertension Relation

Given findings from studies examining hypertensive patients' cognitive appraisals of emotion-laden information and painful stimuli, it could be hypothesized that hypertension is associated with an overall tendency to minimize sensitivity to a broad range of environmental stimuli. Nyklíček et al. (2001) tested this hypothesis by exposing a group of hypertensive patients and normotensive controls to a painful electric current stimulus as well as a variety of stressful laboratory tasks. Findings revealed that hypertensive women, in contrast to normotensive women, exhibited diminished pain sensitivity to the electric current in addition to lower pre-task ratings of state anxiety and less negative appraisal associated with watching a stressful film segment. Pain sensitivity measures were positively correlated with ratings of negative task appraisals, providing some support for this hypothesis. However, these findings were observed only among women, and only with appraisal ratings of the passive film task.

As stated above, there is comparatively less research on the acute cognitive responses of essential hypertensive patients. As with the affective and behavioral responses that have hypothesized roles in the stress–hypertension relation, there is very little prospective evidence supporting the role of acute cognitive responses in predicting onset of

essential hypertension. Without solid prospective empirical support, the evidence suggesting that hypertensives perceive their stressful environments differently from normotensives could easily be interpreted as a consequence of hypertension rather than an etiologic factor. In this regard, patients with essential hypertension may adopt repressive–defensive cognitive styles to avoid acknowledging the fact that they are indeed confronting stressful stimuli at all. Although this 'head in the sand' approach to dealing with stress appears maladaptive, it may serve the function of preventing exaggerated acute physiological reactions known to exacerbate their hypertensive condition. The only prospective study linking an acute cognitive response to onset of hypertension involved a single short-term study on pain perception and subsequent blood pressure status (Campbell et al., 2002). Although the findings support the hypothesis that diminished perception of pain precedes onset of hypertension, more work is needed to determine how pain perception might be etiologically involved in explaining the stress–hypertension relation.

The Acute Physiological Stress Response

Acute psychophysiologic reactivity to stress has long been hypothesized as a mechanism involved in explaining the stress–hypertension connection (see Krantz and Manuck, 1984). In brief, psychophysiologic reactivity refers to the magnitude of change observed in a given psychophysiologic parameter (for example, heart rate, blood pressure, or serum norepinephrine) in response to a standardized stressor. Typically, this response magnitude, or reactivity, reflects a measurable change in physiologic functioning that cannot be predicted by knowing one's resting levels of that same parameter. As an example, the magnitude of a blood pressure response to completing a serial subtraction task is generally independent of one's resting levels of blood pressure. Acute psychophysiologic reactivity generally involves calculating the difference between measures of a given parameter during a stress presentation and an associated rest period, often referred to as a baseline. Although measurement of the physiologic parameter during stressor presentations is fairly straightforward, establishing an adequate base-

line is often more difficult (Turner, 1994). If one chooses to use a pre-task rest period as a baseline, anticipatory arousal may influence the determination of an accurate baseline assessment. If one chooses to use post-task rest periods as a baseline, residual effects of the stressor may still be observed. It is known, for example, that for some stressors (physical exercise or the cold pressor task) lengthy recovery periods are required to obtain basal psychophysiologic measures following task presentations. For this reason, Turner (1994) recommends obtaining baseline measures on another day when the participant is not exposed to any stress at all. Perhaps the best measure of 'true' baseline functioning, although impractical, would be to obtain measures from the middle of the night, when a person's physiologic state presumably reaches an actual baseline level.

Regarding cardiovascular disease and essential hypertension, research has focused on heart rate and blood pressure reactions to stress as playing a potential role in the stress–hypertension relation. Although the reason to focus on cardiovascular parameters may appear obvious, research in this area was based soundly on the work of Malmo, Shagass, and Davis (1950), who first proposed the principle of 'symptom specificity,' the notion that stress responses associated with a specific organ system were most likely to be involved in the expression of specific diseases of that system. Early support for this perspective was derived from studies like that of Moos and Engel (1962) who contrasted physiological response profiles of essential hypertensive patients with rheumatoid arthritic patients. Consistent with the symptom specificity hypothesis, hypertensive patients responded to stress with increased blood pressure responses while arthritic patients responded to stress with increased muscle activity in symptomatic joints. Based upon decades of laboratory investigations of cardiovascular reactivity to a number of different stressors, the 'reactivity hypothesis' was constructed around three premises: (a) patterns of cardiovascular reactivity were stable across time; (b) patterns of cardiovascular reactivity were stable across situations, including those within and external to laboratory settings, and (c) persons with exaggerated cardiovascular reactivity were at greater risk for cardiovascular disease and essential hypertension later in life (Manuck et al., 1989).

Stability of Measures of Cardiovascular Reactivity to Stress

Although there has been some disagreement regarding the stability of measures of cardiovascular reactivity across task and time (see Pickering and Gerin, 1990), a significant amount of empirical work has attested to the moderate stability of these individual difference variables (see Manuck, 1994). This is particularly evident among studies that have aggregated measures of cardiovascular response across multiple stressors (Davig, Larkin, and Goodie, 2000; Kamarck, Debski, and Manuck, 2000). In general, high reactors to mental stressors tend to maintain their heightened reactivity to those same stressors if delivered again in the future or to different stressors administered at a later time or place, although short-term stability is better documented than long-term stability (Kamarck and Lovallo, 2003).

The demonstration of generalization of cardiovascular reactions to stress from the laboratory to real-life settings is of particular importance to the reactivity hypothesis. In this regard, if measurement of laboratory task-elicited cardiovascular reactivity had no correspondence to reactions observed to naturally occurring stressors, it would be difficult to imagine how exaggerated responses only to standardized laboratory stressors, which happen rarely if at all in one's life, would lead to the development of essential hypertension. In this regard, it is important to document that measures of cardiovascular response to laboratory stimuli are related, to some extent, to the reactions individuals typically exhibit in response to daily life stressors. Some investigators have attempted to demonstrate the association between laboratory and real-life stressors by contrasting laboratory-determined measures of cardiovascular response to mental tasks with the variability of blood pressures observed during ambulatory monitoring of regular daily living (Floras et al., 1987; Melville and Raftery, 1981), while others have contrasted the laboratory-based reactivity measures with measurements of cardiovascular reactivity to discrete environmental stressors like a public speech, performance, or thesis or dissertation defense meeting (Abel and Larkin, 1991; Davig, Larkin, and Goodie, 2000; Matthews, Manuck, and Saab, 1986). According to the most recent review of this body of literature by Kamarck and Lovallo (2003), findings from both types of studies have been inconsistent, with only about 20

to 25 percent of the reported associations being significant in the hypothesized direction. However, rather than concluding that very little association exists between laboratory task-elicited cardiovascular reactivity and reactions to real-life stressful encounters, Kamarck and Lovallo suggest that the typical less-than-optimal findings reported among these studies might reflect underlying methodological limitations. In particular, because so many extraneous factors (like activity level, posture, substance use, or level of task demand and control) influence cardiovascular reactions to daily life stressors, it is difficult to disentangle the effects of these extraneous factors from the 'raw' measure of cardiovascular reactivity to stress. For example, for a student who has earned the grade of 'A' on every assignment so far in the semester, giving a speech worth ten points may have a different meaning than for a student who has performed poorly, is barely passing the class, and is in desperate need of points. On the surface, giving a speech appears to be a standard real-life stressor; however, if one considered the motivational factors that might be operating, the situation suddenly appears much less standardized. Kamarck and Lovallo suggest that studies examining the relation between laboratory-based and real-life measures of cardiovascular response to stress employ better assessments of these extraneous parameters that occur during daily life as well as collect data across multiple real-life stressors. To support their position, they cite work by Kamarck, Debski, and Manuck (2000) that confirmed that correlations between laboratory and naturally occurring stressors were significantly improved when multiple tasks were used in both the laboratory and real-life settings. Additionally, the degree of correspondence between laboratory and real-life measures of cardiovascular reactivity has been shown to improve when factors of daily living (activity level, posture, substance use) are controlled during data analysis (Kamarck, Schwartz, et al., 2003). Therefore, if extraneous factors that affect cardiovascular functioning are controlled and responses are obtained across multiple stressors during ambulatory measurement periods, generalization from laboratory to life is more easily demonstrated.

These findings are important in establishing the role of acute cardiovascular reactivity to stress in the stress–hypertension relation. If cardiovascular reactivity to stress lacked stability and the magnitude of

reactions was entirely situationally determined, it would be very difficult to examine the third premise, that exaggerated cardiovascular reactions are associated with increased risk for essential hypertension. For a thorough review of evidence regarding stability of cardiovascular response to stress, see Kamarck and Lovallo (2003).

Exaggerated Cardiovascular Reactivity to Stress and Hypertension

Krantz and Manuck (1984) conducted an initial review of studies examining the relation between acute psychophysiologic response to stress and risk for both cardiovascular disease and essential hypertension. From the evidence available to them at that time, they concluded that 'promising' relations were observed regarding the role of exaggerated cardiovascular responses to stress for both medical conditions. In particular, borderline essential hypertension was shown to be associated with increased behaviorally elicited cardiovascular reactions. Etiologically this was an important finding, in that borderline essential hypertension is often considered a pre-hypertensive state. Regarding the examination of the role of cardiovascular reactivity to stress in the stress–hypertension relation, several types of studies lend support, including animal research, retrospective studies contrasting patients with essential hypertension to normal blood pressure controls, and prospective studies of persons categorized as being either high- or low-reactors to stress.

Animal Studies

There is evidence linking cardiovascular reactivity to stress to hypertension from research conducted on spontaneously hypertensive rats (Hallbäck and Folkow, 1974). In contrast to control rats with normal blood pressures, SHRs exhibit greater heart rate, blood pressure, and catecholamine reactions to laboratory stressors. Interestingly, their exaggerated cardiovascular response profiles appear prior to the onset of hypertension, lending credence to the hypothesis that exaggerated cardiovascular reactivity may be etiologically involved in essential hypertension. Additionally, when these hyper-reactive SHRs are socially isolated to prevent exposure to daily stress, their blood pressures remain

normal (Hallbäck, 1975). Casto and Printz (1990) replicated these findings by demonstrating that SHRs exhibited exaggerated cardiovascular and motor responses to an air puff startle stimulus in contrast to normal WKY control animals. Among the WKY controls, the reduced cardiovascular reactions were shown to be related to parasympathetic activation rather than reduced sympathetic arousal. From these findings, it was concluded that the exaggerated cardiovascular reactions to the novel stimuli that were observed among the SHRs were associated with 'a parasympathetic insufficiency' rather than an overactive sympathetic nervous system.

Research examining cardiovascular response to stress in the development of hypertension has also been conducted using borderline hypertensive rats (Hubbard et al., 1986; Knardahl, Sanders, and Johnson, 1989). Like their progenitors, BHRs were also shown to exhibit increased blood pressure responses to a stressful classical conditioning paradigm in contrast to WKY controls (Hubbard et al., 1986). Although comparable increases in cardiac output were observed for both groups, estimates of total peripheral resistance revealed that the observed differences in blood pressure responses were attributable to vascular factors rather than cardiac factors. Knardahl and colleagues (1989) reported increased mean arterial responses to stress among BHRs exposed to a history of stressful conflict in comparison to unstressed BHRs.

Studies using both SHR and BHR animals have provided support for an association between the magnitude of cardiovascular reactions to acute stress presentations and hypertension. Furthermore, this work indicates that the exaggerated cardiovascular responses that are observed among these animals are present prior to the onset of hypertension, suggesting that either exaggerated cardiovascular reactions are etiologically associated with hypertension or they serve as a significant physiological marker for disease onset.

Retrospective Case–Control Studies

In the initial review conducted by Krantz and Manuck (1984), several studies were cited that found that hypertensive patients exhibited significantly higher cardiovascular responses to laboratory stressors than normal blood pressure controls (Drummond, 1983; Nestel, 1969;

Schachter, 1957; Shapiro, 1961; Shapiro, Moutsos, and Krifcher, 1963). Numerous laboratory stressors have been employed in these retrospective case–control studies, including cognitive tasks, exercise tasks, the cold pressor task, and interpersonal stress manipulations. Some studies have found the nature of the stressful stimuli to be an important factor in determining whether significant differences were observed between hypertensives and normotensives. For example, both Steptoe, Melville, and Ross (1984) and Fredrikson (1992) found differences in blood pressure reactivity between hypertensive and normotensive samples during active-coping stressors (tasks involving instrumental control over task outcome), but not during passive-coping stressors (tasks in which no control over task outcome is evidenced). Fredrikson et al. (1982) found hypertensives exhibited exaggerated blood pressure responses in contrast to normotensives during sensory rejection tasks (mental processing tasks), but not in response to sensory intake tasks (tasks involving continuous attention to sensory input from the environment). Therefore, it appears important to consider the nature of the task used to elicit cardiovascular reactions in evaluating this body of literature.

In 1990, Fredrikson and Matthews conducted a meta-analysis of all retrospective case–control studies contrasting blood pressure and heart rate reactions to a variety of different types of stressors of hypertensives and normotensives. This analysis revealed significant differences in cardiovascular response parameters between both essential hypertensive and borderline essential hypertensive patients and normotensive control participants. For patients with essential hypertension, increased blood pressure responses (both SBP and DBP) were observed across the full range of stressors, including active-coping, passive-coping, and cold pressor challenges, in contrast to normotensives. The association between cardiovascular reactivity to stress and borderline essential hypertension showed a slightly different profile. Borderline essential hypertensive patients, in contrast to normotensives, were shown to exhibit exaggerated heart rate responses in addition to exaggerated SBP and DBP responses mainly to active-coping stressors. The differential cardiovascular response patterns observed between essential hypertensive and borderline essential hypertensive patients provide support for the hyperkinetic circulation hypothesized

to play a role in cases of borderline essential hypertension (Julius and Esler, 1975). No differences between borderline essential hypertensive patients and normotensives were observed in response to either passive-coping stressors or the cold pressor challenge. In a separate review, Conway (1984) reported comparable heightened cardiovascular responses to exercise tasks among essential hypertensive patients.

Suls, Marco, and Wan (1991) conducted a similar meta-analysis to examine the relation between cardiovascular reactivity to stress in essential hypertension at approximately the same time as Fredrikson and Matthews conducted their analyses. The Suls et al. analysis revealed a somewhat different picture. Essential hypertensive patients, in contrast to normotensives, exhibited an exaggerated SBP response, but not DBP response, to active-coping stressors, primarily mental arithmetic. Additionally, young borderline essential hypertensive patients exhibited a tendency for heightened blood pressure, but not heart rate, responses to active-coping tasks in comparison to normotensives; this effect, however, was not observed among older borderline hypertensive patients. Although the pattern of findings across these two meta-analyses is somewhat different, they both indicate that cardiovascular response to stress is associated with essential hypertension. In particular, differences between hypertensive and normotensive patients were most likely to emerge when active-coping tasks were employed as mental stress stimuli.

On the basis of these meta-analyses, it has been generally agreed that hypertensives exhibit greater blood pressure responses to mental stress than normotensives, although the nature of this response is partly dependent upon the specific task chosen. Since the early 1990s, additional studies contrasting hypertensive and normotensive persons have continued to explore physiological factors that might help explain this commonly observed relation. For example, many researchers have examined whether the exaggerated cardiovascular responses of hypertensive patients are related to elevated sympathetic nervous system activity or reduced influence of parasympathetic tone (de Champlain et al., 1991; Fahrenberg and Foerster, 1996; Grossman, Brinkman, and De Vries, 1992; Sherwood, Hinderliter, and Light, 1995). The results of these studies, however, have been inconsistent. While some investigations have found that the exaggerated blood pressure reactions

to stress seen in hypertensive patients were associated with enhanced alpha-adrenergic sympathetic nervous system activity (de Champlain et al., 1991), others have found these reactions to be associated with enhanced beta-adrenergic sympathetic nervous system activity (Fahrenberg and Foerster, 1996; Sherwood et al., 1995), and still others have found no association with sympathetic nervous system activity but associations with reduced parasympathetic activity (Grossman et al., 1992). Studies examining whether the commonly observed heightened cardiovascular reactions to stress in hypertensives are associated with increased plasma levels of norepinephrine or epinephrine have also yielded inconsistent findings (see Pickering and Gerin, 1990). Rather than throwing up one's hands in dismay regarding the inconsistency of these more recent reports, it is probably best to conclude that there are multiple autonomic nervous system pathways involved in blood pressure dysregulation, exaggerated blood pressure responses, and the onset of essential hypertension.

Prospective Studies

Prospective studies provide the best evidence linking potential factors to the resulting disease state. If exaggerated cardiovascular reactivity to stress observed in early adulthood before the onset of essential hypertension was associated with later onset of the condition, considerable support for cardiovascular reactivity to stress as playing a significant role in the stress–hypertension relation would be provided. At the time when Krantz and Manuck (1984) first reviewed the body of evidence linking cardiovascular reactivity to stress to essential hypertension, prospective evidence was entirely lacking. Among the prospective studies that were available at that time (Armstrong and Rafferty, 1950; Barnett et al., 1963; Eich and Jacobsen, 1967; Harlan, Osborne, and Graybiel, 1964; Thomas and Duszynski, 1982), sample sizes were limited and the follow-up periods not long enough to capture an accurate representation of who eventually would be diagnosed with essential hypertension. Furthermore, all of these early prospective studies employed the cold pressor test as a means for categorizing persons into hyper-reactive and normal reactive groups, and consistent evidence associating cardiovascular reactions to the cold pressor test and essential hypertension was lacking (Suls, Marco, and Wan, 1991). Interestingly,

although Pickering and Gerin (1990) concluded from their review of the literature that there was insufficient evidence prospectively linking cardiovascular reactivity to the cold pressor test with hypertension, they cited six prospective studies examining blood pressure response to physical exercise and found that among all of these studies, blood pressure reactivity to physical exercise was a significant predictor of subsequent hypertension. Therefore, the prospective evidence that existed was not based upon studies that employed the typical mental stress tasks used in current research.

Not all prospective studies using the cold pressor stimuli yielded negative findings. Wood et al. (1984) conducted a follow-up study on study participants who were exposed to a cold pressor stress presentation in 1934 and categorized as high and low blood pressure reactors. Hyper-reactors had a fivefold higher risk of developing essential hypertension over the 45-year follow-up period than their low-reactive counterparts. In fact, 71 percent of persons initially categorized as hyper-reactors exhibited essential hypertension at the 45-year follow-up visit compared to only 19 percent of persons categorized as normal blood pressure reactors.

A few years later, Menkes et al. (1989) examined the association between SBP responses to the cold pressor test and subsequent diagnoses of essential hypertension using follow-up data from the sample of medical students initially evaluated and reported by Thomas and Duszynski (1982). During this extended follow-up time interval (20–36 years), in contrast to their previous report, significant associations were observed between initial SBP response to the cold pressor and diagnosis of hypertension, even after controlling for standard known risk factors. Only 2.4 percent of the low SBP reactors developed essential hypertension in contrast to 6.7 percent of the high SBP reactors. These findings lent credence to the notion that associations between cardiovascular reactivity to stress and subsequent diagnoses of hypertension could be observed if follow-up periods were long enough to permit study participants to reach the ages of 45 to 50 where diagnoses of essential hypertension are most likely to be made.

A third prospective study examined the relation between cardiovascular response to a cold pressor task and onset of hypertension over a 28-year period (Kasagi, Akahoshi, and Shimaoka, 1995). Like the pre-

vious two studies, it found SBP response to the cold pressor task to be a significant predictor of essential hypertension, even after controlling for resting blood pressure and body mass index.

Due to the inconsistencies associated with early findings from prospective studies using the cold pressor task and the questionable generalizability of the cold pressor task to typical daily stressors, more recent investigations have conducted prospective studies examining the linkage between cardiovascular reactivity and essential hypertension using cognitive or mentally challenging tasks (Borghi et al., 1986; Falkner et al., 1981; Light, Dolan, et al., 1992; Matthews, Woodall, and Allen, 1993). Unlike studies using the cold pressor task, either these studies have employed samples of persons already diagnosed with borderline essential hypertension (Borghi et al., 1986; Falkner et al., 1981) or follow-up periods have been insufficient to capture all cases of hypertension onset (Light, Dolan, et al., 1992; Matthews et al., 1993). Borghi et al. reported that high DBP reactivity to a mental arithmetic task among a sample of borderline essential hypertensive patients predicted the transition to a diagnosis of sustained essential hypertension five years later. Falkner et al. confirmed these findings using a sample of borderline essential hypertensive children exposed to mental stress and followed for approximately a 17-month period. Using a 10–15 year follow-up period, Light et al. showed that higher blood pressure and heart rate reactions to an initial shock-avoidance reaction time task were associated with increased casual blood pressure measures as well as ambulatory measures of blood pressure during work and leisure activities. Matthews et al. confirmed the association between blood pressure reactivity to cognitive tasks and resting DBPs measured 6.5 years later.

To derive conclusions from this somewhat mixed body of literature, Treiber et al. (2003) recently conducted a thorough review of 25 prospective studies examining cardiovascular reactivity to stress and subsequent onset of essential hypertension or future blood pressure status. Additionally, they examined studies providing prospective evidence linking cardiovascular reactivity to stress and left ventricular functioning as well as carotid atherosclerosis. Although a wide range of mental stressors were employed in the studies reviewed, they concluded that cardiovascular reactivity to mental stress was consistently

associated with the onset of essential hypertension as long as the duration of follow-up was of adequate length (≥ 20 years) to detect new cases of hypertension. Studies using shorter follow-up periods consistently documented that cardiovascular reactivity to stress was associated with increases in resting blood pressure, even though the magnitude of these blood pressure increases was insufficient to warrant diagnoses of essential hypertension. Although a smaller number of studies have examined the prospective association between cardiovascular reactivity to stress and changes in left ventricle mass and carotid atherosclerosis, the findings reported are consistent with findings from studies using hypertensive status or blood pressure status as endpoints. In brief, a greater magnitude of cardiovascular reactivity to mental stress is associated with progression of left ventricle hypertrophy and carotid plaque development.

Hemodynamic Responses to Stress

Although blood pressure reactions of two individuals during a given task might be identical, the underlying hemodynamics may be quite different. Consider the hemodynamic responses of two individuals during delivery of a speech depicted in Figure 5.1. Although mean arterial blood pressure responses are equivalent, Person A's blood pressure response was driven by an increase in cardiac output, which occurred as a result of increased heart rate and an inadequate stroke volume compensation. In contrast, cardiac factors were presumably not responsible for Person B's blood pressure response; Person B's response was primarily determined by increases in total peripheral resistance (vasoconstriction).

Interestingly, different laboratory tasks have been shown to elicit different hemodynamic responses (Hurwitz et al., 1993). For example, the speech task, used in this example, typically elicits the cardiac output response seen in Person A; in this regard, Person B's hemodynamic response is atypical. For other laboratory tasks, like the cold pressor challenge, the vascular response seen for Person B represents the typical response. Eliot, Buell, and Dembroski (1982) hypothesized that the vascular response (like Person B), particularly during a task that typically elicited cardiac responses, was more likely to be associated with

Figure 5.1. Hemodynamic responses from impedance cardiography during speech delivery for two individuals. Note: MAP = mean arterial pressure; HR = heart rate; SV = stroke volume; CI = cardiac index (cardiac output/body surface area); TPRI = total peripheral resistance index (total peripheral resistance/body surface area).

increased risk for onset of essential hypertension and cardiovascular disease than the cardiac response profile.

Although early speculation suggested that vascular-mediated blood pressure responses represented 'hot reactor' profiles associated with increased risk for essential hypertension and other forms of cardiovascular disease, subsequent research did not bear this out. For example, because borderline essential hypertension had been shown to consist of a hemodynamic profile (elevated blood pressures maintained by increased cardiac output) that differed from elevated blood pressures via increased total peripheral resistance in sustained essential hypertension, several investigators examined hemodynamic response to stress among samples of borderline or mild hypertensive patients (Nawarycz, Ostrowska-Nawarycz, and Kaczmarek, 1999; Safer et al., 1975; Schulte et al., 1986). A consistent finding across all of these studies was that blood pressure reactions of borderline essential hypertensive patients were driven by increases in cardiac output, not peripheral resistance. In contrast, studies of obese hypertensive patients have showed the opposite profile; that is, increased blood pressure reactions were associated with increased peripheral resistance responses (Rock-

stroh et al., 1992; Sung et al., 1997). Therefore, elevated blood pressures of borderline essential hypertensive patients and obese hypertensive patients appear to be associated with distinct hemodynamic response profiles to stress.

In addition to findings from case–control studies, a recent study examining the prospective relation between cardiovascular response and future blood pressure status also examined hemodynamic factors in an effort to determine whether cardiac or vascular responses to stress were associated with the commonly observed blood pressure reactivity–hypertension relation (Matthews et al., 2003). Using the cold pressor task, the researchers measured blood pressure and hemodynamic reactivities in a sample of children who were followed for three years. As in previous prospective studies, results revealed that blood pressure reactivity to the cold pressor task predicted both SBP and DBP levels at the three-year follow-up visit. Cardiac output response to the cold pressor task predicted SBP at follow-up, but total peripheral resistance response to the cold pressor task failed to predict either SBP or DBP at follow-up. Consistent with the work of Julius and Esler (1975), these findings supported the role of an overactive cardiac response in predicting subsequent elevations in SBP in children. Since this study examined hemodynamic responses prospectively only among children, it remains for future studies to examine whether peripheral vascular responses to stress play a greater role with adult and older adult samples.

Although other components of the acute stress response have demonstrated stability over time, hemodynamic response profiles have been shown to shift in response to prolonged exposure to stress. For example, in a study of hemodynamic response to stress in monkeys, Forsyth (1971) showed fairly stable blood pressure elevations over three days of exposure to a shock avoidance procedure. Despite the stability of the blood pressure reactions, the hemodynamic profile shifted from a primarily cardiac output-driven blood pressure response early in the stress period to a response driven by peripheral vascular factors as time went on. These shifting hemodynamics have also been observed in healthy normotensives during relatively short-duration (30 min) stress presentations in the laboratory (Carroll, Cross, and Harris, 1990; Ring, Burns, and Carroll, 2002). Therefore, the shifting of resting hemodynamics that occurs as borderline hypertensive patients progress to sus-

tained hypertensive patients can also be observed during relatively brief encounters with stress in the laboratory. These findings suggest that some compensatory mechanism (autoregulation) occurs in response to the exaggerated cardiac output responses that drive early increases in blood pressure.

It should also be noted that hemodynamic responses are associated with two components, the increased physiological response and the failed compensatory response. For example, as cardiac output responses increase, blood vessels are supposed to dilate, leading to a reduction in peripheral resistance and maintenance of a relatively stable blood pressure reaction. If, in the case of borderline essential hypertension, an elevated cardiac output response to stress is observed, one cannot infer that the underlying abnormality is entirely cardiogenic in nature. The failure of the compensatory vasodilatory response could be equally responsible for driving the exaggerated blood pressure response to the stressor. Therefore, a comprehensive understanding of risk for developing essential hypertension based upon analysis of hemodynamic profiling of stress responses requires measuring the magnitude of both the initial hemodynamic response and the associated compensatory response.

Cardiovascular Recovery from Mental Stress

Recall the types of allostatic load outlined in Figure 3.1 (McEwen, 1998), which indicate there are physiological patterns other than exaggerated reactivity that contribute to onset of chronic stress disorders like essential hypertension. In this regard, several investigators have examined cardiovascular recovery from stress rather than cardiovascular reactivity during stress as a potential etiologic mechanism (see Schwartz et al., 2003). If one follows this line of reasoning, essential hypertension may be associated not only with exaggerated heart rate and blood pressure reactions, but also with a failure to show a steady cardiovascular recovery after the task period is over. Supporting this hypothesis, Rutledge, Linden, and Paul (2000) demonstrated that measures of both cardiovascular reactivity *and* recovery predicted blood pressure levels during an ambulatory recording period, and that cardiovascular recovery was actually a better predictor of blood pressure

status than cardiovascular reactivity. In contrast, Seibt, Boucsein, and Scheuch (1998) found no differences in cardiovascular reactivity to mental stress between hypertensive and normotensive participants, but did find delayed blood pressure recovery from stressors among hypertensives. In a meta-analysis of seven studies contrasting hypertensive and normotensive patients on measures of cardiovascular recovery from stress, Schuler and O'Brien (1997) concluded that normotensives exhibited faster DBP recovery from stress than hypertensives. In contrast to the large number of prospective studies examining cardiovascular reactivity to mental stress and subsequent onset of essential hypertension, only a few studies have examined the relation between cardiovascular recovery from stress and onset of hypertension prospectively (Borghi et al., 1986; Stewart and France, 2001; Treiber et al., 2001), and their duration of follow-up interval has been inadequate to test whether such a linkage can be supported.

Environmental Stressors and Cardiovascular Reactivity

Evidence linking stress to essential hypertension presented in Chapter 4 consisted of studies relating high blood pressure to major life events, work stress and strain, and cultural stressors like acculturation or lifestyle incongruity. Direct evidence relating stressful living conditions to onset of elevated blood pressures was also presented using experimental animal work on rats and mice genetically predisposed to develop hypertension. Given the working model illustrated in Figure 4.1, associations between these types of stressors and acute cardiovascular responses to stress would be expected in addition to the established association between stress and hypertension. Let's examine what is known about the relation between cardiovascular reactivity to stress and these types of stressors known to be associated with increased risk for essential hypertension.

Daily Stress and Cardiovascular Reactivity

From the body of evidence showing that rats genetically predisposed to developing hypertension also exhibit exaggerated cardiovascular responses to acute stress presentations (Casto and Printz, 1990; Hallbäck and Folkow, 1974; Hubbard et al., 1986), it could be hypothesized that

persons who have experienced major life events, persons migrating from an undeveloped country to an industrialized country, or persons in high-strain jobs exhibit exaggerated cardiovascular responses to stress. Although the literature examining this hypothesis is not extensive, there is some support for it. For example, Light et al. (1999) compared resting blood pressures of high- and low-reactive men determined during a laboratory session ten years earlier. Although high-reactive men with hypertensive parents exhibited significantly higher resting blood pressures during the ten-year follow-up assessment, this effect was accentuated by exposure to daily stressors. The highest blood pressures at follow-up were observed among high-reactive men with a family history of hypertension who also reported the greatest amounts of stress in their lives. According to this study, exposure to frequent life stressors and an exaggerated cardiovascular response to those stress exposures interacted to increase risk for essential hypertension.

Bongard et al. (2002) reported that acculturated Turkish students in Germany exhibited heightened cardiovascular responses to a mental arithmetic stressor as compared with native Germans. Based upon measures of pre-ejection period, a purported noninvasive measure of beta-adrenergic sympathetic nervous system activity, they concluded that these enhanced cardiovascular reactions were driven by beta-adrenergic activation. Although this study supports the relation between exposure to an environmental stressor (acculturation) and cardiovascular response to stress, clearly additional empirical work is needed in order to make a convincing argument.

Job Strain and Cardiovascular Reactivity

Steptoe and colleagues (1995; 1999; 2000) conducted a series of studies examining the relation between job strain and acute cardiovascular responses to mental stress. In the first study (Steptoe et al., 1995), ambulatory measures of blood pressure of male firefighters with high and low job strain were obtained for both high– and low–SBP reactive men. Ambulatory measures of SBP were elevated only among high–SBP reactive firefighters with high-strain jobs, indicating that acute blood pressure reactivity to stress and job strain interacted to influence resting blood pressures and presumably future risk for essential hypertension.

In a second study (Steptoe, Cropley, and Joekes, 1999), school-

teachers categorized as having high- and low-strain jobs were exposed to two different tasks, one that was self-paced and under the control of the participant and the other in which pacing was externally controlled. Although no differences in resting blood pressures were observed between high and low job strain teachers during the day, the teachers with high job strain exhibited significantly greater blood pressure reactions to the uncontrollable task than did those with low job strain. No differences in reactivity between the two groups were observed for measures of reactivity to the controllable task, indicating that the nature of the task used to elicit cardiovascular reactivity is important to consider when evaluating these findings. Interestingly, during the evening, as teachers relaxed after work, reductions in ambulatory blood pressure were observed among those with low job strain, but not those with high job strain. Presumably, then, high job strain teachers, who are exposed to work demands in which outcomes are not under their control on a daily basis, are more sensitive to uncontrollable tasks presented in the laboratory and less likely to exhibit blood pressure decelerations during nonwork hours than individuals in low-strain jobs.

Finally, in a prospective study, Steptoe and Cropley (2000) compared ambulatory blood pressures of high– and low–SBP reactive school-teachers who were in either high- or low-demand jobs. Although there was no relation between SBP reactivity to mental stress and ambulatory blood pressures measured a year later among teachers in low-demand jobs, the predictive relation between SBP reactivity and ambulatory blood pressure during the workday was significant for teachers in high-demand jobs. Although not all studies examining the relation between work strain and acute cardiovascular reactions to stress have corroborated the findings from Steptoe's laboratory (Blumenthal et al., 1995; Siegrist and Klein, 1990), there is sufficient evidence to support a relation between job strain and increases in cardiovascular response to stress, as long as the laboratory tasks selected for purposes of measuring reactivity tap into important domains (uncontrollability) that pertain to the construct of job strain.

Summary

Gump and Matthews (1999) reviewed 19 studies that have examined the relation between cardiovascular reactivity to stress and the extent of

daily stress experienced in one's life, a phenomenon they termed 'background stress.' Although their review reported that many studies found a direct relation between background stress and magnitude of cardiovascular response to mental stress, there were also a handful of studies that found the opposite relation (more background stress was related to lesser cardiovascular response to mental stress). In this case, participants with high levels of background stress were thought to approach novel stress tasks delivered in the laboratory with fatigue (the defeat reaction) rather than the hypothesized increased vigilance for associated cues of threat in the environment (the defense reaction; Matthews, Gump, and Owens, 2001). It is quite clear that the chronicity of the background stress may influence the direction of the relation with acute cardiovascular reactions to stress and that greater efforts should be made to carefully assess the nature of the background stress in studies examining behaviorally evoked cardiovascular reactions.

In summary, the types of environmental stressors that have been shown to be associated with increased incidence of essential hypertension seem to have been associated with increased cardiovascular responses to stress. It appears that exposure to stressful life events, job stress, and culturally related stress all appear to be associated with increased risk for essential hypertension as well as increased cardiovascular reactions to stressful stimuli. However, there are some instances where the opposite relation is observed, such as under conditions of extreme chronic stress.

Models of the Acute Stress Response

Among all the potential acute stress response variables examined in this chapter, cardiovascular response to stress emerges as the variable that has received the strongest support for linking stress and essential hypertension. Furthermore, it is the only factor reviewed in this chapter that possesses prospective evidence connecting it to both increased incidence of hypertension among middle-aged adults and increases in blood pressure among young adults. This is not to state that the findings pertaining to differences in certain cognitive (repressive cognitive response style) and behavioral responses to stress (inappropriate assertive skills) that have been observed between hypertensive and nor-

motensive patients do not play an important role; rather the evidence linking these other variables to hypertension is currently much weaker, and prospective support for such hypotheses lacking.

Conceptually, cardiovascular response to stress, in contrast to the other types of acute stress response, possesses a plausible mechanism for how it might result in physiological damage to the heart or vasculature, setting the stage for hypertension. For example, it could be hypothesized that the frequent, rapid elevations in blood pressure that occur among persons who exhibit exaggerated cardiovascular response to stress could promote the enlargement of cardiac mass which consequently leads to greater risk for hypertension. Alternately, the increased turbulence of blood flow that occurs among hyper-reactive persons may promote shearing of the vascular wall, particularly at critical points of the circulatory system proximate to the heart (coronary arteries, aorta, and carotid arteries). Over time, due to the excessive cellular damage done through this process of shearing, the vascular walls could become less flexible, leading to elevated blood pressures. Left ventricular hypertrophy may be an additional long-term consequence of exaggerated cardiovascular reactivity, as the heart muscle enlarges to pump blood through an increasingly rigid vascular system.

Manuck, Kasprowicz, and Muldoon (1990) presented four models of how exaggerated cardiovascular responses to stress might result in essential hypertension. Available prospective data enabled them to dismiss the hypothesis that the observed cardiovascular reactions to stress among hypertensive patients were a consequence of essential hypertension. Because the exaggerated cardiovascular response to stress has been measured decades before the onset of essential hypertension in these studies, the decision to eliminate this conclusion appears to be well supported. However, Manuck et al. were not able to derive any conclusions regarding which of the four models depicted in Figure 5.2 best explains the association between cardiovascular reactivity to stress and the onset of essential hypertension.

The first model, the Risk Marker Model, hypothesized that cardiovascular reactivity to stress was not causally linked to essential hypertension at all; rather, this model suggested that cardiovascular reactivity to stress was simply a marker for some other underlying physiological disturbance that causes high blood pressure. In this re-

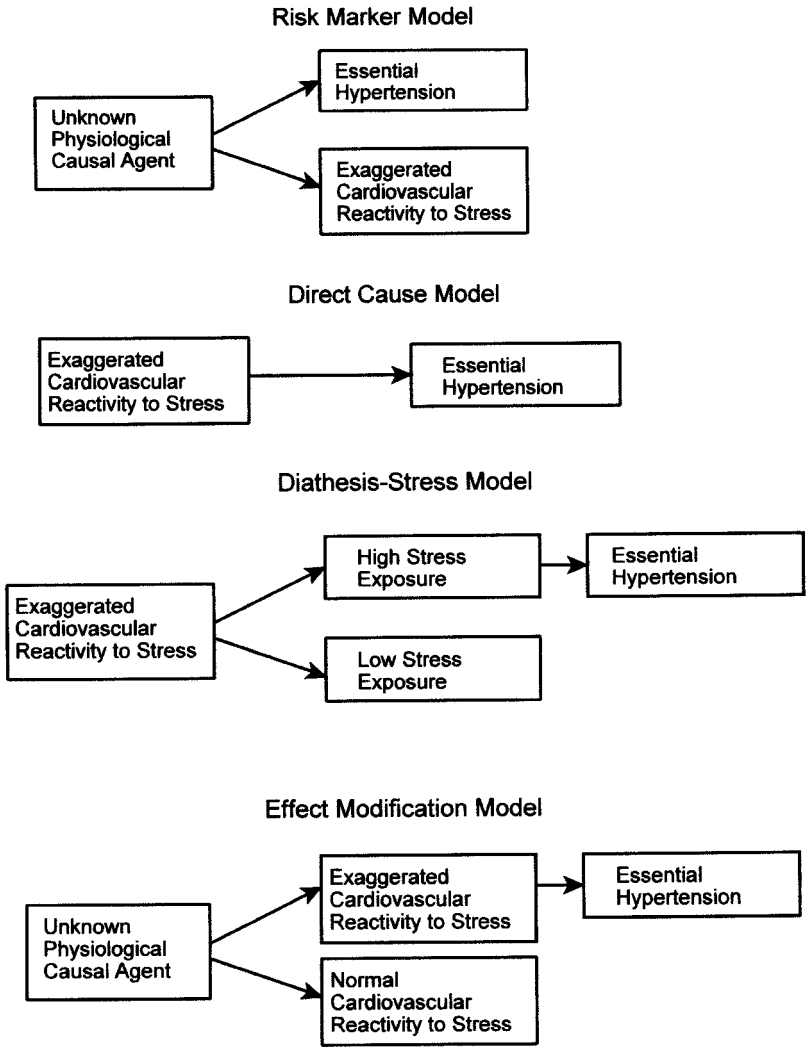

Figure 5.2. The risk marker, direct cause, diathesis–stress, and effect modification models describing the relation between cardiovascular response to stress and onset of essential hypertension. Adapted from S. B. Manuck, A. L. Kasprowicz, and M. F. Muldoon (1990), Behaviorally-evoked cardiovascular reactivity and hypertension: Conceptual issues and potential associations, *Annals of Behavioral Medicine, 12,* 17–29. Copyright © (1990), with permission from Lawrence Erlbaum Associates, Publishers.

gard, cardiovascular reactivity to stress could be a reliable and valid predictor of onset of hypertension, but have no causal role. For example, Manuck et al. suggest that an underlying causal agent, like increased vascular sensitivity to vasoconstricting substances, may predispose a person to develop essential hypertension and also result in increased cardiovascular reactivity to stress. From this perspective, the vascular sensitivity would be the causal agent and the exaggerated cardiovascular response to stress would provide a valid measure of the underlying risk factor.

The second model, the Direct Cause Model, hypothesized a direct causal linkage between exaggerated cardiovascular reactivity to stress and hypertension. According to this model, the exaggerated blood pressure responses exert considerable strain on the heart and vascular walls as hypothesized above. As these frequent, rapid bouts of cardiovascular reactivity occur over an individual's life, the ongoing cumulative strain results in permanent physiological changes to the vasculature that leads to essential hypertension as well as cardiovascular disease.

The third model, the Diathesis–Stress Model, was similar to the model proposed in Figure 4.1, even though the order of stressor and the acute stress response was reversed. According to this model, only persons exposed to some degree of environmental stress *and* who responded to it via elevated blood pressure reactions would develop essential hypertension. Although this also represented a causal model, it was causal only through its association with a stressful environment. For an individual predisposed to be a hyper-reactor, but who rarely encountered life stressors that elicited these reactions, development of hypertension would not be predicted. An extension to this model proposed by Manuck et al. (1990) included personality parameters that were hypothesized to influence hypertensive risk. Accordingly, a particular personality attribute, like anger expressiveness, operated in conjunction with stress, so that a person predisposed to being a hyper-reactor would exhibit elevated risk for hypertension only if exposed to stress and if he or she displayed a tendency to suppress feelings of anger. This feature of the Diathesis–Stress Model is also congruent with the model presented in Figure 4.1, although it is included as an individual difference variable.

Finally, the fourth model, the Effect Modification Model, hypothesized that exaggerated cardiovascular reactivity to stress in conjunction with some underlying causal variable (for example, a genetic factor) led to onset of hypertension. In this model, exaggerated reactivity to stress without the presence of the underlying causal variable would not result in essential hypertension. Like the Diathesis–Stress Model, this represents a variation of the causal model, although in this model, there are really two causal components, one proximal and one distal. Imagine, for example, that there is an underlying genotype that determines whether a person expresses exaggerated cardiovascular reactions to stress or not. Persons with the genotype become hyper-reactors; persons without the genotype exhibit normal cardiovascular responses to stress. Only those who have the genotype and become hyper-reactors proceed to develop hypertension.

Although it has been well over a decade since these models were first proposed, we still do not have the final answer regarding which model best represents the relation between the magnitude of cardiovascular responses to stress and essential hypertension. Given the available evidence to date, the Risk Marker Model cannot be ruled out; therefore, we have still much to learn regarding the causal connection between exaggerated responses to stress and essential hypertension. Although the evidence being presented here supports the model illustrated in Figure 4.1, we must be cognizant that there are other models that may prove useful as additional data become available.

Acute Stress Responses: Mediators of the Stress–Hypertension Relation?

It is clear that the relation between stress and hypertension is not a simple or direct one, and that many variables serve to mediate this relation. After reviewing the evidence pertaining to the various acute stress responses that have been shown to differentiate hypertensive from normotensive patients, it is important to consider whether the observed acute stress responses that have been identified and discussed mediate the relation between stress and hypertension. A mediating variable explains the relation between two other presumably cause-and-effect variables, typically called the predictor and the criterion

variables (Baron and Kenny, 1986). In this case, environmental stress is the predictor variable and the pathophysiological changes that result in essential hypertension is the criterion variable. In this relation, a certain amount of variance of the condition of essential hypertension can be explained or predicted by environmental stress. We certainly know that hypertension cannot be explained by stress alone (100 percent explained); many other factors need to be considered in predicting hypertension, including an individual's genetic constellation, body weight, and dietary salt consumption. We also know that the amount of variance of essential hypertension that can be explained by stress is not 0 percent. Based upon the information presented in Chapter 4, there is clearly some relation between stress and hypertension. For purposes of illustration, let's imagine that stress explains 25 percent of the variance of essential hypertension. If a variable operates as a mediator of this relation, all 25 percent of the predicted variance can be explained by the mediator variable. That is, if the variance associated with the mediator was removed, the association between stress and hypertension would disappear (it would be 0 percent). Note that in the model presented in Figure 4.1 the only linkage between the boxes labeled *Stressor* and *Physiological Change That Maintains Hypertension* occurs through the *Acute Stress Response.* There is no arrow going directly from *Stressor* to *Physiological Change That Maintains Hypertension,* suggesting that the *Acute Stress Response* is hypothesized as a mediating variable of the stress–hypertension relation in this model.

Although the acute affective, cognitive, behavioral, and physiological responses to stress were established as mediating variables in the model depicted in Figure 4.1, what evidence is there to support these variables as mediators of the stress–hypertension relation? To be honest, evidence that any of the variables reviewed actually mediates the stress–hypertension relation is very weak. Only one study among all that were cited in this chapter reported the results of analyses approximating a test for mediation (Beilin et al., 1999). Although they reported a strong association between their proposed mediating variable (lifestyle behaviors) and blood pressure status, their data did not indicate a significant relation between stress and blood pressure status; therefore, a complete test for mediation could not be conducted.

Realistically, cardiovascular reactivity to stress appears to hold the

most promise as a potential mediating variable of the stress–hypertension relation, due to both the strength of prospective evidence linking it to essential hypertension and the biological plausibility of how exaggerated cardiovascular reactions to stress might lead to tissue damage. The other acute stress response variables covered in this chapter appear to have much less promise as variables that mediate the stress–hypertension relation. Nevertheless, there is sufficient evidence demonstrating differences between hypertensive and normotensive patients among several acute cognitive (repressive–defensive cognitive style; perception of pain) and behavioral (gaze aversion, social competence, lifestyle factors) parameters that indicate that these variables have a place in the model.

Summary

Individuals respond to stress in a variety of ways, only some of which place them at risk for developing chronic health problems like essential hypertension. Although variability exists in the magnitude of acute affective responses to stress, there is very little evidence to link either state anxiety or state anger responses to stress to onset of essential hypertension. For the most part, persons who develop hypertension exhibit the same magnitude of state anxiety and state anger responses to stress as persons who live out their lives without developing hypertension. Furthermore, blood pressure increases that have been observed during episodes of anxiety or anger quickly return to normal levels when the emotion-laden period passes.

Both lifestyle behaviors and interpersonal behaviors have been identified as potential acute behavioral stress responses that differentiate hypertensive from normotensive patients. Although lifestyle factors are related to onset of hypertension, they are likely to have a more direct effect on blood pressure than as mediators of the stress–hypertension relation. Hypertensives have been shown to exhibit less socially competent behaviors, particularly in situations where they are emotionally aroused or requested to engage in interpersonal confrontation. Most noticeable among their behavioral deficits are their nonassertive behaviors and limited eye contact during social con-

frontation. Although the evidence regarding the behavioral response differences between hypertensives and normotensives is consistent across studies, there are no prospective data linking these behavioral deficits to onset of hypertension. As such, it is unclear whether they are consequences of hypertension or involved in the etiology.

Very few data have been generated regarding differences in acute cognitive responses to stress between hypertensives and normotensives. However, some data suggest that hypertensives perceive emotion-laden information differently from normotensives. In these studies, hypertensives generally fail to acknowledge the presence of emotional or threatening stimuli. Additionally, hypertensives perceive less physical pain to standardized pain stimuli as well as exhibit higher pain thresholds than normotensives. In this regard, it has been hypothesized that the repressive–defensive response style of hypertensive patients may serve to minimize the stress they encounter in their environment. This so-called 'head in the sand' approach to dealing with stress may be adaptive by preventing exposure to stress-induced elevations in blood pressure. As with the acute behavioral responses, a general lack of prospective data regarding these cognitive response differences has limited our understanding of the causal nature of this relation.

The strongest evidence for differences in the acute stress response between hypertensives and normotensives focuses on literature examining the magnitude and patterning of cardiovascular reactivity to stress. Animal, case–control, and prospective data all support an association between exaggerated cardiovascular response to stress and essential hypertension, although these relations are often influenced by the nature of the specific task chosen as the stressor and the associated hemodynamic profile of the task. Emerging evidence also supports a relation between delayed cardiovascular recovery from stress and essential hypertension, although long-term prospective studies examining this relation have yet to be conducted.

Among all acute stress response differences observed between hypertensives and normotensives, acute cardiovascular response to stress appears to be the frontrunner for a role in mediating the relation between stress and hypertension. However, it is important to recognize that we are not able to ascertain whether cardiovascular reactivity to

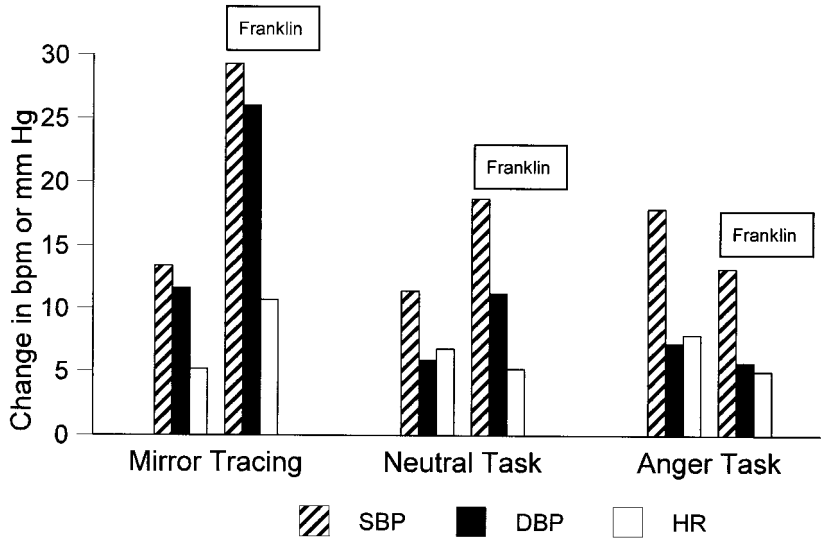

Figure 5.3. SBP, DBP, and HR reactions to the mirror-tracing challenge and both neutral and anger-eliciting role-plays. Within each panel, mean responses for entire study sample (n = 44) are depicted on the left; Franklin's data are depicted on the right. Data collection supported by the American Heart Association, West Virginia Affiliate.

stress serves as a causal factor in essential hypertension or whether it serves as a risk marker for some other underlying pathogenic variable.

Although our patient, Franklin, was convinced that stress caused his elevated blood pressure, he was willing to consider that he perhaps possessed some maladaptive stress coping skills. In order to examine his acute stress response profile more completely, Franklin agreed to complete a comprehensive evaluation of his response to stress. As part of this evaluation, he completed three laboratory tasks (mirror tracing; neutral interaction; confrontation interaction) during which measures of heart rate, blood pressure, and state measures of affect were obtained. Additionally, his behavioral responses were videotaped and coded across a number of different domains of assertive communication. Figure 5.3 shows the results of this evaluation in comparison to average cardiovascular responses of hypertensive patients exposed to the same three stimulus conditions.

In his response to the mirror-tracing challenge, Franklin's heart rate and blood pressure responses were twice that of the hypertensive comparison group, indicating that he might be categorized as exhibiting an exaggerated cardiovascular response. However, the difference between Franklin's blood pressure responses and that of the comparison group was less dramatic during the neutral interpersonal interactions, and not evident at all during the confrontational interactions. Of note, is that the order of task presentation during data collection corresponded to the order depicted in the figure; that is, mirror tracing was presented first, followed by the neutral and confrontational role-plays for all patients. Therefore, the reduction in Franklin's response in comparison to the other patients may simply represent a process of habituation. It is interesting that the degree of habituation that appeared to occur across the three measures of Franklin's task-elicited blood pressure reactivity was similar to the general habituation observed during his blood pressure measurements over three clinic visits (see Table 2.1).

In contrast to other hypertensive patients, who tended to show slightly higher reactions to the confrontational role-play scenes than the other two stressors, Franklin was least reactive to confrontation. Examination of his behavioral data provides additional evidence that the confrontation was not particularly challenging for him, as he possessed a range of anger expression skills. Although he was rated as exhibiting a passive behavioral response to one of the four confrontation scenes, Franklin's responses to the other three scenes were rated from assertive to moderately aggressive. If anything, Franklin was a bit more exuberant in expressing his anger than other hypertensives in this sample. Interestingly, analysis of eye contact duration revealed that while Franklin easily verbalized his anger openly, he exhibited difficulties maintaining eye contact during confrontation. In comparison to an average 37.9 sec of direct eye contact during the confrontational exchange among the other hypertensive patients, Franklin maintained an average response of only 15 sec. This deficit is even more remarkable when contrasted with the average 66.4 sec of direct eye contact among a group of normal blood pressure controls. Therefore, although not accompanied by substantial blood pressure increases during confrontation, the gaze-averting behaviors noted by Baer and colleagues (1980;

1983) were characteristic of Franklin's acute behavioral response profile. Because no prospective data have linked gaze aversion with increased risk for hypertension, however, it is premature to conclude that this nonverbal behavioral response to confrontation is involved in the etiology of Franklin's high blood pressure.

6

Individual Differences and Essential Hypertension

Constitutional and Lifestyle Factors

From evidence presented in Chapter 5, it appears that the intensity, duration, or patterning of the acute physiological response to stress is the most likely candidate for mediating the stress–hypertension relation. Certainly, among all other aspects of the acute stress response, physiological reactions are the most plausible mediators. If acute cognitive, behavioral, or affective responses were shown to mediate the stress–hypertension relation, we would still be left with quite a challenge of establishing how a specific thought, behavior, or emotion could possibly lead to vascular hypertrophy or baroreceptor insensitivity associated with the condition of prolonged essential hypertension. At least, with regard to acute physiological stress responses, plausible explanations exist regarding how hyper-responsive circulatory systems evolve into chronic problems in blood pressure regulation. For example, the description of the hyperkinetic borderline hypertensive patients established by Julius and Esler (1975) and the evolution of problems in blood pressure regulation from cardiac-mediation to subsequent vascular involvement (Laragh, 1983; Lund-Johansen, 1991) are both consistent with a focus on the sympathetic nervous system in the

etiology of hypertension, at least for a subgroup of hypertensive patients.

Although acute physiological responses to stress are likely candidates for mediating the stress–hypertension link, it is obvious that individual differences in physiological responses to stress exist and need to be considered in any model of hypertension. For example, exposure to stressful life events, jobs, or cultures leads to acute elevations in blood pressure among some individuals, whereas other individuals exposed to identical stressful life events, jobs, or cultures maintain normal blood pressure responses. A wide array of individual difference variables has been examined that have been hypothesized to influence the magnitude and pattern of physiological stress responding, including constitutional parameters (like gender or ethnicity) and psychosocial characteristics (like coping skills, personality, and social support). These variables cannot technically be considered candidates for mediating the stress–hypertension relation in the model presented in Figure 4.1, because they are not elicited by stress; rather, they represent independent factors that are present regardless of whether an individual is exposed to stressful stimuli or not. For example, stress does not lead to altered constitutional characteristics like a change in gender or ethnicity. Likewise, personality and related trait-like phenomena are not typically influenced by the sudden onset of an environmental stressor. Nevertheless, these variables have been hypothesized to play a role in the etiology of essential hypertension, perhaps through their association with the acute response to environmental stress.

This chapter will examine evidence for potential individual difference variables pertaining to constitutional and lifestyle factors that influence both the stress–hypertension relation and the stress–cardiovascular reactivity relation. These individual difference parameters may also predict risk for hypertension independently. However, in order for them to be considered individual difference factors associated with the stress–hypertension relation and facilitate our understanding of how stress might lead to hypertension, they must also interact with exposure to stress to influence the magnitude and patterning of the acute cardiovascular stress response. For example, it is well known that obesity is an individual difference variable that is directly associated with increased risk for essential hypertension. The increased risk for

hypertension associated with obesity is evident regardless of the stressfulness of one's life. In this respect, obesity represents a direct influence upon risk for hypertension. If obese individuals with high levels of stress exhibited a greater incidence of essential hypertension than nonstressed obese individuals, obesity might also be said to influence the stress–hypertension relation in addition to its direct effect on risk for hypertension. Additionally, if obese persons were shown to exhibit exaggerated cardiovascular responses to stress in contrast to normal-weight controls, evidence for obesity as affecting the stress–cardiovascular reactivity relation would also be demonstrated. Both sources of evidence are considered for the potential constitutional and lifestyle factors in this chapter. Potential psychological and social factors involved in the stress–hypertension relation are described in Chapter 7.

Constitutional Factors

Age

It is well known that incidence of essential hypertension increases with age in industrialized countries (Wolz et al., 2000). Because comparable age-associated increases in blood pressure have not been observed in less industrialized countries, where exposure to stressful jobs and sedentary lifestyles is minimal (Harper, Crews, and Wood, 1994; Marmot, 1984), age appears to interact with environmental stress in predicting onset of essential hypertension. From the assumption that age influences the stress–hypertension relation, it follows that age could be hypothesized to influence the relation between stress and magnitude of the acute physiological response to stress. Let's consider the evidence for this assertion.

In a review of studies examining the magnitude of cardiovascular response to stress among both young and older adults, Light (1989) reported that younger adults exhibited greater heart rate responses to stress than older adults, and that older adults exhibited greater blood pressure responses to stress than younger adults. These findings corroborated evidence suggesting that beta-adrenergic response to stress declines with age. According to these data, the reduction in beta-adrenergic activity or sensitivity that occurs with age results in a diminished heart rate response to stress. However, because the beta-adrenergic system also regulates vasodilation in the circulatory bed, its reduced sensi-

tivity with aging leads to less arterial dilation and consequently increased total peripheral resistance. Accordingly, Light's analysis of the effect of aging upon physiological response to stress suggests that age indeed influences the magnitude of cardiovascular responses to stress. As such, increased heart rate response to stress would be associated with an increased risk for hypertension only among younger individuals, while an increased blood pressure response to stress would be associated with an increased risk for hypertension among older persons. These findings are consistent with the observations of Lund-Johansen (1991), who has linked early hypertension with cardiac hyper-reactivity and later hypertension with vascular hyper-reactivity.

Genetic Factors

It is well established that essential hypertension runs in families (Hunt, Williams, and Barlow, 1986), leading to considerable research examining potential genetic contributions to the onset of essential hypertension, including twin studies, adoption studies, the selective breeding of animals (SHR, Dahl salt-sensitive rats, and BHRs, as discussed in Chapter 4), and genetic engineering research (see Hamet et al., 2002). According to this body of research, from 30 to 50 percent of the variance of essential hypertension is inherited and the mode of inheritance for the majority of cases is polygenic in origin (Dominiczak et al., 2000). Furthermore, it appears that multiple gene combinations exist that lead to essential hypertension. Therefore, it seems that no single genetic constellation accounts for all cases of essential hypertension. This is certainly the case among the various inbred rat strains that have served as animal models. Although differing genetic constellations were selectively bred among these animal models, they each resulted in the manifestation of heightened blood pressure, albeit through differing physiological mechanisms. Genes that control secretion of renin, nitric oxide, and the formation and sensitivity of beta-adrenergic or angiotensin receptors may each contribute to blood pressure dysregulation and subsequent onset of hypertension via distinctly different genetic pathways. Despite the complexity of the specific genetic structures involved in the etiology of hypertension, it is safe to conclude that multiple genetic factors comprise an important component in the etiology of essential hypertension.

How might genetic structures influence acute cardiovascular response to stress? There have been three different approaches to this question: the selective breeding method, the twin study method, and the family history method. Findings regarding cardiovascular reactivity to stress among various inbred hypertensive strains have already been discussed in the previous chapter (see pp. 156–157). Basically, we know that rats genetically endowed to develop hypertension exhibit exaggerated blood pressure responses to stress in contrast to controls, and that the enhanced responses can be detected before the onset of hypertension.

Twin Studies

Turner and Hewitt (1992) reviewed evidence from ten studies comparing the cardiovascular responses to stress of identical or monozygotic (MZ) twins and fraternal or dizygotic (DZ) twins. Although this group of studies was limited by small sample sizes, the authors concluded that cardiovascular reactivity to stress was 'moderately heritable.' Although a range of heritability estimates have been reported among these studies, the heritability estimate of .48 by Carroll et al. (1985) represents a solid median estimate considering the range of samples and stressors employed in these studies. Furthermore, the estimated heritability for heart rate response to mental arithmetic of .50 between mid-child and mid-parent approximates this value (Ditto, France, and Miller, 1989), suggesting that it represents a good estimate of the portion of variance of cardiovascular response to stress explained by genetic factors. In sum, although far from conclusive, heritability estimates of cardiovascular response to stress appear to approach the range of heritability estimates associated with the expression of the condition of essential hypertension itself.

Parental History of Hypertension

Although twin studies have been valuable in exploring the relation between the genetic contribution to both cardiovascular reactivity to stress and essential hypertension, they are difficult to conduct due to the limited number of twins in the population and limited access to

sets of twin data. Based upon the knowledge that hypertension aggregates in families (Paffenbarger, Thorne, and Wing, 1968; Stamler et al., 1971), a considerable amount of research has examined the genetic foundation of cardiovascular response to stress by comparing persons of different hypertensive parentage (for a review, see Fredrikson and Matthews, 1990). In most of these studies, categorization of young normotensive participants into those with or without a family history of hypertension is conducted through brief interviews of participants' biological parents regarding their hypertensive status, although a few studies have extended this definition to include parents with coronary heart disease and others have included information regarding hypertensive status of grandparents. In a meta-analytic review of 30 studies comparing cardiovascular reactions to stress between young adults with and without hypertensive parents, Fredrikson and Matthews (1990) found that offspring of hypertensive patients exhibited significantly greater heart rate and SBP reactions to all types of mental stressors as well as a significantly greater DBP response to active mental tasks (mental arithmetic, interpersonal encounter) than persons with normotensive parentage. Elevated blood pressure reactions to stress have also been reported among offspring of hypertensive monkeys in comparison to offspring of normotensive monkeys (Kirby et al., 1984). These findings are significant in that these exaggerated cardiovascular reactions are observed in these high-risk persons (and monkeys) before onset of essential hypertension, indicating that the commonly observed hyper-reactivity among borderline and sustained hypertensive patients is likely not a consequence of chronically elevated arterial pressures.

Nervous System Influences and Parental History of Hypertension

Starting from the conclusions of works cited by Fredrikson and Matthews (1990), several investigators began to explore the physiological foundation for the commonly observed differences in cardiovascular response to stress between young adults with and without a parental history of hypertension. Foremost among these investigations were those that tested the hypothesis that these exaggerated cardiovascular reactions emanated from enhanced sympathetic nervous system activation (Anderson et al., 1987; Ditto and Miller, 1989; Manuck et al.,

1996; Miller and Ditto, 1991; Perini et al., 1990). Miller and Ditto (1991) reported significantly greater heart rate, blood volume pulse (reflecting increased vascular resistance via alpha-adrenergic activity), and forearm blood flow responses (reflecting decreased vascular resistance via beta-adrenergic activity) among offspring of hypertensives in comparison to offspring of normotensives, indicating that the enhanced cardiovascular response to mental stress involved both beta-adrenergic and alpha-adrenergic activation. Administration of selective beta-blocking and alpha-blocking agents resulted in attenuations of response parameters in the expected directions (beta-blockade eliminated the heart rate and forearm vascular resistance differences between groups), lending further support to the role of both beta-adrenergic and alpha-adrenergic activity in explaining the cardiovascular response differences observed among persons differing in hypertensive parentage. Other research has confirmed that disrupted vascular resistance may underlie the exaggerated cardiovascular responses that are commonly observed in this literature (Anderson et al., 1987; Ditto and Miller, 1989).

Studies comparing neuroendocrine responses to stress between offspring of hypertensive and normotensive parents also provide information regarding the role of the sympathetic nervous system in driving the observed cardiovascular response differences. In particular, if group differences in measures of epinephrine, norepinephrine, or cortisol were evident, greater sympathetic involvement could be presumed. Although increased levels of resting plasma norepinephrine (Horikoshi et al., 1985) and norepinephrine response to exercise were reported among individuals with hypertensive parents (Nielsen, Gram, and Pedersen, 1989), no differences in epinephrine between offspring of hypertensive and normotensive parents were reported. Other studies, however, have failed to find any differences in either norepinephrine or epinephrine levels or responses to mental and physical stressors among groups of offspring of hypertensive and normotensive persons (Manuck et al., 1996; Perini et al., 1990). Although less attention has been paid to cortisol response to stress than catecholamine response to stress, al'Absi and Wittmers (2003) reported an association between cortisol reactivity and cardiovascular reactivity among men and women at risk for hypertension in contrast to low-risk counter-

parts. Because the high-risk group in this study was defined on the basis of high resting SBPs *and* a parental history of hypertension, they reflected perhaps a subgroup of individuals at even greater risk for developing hypertension than those individuals who have hypertensive parents but relatively normal blood pressures. Therefore, it is unknown whether the increased cortisol response to stress observed in this study is unique to this subgroup of high risk participants.

Although activation of the sympathetic nervous system has been hypothesized to be at the root of the observed differences in cardiovascular response to stress among offspring of hypertensive and normotensive parents, it is also possible that the parasympathetic nervous system may be involved. To test this hypothesis, Miller (1994) measured cardiovascular responses to a variety of mental stressors among a group of persons with and without hypertensive parents. Congruent with previous work, they found elevated heart rate responses among participants with a hypertensive parent in contrast to those with normotensive parents. Parasympathetic involvement, as determined by measures of respiratory sinus arrhythmia, however, were not different between groups, suggesting that the observed difference in the magnitude of heart rate reactions was due to sympathetic, not parasympathetic, influences.

Despite the initial promise of this line of inquiry, several well-designed studies have failed to find any significant differences in cardiovascular reactivity to stress between young adults with and without hypertensive parents (Manuck et al., 1996; Perini et al., 1990; Ravogli et al., 1990). In response to the discrepant findings among studies examining the relation between cardiovascular response to stress and parental history of hypertension, Muldoon et al. (1993) conducted a comprehensive review of the entire literature exploring family history of hypertension, including studies that examined differences in intracellular sodium transport, renal functioning, cardiovascular morphology, and cardiovascular reactivity to stress. Among all of the physiological parameters considered, they found solid evidence for only two conclusions. First, persons with hypertensive parents tended to show enhanced left ventricular thickness and mass earlier than persons without hypertensive parents. And second, offspring of hypertensives exhibited abnormalities of the peripheral vasculature, as evidenced by in-

creased forearm blood flow responses to mental stress or the cold pressor task. According to these authors, evidence for the remaining variables, including direct comparisons of heart rate and blood pressure response to mental stress between persons with and without hypertensive parents, was insufficient for making definitive conclusions.

Parental History of Hypertension and Individual Difference Variables

One reason that consistent observations of exaggerated cardiovascular responses to stress among offspring of hypertensive patients have not been made may be that the relation between these two variables is influenced by other individual difference variables. For example, as mentioned in Chapter 5, Light et al. (1999) found that the interaction between family history of hypertension and acute cardiovascular response to stress in predicting casual blood pressures prospectively was influenced by occurrence of high daily stress. In other words, the elevated cardiovascular reactions among persons of hypertensive parentage predicted onset of essential hypertension only among persons reporting regular exposure to high life stress. Presumably, persons who lead relatively stress-free lives may not develop chronically heightened blood pressures even if they have a positive family history of hypertension.

Several psychological individual difference parameters have also been shown to interact with parental history of hypertension in affecting the magnitude of behaviorally elicited cardiovascular reactivity. For example, research has shown that relations between parental history of hypertension and cardiovascular response to stress were observed among participants who inhibit anger expression, but not those who express anger openly (Holroyd and Gorkin, 1983; Vögele and Steptoe, 1993), among participants reporting heightened anxiety (Manuck et al., 1985; Miller, 1992), among individuals high on measures of defensiveness (Shapiro, Goldstein, and Jamner, 1995), and among persons who deny the experience and expression of emotion, particularly in association with a high need for social approval (Jorgensen, Gelling, and Kliner, 1992; Jorgensen and Houston, 1986; 1988). Several of these psychological characteristics (anger inhibition, defensiveness, anxiety) have also been shown to be related to increased ambulatory blood pressures during workdays among working women with hyper-

tensive parents (Goldstein and Shapiro, 2000). In this study, associations between these psychological characteristics and ambulatory blood pressures were not observed for offspring of normotensives or offspring with only one hypertensive parent. Although there has not been a substantial amount of empirical work in this area, studies that exist provide obvious hints that certain individual difference variables are worthy of further exploration with regard to their association with cardiovascular response to stress. Perhaps additional exploration of selected individual difference variables will result in a better understanding of the sources of inconsistent observations between parental history of hypertension and acute cardiovascular responses to stress that are prevalent in the literature.

Parental History of Hypertension and Behavioral Responses to Stress

The relation between parental history of hypertension and acute cardiovascular reactivity is further complicated by observations that individuals with hypertensive parents have also been shown to exhibit behavioral response differences from offspring of normotensive parents (Baer et al., 1980; Frazer, Larkin, and Goodie, 2002; Semenchuk and Larkin, 1993). In addition to observing the clear behavioral differences during family interactions between hypertensive and normotensive fathers described in Chapter 5, Baer et al. (1980) also analyzed behavioral data of the children during these interactions. Thus this study provided a unique opportunity to evaluate behavioral responses of both hypertensive patients and their offspring within a single experimental session. Congruent with behavioral deficits of the hypertensive father, children of hypertensive fathers exhibited greater negative nonverbal (gaze aversion) and lesser positive verbal behaviors (agreements) than children of normotensive fathers. These findings suggest that hypertensive fathers may model a distinct behavioral style of coping with confrontation that is learned and practiced by their children.

Using multiple measures of behavioral and cardiovascular responses to social confrontation with a confederate, Semenchuk and Larkin (1993) reported that male offspring of hypertensives exhibited both increased SBP responses and less adaptive behavioral responses to the interpersonal challenges in comparison to sons of normotensives. Analysis of the specific behavioral rating categories showed that per-

sons with hypertensive parents paid less attention to the confederate's responses, used humor less, grimaced more, and used more disagreeing statements than persons of normotensive parentage. Frazer, Larkin, and Goodie (2002) replicated these findings using a sample of both young men and women with and without parental histories of hypertension. Similar behavioral differences were observed across interpersonal and non-interpersonal laboratory tasks; that is, offspring of hypertensives showed more disagreeing statements, put-downs, eye rolling, and sighing than offspring of normotensives. Correlational analyses from both of these studies revealed no correspondence between cardiovascular and behavioral response differences even though both were observed when contrasting persons with and without hypertensive parents. This suggests that offspring of hypertensive patients with the greatest SBP responses are not necessarily the same participants exhibiting the less adaptive social behaviors. In this regard, two orthogonal response differences exist among young adults with hypertensive parents, one involving elevated cardiovascular reactions and the other involving the display of less socially competent behaviors during confrontation and stress provocation.

Parental History of Hypertension and Neuropsychological Performance

As described in Chapter 1, significant differences in performance on an array of neuropsychological tests have been observed between essential hypertensive and normotensive patients (see Waldstein et al., 1991). For the most part, based upon evidence that these differences in information processing disappeared following successful blood pressure regulation using anti-hypertensive treatment (Miller et al., 1984), it had been thought that the observed differences in information-processing speed and abstract reasoning that existed between hypertensive and normotensive patients represented a consequence of high blood pressure rather than a factor involved in its etiology. Despite this assumption, a few investigators have attempted to examine whether these neuropsychological deficits were apparent among individuals with hypertensive parents (McCann et al., 1990; Pierce and Elias, 1993; Thyrum et al., 1995; Waldstein et al., 1994). Although McCann et al. (1990) reported no differences on performance on a variety of neuropsychological tests between persons with and without hypertensive

parents, the other three studies reported poorer performance among persons with hypertensive parents on tests of attention and memory (Pierce and Elias, 1993; Thyrum et al., 1995) as well as tests of visual perceptual and spatial skill and reaction time (Waldstein et al., 1994). Because the nature of the information-processing differences between persons with and without hypertensive parents was similar to deficits reported in comparisons of neuropsychological test performance between hypertensive and normotensive patients, these data suggested that perhaps these subtle deficits in information processing preceded onset of essential hypertension. Hypothetically, if these information-processing differences between persons differing in hypertensive parentage serve as a marker for underlying acute alterations in diminished cerebral blood flow during task performance, it might explain how these differences are apparent prior to the onset of essential hypertension. Alternatively, if young adults at risk for hypertension were aware of their deficits in information processing, they might find performance of cognitive stressors often used in studies of cardiovascular reactivity to stress among offspring of hypertensives more stressful than offspring of normotensives with relatively superior information-processing skills. However, these thoughts represent speculation at this point, as studies of cerebral blood flow during neuropsychological task performance among persons with and without hypertensive parents have yet to be conducted.

Parental History of Hypertension and Perception of Pain

As described in Chapter 5, essential hypertension is associated with an increased tolerance of pain and decreased perception of pain (see France, 1999). As with research on cardiovascular reactivity to stress, behavioral responses to stress, and deficits in neuropsychological task performance, France and colleagues have extended this body of literature by examining perception of pain among individuals with a familial history of hypertension (Ditto, France, and France, 1997; France et al., 1994; France, Froese, and Stewart, 2002; France and Suchowiecki, 2001). Although various pain manipulations have been used in these studies, each reports significantly lower perception of pain accompanied by a higher tolerance of pain among individuals with a parental history of hypertension. These findings suggest that whatever the

physiological mechanism is that is responsible for the reduced perception of pain among essential hypertensive patients (for example, baroreceptor activation), it is also present among offspring of hypertensives.

Summary of Research on Hypertensive Parentage

Some studies comparing young adults with and without a parental history of hypertension have revealed that the same exaggerated cardiovascular reactivity to stress that has been shown to distinguish hypertensive and normotensive patients is also observed among their offspring. Congruent with the literature on hypertensive patients, the observed differences in cardiovascular reactivity to stress between persons with and without hypertensive parents appears to be influenced by additional individual difference variables like exposure to daily stress, mode of anger expression, or degree of the need for social approval. Additionally, because persons with hypertensive parents have been shown to exhibit different behavioral responses during social confrontation, neuropsychological task performance, and sensitivity to pain than persons with normotensive parents, it is unclear to what extent each of these attributes contributes to the magnitude of their cardiovascular reactions to stress as well as their future risk for essential hypertension. From these observations, it is apparent that parental history of hypertension represents an important individual difference variable in explaining the relation between exposure to environmental stress and incidence of essential hypertension. However, the relation of this variable with hypertension is quite complex, involving interactions with acute behavioral and cognitive responses in addition to the hypothesized acute physiological response to stress.

Gender

As discussed in Chapter 1, incidence of hypertension is influenced by gender. Basically, males exhibit higher incidence rates of essential hypertension than females until menopause. Following this stage in life, females' incidence rates increase and actually exceed incidence rates for males (Wolz et al., 2000). Naturally, this has alerted researchers to the importance of the menstrual cycle in protecting women from onset of

high blood pressures until later in life (von Eiff et al., 1971). The relation between blood pressure and gender is clearly age-related. In general, males and females have comparable blood pressure levels in childhood and early adolescence. However, blood pressures in men begin to become higher than in women in mid-adolescence and remain that way until ages in the late 50s (National Center for Health Statistics, 1977). Furthermore, because smaller body sizes are associated with higher heart rates and males are typically larger than females, mean resting heart rates of women are generally higher than mean resting heart rates of men (Berkow, 1982). Although risk for hypertension clearly differs between males and females, the evidence that men who lead stressful lives are more susceptible to hypertension than women who lead such lives is largely based upon data on job stress and strain (Cesana et al., 2003; Schnall et al., 1992). When measures of home and family stress are measured in addition to work-related stress, these gender effects are less compelling (Brisson et al., 1999; James et al., 1993).

In a meta-analysis of 12 studies that compared cardiovascular responses to stress between males and females, Stoney, Davis, and Matthews (1987) found evidence to support gender differences in acute physiological response to stress. Males, in contrast to females, exhibited significantly higher SBP and epinephrine responses, but lower heart rate responses to stress. Measurement of hemodynamic responses of males and females using impedance cardiography has also revealed consistent gender differences, with males showing more of a total peripheral resistance response to mental stress than females, and females showing more of a cardiac output response to mental stress than males (Allen et al., 1993; Girdler et al., 1990). Furthermore, postmenopausal women were shown to exhibit higher heart rate, SBP, and epinephrine responses to stress than premenopausal women, suggesting that after menopause, women more closely resemble male acute physiological response profiles than prior to menopause (Saab et al., 1989). Interestingly, in some studies, postmenopausal women undergoing hormone replacement therapy have been shown to have lower blood pressure responses to mental stress than postmenopausal women not receiving hormone replacement (Matthews et al., 2001; von Eiff et al., 1971). Coupled with observations of elevated heart rate responses to stress in

postmenopausal women (Burleson et al., 1998), these findings suggest that hormone replacement therapy returns women to their premenopausal cardiovascular reactivity pattern.

Comparable reductions in cardiovascular reactivity to stress with hormone replacement therapy have also been observed among women at risk for developing essential hypertension (McCubbin et al., 2002). In this study, as in many previous studies, postmenopausal women with either elevated blood pressures or a family history of coronary heart disease exhibited increased blood pressure responses to stress in comparison to women with normal blood pressures and no family history of heart disease. However, this effect was not observed among women on hormone replacement therapy, indicating that hormone replacement normalizes the acute cardiovascular response to stress, presumably lowering women's risk for subsequent development of essential hypertension.

Some contradictory findings regarding the effect of menopause and hormone replacement have also been reported (see Saab, 1989). In a more recent study in which young women were administered hormones to reduce estrogen to postmenopausal levels, no differences in cardiovascular or neuroendocrine responses to stress were detected (Matthews et al., 1998). Although this study did not examine the long-term effect of estrogen loss, the findings clearly failed to support previous work that suggested that normal ovarian functioning served a protective role for both acute physiological responses to stress and incidence of essential hypertension.

Studies investigating gender differences in cardiovascular response to stress, however, have been criticized on the grounds that they typically employ competitive mental tasks that can be characterized as masculine in nature (like mental arithmetic or a handgrip challenge). As such, the heightened cardiovascular responses commonly observed among males may represent the fact that men are more threatened or engaged by these sorts of tasks than women. In fact, studies comparing responses of men and women to tasks that might be characterized as being more challenging to the traditionally female gender role, like interpersonal cooperation with one's spouse or talking about one's physical appearance, have yielded greater cardiovascular responses among

women (Fritz, Matthews, and Cohen, 2001; Smith et al., 1998; Stroud, Niaura, and Stoney, 2001).

Ethnicity

Among the various ethnic groups living in the United States, incidence of essential hypertension is highest among black Americans, with blacks exhibiting at least a two times greater risk than whites and most other ethnic groups (Kaplan, 2002). One of many studies that have supported this finding is the CARDIA study, a multi-site longitudinal investigation of over 5000 young adults conducted in the 1980s. Congruent with other findings, the CARDIA investigators reported significantly higher blood pressures among black than white young adult men and women (Liu et al., 1989). However, these authors noted that several lifestyle factors that differed between blacks and whites accounted for much of the observed blood pressure difference, including body mass index, fitness, and use of cigarettes and alcohol. Therefore, it is important to consider differences in these lifestyle variables when examining ethnic differences in blood pressure status, as they appear to interact with ethnicity to determine overall risk for essential hypertension. Additionally, darker-skinned blacks have been shown to exhibit higher blood pressures than lighter-skinned blacks, a finding Dressler (1991) attributes to the greater degree of sociocultural struggle that darker-skinned blacks confront as they attempt to maintain their quality of life in what he refers to as a 'color-conscious society.'

Given the unique stressors confronting black Americans both historically (slavery) and currently (racial discrimination), it is only natural that a considerable body of literature has emerged comparing the acute physiological stress responses of black and white Americans. In a review examining this body of literature, Anderson, McNeilly, and Myers (1992) cited evidence that blacks consistently exhibit elevated blood pressure responses to laboratory stressors in contrast to whites. Schuler and O'Brien (1997) also reported delayed DBP recovery from stress among blacks in contrast to whites, indicating that not only do blacks experience more intense blood pressure reactions than whites, but these reactions are more prolonged. Research employing assessment of hemodynamic functioning, also cited in the review by Ander-

son et al., revealed that the exaggerated blood pressure responses to stress observed among blacks were more closely associated with increases in total peripheral resistance than with cardiac output. In contrast, blood pressure responses to the same tasks among whites reflected the opposite hemodynamic pattern (increased cardiac output). Furthermore, several of these studies found a reduced heart rate response to mental stress among blacks in comparison to whites, providing further evidence that the increased blood pressure responses were mediated by vascular rather than cardiac hyper-reactivity. Congruent with the model proposed by Anderson et al., there is evidence that the exaggerated vascular reactions observed among blacks in response to stress are related to enhanced sympathetic nervous system activity as opposed to structural changes in the vasculature (Calhoun et al., 1993). Additionally, under conditions of stress, blacks have been shown to secrete more endothelin-1, a vasoconstrictive peptide released by the blood vessel wall, than whites (Treiber et al., 2002). It appears, then, that the exaggerated vascular response observed among blacks is mediated by both the sympathetic nervous system and local vasoactive substances.

It has been hypothesized that exposure to racism may serve as a common environmental stressor that may promote acute blood pressure responses (Armstead et al., 1989). Because blacks are more likely than whites to experience racism and associated racial discrimination in daily life, it has been argued that their more frequent episodes of cardiovascular reaction to racism may be associated with increased risk for essential hypertension. In a review of the relation between racism and blood pressure status, Brondolo, Rieppi, Kelly, et al. (2003) reported that there were no consistent findings relating exposure to racism and either resting blood pressure or hypertensive status. In the same paper, Brondolo and colleagues reviewed the literature examining the magnitude of cardiovascular reactions to a wide range of strategies of exposing study participants to racist stimuli. Although they concluded that racist stimuli evoked substantial blood pressure reactions, the magnitude of these responses was similar among blacks and whites. However, DBP responses to exposure to racist stimuli were accentuated among women who had a significant personal history of being exposed to racial discrimination (Clark, 2000; Guyll, Matthews, and Bromberger, 2001).

Black Americans also differ from white counterparts in how their bodies respond to and excrete sodium, and this effect appears to be independent of the amount of dietary sodium consumed (Anderson et al., 1992). In particular, it has been shown that blacks exhibit a higher blood pressure elevation following sodium loading accompanied by lower sodium excretion (Luft, Grim, and Weinberger, 1985). Therefore, black Americans are more sensitive to the blood pressure–elevating effects of sodium and their kidneys do a better job of retaining sodium. It has been speculated that these unique physiological sensitivities to sodium are partly the result of the genetic lineage associated with the physiological traits of those African slaves who survived the middle passage (Wilson and Grim, 1991). In other words, slaves endowed with a physiology that retained sodium were more likely to survive the tortuous conditions of slave ships as they crossed the mid-Atlantic; those equipped with a less sodium-retaining exocrine system failed to survive. Thus the African slaves that arrived in America were genetically predisposed to survive under conditions of substantial overheating, starvation, and exposure to fluid-depleting diseases. Although this hypothesis has some appeal, historians have discounted support for its assertions (Curtain, 1992).

Less research has been done examining cardiovascular responses to stress among other ethnic groups. Although questions regarding differences in cardiovascular response to stress among persons with different ethnic backgrounds would be worthy of additional attention, the drive to conduct this type of research may be dampened by findings that incidence of essential hypertension is not notably elevated among these other ethnic groups.

Diabetes

It is well known that diabetes mellitus is associated with essential hypertension, although part of this relation may be owing to the fact that both medical conditions are associated with obesity (Kaplan, 2002). It is also known that living with a chronic medical condition like diabetes presents the patient with additional stressors in life (hospitalizations or medical complications) that may further increase risk for hypertension. In contrast to some of the other constitutional factors discussed,

much less is known regarding the relation between acute physiological response to stress and diabetes. It has been shown, however, that diabetic patients exhibit elevated blood pressure responses to stress in contrast to non-diabetic normotensives (Shapiro, Moutsos, and Krifcher, 1963), and that the relation between elevated blood pressure response and diabetes becomes apparent only after the patient has been diagnosed with diabetes mellitus for some time (Kraemer, 1985). In a study assessing hemodynamic response parameters, diabetic hypertensive patients exhibited greater vascular resistance and temperature reduction responses than non-diabetic hypertensives, indicating that the degree of vascular impairment was much greater among patients with diabetes (Nazzaro et al., 1994). Although there is some evidence that diabetic patients exhibit exaggerated cardiovascular responses to mental stress like that observed among hypertensive patients, there are simply an insufficient number of studies examining this hypothesis to draw any firm conclusions.

Obesity

Although the relation between obesity and hypertension has been clearly established and obesity ranks as one of the primary risk factors for the development of essential hypertension (Kaplan, 2002), there is very little empirical work examining whether obesity affects the stress–hypertension relation. Although one could hypothesize that living with obesity presents the patient with an additional set of stressful life circumstances that normal-weight individuals do not confront (decreased mobility and social disapproval), it is unknown whether these types of stressors place the obese patient at any greater risk for hypertension than obese patients not exposed to stressful life events. Furthermore, very little is known about the relation between obesity and cardiovascular response to stress. Putnam and Rennert (1984) compared cardiovascular responses of obese and normal-weight women to a mental arithmetic task and found that heart rate responses were significantly higher among the obese women. More recently, a few investigators have reported that increased central adiposity (waist circumference) was associated with increased heart rate and blood pressure responses to mental stress (Barnes et al., 1998; Waldstein et al., 1999).

Finally, blood pressure reactions to stress among obese patients have been shown to be associated with increased peripheral resistance responses rather than cardiac output–mediated responses (Rockstroh et al., 1992; Sung et al., 1997), as have blood pressure responses for women with higher levels of central adiposity (Davis et al., 1999). Although these findings support the hypothesis linking obesity to hypertension through acute cardiovascular reactivity to stress, not enough research has been conducted in this area for us to make this statement convincingly.

Lifestyle Factors

Several lifestyle variables are associated with an increased risk for essential hypertension, including physical inactivity, smoking, and consumption of alcohol, caffeine, and a high-sodium diet (Kaplan, 2002). Surprisingly, many of these variables have also been shown to affect cardiovascular reactivity to stress, suggesting that perhaps their influence on risk for hypertension is expressed via the sympathetic nervous system. Let's examine the evidence linking each of these lifestyle factors with measures of cardiovascular response to stress.

Physical Activity

Physical inactivity is associated with both obesity and diabetes, and similarly has been commonly linked to the etiology of essential hypertension (Blair et al., 1984). Among its many benefits, engaging in aerobic exercise is associated with reduced blood pressures, lower heart rate, reduced sympathetic nervous system activity, and increased parasympathetic activity (Scheuer and Tipton, 1977). In a review of the literature, Light (1989) cited two studies that contrasted subjects categorized as low versus high in physical fitness on measures of cardiovascular response to stress (Holmes and Roth, 1985; Light et al., 1987). In both of these studies, physical fitness was associated with lower cardiovascular responses to mental stress. Light also cited other studies that failed to find an association between physical fitness and cardiovascular reactivity to stress, but did find an association between physical fitness and heart rate recovery from stress (Cantor, Zillman, and Day,

1978; Cox, Evans, and Jamieson, 1979). As she stated in her review, however, the findings of these studies must be interpreted with caution, as persons who chose to avoid exercise and were not physically fit may be in that state due to other factors like obesity or personality characteristics.

To address problems interpreting findings from studies of participants who were self-selected into fitness groups, experimental studies are needed in which cardiovascular reactivity to stress is assessed during periods of fitness and unfitness among the same participants. This type of study typically involves assessing cardiovascular reactivity to stress on unfit participants and then again later after these participants engage in an exercise program designed to enhance physical fitness. Fillingim and Blumenthal (1992) reviewed eight studies employing prospective designs and reported mixed findings, with only half of the studies reviewed demonstrating reductions in cardiovascular response to stress with aerobic exercise training. Furthermore, most of the studies cited by Fillingim and Blumenthal were conducted on men, and recent evidence has suggested that reductions in blood pressure response that are associated with fitness are observed only among samples of females (Dishman, Jackson, and Nakamura, 2002; Dishman et al., 2003). Because of these inconsistencies, definitive conclusions regarding the relation between cardiovascular response to stress and physical fitness cannot be made.

Smoking

Ingestion of nicotine, one of many psychoactive ingredients in tobacco, results in acute increases in blood pressure that are maintained during smoking but decrease following smoking cessation (Verdecchia et al., 1995). Research on the more enduring effects of smoking on essential hypertension, however, have yielded mixed findings. In some studies, smokers have higher ambulatory blood pressures than nonsmokers (Poulsen et al., 1998); yet in other studies, smoking is associated with lower daily blood pressures (Mikkelsen et al., 1997). Although evidence for smoking as a risk factor for essential hypertension is not as strong as some other established risk factors (for example, obesity or sodium consumption), it is well known that smoking represents

a major risk factor for coronary heart disease in conjunction with essential hypertension and high cholesterol.

Not surprisingly, findings relating smoking to the magnitude of cardiovascular responses to stress have also been mixed. Some studies have reported greater blood pressure responses to stress among smokers (Emmons and Weidner, 1988; Tsuda et al., 1996), but others have reported no differences in cardiovascular response to stress between smokers and nonsmokers (Ward et al., 1994) or even attenuated cardiovascular responses to stress among smokers in contrast to nonsmokers (West et al., 2001). It would appear that the increased risk of coronary heart disease associated with smoking follows a different pathway that is perhaps not mediated by the sympathetic nervous system. In fact, in a model of psychosocial risk factors for cardiovascular disease, Larkin and Semenchuk (1995) suggested that smoking may exert its damaging effect by releasing toxins like carbon monoxide into the bloodstream that cause direct tissue damage to the endothelium.

Alcohol Consumption

It is well known that consumption of alcohol is associated with increased risk for essential hypertension, even though light drinking has been shown to be associated with reduced risk for coronary heart disease (Thun et al., 1997). In general, the most recent data suggest that the relation between alcohol consumption and blood pressure is a linear one, with increased alcohol consumption associated with increases in blood pressure (Puddey et al., 1997), although some earlier reports positing a J-shaped relation have been cited, in which slight increases in incidence of high blood pressure occur with total abstinence (Shaper, Wannamethee, and Whincup, 1988). Reductions in alcohol intake are typically associated with reductions in blood pressure within a week or two (Puddey et al., 1997).

Given that alcohol consumption is associated with higher blood pressures, what is the relation between alcohol consumption and acute physiological responses to environmental stress? There is evidence suggesting that the relation between job stress and risk for hypertension is apparent only among men who consume alcohol (Schnall et al., 1992),

suggesting that it may be an important variable influencing the stress–hypertension link. Most studies of the alcohol–cardiovascular reactivity association have showed that administration of alcohol results in a diminished cardiovascular response to stress among alcohol-dependent patients (Panknin et al., 2002) as well as among individuals at risk for alcoholism based upon having a positive family history of alcoholism (Conrod, Pihl, and Ditto, 1995; Finn and Pihl, 1987; Finn, Zeitouni, and Pihl, 1990; Sher and Levenson, 1982). A few studies have also reported that the diminished cardiovascular response to stress associated with administration of alcohol was observed primarily among individuals with Type A (coronary-prone) behavior pattern (Niaura, Wilson, and Westrick, 1988; Zeichner, Edwards, and Cohen, 1985). Interestingly, exposure to stress during sober test sessions revealed that men with a family history of alcoholism exhibited greater cardiovascular reactions to stress than persons with no family history of alcoholism (Finn et al., 1987; 1990). These authors have speculated that perhaps offspring of alcoholics who exhibit exaggerated acute stress responses use alcohol to regulate these stress responses; because alcohol successfully attenuates their acute stress reactions, they use it more frequently, resulting in an increased risk for developing problems with alcohol abuse and dependence.

In summary, although the use of alcohol is associated with an increased incidence of essential hypertension and there is evidence that the use of alcohol affects the association between stress and hypertension, the relation between alcohol consumption and cardiovascular reactivity appears to be in the opposite direction. Therefore, the association between alcohol and risk for hypertension does not appear to operate through an exaggerated cardiovascular response to stress.

Caffeine Consumption

Although ingestion of caffeine has been shown to be associated with acute increases in blood pressure, the long-term relation between caffeine use and essential hypertension is far from established (Myers, 1988). Some studies have found chronic consumption of caffeinated beverages to be associated with increases in casual blood pressures (Jee et al., 1999; Savoca et al., 2004), while others have reported lower

blood pressures among heavy consumers of caffeine (Stamler, Caggiula, and Gandits, 1997). Additional evidence regarding the effect of caffeine on blood pressure indicates that the body develops a tolerance to the chronic consumption of caffeine and that the intensity of the acute blood pressure responses observed when nonusers ingest caffeine dissipates over time (Myers, 1988).

Although the relation between caffeine consumption and essential hypertension has yet to be established, several investigators have examined the relation between caffeine use and cardiovascular response to mental stress. In general, studies comparing acute cardiovascular responses to mental stress between participants given caffeine versus placebo have revealed that administration of caffeine results in elevated blood pressure responses to stress (France and Ditto, 1988; Lane and Williams, 1985; Pincomb et al., 1987). Even Henry and Stephens (1980) reported that administration of caffeinated coffee instead of water to mice living in stressful living environments resulted in elevated blood pressures. Furthermore, the magnification of the observed blood pressure responses to stress that occurs with caffeine ingestion is even more marked among persons at risk for developing hypertension (having a parental history of essential hypertension or borderline blood pressures; Lovallo et al., 1989; 1996) and in conjunction with smoking (MacDougall et al., 1988). Unlike the relation between regular caffeine use and resting blood pressure, the exaggerated blood pressure response to stress associated with caffeine ingestion does not appear to habituate over time (Ratliff-Crain, O'Keefe, and Baum, 1989). Therefore, even among long-time users of caffeinated beverages, exaggerated cardiovascular reactions to stress can be observed.

In a recent review of the literature linking caffeine use with the incidence of essential hypertension, James (2004) concludes that while evidence showing the influence of caffeine upon acute blood pressure responses to stress is quite strong, the overall link between caffeine use and incidence of essential hypertension in epidemiologic studies is only modest. Nevertheless, James suggests that the magnitude of the relation between caffeine use and increased blood pressure is substantial enough to consider caffeine use an important cause of premature deaths associated with coronary heart disease and stroke.

Dietary Factors

Sodium

Among all dietary factors that have been examined with respect to essential hypertension, ingestion of sodium, mainly in the form of salt, has the most consistent linkage (Law, 1997). INTERSALT, the largest multi-culture study conducted examining the relation between sodium excretion and blood pressure, found that a relation was evident in each of its 52 international sites (Stamler et al., 1991; Elliott et al., 1996). The association between sodium excretion and blood pressure was strongest in the older age groups, demonstrating perhaps the effect of chronic exposure to high salt intakes. In another line of research, sodium restriction has been shown to be reliably associated with reductions in blood pressure (Cutler, Follman, and Alexander, 1997), providing further confirmation of the strong association between sodium intake and blood pressure status.

Despite the consistent findings relating sodium intake to blood pressure status, there is evidence to suggest that blood pressure elevations associated with sodium consumption occur in only some individuals. Very simply, some persons display substantial blood pressure elevations following ingestion of sodium while others exhibit minimal alterations in blood pressure given the same amount of sodium (Sullivan, 1991). These observations have led toward investigations of these so-called salt-sensitive hypertensive patients that parallel laboratory observations of the Dahl salt-sensitive rats. Like the DS and DR rats, salt-sensitive essential hypertensive humans exhibit no difference in blood pressure from salt-resistant hypertensives, unless exposed to sodium (Sullivan, 1991). In a review of the literature on salt sensitivity, Sullivan (1991) reported that altered vascular resistance and suppressed plasma renin activity as well as aldosterone were characteristics of salt sensitivity among both humans and animals. Examinations of differences across various demographic variables on salt sensitivity have revealed no significant differences in salt sensitivity associated with gender or body weight (Chrysant et al., 1997). Although there do not appear to be significant differences in sodium sensitivity associated with some demographic variables associated with essential hypertension, there is strong evidence that elevated sodium sensitivity

is more prevalent among hypertensive patients (Weinberger et al., 1986).

Given the premise that individual differences in salt sensitivity exist, it could be hypothesized that salt sensitivity affects acute cardiovascular reactions to stress as well as subsequent risk for essential hypertension. Accordingly, salt-sensitive persons who have consumed sodium would be hypothesized to exhibit exaggerated blood pressure responses to stress in contrast to salt-resistant persons or salt-sensitive individuals consuming salt-restricted diets. Let's examine the evidence for this hypothesis.

Falkner, Onesti, and Angelakos (1981) conducted one of the first studies to examine this hypothesis using normotensive adolescents with and without a family history of essential hypertension. In this study, elevated heart rate and blood pressures during a mental arithmetic challenge were observed among individuals with a family history of hypertension, but only during a salt-loading condition; that is, differences between adolescents with and without a family history of hypertension were not significant during the no-salt control condition. Ambrosioni and colleagues corroborated these results using direct measures of intracellular electrolytes and sodium transport (Ambrosioni et al., 1981; 1982). In these studies, increased intracellular sodium in lymphocytes was observed in both hypertensive patients and normotensive offspring of hypertensive patients, and was related to exaggerated blood pressure responses to stress and exercise. Furthermore, restriction of salt among borderline hypertensives was shown to be associated with reductions in blood pressure response to stress and exercise (Ambrosioni et al., 1982). In this regard, sodium intake was clearly linked to the magnitude of blood pressure responses to both mental and physical stressors.

The effects of sodium homeostasis among essential hypertensive patients as well as their normotensive offspring have also been examined by measuring sodium excretion (Light et al., 1983; Light and Turner, 1992). Presumably, if salt sensitivity is associated with increased intracellular sodium concentrations, this would indicate that sodium is being retained in response to stress and that less sodium would be evident in urine output. In a study examining this hypothesis, Light et al. (1983) compared mental stress reactions of young adults at high and

low risk for developing hypertension based upon presence of borderline resting blood pressures or parental history of hypertension. No relation between sodium excretion and heart rate response to stress was observed among low-risk participants; however, a highly significant inverse correlation was observed between sodium excretion and heart rate response to stress among the high-risk group. The highest heart rate responders to stress exhibited the most sodium retention. Furthermore, this reduction in sodium excretion was maintained during a post-stress recovery hour, suggesting that the fluid retention persisted long after exposure to stress was terminated. In a related study, Light and Turner (1992) confirmed that reduction in sodium excretion was associated with enhanced blood pressure, heart rate, and cardiac output responses to mental stress; additionally, the reduced sodium excretion response to stress was more likely to be observed among black than white participants. More recent reports have corroborated these findings relating sodium sensitivity and blood pressure response to mental stress (Deter et al., 1997), but have also suggested that the presence of certain psychological characteristics, like anxiety, emotional irritability, or anger, may be associated with increased sodium sensitivity (Deter et al., 2001). Furthermore, demographic variables have also been shown to impact the relation between salt sensitivity and cardiovascular response to stress, with some studies showing a stronger relation with age (Overlack et al., 1995) and among blacks (Falkner and Kushner, 1990).

Potassium

Another electrolyte, potassium, has received considerable attention regarding its role in the etiology of essential hypertension (He and Whelton, 1999). In contrast to dietary sources of sodium, most of our dietary sources for potassium are vegetables and fruits, foods that individuals in most industrialized countries do not consume in adequate amounts. Therefore, unlike sodium, if potassium is related to onset of problems with blood pressure regulation, it is due to inadequate consumption. Because of the overconsumption of sodium-rich foods and underconsumption of potassium-rich foods in modern industrialized countries, it is difficult to disentangle the unique contributions to hypertension risk associated with each electrolyte. Analysis

of data from the TONE study, however, indicated that risk for high blood pressure was independently associated with increased sodium consumption and decreased potassium consumption (Espeland et al., 2002). Additionally, there is convincing epidemiologic evidence that increased dietary intake of potassium is related to lower blood pressures (He and Whelton, 1999).

Only a few studies have examined the relation between potassium and cardiovascular response to stress (Sudhir et al., 1997; West et al., 1999). Although Sudhir et al. (1997) did not observe any cardiovascular response differences to stress following salt loading, they did report that reductions in potassium were associated with increased blood pressure response to the cold pressor in blacks. West et al. (1999) examined the relation between electrolytes and cardiovascular response to stress by measuring responses to stress after participants consumed each of three different controlled diets (low salt, high salt, high potassium) for 8–10–day periods. Among salt-sensitive participants, both low-salt and high-potassium diets resulted in reductions in resting blood pressures. Change scores, representing standard measures of cardiovascular reactivity, did not differ across groups. Comparable reductions in resting blood pressure were obtained for participants during the low-salt and high-potassium intervention weeks, suggesting that alterations to either electrolyte were beneficial regarding blood pressure status but had no effect on acute cardiovascular reactivity to stress. However, due to the inconsistency of these two studies and general paucity of the data examining cardiovascular response to stress and potassium, there is inadequate evidence supporting a relation between potassium and cardiovascular reactivity to stress at this point in time.

Calcium

Several studies have explored the relation between calcium intake and blood pressure. As with potassium, there is an inverse relation between calcium intake and blood pressure (lower calcium intake is associated with higher blood pressures; Griffith et al., 1999). Studies of dietary supplementation have generally found that increased calcium intake was related to reductions in blood pressure, although it was often difficult to disentangle the unique effect of calcium from other dietary alterations that occurred in these studies such as lower sodium intake or

increased potassium intake. In fact, MacGregor and Cappuccio (1993) hypothesized that the lower calcium observed in studies of hypertensive patients might be a consequence of increased sodium intake and that calcium had no unique predictive relation to onset of essential hypertension. Although studies examining the relation between calcium consumption and cardiovascular response to mental stress are few, calcium supplementation has been shown to reduce blood pressure responses to stress in salt-sensitive SHRs fed high-sodium diets (Scrogin, Hatton, and McCarron, 1991).

Magnesium

Only a few studies have examined the relation between magnesium and blood pressure. Although one study found a relation between lower magnesium intake and increased incidence for essential hypertension in a sample of female nurses (Ascherio et al., 1996), only minimal effects of magnesium supplementation on blood pressure have been observed (Kawano et al., 1998). As with calcium, no research has been conducted examining the relation between magnesium and cardiovascular response to stress in humans.

Omega-3 Polyunsaturated Fatty Acids

Consumption of eicosapentanoic (EPA) and docosahexanoic (DHA) acids, two omega-3 polyunsaturated fatty acids commonly found in fish, has been shown to be associated with reduced risk for coronary heart disease as well as essential hypertension (Mori et al., 2000). Additionally, significant reductions in blood pressure have been observed among hypertensives who increased consumption of omega-3 polyunsaturated acids (Bao et al., 1998). However, no studies to date have examined the relation between consumption of omega-3 polyunsaturated fats and cardiovascular reactivity to stress.

Summary

It is evident that there are many constitutional and lifestyle variables that may influence the stress–hypertension relation. These variables are not thought to be direct 'causes' of essential hypertension; rather, these variables influence the strength of other variables in increasing or

decreasing risk for hypertension. In many cases, these individual difference variables interact with one another in exerting their effect in predicting who will and who will not develop essential hypertension. To see a summary of findings regarding each of the variables discussed in this chapter, look at Table 6.1. Briefly, the table lists each variable presented and provides a rating regarding whether evidence exists linking the variable with (a) the relation between stress and risk for essential hypertension, and (b) the relation with cardiovascular response to stress. In addition the table lists any potential interactions with other individual difference variables that have received at least some attention in the literature. One needs only a brief glance at the table to acknowledge that a multitude of interacting variables exists influencing the stress–hypertension relation. Considering the sheer number of these overlapping interactions, one can only imagine the complexity of

Table 6.1. Summary of Constitutional and Lifestyle Variables That Influence the Stress–Hypertension Relation

Variable	*Differential Relation between Stress and Essential Hypertension?*	*Related to Increased Cardiovascular Response to Stress?*	*Potential Interaction Variables That Have Been Studied*
Constitutional Factors			
Increased Age	Yes	Yes	gender; sodium sensitivity; neuropsychological deficits
Heritability	Yes	Yes	sodium sensitivity
Parental History of Hypertension	Yes	Partial Support	suppressed hostility; anxiety; defensiveness; behavioral responses to stress; hostility; neuropsychological deficits; perception of pain; caffeine use; sodium sensitivity; cognitive coping
Male Gender	Mixed	Yes (BP only)	age; physical fitness; hostility; cognitive coping; social support

continued

Table 6.1.(*Continued*)

Variable	*Differential Relation between Stress and Essential Hypertension?*	*Related to Increased Cardiovascular Response to Stress?*	*Potential Interaction Variables That Have Been Studied*
Black Ethnicity	Yes	Yes	lifestyle factors; history of exposure to racism; sodium sensitivity; anxiety; depression; cognitive coping; social support; religious support
Presence of Diabetes	?	?	obesity; physical inactivity
Obesity	?	?	physical inactivity; hostility
Lifestyle Factors			
Less Physical Fitness	?	Mixed	obesity; presence of diabetes; gender
Smoking	?	?	caffeine and alcohol use; ethnicity; hostility
Alcohol Consumption	Yes	No (reduced)	nicotine use; Type A behavior pattern; family history of alcoholism; ethnicity; hostility
Caffeine Consumption	?	Yes	smoking; parental history of hypertension
High Sodium Intake	Yes	Yes	age; heritability; parental history of hypertension; ethnicity; anger; anxiety
Low Potassium Intake	?	?	sodium sensitivity; ethnicity
Low Calcium Intake	?	?	sodium and potassium intake
Low Magnesium Intake	?	?	
Low Omega-3 Fatty Acids Intake	?	?	

the Venn diagram that would be needed to portray them. Suffice it to say that I will not attempt to construct such a Venn diagram for purposes of illustration.

In the first two columns, summary ratings for each potential individual difference variable are made based upon the quality and con-

sistency of the empirical findings from the literature. The first column examines empirical evidence linking each variable to the stress–hypertension relation. Note that although some of these variables may be directly related to risk for hypertension (obesity, gender, and age), this table considers the variable only within the context of the stress–hypertension relation. As stated earlier, if being obese can be shown to be associated with increased stress in one's life due to factors like increased health problems, decreased mobility, and exposure to societal discrimination against obesity, then evidence suggests that obesity influences the stress–hypertension association above and beyond the direct link obesity has with hypertension. In the second column, empirical evidence is examined regarding whether each variable has been shown to be associated with exaggerated cardiovascular reactivity to stress, the hypothesized mediator of the stress–hypertension relation. For both columns, a rating of 'Yes' indicates that the data support the relation in question. A 'No' rating indicates that either the available evidence finds no support for the relation in question or finds the opposite relation. Obviously, a rating of 'Partial Support' indicates that there is some support for the relation in question, and a rating of 'Mixed' indicates that the available data are inconsistent. Finally, a rating of '?' indicates that there are not enough data available to attempt to answer that particular question.

Although there is a need to learn more about these variables and the potential interactions among them, for many, there already is sufficient evidence to warrant consideration in evaluating a patient's risk for hypertension. Let's return to Franklin for a moment and consider which constitutional and lifestyle variables may help us better understand his hypertensive condition and any stress-related variables that may be operating. Certainly, as a middle-aged, African American man, he exhibits several constitutional variables known to influence the association between stress and onset of hypertension. He is genetically predisposed to developing high blood pressure, as evidenced by his parents' hypertension and his father's consequent cardiac problems. Fortunately, Franklin is in fairly decent physical condition and possesses adequate health habits. He does not drink or smoke, and he works out four to five times per week. However, he is somewhat overweight, a condition that runs in his family. Therefore, Franklin ex-

hibits several constitutional factors that potentially increase his risk for the development of high blood pressure that appear to be partially offset by some healthy lifestyle factors that decrease overall risk. Although we know a good bit about constitutional and lifestyle factors that may influence Franklin's risk for hypertension, we know very little about any psychological or social parameters that may have contributed to the onset of his hypertension. This is unfortunate because we know that his experience of a significantly stressful life event, the death of the child, corresponded with the diagnosis of his hypertension. We do not know whether he experienced any problems with anxiety or depression prior to or following this incident. We also do not know how he typically copes with stress and whether his strategy facilitated coping with this stressor, although, from the behavioral observations of his response to confrontation in the laboratory, hypotheses regarding his ability to express anger appropriately could be generated. We also do not have any information regarding whether he confided in co-workers or parents and shared his feelings regarding this incident. Has he made use of his close family support network or used his religious beliefs to cope with this stressful time in his life? Although it appears reasonable to conclude that these psychological and social factors may have influenced the onset of Franklin's hypertensive state, just what do we know regarding the relation between psychological and social factors and risk for hypertension? The answers to these questions are considered in the following chapter.

7

Individual Differences and Essential Hypertension

Psychological and Social Factors

From evidence presented in Chapter 6, it is quite obvious that constitutional and lifestyle factors influence the relation between stress and hypertension. They probably did in Franklin's case. Many of these same variables were shown to also be associated with elevated cardiovascular responses to stress, a hypothesized mediator of the stress–hypertension relation. However, when we applied our knowledge of these constitutional and lifestyle variables in the case of Franklin's hypertension, it became clear that the influence of several other variables was still unknown, namely, those pertaining to Franklin's psychological state both prior to and following the traumatic incident. Additionally, the influence of Franklin's social network and the support he either received or failed to receive were unknown. In this regard, it seems important to also consider psychological and social factors that may influence the stress–hypertension relation. In the same format applied in Chapter 6, both psychological and social individual difference variables that have been hypothesized to influence the stress–hypertension relation are considered and reviewed in this chapter.

Psychological Factors

Personality factors have been long hypothesized to be associated with the etiology of essential hypertension (Alexander, 1939; Diamond, 1982). As mentioned in Chapter 1, even the term 'hypertension' connotes involvement of emotional or psychological factors. Historically, three different, but related, perspectives have been identified regarding the interrelation between personality factors and risk for essential hypertension: the Negative Affect Hypothesis, the Suppressed Hostility Hypothesis, and the Emotional Defensiveness Hypothesis (Jorgensen et al., 1996). Very briefly, the Negative Affect Hypothesis stems from observations of psychoanalysts who worked with hypertensive patients in the early part of the twentieth century (Ayman, 1933; Dunbar, 1943), who described hypertensives as 'neurotic' patients, characterized by frequent bouts of intense negative affect, including anxiousness, anger, and depression. Based upon these observations, it was hypothesized that persons who exhibited this degree of negative affect throughout life also exhibited an increased risk for onset of essential hypertension as they aged. The Suppressed Hostility Hypothesis was also derived from observations of psychoanalysts (Alexander, 1939), as well as the work recognizing that behavioral responses of hypertensive patients to confrontation were quite distinct from behavioral responses of persons with normal blood pressures (see pp. 142–146). This perspective was not concerned with the degree of emotionality that hypertensives reported across a range of measures of negative affect; rather, the focus was on the strategy hypertensive patients employed to express one type of negative affect, namely, anger. In particular, failure to express anger (anger suppression) was hypothesized to be associated with increased blood pressures and increased risk for hypertension. Finally, the Emotional Defensiveness Hypothesis was based upon observations that hypertensive patients avoided dealing with emotional content of any type (Handkins and Munz, 1978) and more recent evidence linking hypertension with diminished negative appraisals during exposure to stressors (see pp. 147–150) or painful stimuli (see pp. 150–151). It is probably obvious that these three hypotheses are not mutually exclusive and that certain hypertensive patients could be characterized by increased expe-

rience of negative affect, suppression of anger, and emotional defensiveness. Indeed, many of the studies that provide support for a given perspective also provide information pertinent to one of the remaining perspectives. Nevertheless, because they represent specific hypotheses regarding the relation between personality factors and hypertension, they will be considered individually.

Negative Affect Hypothesis

Because broad measures of neuroticism have revealed no consistent relation with essential hypertension (Cochrane, 1973; Davis, 1970; Kohler et al., 1993; Sainsbury, 1964; Spiro et al., 1995), most investigators have explored the Negative Affect Hypothesis by administering trait measures of negative affect, most commonly anxiety, anger, and depression. Although measurement of the experience of negative affect can be conducted using behavioral coding of facial displays of emotion (Ekman and Friesen, 1978), most investigators of the relation between personality factors and hypertension have used self-report questionnaires. Behavioral coding of emotions is simply too labor-intensive to conduct during the large-scale epidemiologic investigations that are typically used to address these relations.

Trait Anxiety

In contrast to the acute alterations in anxiety that occur in response to exposure to a threatening stimulus, trait anxiety refers to the relatively enduring anxiousness that persons experience on a daily basis. High-trait-anxious individuals simply tend to be more nervous or 'high-strung' than low-trait-anxious individuals. Elevated trait anxiety is associated with an increased sensitivity to physiological cues of arousal as well as cognitive symptoms of chronic worry and the tendency to view the environment as threatening or dangerous. The hypothesis that high-trait-anxiety persons exhibit an increased risk for hypertension makes intuitive sense; if an individual goes through life with a characteristic hyper-vigilance for internal cues of anxiety and sources of threat from the environment, one could easily speculate that high blood pressure might be a potential medical consequence. Let's exam-

ine the literature that has tested the relation between trait anxiety and risk for essential hypertension.

Although increased levels of trait anxiety have been reported among hypertensive patients in comparison to normal blood pressure controls (Markovitz et al., 1991; Sullivan et al., 1981), others have reported no relation between trait anxiety and blood pressure status (Friedman et al., 2001; Shinn et al., 2001; Siegel and Leitch, 1981). Because definitive conclusions cannot be drawn from case–control research, the more convincing data associating trait anxiety with risk for hypertension come from epidemiological cohorts in which larger samples of individuals are followed for extended periods of time. For example, data from the Framingham Study, an epidemiologic study that has spanned almost half a century, revealed that there was more than a twofold increased incidence of hypertension associated with a measure of anxiety (or tension) among men but not among women (Markovitz et al., 1993). Even stronger associations between anxiety and hypertension were reported by Jonas, Franks, and Ingram (1997) in a national sample of both black and white men and women (NHANES I). Interestingly, in this study, significant risk for hypertension associated with trait anxiety was observed for black men and women of all ages, but only for older white men and women. Findings from a four-year prospective study relating psychosocial factors to onset of hypertension among white and black students at the University of Zimbabwe confirmed the association between trait anxiety and increased risk for hypertension among black students (Somova, Connolly, and Diara, 1995). However, no relation between trait anxiety and hypertension was observed among white students. Data from three other large-scale epidemiologic studies, the CARDIA Study (Yan et al., 2003), the Tecumseh Study (Young et al., 1998), and a study of Australian government workers (Chapman et al., 1990), however, failed to confirm any increased risk for hypertension for persons with high trait anxiety.

Although findings regarding the relation between trait anxiety and hypertension have been mixed, there is some evidence that anxiety is related to autonomic nervous system functioning, which in turn may lead to elevated blood pressures. For example, Piccirillo et al. (1998) measured parameters of the autonomic nervous system and

morphological characteristics of the heart among groups of high- and low-anxious hypertensive and normotensive adults. Congruent with their hypotheses, higher anxiety scores were associated with the increased sympathetic nervous system influence on heart rate as well as left ventricular hypertrophy. Comparable associations between anxiety and physiological parameters were observed for both hypertensive and normotensive participants, indicating that this relation was not unique to those diagnosed with hypertension. High trait anxiety has also been shown to be associated with diminished baroreceptor sensitivity, consequently resulting in increased SBP variability (Virtanen et al., 2003; Watkins et al., 1998), indicating heightened sympathetic nervous system activation and reduced parasympathetic tone. Although trait anxiety appears to be associated with alterations in autonomic nervous system activity, there is currently no evidence that hypertensive and normotensive patients differ regarding how trait anxiety is linked to autonomic nervous system activity.

A few studies have explored the relation between trait anxiety and cardiovascular response to stress. Like the results of research on state anxiety (see pp. 132–135) and the epidemiologic research examining the role of trait anxiety as a psychological predictor of hypertension, these findings have been mixed. Although some researchers have found exaggerated cardiovascular reactions among individuals high in trait anxiety (Glass et al., 1983; Houston, 1977), others have found high trait anxiety to be associated with lower cardiovascular reactions to stress (Young et al., 1998). Anxiety has also been reported to interact with parental history of hypertension in affecting the magnitude of cardiovascular responding to mental stress (Manuck et al., 1985; Miller, 1992). In these studies, high-anxious young adults with a parental history of hypertension exhibited higher cardiovascular reactions to mental stress than either persons low in anxiety or those without a parental history of hypertension.

In summary, the evidence for a causal link between high trait anxiety and increased risk for developing essential hypertension is modest. Findings from both case–control and prospective studies examining the relation have been mixed. Likewise, anxiety does not appear to be directly linked to cardiovascular response to stress; rather it may exert its influence on the magnitude of cardiovascular reactions in

conjunction with other individual difference variables, like parental history of hypertension.

Trait Anger

Another component of negative affect that has been examined in relation to risk for essential hypertension is the constellation of variables referred to as trait anger or hostility. To be quite frank, these terms are often used interchangeably, although there is good reason to make careful distinctions between them. Using a comprehensive strategy for distinguishing among anger-related variables, Spielberger et al. (1985) described three distinct anger-related elements: anger, aggression, and hostility. Anger, according to Spielberger, referred to an emotional experience that was comprised of physiological arousal and a whole range of cognitive appraisals associated with the experience of anger (perceptions of unfairness or experiencing goal blockage). As stated in Chapter 5, the experience of anger can be assessed using state measures regarding how the respondent feels "right now" as well as using trait measures which request information regarding how one "typically feels." Individuals with high trait anger scores are typically temperamental and prone to overt expressions of the intense anger that 'hovers below the surface.' Aggression, the second anger-related variable described by Spielberger, referred to a prominent type of behavioral display of anger that can occur physically or verbally. Anger suppression, or the failure to express anger overtly, represents another type of behavioral response to anger; because data linking anger expression/suppression to hypertension are more pertinent for the Suppressed Hostility Hypothesis, it will be considered in the next section. Finally, Spielberger and colleagues distinguished hostility from both the experience of anger and the observable expressions of anger (expression or suppression). Although hostility is often confused with aggressiveness, in the psychological literature hostility represents an attitude of general cynicism and mistrust. As such, hostile persons believe that others are self-serving and frequently take advantage of those around them. Naturally, this suspicious demeanor results in heightened vigilance during interpersonal interactions and a tendency to perceive angry intent among others when in fact none may be present (Larkin, Martin, and McLean, 2002). Consequently, hostile persons may be more likely to

experience bouts of anger than low-hostile individuals and thus more likely to express anger aggressively.

As with research on trait anxiety, some case–control studies have found support for a link between trait anger and blood pressure status (Crane, 1982; Jern, 1982; Siegel and Leitch, 1981; Sullivan et al., 1981), while others have found no association between measures of trait anger and blood pressure (Durel et al., 1989; Friedman et al., 2001). In contrast to the copious literature relating anxiety and hypertension, only two prospective studies have examined the relation between measures of trait anger and onset of hypertension (Markovitz et al., 1991; 1993). In the study of middle-aged women reported by Markovitz et al. (1991), initial levels of trait anger did not predict onset of high blood pressure. However, change in trait anger over the study duration was associated with change in both SBP and DBP; therefore, increases in trait anger among these women were associated with increased blood pressures, even after controlling for traditional risk factors. In contrast, trait anger data from the Framingham Study were not associated with subsequent risk for essential hypertension (Markovitz et al., 1993).

Suls, Wan, and Costa (1995) conducted a meta-analysis of all studies conducted from 1963 to 1993 to clarify the inconsistent findings observed between hypertension and measures of trait anger. Overall effect sizes were quite small, indicating that even among those anger-related variables that were correlated with blood pressure, the magnitude of the association was not remarkable. Parameters most closely associated with blood pressure included measures of anger expression, not measures of trait anger.

Congruent with findings relating trait anger to risk for hypertension, findings relating trait anger to cardiovascular reactivity to stress have also been mixed. While some studies have reported a relation between increased trait anger and exaggerated cardiovascular reactions to stress (Durel et al., 1989; Johnson, 1989a), others have failed to find such a relation (Laude et al., 1997). Therefore, as with trait anxiety, even if trait anger is associated with increased risk for essential hypertension, it is unclear whether it influences cardiovascular reactivity to stress.

Hostility

Given the substantial body of evidence linking measures of hostility to coronary heart disease (see Smith, 1992), several researchers have examined the association between hostility and blood pressure. As with trait anxiety and anger, several studies have reported a significant association between hostility and blood pressure levels (Benotsch, Christensen, and McKelvey, 1997; Durel et al., 1989; Jamner et al., 1991; 1993; Räikkönen et al., 1999), but other studies have found no relation between measures of hostility and blood pressure (Friedman et al., 2001; Pasic et al., 1994). Guyll and Contrada (1998) reported a significant association between DBP and hostility among men, but not women. Unfortunately, very few case–control studies comparing hypertensive and normotensive patients on measures of hostility or prospective studies linking hostility to hypertension have been conducted; among those that have been conducted, no relation between hostility and essential hypertension has been observed (Steptoe, Melville, and Ross, 1982). Findings from two prospective studies examining the relation between hostility and onset of hypertension have likewise been mixed. Although Siegler et al. (1992) found no prospective relation between hostility and onset of hypertension, Yan et al. (2003) reported a significant relation between high hostility and increased risk for essential hypertension in the CARDIA Study.

Although very little work has been conducted examining the relation between hostility and hypertensive status, a considerable amount of research has investigated the relation between hostility and cardiovascular response to stress. Suls and Wan (1993) conducted a meta-analysis of all studies between 1965 and 1992 examining the relation between the magnitude of cardiovascular reactions to stress and various measures of hostility. Although no consistent relations were observed between measures of cardiovascular response to stress and the various indices of hostility, elevated DBP reactivity to interpersonal challenges was associated with high hostility as measured by the Cook-Medley Hostility Scale (Cook and Medley, 1954), but only under conditions of provocation or harassment. Subsequent studies of the relation between cardiovascular reactivity to stress and hostility have tended to use interpersonal tasks rather than the traditional laboratory mental stress

tasks. Congruent with the findings of Suls and Wan, these studies have confirmed the association between greater blood pressure reactions and high hostility during interpersonal tasks involving confrontation, marital interaction, harassment, or disclosure of a personally troubling issue (Brondolo, Rieppi, Erickson, et al., 2003a; Christensen and Smith, 1993; Powch and Houston, 1996; Smith and Gallo, 1999; Suarez et al., 1993; Suarez, Kuhn, Schanberg, et al., 1998a).

In general, the linkage between blood pressure reactivity to provocation and hostility has been demonstrated more consistently among samples of men than women, suggesting that gender may play an important role in impacting this association. It is important to remember, however, that males may be more likely to be threatened by the sorts of interpersonal challenges used in this body of literature, due to their focus on achievement, confronting the source of harassment, or winning at all costs. In fact, high-hostile women have been shown to exhibit comparable elevated cardiovascular responses to stress to those seen among high-hostile men when a less competitive task is used (Davis, Matthews, and McGrath, 2000). Additionally, there is evidence that parental history of hypertension interacts with hostility to determine magnitude of cardiovascular response to stress (Miller et al., 1998). In this study, high-hostile and low-hostile young adult males with and without a parental history of hypertension engaged in either a harassment or non-harassment condition. High-hostile offspring of hypertensives exhibited significantly greater cardiac output and forearm blood flow responses than individuals in the other groups, but only during the harassment condition. In this regard, both dispositional and situational characteristics influenced whether exaggerated cardiovascular responses were observed.

The most consistent cardiovascular parameter associated with hostility during provocation stressors has been DBP, although increased forearm blood flow among high-hostile persons has also been reported (Miller et al., 1998; Suarez et al., 1998a). Differences in heart rate response to these stressors among high- and low-hostile persons are rarely, if ever, observed. Based upon this constellation of findings, both cardiac (lack of heart rate response differences) and vascular (differences in increased forearm blood flow response) involvement could be hypothesized to be associated with the commonly observed differ-

ence in DBP response to provocation between high- and low-hostile individuals. To examine the nature of the hemodynamic factors underlying this blood pressure response difference, a few studies employing impedance cardiography have revealed that blood pressure increases during provocation for high-hostile persons are associated with greater total peripheral resistance and lesser cardiac output than those for low-hostile persons (Bongard, al'Absi, and Lovallo, 1998; Davis et al., 2000). In an examination of nervous system influences upon this exaggerated peripheral resistance response, Suarez, Sherwood, and Hinderliter (1998b) contrasted alpha- and beta-adrenergic receptor responsiveness to pharmacological agonists of high- and low-hostile men. Although no differences in alpha-adrenergic receptor responsivity was observed between high- and low-hostile men, decreased beta-adrenergic receptor responsiveness was observed among the high-hostile participants. These findings were recently replicated using a sample of middle-aged women (Sherwood et al., 2004). This pattern of results indicates that the vascular response observed among high-hostile individuals is more closely associated with a diminished vasodilatory response of the beta-adrenergic nervous system than an increased vasoconstrictive response of the alpha-adrenergic nervous system. Additionally, hostility has been shown to be associated with reduced baroreceptor sensitivity (Virtanen et al., 2003) and lower parasympathetic regulation of the heart (Sloan et al., 2001), suggesting that the linkage between hostility and cardiovascular response to stress is not entirely mediated by peripheral vascular influences. It appears that both beta-adrenergic and parasympathetic nervous systems have a role in generating the increased blood pressure response to provocation observed among high-hostile participants in laboratory studies of the cardiovascular reactivity to stress–hostility relation.

Although a considerable amount of research has supported the hypothesis that hostility is related to an increased magnitude of cardiovascular reactivity to stress, in particular in response to situations involving confrontation, harassment, or self-disclosure, it is important to consider alternative hypotheses as well. For example, risk for essential hypertension associated with hostility has been hypothesized to be associated with differential lifestyle habits, including smoking, alcohol use, and eating and exercise habits (Leiker and Hailey, 1988). In their

examination of the relation between hostility and lifestyle factors, Musante et al. (1992) found some support for this alternative hypothesis. Increased hostility was related to poorer health habits, including consumption of a less healthy diet (increased fat and sugar consumption accompanied by decreased fiber intake) and a greater tendency to smoke cigarettes. Data from the CARDIA Study support these conclusions as well, with hostility being associated with higher frequency of smoking cigarettes and marijuana as well as consumption of a higher number of calories (Scherwitz et al., 1992). Finally, prospective links between measures of hostility taken during the undergraduate years and health behaviors in adulthood have provided additional evidence for this hypothesis. Data from the UNC Alumni Heart Study showed that high hostility during young adulthood was associated with increased smoking and consumption of alcohol and a high-fat diet, obesity, and low social support at midlife (Siegler et al., 2003). Therefore, there is evidence that the association between hostility and risk for essential hypertension may not reflect a simple linear relation and that multiple pathways may be involved.

Depression

Depression represents another emotion that comprises negative affect. Unlike anxiety and anger, which are thought to be associated with increased physiological arousal or irritability, depression is commonly associated with under-arousal or the lack of activity. Depressed individuals often sleep more and engage in less activity than nondepressed counterparts, and this inactivity is often associated with increased complaints of fatigue and loss of energy. If we recall the defense and defeat reactions described by Henry and Stephens (1977) in Chapter 3, anger and anxiety appear to be classic defense reactions, while depression would be categorized as a defeat reaction. Based upon observations of psychiatric outpatients that revealed an increased incidence of essential hypertension associated with diagnoses of depression (Rabkin, Charles, and Kass, 1983), speculations that perhaps a causal relation existed between depression and hypertension have been entertained (Dilsaver and Coffman, 1988). Accordingly, individuals who experience depressive episodes throughout life were hypothesized to be

at increased risk for subsequent onset of essential hypertension. Let's examine the evidence supporting this hypothesis.

Given the strong association between depression and coronary heart disease (see Rozanski et al., 1999), it is certainly important to examine whether a comparable relation exists between depression and essential hypertension, a primary risk factor for coronary heart disease. The majority of case–control studies aimed at measuring symptoms of depression in hypertensive patients, however, have failed to find any relation between depression and hypertension (Edlavitch et al., 1987; Friedman and Bennet, 1977; Friedman et al., 2001; Jones-Webb et al., 1996; Kim et al., 2003). In contrast, Grewen et al. (2004) reported a relation between depression and level of blood pressure during ambulatory monitoring, but only among participants with a parental history of high blood pressure. If depression is linked with increased blood pressure or increased incidence of hypertension, it may exert this influence only among a certain subgroup of individuals.

In contrast to case–control studies, there is some prospective evidence linking indices of depression with onset of essential hypertension among blacks, but not whites (Davidson et al., 2000; Jonas et al., 1997). However, the evidence is not that consistent, as other prospective studies have failed to find any elevated risk for hypertension associated with depression at all (Levenstein, Smith, and Kaplan, 2001; Shinn et al., 2001; Yan et al., 2003). Although Räikkönen, Matthews, and Kuller (2001) did not find a relation between initial depression and subsequent risk for hypertension, they reported a significant association between increased depression and increased SBP among women participating in a nine-year prospective study. Although findings from the Kuopio Ischemic Heart Disease Risk Factor Study in Finland also failed to find a significant relation between depression and hypertension, a highly significant association was uncovered between hopelessness, an important component of depression, and risk for hypertension (Everson et al., 2000). In this study, high levels of hopelessness were associated with an increased relative risk (RR) of 3.22, indicating that persons high in hopelessness had over a three times greater risk of developing hypertension than low-hopelessness counterparts. Although the body of evidence supporting a link between depression and

risk for hypertension is not large, there are some indications that depressed mood may indeed be an important psychosocial risk factor to consider in predicting onset of essential hypertension.

Despite the potential importance of depression for predicting essential hypertension, the literature examining the relation between depression and acute cardiovascular responses to stress is not substantial. Perhaps it may go without saying that because depression is typically thought to be associated with a dampened rather than an accelerated sympathetic nervous system response, fewer investigations of this hypothesis have been conducted. However, on the assumption that both depression and cardiovascular response to stress involve autonomic nervous system functioning, a few studies have examined this potentially important relation (Delehanty, Dimsdale, and Mills, 1991; Light, Kothandapani, and Allen, 1998). Although both studies found very limited support for the relation between depression and blood pressure response to stress, clear evidence was uncovered for the relation between depression and increased heart rate response to stress. The exaggerated heart rate response observed among persons with higher depression scores was accompanied by a shorter pre-ejection period (Light et al., 1998), indicating that the observed autonomic imbalance involved the sympathetic nervous system. In a recent pharmacologic investigation on depressed patients (Straneva-Meuse et al., 2004), SBP, cortisol, and epinephrine reactivity to mental stress was dampened following intervention with one of two common anti-depressant medications. Although data addressing the relation between depression and acute cardiovascular response to stress are limited, there is some indication that depression is associated with increased cardiovascular response to stress (particularly heart rate) and that this exaggerated reactivity can be attenuated with the successful treatment of depression.

Negative Affect and Mood

A few studies have examined the Negative Affect Hypothesis by lumping together measures of anxiety and depression into an amalgamated measure of negative affect or mood. For example, analysis of psychosocial risk factors of hypertension in the follow-up study associated with NHANES I was conducted by deriving a single negative affect factor comprised of symptoms of both anxiety and depression. As with

NHANES I, the follow-up data showed a significant association between negative affect and subsequent risk for hypertension for both men and women (Jonas and Lando, 2000). The relative risk for hypertension was particularly elevated among black women (RR = 3.12). Ewart and Kolodner (1994) also employed a measure of negative affect based upon combined scores on standardized measures of depression and anxiety in a study examining ambulatory blood pressures of adolescents. Congruent with previous work on measures of negative affect, they found that negative affect was a significant predictor of ambulatory blood pressures, even after controlling for resting blood pressure, body size, and substance use. In an 18-month study of the relation between mood and blood pressure, Pollard and Schwartz (2003) reported an association between increases in negative affect and increases in SBP; however, Brondolo et al. (1999) reported no relation between negative affect and blood pressure change in a similar study. Like the findings relating both anxiety and depression to measures of blood pressure or hypertensive status, results of research examining the relation between negative affect and blood pressure status are mixed. However, this should not be that surprising, as measures of negative affect are generally comprised of combining scores from traditional measures of anxiety and depression. Furthermore, no empirical work has examined the relation between trait measures of negative affect and cardiovascular reactivity to stress.

Summary of Findings Supporting the Negative Affect Hypothesis

The Negative Affect Hypothesis stipulates that persons who experience a range of negative emotions more frequently or more intensely will exhibit a greater risk for developing essential hypertension than persons who experience such emotions less often or with less intensity. Studies designed to examine this hypothesis have approached it by defining negative affect broadly to include a number of different types of negative emotions or more narrowly to focus on an individual source of negative affect like anxiety, anger, hostility, or depression. Although findings across these studies have been mixed, there is enough prospective evidence available to suggest that at least for some individuals the frequent, intense exposure to negative emotions may play a role in the etiology of essential hypertension. In particular, prospective

evidence linking both anxiety and depression (as well as their combination, negative affect) with subsequent risk for developing essential hypertension suggests that these variables may be important individual difference factors to consider. However, it is important to recognize that the specific type of negative affect associated with increased risk for hypertension varies among these prospective studies. For example, Markovitz et al. (1993) found prospective evidence linking anxiety to onset of hypertension, but not anger. Yan et al. (2003) found no linkage for either anxiety or depression with onset of hypertension, but found a relation between hostility and subsequent hypertension. Therefore, although there is some support for the Negative Affect Hypothesis within each prospective study, the parameter related to onset of hypertension differs from study to study. Finally, because evidence linking both anxiety and depression to acute cardiovascular response to stress is generally limited, it is possible that their influence may exert its effect through an alternate pathway.

Prospective evidence linking trait anger and hostility to hypertension is not as convincing as the data on anxiety and depression. However, evidence linking hostility to the magnitude of cardiovascular response to stress is quite strong. Therefore, it appears that if anger or hostility is related to risk for hypertension, it is likely that their influence occurs as a result of the elevated cardiovascular reactions to stress associated with these variables.

Suppressed Hostility Hypothesis

The belief that essential hypertension is associated with the tendency to suppress angry feelings is one of the longest-standing psychosomatic hypotheses. As first stipulated by Alexander (1939), hypertension was associated with conflict between hidden hostile urges and dependency needs that resulted in the inadequate overt expression of anger. Accordingly, individuals who experienced angry feelings but failed to express them due to fears that by doing so they might damage important interpersonal relationships tended to develop essential hypertension. In contrast to the Negative Affect Hypothesis which focuses upon the intensity of the emotional experience, the Suppressed Hostility Hypothesis centers around the expression of presumably normal anger ex-

periences. Like a 'pressure cooker,' in which steam (anger) accumulates with no mechanism for release (inhibited anger expression), suppressing such anger can have a dangerous outcome (chronically elevated blood pressure), particularly when more heat (environmental stress) is applied.

Evidence supporting the Suppressed Hostility Hypothesis of essential hypertension has been derived from several bodies of literature (see Diamond, 1982), including psychodynamic evaluations of personality characteristics of essential hypertensive patients, studies employing both projective and objective measures of hypertensive personalities, behavioral observations of hypertensive patients exposed to interpersonal challenges (see pp. 142–146), and social psychological investigations of the frustration–aggression hypothesis. Across studies comprising these varying experimental domains, expression of anger has been shown to be generally associated with reduced blood pressures while suppression of anger has been more likely to be associated with blood pressure elevations and increased incidence of essential hypertension. Despite consistent findings, Diamond cited obvious methodological concerns regarding the assessment of the 'hypertensive personality' via psychiatric interviews, rating systems, or projective assessment devices with questionable reliability and validity.

Anger-Expressive Style

Investigations of anger-expression style that followed Diamond's (1982) review of the literature tended to employ assessment strategies that were designed to measure anger-expression style directly. In particular, the methods for assessing anger-expressive style employed in the epidemiological work of Harburg and colleagues as well as the contributions pertaining to the development of Spielberger's (1985) anger-expression scales represent important advances in the assessment of anger suppression/expression. The focus of both of these assessment strategies was not uncovering broad personality dimensions that may comprise the hypertensive personality; rather, these instruments were designed specifically to measure styles of anger expression. Persons scoring high on the Anger-Out dimension typically expressed anger overtly by confronting the source of the anger provocation directly. In contrast, persons who scored high on the Anger-In dimension were

more likely to inhibit expression of anger and avoid confronting the source of provocation. Although on the surface it appears that Anger-Out and Anger-In might represent opposite ends of a single continuum of anger expressiveness, Spielberger's data indicated that Anger-Out and Anger-In reflected two independent dimensions of anger expression. Thus individuals who tend to suppress anger expression in most situations, only to have their anger 'boil over' during periods of explosive anger expression, can exhibit elevated scores on both dimensions of Anger-Out and Anger-In.

Harburg and colleagues have conducted several population-based investigations exploring the relation between anger expression and blood pressure that have now spanned over four decades (Gentry, Chesney, Gary, et al., 1982; Harburg, Blakelock, and Roeper, 1979; Harburg et al., 1964; 1973; 1991; 2003; Julius et al., 1986). Their paradigm for assessing anger suppression involves asking study participants to imagine a few scenarios in which they have been the target of an unfair accusation by an authority figure, like a policeman, and to report their most likely response. Based upon responses to these sorts of questions, participants are categorized into those who report suppression of anger (Anger-In) and those who report overt anger expression (Anger-Out). Findings regarding the relation between anger suppression/expression and blood pressure from these studies have been mixed, with some finding higher blood pressures among individuals who typically suppress anger (Gentry et al., 1982; Harburg et al., 1973), some finding higher blood pressures among individuals who typically express anger (Harburg et al., 1991), and some finding no difference in blood pressures between individuals who typically suppress and express anger (Julius et al., 1986; Harburg et al., 2003). Although these latter two studies failed to find any difference between anger-suppressing and anger-expressing individuals on blood pressure, resting blood pressure interacted with anger suppression in predicting cardiovascular mortality; that is, high anger suppression in conjunction with high blood pressure resulted in increased mortality rates, a relation not observed among persons with low or normal blood pressure.

Mixed findings have also been observed using Spielberger's measures of anger expression, with some studies demonstrating a relation between Anger-In (anger suppression) and elevated blood pressure

(Johnson et al., 1987a; 1987b; Perini et al., 1990), and others demonstrating a relation between Anger-Out (anger expression) and elevated blood pressure (DeShields, 1985; Johnson, 1989a). Still other studies have failed to find any differences between hypertensives and normotensives on measures of Anger-In or Anger-Out (Friedman et al., 2001; Larkin and Zayfert, 2004; Porter et al., 1999).

Suls et al. (1995) examined studies exploring the relation between anger expression and hypertension in their meta-analysis of all studies of hypertension and measures of anger expression. There was modest support for a positive relation between the suppression of anger and blood pressure, with the two measures highlighted by the authors as yielding the most consistent relations with blood pressure as Harburg's (1973) Anger-In/Anger-Out Index and Spielberger's (1985) Anger-In Scale, both showing relations between anger suppression and increased blood pressures. A comparable meta-analysis of studies examining the relation between the expression of anger and ambulatory measures of blood pressure also yielded only modest associations between anger suppression and DBP, but not SBP (Schum et al., 2003).

Type A Behavior Pattern

Although investigations of anger-expressive style have commonly linked anger suppression with essential hypertension and cardiovascular disease, there is also evidence that persons who are easily provoked into anger and readily display hostile behaviors have an increased risk for cardiovascular disease. Foremost in this literature is the empirical work on the Type A Behavior Pattern (TABP), initially identified by Friedman and colleagues (1960). Very briefly, TABP is comprised of a constellation of behaviors, including the outward expression of anger as well as intense competitiveness and a chronic sense of time urgency. In addition to increased verbal expressions of anger, individuals characterized as exhibiting the TABP employ loud, terse vocal characteristics, frequently interrupt others in conversation, and display obvious facial expressions of dislike and anger. In the prospective Western Collaborative Group Study of executives, twice the risk for coronary heart disease among Type A was observed in contrast to Type B men (Roseman et al., 1975). Because of the strong association between TABP and heart disease, it was logical to consider ex-

ploring the relation between TABP and risk factors for heart disease, including essential hypertension. Although this direction of research appeared promising, findings have been inconsistent, with some researchers reporting increased TABP among hypertensive patients (Irvine et al., 1991; Lázaro et al., 1993), some reporting increased TABP among normotensive controls (Steptoe et al., 1982), and yet others reporting no difference in TABP characteristics between hypertensives and normotensives (Friedman et al., 2001; Russell, 1983; Steptoe et al., 1984). In the only prospective trial examining TABP characteristics and risk for essential hypertension, Yan et al. (2003) reported a significant predictive association between a measure of time urgency and impatience and subsequent incidence of hypertension at the 15-year follow-up period of the CARDIA Study. There was no association, however, between achievement striving/competitiveness and risk for hypertension.

Although evidence linking TABP to essential hypertension has been inconsistent, several investigators have explored the relation between TABP and cardiovascular response to stress. Like studies linking hostility to cardiovascular response to stress, these studies have also shown that the linkage between TABP and cardiovascular response to stress depends on the experimental context employed (see Houston, 1986). If the task involves harassment and a moderate degree of engagement or effort, persons with TABP tend to exhibit greater cardiovascular reactions than Type B counterparts (Glass et al., 1980; Jorgensen and Houston, 1981; Manuck and Garland, 1979).

Curvilinear Hypothesis

From the mixed findings relating anger suppression and expression with blood pressure status, Harburg et al. (1979) hypothesized that both overt aggressive displays of anger *and* anger suppression represented forms of resentful anger expression that were related to development of essential hypertension. As such, they concluded that hypertensives "may be inappropriately assertive as well as inappropriately submissive" (p. 199). These findings suggested that a curvilinear relation best described the relation between typical anger-expressive style and blood pressure. There is actually now some very convincing evidence that this may indeed be the case. In a four-year prospective

study, Everson et al. (1998) reported an increased incidence of essential hypertension for men with high Anger-Out scores as well as men with high Anger-In scores. The authors reported that a 12 percent increase in incidence of hypertension was associated with each one-point increase on the measure of either Anger-In or Anger-Out. Furthermore, these associations were maintained after controlling for a number of standard risk factors for hypertension, including body mass index, family history, smoking, alcohol consumption, physical activity, and baseline blood pressures.

The conclusions of Harburg et al. (1979) and data supporting a curvilinear model of anger expression and blood pressure have led to more attention being paid to identifying more constructive styles of anger expression. If both passive-submissive and overt aggressive anger-expression styles are associated with elevated blood pressures, presumably the optimal anger-expression strategy involves the assertive expression of anger. Starting from this premise, Davidson et al. (2000) devised the Constructive Anger Behavior–Verbal Style Scale, a rating scale that can be applied to assess constructive anger-expressive behaviors (or what Harburg called reflective anger coping) that occurred during structured interviews aimed at discussing typical anger-expression styles. In this study, high scores in constructive anger were shown to be associated with lower blood pressures, even after controlling for a variety of standard hypertension risk factors, including body mass index, smoking and alcohol use, diabetic status, and family history of heart disease.

Prospective Trials of Anger Expression

Several prospective studies that have examined the relation between anger-expressive style and onset of hypertension have now been conducted (Everson et al., 1998; Kahn et al., 1972; Markovitz et al., 1991; 1993; Somova et al., 1995). Findings, however, have been mixed, with anger suppression (Anger-In) predicting subsequent onset of hypertension in two studies (Kahn et al., 1972; Somova et al., 1995), Anger-Out predicting subsequent hypertension onset in one study (Everson et al., 1998), and no association with either Anger-In or Anger-Out in two prospective trials (Markovitz et al., 1991; 1993). These mixed findings have led researchers to explore variables that may help explain why

risk for hypertension is associated with anger-expression style only among some individuals.

Although modest associations between anger-expression styles and blood pressure using both case–control and prospective methods have been reported, it is possible that more robust findings have not been observed because anger expression is related to blood pressure only among a subgroup of patients who develop essential hypertension. For example, Cottington et al. (1986) found that suppression of anger interacted with job stress in predicting hypertensive status among factory workers. Workers with high job stress who suppressed anger exhibited higher blood pressures than either workers who had less job stress or who expressed anger openly. In this study, the relation between anger suppression and blood pressure was evident only under conditions of high stress, suggesting that suppression of anger may not be related to onset of hypertension within low-stress occupations. Additionally, Gentry (1985) hypothesized that ethnicity interacted with suppression of anger in predicting hypertension, based upon evidence that black males who engaged in more anger suppression than white males had a greater risk for onset of hypertension.

A classic study conducted by Esler et al. (1977) implicated a subgroup of hypertensive patients that were categorized according to their propensity for anger suppression and other unique physiological characteristics. In this study, a subgroup of mild hypertensive patients was identified as having 'neurogenic' hypertension, based upon observations that their blood pressures returned to normal levels following pharmacologic blockade of the autonomic nervous system. These patients also exhibited other signs of sympathetic nervous system involvement including increased plasma norepinephrine levels and elevated plasma renin activity. Not surprisingly, this group of 'neurogenic' or high-plasma-renin hypertensive patients had higher scores on measures of suppressed anger than either low-renin hypertensives or normotensives. The authors concluded that for at least some hypertensive patients, suppression of anger is associated with their higher recorded blood pressures. Subsequent empirical work has also reported increased levels of depression, hostility, and anxiety among high-plasma-renin hypertensives, suggesting that their 'neurogenic' profile is not confined just to problems expressing anger (Thailer et al., 1985).

Anger Expression and Cardiovascular Response to Stress

Given that significant associations have been observed between anger-expression style and essential hypertension, many investigators have also explored the relation between anger suppression/expression and acute cardiovascular responses to stress. As in the literature examining the relation between anger suppression/expression and essential hypertension, the evidence relating anger suppression/expression to cardiovascular reactivity to stress is mixed. While some investigations have reported increased cardiovascular reactions during anger suppression (Van Egeren, Abelson, and Thornton, 1978), others have reported increased reactions during anger expression (Siegman, 1993; Suchday and Larkin, 2001).

In considering the lack of consistency of these findings, Engebretson, Matthews, and Scheier (1989) hypothesized that individuals exhibited exaggerated cardiovascular reactions only if they were instructed to engage in a type of anger expression that was different from their typical mode of expressing anger. Accordingly, persons with high Anger-In scores were hypothesized to have exaggerated cardiovascular responses only if they were instructed to express their anger overtly during the laboratory session in contrast to their typical anger-suppressive style. Likewise, persons with high Anger-Out scores would display exaggerated cardiovascular responses, but only during conditions in which they were expected to suppress their anger. Congruent with expectations, participants who engaged in their typical modes of anger expression during the laboratory session exhibited faster SBP recovery from harassment than participants who engaged in modes of anger expression different from their typical modes. Thus, both anger suppression and anger expression were shown to be associated with delayed cardiovascular recovery from stress when mode of anger expression did not match the participant's typical mode. Although findings from this study appeared to explain how both anger suppression and anger expression were associated with delayed cardiovascular recovery, other comparable investigations have failed to replicate these findings (Lai and Linden, 1992; Suchday and Larkin, 2001).

An alternate hypothesis explaining the lack of consistent findings between anger-expression styles and magnitude of cardiovascular responses to stress focuses on potential interactions with other variables.

For example, research has shown that relations between anger suppression and cardiovascular response to stress were observed only among participants with a positive family history of hypertension (Goldstein and Shapiro, 2000; Holroyd and Gorkin, 1983; Vögele and Steptoe, 1993). If the relation between anger suppression and acute cardiovascular response to stress was dependent upon presence of another individual difference variable like parental history of hypertension, one would expect significant associations between anger suppression and cardiovascular reactivity to be observed only if the study sample included a sufficient representation of offspring of hypertensive parents.

Summary of Findings Supporting the Suppressed Hostility Hypothesis

Although a wealth of empirical work has examined the Suppressed Hostility Hypothesis, definitive support for its basic assumptions cannot yet be made. Although it is fairly safe to conclude that hypertensive patients exhibit characteristic social skill deficits regarding emotional expression, particularly the expression of anger, it has yet to be determined whether these behavioral differences are involved in the etiology of essential hypertension. Certainly the inconsistent findings from both case–control comparisons and prospective trials have led to additional skepticism regarding the potential etiologic role of suppressed hostility.

It is of interest that higher blood pressures appear to be associated with both passive nonassertive and overtly hostile responses to provocation. Because both case–control and prospective studies conducted to date have explored the relation using linear models of prediction, their inconsistent findings would not be unexpected if this curvilinear model appears to fit the data best. Prospective studies based upon Harburg's (1979) definition of 'reflective' methods of anger expression or Davidson et al.'s (2000) constructive anger verbalizations may prove to be worthy in the pursuit of identifying anger expression variables that may be consistently linked with risk for essential hypertension.

Emotional Defensiveness Hypothesis

A final personality characteristic that has been associated with essential hypertension is emotional defensiveness. Research in this area was

grounded in the observations that hypertensive patients exhibit an acute cognitive response to stress characterized by underreporting or acknowledgment of emotional or painful stimuli (see pp. 147–151). According to the Emotional Defensiveness Hypothesis, persons who are uncomfortable in emotionally arousing situations adopt strat-egies to avoid these contexts, and when forced to engage emotionally salient information, they may resort to denial or underreporting of emotionality. Due to the degree of discomfort associated with emotionally salient information, defensive individuals become chronically vigilant of their environment, searching for cues of emotionality and developing appropriate preemptive avoidance responses. Over time, according to the Emotional Defensiveness Hypothesis, this heightened state of vigilance and the associated state of cortical arousal predispose individuals to developing essential hypertension. Let's examine evidence for the Emotional Defensiveness Hypothesis.

Defensiveness and Repression

Defensive individuals underreport negative affective states in an effort to portray a more positive and emotionally controlled image to those around them. Paulhus (1984) suggested that there were two distinct dimensions associated with defensive responding: self-deception and impression management. Although self-deception involves adopting socially desirable responses due to an individual's enhanced need for approval, impression management represents a more conscious effort to present a positive picture of oneself. Although several instruments are available to measure defensiveness, the most frequently used is a social desirability scale, like the Marlowe-Crowne Social Desirability Scale (Crowne and Marlowe, 1964). Persons who score high on social desirability exert energy to deceive those around them in an effort to maintain a positive impression. Repression (or self-deception) is a particular type of defensiveness that is characterized by both high scores on defensiveness and low scores on negative affect (Nyklíček, Vingerhoets, and Denollet, 2002). Presumably, repression represents a form of defensiveness that occurs unconsciously. There is some evidence that higher scores on either defensiveness or repression are associated with a greater incidence of essential hypertension (Mann and James, 1998; Wennerholm and Zarle, 1976) or higher resting or ambulatory

blood pressures (Jamner et al., 1991; Nyklíček et al., 1998; Shapiro et al., 1995). However, data from several studies examining the Negative Affect Hypothesis that have revealed relations between hypertension and higher scores on self-reported measures of negative affect (Ewart and Kolodner, 1994; Markovitz et al., 1991; Sullivan et al., 1981) or emotional reactivity (Melamed, 1987) seem to contradict these findings. Because hypertensive patients reported significantly higher levels of negative affect than normotensives in these studies, it seems unlikely that they adopted defensive postures in which they underreported their emotions. In a meta-analytic review of various personality factors and blood pressure status, Jorgensen et al. (1996) acknowledged the mixed findings relating defensiveness and blood pressure status, but concluded that the effect sizes among studies examining the relation of defensiveness and blood pressure were much larger than effect sizes from studies examining links between hypertension and any negative affect variable or measure of anger expression/suppression. Only one prospective study has examined the relation between defensiveness and blood pressure status (Rutledge, Linden, and Davies, 2000a), and found that higher scores on measures of defensiveness predicted greater SBP after three years.

Given the nature of the mixed findings relating defensiveness and hypertension, Perini et al. (1994) hypothesized that only a subgroup of hypertensive patients exhibited a repressive coping style. In contrast to previous work showing that high-plasma-renin-activity hypertensive patients were characterized by anger suppression (Esler et al., 1977), Perini et al. found a repressive coping style among *low*-plasma-renin-activity hypertensive patients. Taken together, these findings suggest that renin activity may be related to 'neurogenic' hypertension at both extremes; high-plasma-renin activity in hypertension is associated with suppressed anger and low-plasma-renin activity in hypertension is associated with emotional defensiveness.

Several studies have examined the relation between emotional defensiveness or repression and the magnitude of cardiovascular reactivity to mental stress, with some finding an association between elevated defensiveness or repression and increased cardiovascular reactions to stress (Coy, 1998; King et al., 1990; Miller, 1993; Weinberger, Schwartz, and Davidson, 1979) and others finding an inverse associa-

tion between defensiveness or repression and measures of cardiovascular reactivity (Melamed, 1996; Warrenburg et al., 1989). Given these mixed findings, investigators began to consider that risk for hypertension associated with defensiveness may be related to another individual difference variable. For example, other studies of cardiovascular reactivity to mental stress have reported that emotional defensiveness has been consistently associated with elevated blood pressure responses to mental stress among offspring of hypertensive patients (Jorgensen et al., 1992; Jorgensen and Houston, 1986; Shapiro et al., 1995) and persons with high scores on cynical hostility (Jamner et al., 1991; Jorgensen et al., 1995; Larson and Langer, 1997), suggesting that emotional defensiveness, in conjunction with either a parental history of hypertension or the presence of hostility, is more closely associated with exaggerated cardiovascular responses to stress.

Alexithymia

Alexithymia literally refers to the lack of words that describe emotion. Not surprisingly, persons who score high on measures of alexithymia have difficulty identifying and expressing feelings and distinguishing them from other bodily sensations. This is not to say that alexithymic individuals do not experience feelings; rather they have no conscious awareness of them (Sifneos, 1996). Although alexithymia may appear to be related to emotional defensiveness, it can be distinguished in that a defensive individual is presumably aware of his or her efforts at impression management whereas an alexithymic individual lacks this awareness. Similarly, although alexithymia may appear to resemble repression, repression typically is associated with a distinct emotion or emotionally arousing memory whereas alexithymia involves the entire emotional spectrum, including both positive and negative emotions. As such, a person scoring high on a scale of alexithymia would respond to episodes of extreme joy (for example, the birth of a baby), extreme sorrow (for example, the death of a loved one), and extreme anger (for example, being treated unfairly) in much the same way, with rather flat, monotone vocal characteristics and no facial displays of emotion. According to the Emotional Defensiveness Hypothesis, persons high in alexithymia should exhibit increased risk for essential hypertension. Let's see whether the literature supports this hypothesis.

Not many studies have examined the relation between alexithymia and hypertension. Among those that have been conducted, however, some have observed positive relations between measures of alexithymia and blood pressure (Jula, Salminen, and Saarijarvi, 1999; Todarello et al., 1995), while others have shown no relation (Newton and Contrada, 1994). Studies examining whether persons with higher scores on alexithymia had exaggerated cardiovascular responses to mental stress or exposure to emotional stimuli in comparison to low-alexithymic individuals have also been mixed, with some finding lower heart rate reactions to stress among alexithymic individuals (Newton and Contrada, 1994) and others finding no relation (Linden, Lenz, and Stossel, 1996; Roedema and Simons, 1999). If any relation exists, however, it appears that high alexithymia is more closely linked to attenuated rather than elevated heart rate reactions to stress.

Blunting and Monitoring

The dimension of monitoring–blunting represents another psychological individual difference parameter that may shed light on the relation between the purported repressive–defensive cognitive style and essential hypertension (Miller, 1987). Monitoring involves confronting stressors by learning as much as possible about the nature of the stress. Blunting, in contrast, involves minimizing threat-related cues associated with the confrontation of a particular stressor. Miller, Leinbach, and Brody (1989) compared hypertensive and normotensive patients on standardized measures of monitoring–blunting. Surprisingly, they found that hypertensive patients reported using significantly higher monitoring modes of coping with stress than the normotensive patient control group. Additionally, hypertensives reported being more concerned regarding the reason for their visit to the primary care clinic than normotensives. Although these findings appear to be at odds with other research supporting the repressive–defensive coping style among hypertensives, it is important to remember that evidence linking monitoring rather than blunting with hypertension was generated from studying how persons coped specifically with medical information. Strategies for coping with medical information may be quite different from the ways individuals typically respond to or admit emotionality.

Summary of Findings Supporting the Emotional Defensiveness Hypothesis
Although there has been much less research conducted examining the Emotional Defensiveness Hypothesis than either the Negative Affect Hypothesis or the Suppressed Hostility Hypothesis, some of it supports a link between hypertension and the various measures of emotional defensiveness, repression, and alexithymia. However, only one prospective study has examined this relation, and it was of a relatively short duration (Rutledge et al., 2000). To complicate matters further, there does not appear to be convincing evidence that emotional defensiveness is directly related to measures of cardiovascular reactivity to stress. If support for the linkage between emotional defensiveness and risk for hypertension continues to accumulate, it may operate via indirect means with another existing individual difference variable like parental history of hypertension or presence of cynical hostility.

Cognitive Factors and Information Processing

The lack of consistent findings in support of the Negative Affect, Suppressed Hostility, and Emotional Defensiveness Hypotheses has led investigators to explore new and different avenues of research to find psychological characteristics linked to the stress–hypertension relation. In particular, there is renewed interest in hypotheses pertaining to how patients with hypertension process information differently from persons with normal blood pressures. In this regard, these hypotheses take us from a concentration on the autonomic nervous system to differences presumably embedded in central nervous system activity.

Information-Processing Deficits
As mentioned in Chapter 1, essential hypertension has been associated with numerous deficits in information processing, including reduced reaction times and lower scores on attention, memory, and abstract reasoning tasks (for review, see Waldstein et al., 1991). Although adequate comparisons between samples of hypertensive and normotensive middle-aged and older adults have been made using these information-processing tests, many studies have noted that the most pronounced differences between hypertensives and normotensives were observed among younger adult samples (Elias et al., 1990; Wald-

stein et al., 1996), and even among young adult normotensives with hypertensive parents (Pierce and Elias, 1993; Thyrum et al., 1995; Waldstein et al., 1994). This might suggest that these information-processing deficits are most apparent early in the etiology of essential hypertension and perhaps may play a causal role. Indeed, if persons at risk for hypertension exhibited subtle information-processing deficits, dealing with daily hassles and conflicts may be more stressful to them due to their limited problem-solving skills and memory capacities. Although there is evidence linking deficits in information processing to both the condition of hypertension and risk for hypertension, very little is known regarding the relation between performance on information-processing tasks and the magnitude of acute cardiovascular responses to stress. If it can be established that individuals who exhibit poorer performance on these information-processing tasks also experience exaggerated cardiovascular reactions as they attempt to complete the tasks successfully, support for this perspective can be generated.

Locus of Control

The importance of control has been illustrated in eliciting acute stress responses in the animal literature (see pp. 79–80), identifying aspects of job environments (job strain) that are related to increased blood pressures (see p. 98), and in identifying the nature of mentally stressful tasks that have been shown to elicit cardiovascular response differences between hypertensives and normotensives (see p. 158). Given the consistent findings that a lack of control is associated with negative health outcomes, some investigators have focused on the individual difference variable of locus of control. Locus of control is conceptualized as a characteristic of the individual that typifies how much control one perceives he or she has in determining outcomes of important events in life (Rotter, 1966). Persons categorized as being 'internal' in locus of control tend to believe their actions can influence outcomes of these life events, whereas persons categorized as being 'external' in locus of control tend to attribute outcomes of life events to the actions of others or to good or bad luck. For example, persons with an internal locus of control may believe that their ability to gain employment and develop successful relations with others is due to the amount of effort and

work they put into pursuing these ends. In contrast, persons with an external locus of control tend to perceive positive outcomes in work and relationships as being associated with 'being in the right place at the right time' or being successful due to 'knowing the right people.'

From the association between lack of control and health consequences, it could be hypothesized that persons with an external locus of control might exhibit a greater incidence of essential hypertension. However, the data fail to support this association; most studies that have compared hypertensive and normotensive patients have showed no group differences on measures of locus of control (Friedman et al., 2001; Wennerholm and Zarle, 1976). Regarding empirical work examining the relation between locus of control and cardiovascular reactivity to stress, some studies have shown elevated cardiovascular reactions to stress among those with an internal locus of control (DeGood, 1975; Manuck, Craft, and Gold, 1978) and some have shown no differences in reactivity between persons with an internal or external locus of control (Larkin, 1982). Interestingly, the relation between internal locus of control and cardiovascular response to stress reported by DeGood was found only during presentation of an uncontrollable experimental stressor; when a controllable stressor was used, the opposite pattern was observed, with persons of external locus of control exhibiting higher DBP responses than internal-locus-of-control participants. Therefore, increased cardiovascular reactions to stress were observed when the type of controllability involved in the task did not match the typical locus of control of the study participant. Across these studies no consistent relation between locus of control and either diagnosis of hypertension or cardiovascular response to stress has been observed, suggesting that locus of control is not a likely candidate for influencing the stress–hypertension relation.

Cognitive Coping Strategies

The relation of cognitive coping, measured via standardized coping checklists, to blood pressure status has infrequently been examined. Although DBPs have been reported to be inversely correlated with various cognitive coping strategies, including wishful thinking, avoidance, and minimization of threat (Wright and Sweeney, 1989), other

studies contrasting coping strategies of essential hypertensive patients with normotensive counterparts have yielded no significant differences in coping strategies (Larkin et al., 2004).

In a study of Italian men and women, Krogh et al. (1992) found that the relations between cognitive coping strategies and blood pressure differed among men and women. Although higher SBP was associated with lower scores on resignation coping (acceptance and compromise) for both men and women, higher SBP was also associated with lower emotional-expression coping (getting angry or nervous) and higher DBP was associated with lower resignation coping and higher sympathy seeking (seeking comfort from others or through substance use) among males, but not females. In this regard, acceptance of the stressor was associated with lower blood pressure for both genders; additionally, low blood pressures among males were associated with use of emotional coping strategies, but not with use of substance or support from others.

Several studies have examined the relation between cognitive styles of coping and cardiovascular responses to stress. For example, the use of avoidance coping, a form of emotion-focused coping, has been associated with increased blood pressure reactions to stress (Holroyd and Gorkin, 1983; Kohlmann, Weidner, and Messina, 1996; Suzuki, Kumano, and Sakano, 2003). In contrast, Hahn, Brooks, and Hartsough (1993) showed that a composite form of emotion-focused coping was associated with reduced cardiovascular reactions. To confuse matters further, Gump and Matthews (1998) found that induction of vigilant coping, which presumably is a form of problem-focused coping, was also associated with increased blood pressure responses to subsequent stressors.

In studies examining the association between both problem-focused and emotion-focused coping and cardiovascular reactivity to stress, Clark (2003b) reported that both forms of coping were associated with increased DBP reactivity to stress; problem-focused coping was associated with increased DBP under high-stress conditions, while emotion-focused coping was associated with increased DBP under low-stress conditions. Other studies have also found exaggerated cardiovascular reactivity to be associated with both active problem-solving efforts at coping and passive strategies like avoidance (Clark

and Anderson, 2001; Suzuki et al., 2003). In contrast, Fontana and McLaughlin (1998) found certain forms of emotion-focused coping (distancing) were associated with greater blood pressure reactivity and other forms were associated with lesser reactivity (tension reduction and positive reappraisal), and no associations were observed between forms of problem-focused coping and cardiovascular reactivity to stress. Finally, Clark (2003a) reported that the relation between coping strategies and cardiovascular response to stress interacted with parental history of hypertension. In this study, SBP response to stress was elevated among offspring of hypertensive patients, but only among those who employed the problem-focused coping strategy of planning and the emotion-focused coping strategy of denial. Therefore, evidence exists to support the contention that some specific styles of coping are related to elevated cardiovascular reactivity to stress, including both problem-focused and emotion-focused coping strategies.

Various measures of coping have been hypothesized to interact with ethnicity in influencing the relation between stress and hypertension (Brondolo et al., 2003b). For example, the effort to succeed at all costs, as typified by high scores on the John Henryism Scale, has been shown to influence the stress–hypertension relation, although it remains unclear whether the increased risk for hypertension associated with high John Henryism scores generalizes to samples other than black men (James et al., 1984; 1987; Wright et al., 1996). Only two studies have examined whether John Henryism scores were related to the magnitude of cardiovascular response to stress, with one finding support for increased blood pressure response among women scoring high on John Henryism (Clark, Adams, and Clark, 2001) and the other finding no differences between persons with high and low scores on John Henryism (Wright et al., 1996).

Regarding the relation between cognitive coping strategies, as measured by standard coping scales, and blood pressure status, few consistent relations have been observed, rendering them unlikely candidates for systematically affecting the stress–hypertension relation. Various forms of problem-focused coping and emotional-focused coping have been associated with increased cardiovascular reactions to stress. However, there have been very few studies examining the types of coping strategies that hypertensive patients employ, and studies ex-

amining this relation are difficult to compare due to reliance on different strategies for measuring coping. Additional research in this area may illuminate a relation that has yet to be observed.

Social Factors

Social Support

A coping strategy employed by a significant number of individuals as they confront stressors in their lives is to rely on social support. Unlike some of the other hypothesized individual difference variables associated with the stress–hypertension relation, the lack of social support has broad evidence of importance as predictor not only for coronary heart disease and stroke (Rozanski et al., 1999), but also for other causes of mortality (see Cohen and Syme, 1985). There are two general methods for assessing an individual's social support: structural and functional (Uchino et al., 1996). Structural measures typically assess size of social network, number of persons living in the household, or number of people interacting with the respondent on a daily basis. However, it is well known that the quality of these interactions varies, from warm, supportive relations with loved ones to aggravating exchanges with less desirable individuals, like a nagging spouse or a hostile boss. Functional measures, in contrast, assess the quality of the support (emotional support) received from all interpersonal sources available in the environment. Let's examine the evidence relating social support to onset of essential hypertension.

Social Support and Hypertension

Given the convincing evidence linking the presence of social support with lower overall mortality, it would be expected that hypertensive patients exhibit less dense social networks and/or lower quality of social support than normal blood pressure controls. Uchino et al. (1996) conducted a meta-analysis of 28 studies that investigated the relation between social support and levels of blood pressure. Their results confirmed that persons reporting more social support exhibited significantly lower blood pressures than persons with lesser social support, and that this effect was observed for both structural and functional measures of social support. More recent research, for the most part, has confirmed and extended the findings of this meta-analysis (Carels, Blu-

menthal, and Sherwood, 1998; Holt-Lunstad et al., 2003; Karlin, Brondolo, and Schwartz, 2003). In a prospective study, Räikkönen et al. (2001) found that a reduction in social support over nine years was associated with an increased risk for essential hypertension. Daniels et al. (1999), however, failed to show an association between social support and risk for onset of hypertension in a comparable prospective trial.

Although both men and women appear to benefit by having strong socially supportive ties in their environment, Uchino stated that the specific type of social support may differ between men and women. For example, Bland et al. (1991) found that lower blood pressures were observed among men who participated in social clubs, but for women, lower blood pressures were associated with a greater number of siblings. Similarly, Janes (1990) found that lower blood pressure was associated with increased social resources among men and with increased instrumental support among women, providing additional evidence that the specific type of support associated with lower blood pressure differs by gender. Karlin et al. (2003) found that men's lower ambulatory blood pressures were associated with support from co-workers, while women's lower blood pressures were associated with having a supportive work supervisor. Although the specific findings relating social support to blood pressure status differ across studies, there is consistent evidence that the relation between social support and blood pressure status may differ between men and women.

Social Support and Cardiovascular Response to Stress

The relation between social support and cardiovascular response to stress has also been widely studied (see Uchino et al., 1996). In most of these investigations, the magnitude of cardiovascular reactions to stress is compared during conditions where a mentally stressful task is completed in the presence of a supportive friend versus completing the task alone. Fifteen studies of this nature were also reviewed by Uchino and colleagues (1996). Overall effect sizes calculated across these studies revealed a very strong association between the presence of a socially supportive person and reduced cardiovascular responses to stress. In fact, more recent work has shown that this finding is so robust that a supportive person does not have to be present in the laboratory to reduce cardiovascular response to stress (Smith, Ruiz, and Uchino, 2004;

Uchino and Garvey, 1997); merely thinking about a supportive individual elicits the same attenuated response.

Interestingly, the reductions in cardiovascular reactivity associated with social support are not typically observed among high-hostile individuals (Lepore, 1995a; Smith et al., 2004), suggesting that high levels of hostility block the salubrious effects of social support on cardiovascular reactivity to stress. Furthermore, negative interactions with others have been shown to be related to higher ambulatory DBPs among high- but not low-hostile men and women (Brondolo et al., 2003a), indicating that not only do high-hostile persons fail to benefit from positive interactions, but their negative interactions are associated with higher DBPs. In a related study, reductions in cardiovascular reactivity associated with social support have been observed among blacks, but only among those experiencing low perceptions of racism (Clark, 2003a); in fact, presence of a presumably supportive person was associated with exaggerated blood pressure responses among blacks reporting high levels of perceived racism. Clark suggested that the presence of another person, for participants with high perceived racism, may elicit less adaptive coping strategies like blaming oneself, resulting in elevated cardiovascular reactions to stress. Finally, based upon evidence that men and women obtain their social support differently, Wilson et al. (1999) showed gender differences in the relation between social support and cardiovascular response to stress in a sample of adolescents. For boys, lower SBP reactivity and faster SBP recovery were observed among those assigned to an instrumental support condition in comparison to an emotional support or control condition; for girls, although SBP tended to be lower in the emotional support condition, this difference was not significant. In sum, hostility, perceptions of racism, and gender each appears to affect the relation between social support and cardiovascular response to mental stress.

Family Support and Environment

Given the solid inverse relation between social support and a wide array of health-related variables including hypertension, it is not surprising that a number of investigators have examined the types of home environments associated with an individual's family of origin and sub-

sequent blood pressure status. In particular, it was hypothesized that specific parenting behaviors might characterize households of hypertensive patients and set the stage for subsequent onset of hypertension. This hypothesis stemmed from cross-fostering studies of inbred strains of SHRs and Dahl salt-sensitive rats that demonstrated that young rats, genetically endowed to develop hypertension but raised by normotensive mothers, developed adult blood pressures much lower than young rats raised by their natural hypertensive mothers (Azar and Hrushesky, 1985; Blizard, 1992; Cierpial and McCarty, 1991; DiNicolantonio et al., 1986). Although the specific nature of these maternal environmental differences is unclear, evidence suggesting that hypertensive mothers fail to nurture their pups is lacking. In fact, quite the contrary, hypertensive mother rats tend to maintain closer contact with their pups and groom them more frequently than mothers from control strains (Cierpial et al., 1987). To account for this unexpected finding, Myers et al. (1989) hypothesized that these young rat pups' blood pressures increased as a result of the frequent feedings; to support this hypothesis, they provided data showing substantial increased blood pressures during feeding among these pups. Findings from the animal literature suggest that the genetic predisposition and being raised by a hypertensive mother interact to place the young rat at risk for elevated blood pressures in adulthood.

In addition to these findings on animals, there is evidence that risk for essential hypertension in humans is increased among spouses of hypertensive patients who share no genetic variance, even after controlling for traditional risk factors (Carmelli et al., 1989; Hippisley-Cox and Pringle, 1998; Speers, Kasl, Freeman, et al., 1986). Like findings from research on cross-fostering of rats, these findings suggest that there is a unique environmental contribution to the development of hypertension that appears to occur independently of any genetic or behavioral lifestyle factors, including smoking status, obesity, and dietary and exercise habits. Just what might these family environmental factors be?

Unfortunately, very few studies have examined family environmental characteristics of hypertensive families. Certainly, the work of Baer and colleagues (1980; 1983) illustrating differential behavioral styles of interacting in families of hypertensive and normotensive patients (see pp. 144–145 and 190) stands out as an example of this type of

empirical research. In these studies, hypertensive families were characterized as exhibiting less sophisticated social skills when the members interacted. As a result, conflict resolution may be much more difficult to attain in hypertensive families. In other studies of hypertensive and normotensive family environments, hypertensive parents have been reported to be less supportive and caring (Russek and Schwartz, 1997) and more prone to having a dissatisfying job and experiencing a divorce (Lindgarde, Furu, and Ljung, 1987). This is really all that is known about family environments of hypertensive patients. Furthermore, the contribution of these family environmental characteristics to the etiology of hypertension is unclear because genetic and environmental influences cannot be disentangled in these studies.

Despite the limited data relating family environment characteristics with onset of hypertension, a few studies have examined the relation between family environmental factors and cardiovascular reactivity to stress, the hypothesized mediator of the stress–hypertension relation. Interestingly, there is one cross-fostering study on blood pressure reactivity to stress conducted on young borderline hypertensive rats raised with either hypertensive or normotensive mothers (Sanders and Gray, 1997). In this study, BHRs raised by normotensive mothers had significantly reduced blood pressure reactivity to stress in comparison with BHRs raised by hypertensive mothers, lending some support to the hypothesis that environmental parenting influences the magnitude of blood pressure reactions to acute stress presentations. There have been some findings that family environmental characteristics influence cardiovascular response to stress in humans as well (El-Sheikh, 1994; Larkin, Frazer, and Semenchuk, 1996; Woodall and Matthews, 1989; Wright et al., 1993). In all four of these studies, young adults or children from less functional families (that is, less cohesive, less adaptive, or high-conflict families) exhibited higher heart rate reactions to stress than participants from more stable families. Interestingly, there is some evidence to suggest that these less functional families are more likely to consist of at least one hypertensive parent than stable families (Larkin et al., 1996), and young adults from these less functional families are more likely to establish hostile attitudes and express their anger overtly than young adults from stable families (Matthews et al., 1996). The association between lesser cardiovascular reactivity to stress and

family stability (less family conflict) appears to be mediated by increased parasympathetic activity (Salomon, Matthews, and Allen, 2000). Finally, in addition to the association between family structural characteristics and cardiovascular response to stress, there is evidence that loss of a parent results in higher blood pressure responses to mental stress (Luecken, 1998). Therefore, although there is not a strong association with family environmental characteristics and onset of hypertension, there is some support for the proposition that specific maladaptive family environmental characteristics are associated with increased cardiovascular reactions to stress. Again, these findings should be considered only tentative because the genetic and environmental influences upon cardiovascular responses to stress cannot be easily separated in these studies.

Religious Support

Seeking support and comfort from one's religious beliefs is another coping strategy that has been associated with blood pressure status. A number of studies have shown that higher levels of religious involvement are associated with lower blood pressures (Graham et al., 1978; Hixson, Gruchow, and Morgan, 1998; Larson et al., 1989). In particular, religious coping has been associated with lower ambulatory blood pressures among blacks more than whites (Steffen et al., 2001). One coping element often associated with religiosity, the ability to engage in forgiveness, has also been associated with lower blood pressures as well as more rapid blood pressure recovery following recollection of an interpersonal betrayal (Lawler et al., 2003). Although studies examining the relation of religiosity to cardiovascular response to stress have yet to be conducted, emerging evidence linking forgiveness with lower cardiovascular reactions has already been reported (Lawler et al., 2003; Witvliet et al., 2001).

Summary

Applying the same ratings used to evaluate constitutional and lifestyle factors, Table 7.1 summarizes the findings associated with the psychological and social individual difference variables presented in this chap-

Table 7.1. Summary of Psychological and Social Variables That Influence the Stress–Hypertension Relation

Variable	*Differential Relation between Stress and Essential Hypertension?*	*Related to Increased Cardiovascular Response to Stress?*	*Potential Interaction Variables That Have Been Studied*
Psychological Factors			
High Trait Anxiety	Partial Support	?	parental history of hypertension; ethnicity; renin status
High Trait Anger	Mixed	?	sodium sensitivity; hostility
High Hostility	Mixed	Yes	gender; parental history of hypertension; smoking; dietary habits; alcohol use; obesity; social support; drug use; anger; renin status; defensiveness; family environment
High Depression	Partial Support	Partial Support	ethnicity; renin status; parental history of hypertension; gender
High Negative Affect	Partial Support	?	
Anger Expressive Style (e.g., Suppression)	Partial Support	Partial Support	parental history of hypertension; ethnicity; renin status
Type A Behavior Pattern	Mixed	Yes	alcohol use
Defensiveness and Repression	Partial Support	Mixed	renin status; parental history of hypertension; hostility
High Alexithymia	Mixed	No	
Low Monitoring and High Blunting	No	No	
Information-Processing Deficits	?	?	age; parental history of hypertension
External Locus of Control	No	No	
Maladaptive Cognitive Coping Strategies	Mixed	Mixed	gender; parental history of hypertension; ethnicity

continued

Table 7.1. (*Continued*)

Variable	*Differential Relation between Stress and Essential Hypertension?*	*Related to Increased Cardiovascular Response to Stress?*	*Potential Interaction Variables That Have Been Studied*
Social Factors			
Reduced Social Support	Yes	Yes	gender; hostility; ethnicity
Poor Family Environments	?	Partial Support	behavioral response to stress; hostility
Low Religious Support	Partial Support	Partial Support	ethnicity

ter. As with the constitutional and lifestyle factors, there is evidence of many significant interactions among psychological and social variables. Not only are there interactions among the variables presented in this chapter; there is also evidence that psychological and social variables interact with the constitutional and lifestyle variables presented in Chapter 6. Therefore, a wide range of individual difference variables needs to be considered in predicting who will or will not develop hypertension in response to living a stress-filled life.

Three different psychological hypotheses have been proposed that represent individual difference variables that influence the stress–hypertension relation: the Negative Affect Hypothesis, the Suppressed Hostility Hypothesis, and the Emotional Defensiveness Hypothesis. There is some evidence supporting a role for each of these. Although the specific measure of negative affect varies from study to study, several measures of negative affect have been shown to be associated with onset of hypertension in prospective trials. There is also evidence to support a curvilinear relation between anger expression and blood pressure status. Both extreme anger suppression and extreme anger expression have been shown to be associated with increases in blood pressure, and constructive anger expression is associated with lower blood pressures. Finally, the tendency to minimize emotionality has also been linked with an increased risk for hypertension. In addition to the link-

ages between these variables in risk for hypertension, they have also each been shown to be partly associated with increased cardiovascular reactivity to stress, a hypothesized mediator of the stress–hypertension relation.

There is also solid evidence linking both the quantity and quality of social support to both risk for hypertension and the magnitude of cardiovascular responses to stress. In both cases, high levels of social support are associated with reduced risk for hypertension and attenuated cardiovascular reactions to stress. Emerging evidence relating family environmental characteristics and use of religion as a supportive aid has also shown promise in predicting onset of essential hypertension and the extent of behaviorally elicited cardiovascular reactivity. In the case of family environmental characteristics, dysfunctional families of origin are more closely linked to increased incidence of hypertension and greater cardiovascular responses to stress. Evidence linking religion to hypertension has generally shown a lowered incidence of hypertension among persons who engage religion to deal with stress or who practice forgiveness in their lives.

In contrast to the constitutional and lifestyle factors, which can often be observed directly, the vast majority of psychological and social variables are assessed through self-report measures. Thus if hypertensive patients employ defensive postures when asked to report on emotional states or traits, as hypothesized by several investigators (Jamner et al., 1991; Mann and James, 1998; Nyklíček et al., 1998; Shapiro et al., 1995), then the accuracy of these measures among this group must be called into question. For example, if hypertensives indeed engage in emotional defensiveness, it could be hypothesized that they would have lower scores on measures of anxiety, depression, negative affect, anger, or hostility than normotensives, as each represents a measure of an emotional state or trait. In this regard, the failure to demonstrate consistent findings showing that hypertensives experience more negative affect than normotensives may reflect more of a limitation of the reliance on self-report methods for measuring negative affect than a failure to support the Negative Affect Hypothesis. It is possible, for example, that many hypertensives truly experience more negative affect than normotensives, but fail to endorse this experience on self-report inventories due to their emotional defensiveness.

A second methodological limitation that influences interpretation of findings pertaining to psychological and social variables associated with risk for hypertension is the well-established association between knowledge of hypertensive status and responses to assessments of psychological parameters (Irvine et al., 1989; Zonderman et al., 1986). In these studies, hypertensives who were aware of their hypertensive diagnosis reported more psychological distress than hypertensives unaware they had high blood pressure. In this regard, knowledge of having a chronic blood pressure problem appears to lead toward increased psychological symptom endorsement. On one hand, this effect may be associated with increased distress upon receiving this diagnosis; on the other hand, it could be associated with patients' belief that if they have high blood pressure, they must be under a lot of stress and should be endorsing a lot of psychological symptoms. In the meta-analysis relating psychological parameters with risk for hypertension, Jorgensen et al. (1996) conducted analyses separately among studies in which patients were aware of their hypertension versus those in which patients did not know they had high blood pressure. A very interesting finding emerged. Whereas the endorsement of psychological symptoms was positively related to hypertension among patients who were aware of the diagnosis, endorsement of symptoms was *negatively* related to hypertension among patients unaware of their diagnosis. This finding seems to suggest that hypertensive patients who are unaware of their diagnosis tend to underreport psychological symptoms, but once made aware of their diagnosis, they report emotional symptoms freely.

Interestingly, findings relating awareness of hypertension to increased symptom endorsement have been replicated using measures of acute physiological reactivity to stress (Rostrup and Ekeberg, 1992; Rostrup et al., 1990; 1991). In these studies, hypertensive men aware of their diagnosis exhibited greater cardiovascular and neuroendocrine reactions to mental stress than hypertensive patients unaware of their diagnosis. Therefore, it is clear that knowledge of the diagnosis of hypertension must be considered when evaluating differences between hypertensive and normotensive samples on both self-reported measures of psychological functioning and measures of cardiovascular reactivity to stress. Awareness of having high blood pressure seems to alter multiple response pathways, making it difficult to determine which

psychological or physiological response patterns play an etiologic role in essential hypertension.

Given the observation of Franklin's tendency to exhibit overly assertive behaviors during the confrontational role-plays described in Chapter 5, one might expect him to endorse elevated scores on measures of anger expression (Anger-Out). However, when he was administered Spielberger's State-Trait Anger Expression Inventory, all scaled scores for state and trait anger as well as anger expression were within normal limits. In contrast, he scored in the 'aggressive' range on a scale of assertiveness (Rathus, 1973) and was categorized as exhibiting Type A behavioral characteristics on the Framingham Scale of Type A Behavior. In a sense, interpretation of Franklin's self-report measures yielded mixed findings. Although the data from the assertiveness scale and Type A categorization are congruent with behaviors observed in the laboratory, his relative normal scores on anger and anger expression are perplexing. In that some degree of emotional defensiveness has been shown to be common among hypertensive patients, however, it is not entirely surprising that these scores fell within normal limits. Although Franklin may exhibit problems with his overly exuberant expression of anger when engaged in confrontational situations, he may be unaware of this difficulty or he may be attempting to portray himself as having more control over his emotions than he really might have. Despite the finding that he exhibited several psychological phenomena consistent with the hypotheses linking psychological factors with hypertension presented in this chapter, there is no clear evidence implicating Franklin's observed behavioral tendencies in the onset of his hypertensive condition.

8

Treatment and Prevention of Essential Hypertension

Given the evidence that has accumulated over the past half century, it is not surprising that Franklin's physician prescribed an antihypertensive medication to treat his hypertensive condition. Among all interventions that have been tested to lower blood pressure, antihypertensive medications have clearly shown the most efficacy. However, like many patients, Franklin experienced some noticeable side effects associated with the medicine that led to periods of non-adherence and, consequently, his current state of uncontrolled blood pressure. Franklin was not taking his medication during the day in which ambulatory measures of his blood pressure were obtained (see Figure 2.1), and the profile that was observed showed that his blood pressure was not well controlled.

According to the JNC-7 Report (Chobanian et al., 2003), the primary goal of treating essential hypertension is to reduce mortality associated with cardiovascular and cerebrovascular disease. Reducing blood pressure to less than 140/90 mm Hg is the specific aim of antihypertensive therapies, although it is clearly recognized that any blood pressure reduction, even if it does not achieve these benchmarks, is beneficial. Often good blood pressure control requires use of more

than one antihypertensive medication (Cushman et al., 2002), indicating that patients and physicians must collaborate in reaching optimal treatment outcomes. Unfortunately, Franklin and his physician were not working as a team in confronting his essential hypertension. Before considering what could be done to provide a better treatment outcome for Franklin, let's examine briefly the various antihypertensive medications that could be prescribed to treat his high blood pressure.

Pharmacologic Treatment of Hypertension

Like many other early medicines, the first known antihypertensive medication, reserpine, was uncovered more or less by accident during investigations of the medicinal properties of common plants and herbs. Reserpine is a pharmaceutical compound derived from the Indian snakeroot, *Rauwolfia serpentine,* whose antihypertensive properties were first described by Bhatia in 1942. After years of use, reserpine's mechanism of action was determined to be associated with its ability to deplete storage of norepinephrine in neurons (Cohen et al., 1968), leading to a reduction in sympathetic nervous system activity and vascular resistance. In this regard, it is of interest that the very first antihypertensive medication to be used regularly exerted its effect via sympathetic nervous system involvement. Unfortunately, the norepinephrine depletion responsible for reserpine's antihypertensive effect also led to severe clinical depression in a substantial number of patients, resulting in reduced prescription of this avenue for treating hypertension as more promising agents emerged.

Since the advent of pharmacologic treatment of hypertension, there have been approximately a hundred different antihypertensive medications developed and marketed for treating high blood pressure. Unlike reserpine, most of these pharmacologic agents were derived based upon knowledge of the hypothesized physiological mechanisms of blood pressure control. Whereas some of these drugs exert their effect by altering fluid regulation maintained by the kidneys, others promote lower blood pressure due to their effects on the sympathetic nervous system or the vascular system. A list of the primary categories of antihypertensive agents and selected examples of each are shown in Table 8.1. With this table as a guide, let's briefly consider how drugs in

Table 8.1. Classes of Antihypertensive Medications

Drug Class	*Selected Examples—Generic (Trade) Names*
Diuretics	
Thiazides and Sulfonamides	Chlorothiazide (Diuril)
	Chlorthalidone (Hygroton; Thalitone)
	Hydrochlorothiazide (Esidrix; HydroDIURIL; Microzide)
	Indapamide (Lozol)
Loop Diuretics	Bumetanide (Bumex)
	Ethacrynic acid (Edecrin)
	Furosemide (Lasix)
Potassium-Sparing agents	Amiloride (Midamor)
	Spironolactone (Aldactone)
Adrenergic Inhibitors	
Alpha-Blockers	Doxazosin (Cardura)
	Prazosin (Minipress)
Beta-Blockers	Atenolol (Tenormin)
	Metoprolol (Lopressor; Toprol XL)
	Propranolol (Inderal)
	Nadolol (Corgard)
Central Alpha-Agonists	Clonidine (Catapres)
	Methyldopa (Aldomet)
Combined Alpha/Beta-Blockers	Carvedilol (Coreg)
	Labetalol (Normodyne; Trandate)
Peripheral Inhibitors	Guanethidine (Ismelin)
	Reserpine (Serpasil)
Vasodilators	
Angiotensin-Converting Enzyme (ACE) Inhibitors	Captopril (Capoten)
	Enalapril (Vasotec)
	Lisinopril (Prinivil; Zestril)
Angiotensin II Receptor Blockers	Candesartan (Atacand)
	Losartan (Cozaar)
	Valsartan (Diovan)
Calcium Channel Blockers	Amlopidine (Norvasc)
	Diltiazem (Cardizem; Dilacor; Tiazac)
	Nifedipine (Procardia XL; Adalat CC)
	Verapamil (Isoptin SR; Calan SR)
Direct Vasodilators	Hydralazine (Apresoline)
	Minoxidil (Loniten)

continued

Table 8.1. (*Continued*)

Drug Class	*Selected Examples—Generic (Trade) Names*
Combination Drugs	
Diuretics and Potassium-Sparing Diuretics	Amiloride and hydrochlorothiazide (Moduretic)
Beta-Blockers and Diuretics	Metroprolol and hydrochlorothiazide (Lopressor HCT)
ACE Inhibitors and Diuretics	Benazepril and hydrochlorothiazide (Lotensin HCT)
Angiotensin II Receptor Antagonists and Diuretics	Candesartan and hydrochlorothiazide (Atacand HCT)
Calcium Channel Blockers and ACE Inhibitors	Amlodipine and benazepril (Lotrel)

each of these classes exert their antihypertensive effect. Because a complete description of these classes of medicines and their modes of action is already available (Kaplan, 2002), only a brief summary is presented here. In particular, attention will be paid to how each pharmacologic agent might influence the stress–hypertension relation and how treatment with these agents may impact acute cardiovascular reactions to stress, the hypothesized mediator of the stress–hypertension relation.

Diuretic Antihypertensive Pharmacologic Agents

Diuretic medications were the earliest form of antihypertensive therapy that followed the discovery of reserpine. In fact, the first trials demonstrating that reduction in blood pressure was accompanied by a decreased risk for cardiovascular and cerebrovascular disease employed diuretic medications (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967; 1970). As their name implies, diuretic medications work by blocking sodium retention in the kidney, which results in an increased excretion of sodium and water. Consequently, cardiac output drops and blood pressure is reduced. Although the initial reduction in blood pressure is associated with di-

minished cardiac output, reduced peripheral resistance follows with continued diuretic use, as the body accommodates to its new fluid volume. There are three classes of diuretic agents: thiazide diuretics, loop diuretics, and potassium-sparing diuretics. Although widely and safely used, thiazide and loop diuretics can deplete the body of important nutrients and electrolytes. In particular, because the depletion of potassium can lead to ventricular arrhythmias as well as other metabolic imbalances, potassium-sparing diuretics were developed. Although use of the potassium-sparing diuretics results in fewer side effects, they have a somewhat weaker antihypertensive effect than thiazide diuretics. Therefore, the two are often used in conjunction.

Because the site of pharmacologic action for diuretic antihypertensives is in the kidney, it could be argued that diuretics do not affect nervous system functioning. However, several side effects associated with diuretic use (fatigue, weakness, and impotence in men) suggest that these medications influence nervous system activity in some way. Given the complexity of the feedback systems involved in the renin-angiotensin-aldosterone and broader neuroendocrine systems, it is quite plausible that the reductions in blood pressure that occur with diuretic therapies indirectly affect central and peripheral nervous system functioning.

Adrenergic-Inhibiting Antihypertensive Pharmacologic Agents

A number of different types of antihypertensive agents directly target blood pressure control through altering the nervous system regulation of blood pressure, including central alpha-agonists, peripheral adrenergic inhibitors, and both alpha- and beta-adrenergic blockers. In all cases, these pharmacologic agents decrease sympathetic nervous system activation on the circulatory system. Central alpha-agonists decrease sympathetic nervous system activity through their action on brain mechanisms responsible for blood pressure regulation, including baroreceptor functioning. Peripheral adrenergic inhibitors, including reserpine, exert their blood pressure–lowering effect on the release of norepinephrine in the peripheral nervous system. Both alpha- and beta-adrenergic blocking medications influence blood pressure regula-

tion by blocking neural signals that lead to vasoconstriction and heart rate activation, respectively. Unlike with diuretic antihypertensive agents, metabolic problems associated with electrolyte depletion do not occur with adrenergic-inhibiting antihypertensives. Rather, adrenergic-inhibiting pharmacologic agents, due to the general dampening of sympathetic nervous system activity associated with their use, can cause sedation, tiredness, and fatigue. In particular, fatigue associated with use of beta-blockers is problematic among athletes or individuals on strenuous exercise programs (Gordon, Scott, and Duncan, 1997). Additionally, a number of adrenergic-inhibiting antihypertensive agents have been occasionally shown to be associated with impaired performance on memory and psychomotor tasks (Light, 1980; Shapiro et al., 1989; Solomon et al., 1983), indicating that many of these agents affect central nervous system adrenergic functioning as well. The role of dampening the nervous system to achieve lowered blood pressures is quite obvious among the adrenergic-inhibiting antihypertensive medications, unlike the diuretics.

Vasodilating Antihypertensive Pharmacologic Agents

In contrast to the diuretics, which act on the kidneys, and the adrenergic-inhibiting drugs, which act on the sympathetic nervous system, other antihypertensives exert their effect by directly attacking the extent of vasoconstriction associated with high blood pressure that occurs in vascular smooth muscle cells. Although each medication in this category has a distinct mechanism of action, all result in increased vasodilation of vascular muscle cells; hence, they are grouped together as vasodilators. They include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, and direct vasodilators. Whereas direct vasodilators exert an immediate relaxing effect upon the smooth muscle cells of the vasculature, other vasodilating agents exert their effect by altering local substances known to affect vasodilation (Kannel, 2002). For example, calcium channel blockers, as their name indicates, disrupt the flow of calcium into the smooth muscle vascular cells. Because calcium is needed to induce contraction of both cardiac and vascular muscles, its disruption

via calcium channel blockade results in vasodilation among vascular cells as well as heart rate slowing and diminished contractility (Meredith, 2002). In contrast, the ACE inhibitors cause vasodilation by reducing the circulation of angiotensin II, a potent vasoconstricting peptide. Basically, a converting enzyme is needed to form angiotensin II from angiotensin I; if production of this enzyme is inhibited via administration of ACE inhibitors, levels of angiotensin II are diminished. Finally, angiotensin II receptor blockers cause vasodilation in yet another way. In contrast to ACE inhibitors, which interfere with the production of angiotensin II, the angiotensin receptor blockers work by interfering with the action of angiotensin II. If circulating angiotensin II cannot stimulate its receptors, its vasoconstrictive properties are nullified. Therefore, while each of these classes of antihypertensive medications operates in physiologically distinct ways, they all result in vasodilation and reduced arterial pressures.

The effect of vasodilating antihypertensives upon nervous system functioning is unclear. In fact, because several forms of vasodilators do not cross the blood-brain barrier (ACE inhibitors), very little influence on the central nervous system is presumed to occur. However, given the interrelations between the nervous and circulatory systems in regulating blood pressure, it is plausible that vasodilators do influence nervous system activity, at least in the periphery.

Combination Antihypertensive Agents

Although all three of the broad categories of antihypertensive medications have been shown to reduce blood pressure, several possess physiological or metabolic side effects that are associated with increased risk for other pathological conditions. Already mentioned is the potassium-depleting characteristic of thiazide and loop diuretics, which results in an increased risk for arrhythmias and other metabolic disturbances. Similarly, beta-blockers have been shown to raise triglycerides and alter one's lipid profile (Kaplan, 2002). Because multiple antihypertensive agents may be needed to achieve optimal blood pressure control and to counteract some of the negative side effects associated with taking a single antihypertensive agent, many combination drugs

have been made available. Demonstrating a synergy between agents, many of these combination agents have yielded better blood pressure control than single agents, often without producing negative side effects (Kaplan, 2002). As shown in Table 8.1, most of these pharmacologic agents involve the addition of a diuretic to other forms of antihypertensive medications.

Effect of Antihypertensive Agents on Cardiovascular Reactivity to Stress

If cardiovascular reactivity to stress mediates the stress–hypertension relation, it follows that interventions aimed at lowering blood pressure might also reduce the magnitude of cardiovascular response to stress. Although there is clear evidence that use of diuretics, adrenergic inhibitors, and vasodilators leads to diminished arterial pressures, we have not yet considered whether they exert this effect by dampening cardiovascular responses to stress. Given the differential physiological mechanisms through which these classes of antihypertensive medications exert their blood pressure–lowering effect, it is possible that they impact cardiovascular reactions to stress differently. For example, because beta-blockers lower blood pressure by blocking sympathetic nervous system activation of the heart, it would certainly be expected that heart rate reactions to stress would be tempered by beta-blockade. Conversely, treatment with diuretics might be expected to influence heart rate or blood pressure response to stress less than beta-blockers because of the indirect effect that diuretic action has on the sympathetic nervous system. Let's examine whether any class of antihypertensive medications affects cardiovascular reactivity to stress.

Research examining whether treatment with antihypertensive medications influences acute cardiovascular reactivity to stress is founded on empirical work demonstrating reductions in cardiovascular reactivity with antihypertensive therapy in SHRs (Weiss and Lundgren, 1978). In this study, blood pressure responses to stress were reduced following treatment with direct vasodilators and a cardiac-selective beta-blocker, metoprolol, but not following treatment with a nonselective beta-blocker, propranolol. Presumably, the failure to observe reduced blood pressure reactions to stress with propranolol was associ-

ated with dual blockade of both cardiac-enhancing and vasodilating beta-adrenergic effects of the nonselective medication. Although these findings suggested that treatment with a number of antihypertensive medications resulted in reductions in both blood pressure and blood pressure response to stress among SHRs, it was unknown whether comparable findings would emerge when these same pharmacologic agents were tested on humans with hypertension.

Because of the obvious involvement of the sympathetic nervous system in eliciting cardiovascular responses to stress, the vast majority of studies conducted on humans have examined adrenergic-inhibiting agents, in particular beta-blockers. Presumably, when the beta-adrenergic system is blocked pharmacologically, heart rate reactions to stress will be dampened, resulting in lowered cardiac output and blood pressure responses to stress as well as overall reductions in resting blood pressure. Although this hypothesis has appeal due to its simplicity, support for it is generally lacking. Empirical investigations of the influence of beta-blockers on stress-elicited cardiovascular reactions have been mixed, with some studies observing the hypothesized reduction in cardiovascular reactivity to stress during beta-blockade (Schmieder, 1983), some finding no change in cardiovascular reactivity (Nyberg, Graham, and Stokes, 1977), and still others finding reduced cardiovascular reactions, but only to certain types of experimental tasks (Dunn, de Carvalho, and Frohlich, 1978; Floras et al., 1985). Research on other classes of antihypertensive medications has also failed to demonstrate the hypothesized reductions in cardiovascular response to stress associated with effective pharmacologic intervention, including studies employing centrally acting adrenergic agonists (Boyar et al., 1980), alpha-blockers (Mancia et al., 1980), diuretics (Bateman et al., 1979), and calcium channel blockers (Stevinkel et al., 1997). In contrast, use of ACE inhibitors has been shown to be associated with reductions in both SBP and DBP response to stress (Kahan and Eliasson, 1999; Nazzaro et al., 1994), although this relation has been relatively infrequently studied.

Although evidence indicates that most of the antihypertensive agents, including diuretics, adrenergic inhibitors, and vasodilators, do not appear to impact the degree of blood pressure reactivity to stress, there is clear evidence that administration of beta-blockers results in an

attenuated heart rate response to stress (Mills and Dimsdale, 1991). Recognizing that these diminished heart rate responses to stress occurred in conjunction with no change in blood pressure reactivity, several investigators conducted subsequent studies to explore the underlying hemodynamics responsible for the disparate heart rate and blood pressure response alterations (Garavaglia et al., 1988; Rüddel et al., 1988; Schmieder et al., 1987). Consistent findings emerged across all three studies; the attenuated heart rate response that occurred with beta-blockade was accompanied by increased peripheral resistance during stress presentations, thereby maintaining the blood pressure response. Comparison drugs used in these studies (calcium channel blockers, central adrenergic agonists), in contrast, lowered blood pressure without altering the hemodynamic response profile to stress. Therefore, although the hemodynamic profile associated with blood pressure reactivity to stress is altered through administration of beta-blockers, the magnitude of the blood pressure response remains unaffected.

With perhaps the exception of ACE inhibitors, then, there is very little evidence indicating that antihypertensive medications exert their blood pressure–lowering effect by altering the magnitude or profile of cardiovascular reactivity to stress. Therefore, the blood pressure–lowering effect of these medicines appears to be caused by other mechanisms involved in blood pressure regulation, like altering fluid retention or local vascular effects. Although demonstrating a link between the mechanism of action of antihypertensive agents and diminished cardiovascular reactivity to stress would have clearly supported the hypothesis that cardiovascular reactivity to stress mediates the stress–hypertension relation, the lack of evidence does not suggest that this hypothesis should be abandoned. Clearly, there are multiple physiological adjustments that lead to reductions in blood pressure, and exaggerated cardiovascular reactivity to stress has been proposed to explain only one of them, how stress leads to high blood pressure. In a sense, drugs are not intelligent; that is, they do not need to know the cause of a physiological imbalance in order to have a positive treatment outcome. In this regard, any given antihypertensive agent will lower blood pressure to some extent, whether the hypertensive condition is caused by obesity, a high-salt diet, a genetic propensity for hypertension, or a stress-filled life.

Effect of Antihypertensive Agents on Cognitive Functioning

As stated in Chapter 1, it has been well documented that essential hypertension is associated with subtle cognitive impairments that can often be detected only by means of specific neuropsychological assessment strategies (see Waldstein et al., 1991). If hypertensive patients are generally aware of these cognitive deficits, they may need to exert more effort or become more engaged with mental tasks in order to perform at an acceptable level. Their exaggerated cardiovascular response to mental stress may reflect their increased effort or engagement. If pharmacologic interventions result in improved cognitive ability, as initially hypothesized by Miller et al. (1984), the mechanism of action for antihypertensive medications may involve cognitive functioning. As such, one would expect antihypertensive agents to 'normalize' the cognitive deficits commonly observed in hypertensive patients with ongoing treatment. Let's examine the body of evidence examining the effect of antihypertensive agents on various measures of cognitive functioning.

Muldoon et al. (1991) conducted a review of over 50 studies that have examined the effect of antihypertensive pharmacologic agents on various measures of cognitive performance. Although their review of the literature uncovered some studies finding improvement in cognitive functioning with antihypertensive therapy, the vast majority of studies have found that treatment with most types of antihypertensive agent had very little effect on measures of cognitive activity. There was some evidence, however, linking administration of adrenergic inhibiting agents (beta-blockers or central-acting alpha-agonists) to poorer performance on speeded psychomotor tasks. Conversely, improvements on psychomotor tasks were noted in conjunction with use of ACE inhibitors, although only in a few studies.

Although diminished performance on tasks involving psychomotor speed has been associated with numerous antihypertensive agents, more recent research has found improved performance on working memory tasks with these same pharmaceutical agents (Muldoon et al., 2002), particularly ACE inhibitors or calcium channel blockers (Amenta et al., 2002). Therefore, the newer classes of antihypertensive drugs appear to exhibit a more positive outcome with respect to specific cognitive functions than the older classes of drugs.

Selection of Appropriate Antihypertensive Therapy

Although diuretics, adrenergic inhibiting agents, and vasodilators will each lower blood pressure in their own distinct way, it seems obvious that optimal blood pressure control might be achieved using a lower dose of a medication or combination of medications that directly attacks the mechanisms suspected of causing essential hypertension for a given patient. Given such a broad array of available and effective antihypertensive agents, what determines which medication the physician will choose for a given patient? Despite the standing joke that the physician's choice for an antihypertensive medication depends upon which drug representative visited the clinic most recently, several pieces of information are typically considered when selecting the optimal therapy, including demographic variables associated with differential treatment response to a particular agent, the presence of any comorbid medical conditions like heart disease or diabetes, and potential side effects that may interfere with a patient's quality of life.

Of foremost importance in determining an appropriate antihypertensive agent is consideration of the relative efficacy of medications in controlling blood pressure and their ability to reduce cardiovascular and cerebrovascular mortality. In general, all classes of medications described in this chapter have been shown to lower blood pressure, and the extent of reduced mortality associated with cardiovascular and cerebrovascular disease is comparable across classes of antihypertensive agents in most studies (Neaton et al., 1993; Pepine et al., 2003; Staessen et al., 1997; Wing et al., 2003). Mean blood pressure reductions commonly observed with this array of antihypertensive medications range from an average of 8 mm Hg to more than 17 mm Hg (Linden and Chambers, 1994). Although reduced morbidity and mortality have long been associated with treatment of high blood pressure with diuretics or beta-blockers (Psaty et al., 1997), these findings have also been observed more recently among the few prospective trials that have been conducted with calcium channel blockers and ACE inhibitors (Blood Pressure Lowering Treatment Trialists' Collaboration, 2000; Julius et al., 2004). Therefore, if one has to choose a drug based upon overall efficacy in reducing blood pressure and mortality, a flip of the coin appears as good as any other method.

Based upon findings that antihypertensive medications were generally comparable in efficacy, clinical recommendations, as developed through reports from various panels of hypertensive specialists (Joint National Committee, 1977), have historically employed what was called the 'stepped care' approach to treating hypertension. According to this approach, the first step in initiating treatment involved administering a diuretic, because of its extensive history of reducing high blood pressure. If blood pressure control was not achieved with this alone, then adrenergic-inhibiting agents could be added in the second step. Finally, if blood pressure control was still not achieved, a vasodilator could be added to the treatment regimen in Step 3. This stepped care approach was demonstrated to be highly effective in both lowering blood pressure and preventing cardiovascular-related mortality in the Hypertension Detection and Follow-up Program conducted in the 1970s (Hypertension Detection and Follow-up Program Cooperation Group, 1979).

Although many individuals were treated successfully using the stepped care approach over the decades, as newer antihypertensive agents were developed and marketed it became apparent that some of the newer agents, with more tolerable side effect profiles, might serve equally well as diuretics as Step 1 medications. Therefore, recommendations from national and international committees of hypertension researchers (Guidelines Committee, 1999; Joint National Committee, 1988), moved away from the stepped care approach, giving more liberty to clinicians to choose from a menu of antihypertensives, including diuretics, beta-blockers, calcium channel blockers, and ACE inhibitors. The 'one size fits all' approach of stepped care was replaced with what was appropriately termed 'tailored therapy' (Poulter, 1991). The tailored therapy approach gave rise to altered patterns of prescribing among physicians, resulting in increased usage of beta-blockers, calcium channel blockers, and ACE inhibitors as first-line antihypertensive agents (Kaplan, 2002).

Reluctant, however, to support the rapid increase in the use of calcium channel blockers and ACE inhibitors as first-line agents in the absence of a substantial body of prospective evidence showing these agents were associated with decreased cardiovascular and cerebrovascular morbidity and mortality, national experts resumed their endorse-

ment of either diuretics or beta-blockers as first-line agents until more complete data could be generated (Joint National Committee, 1993). This return to the traditional stepped care approach did not occur without controversy, as many investigators believed that ACE inhibitors, calcium channel blockers, and alpha-blockers were perfectly reasonable first-line agents for certain types of patients (Weber, 1993). Evidence that recommendations have come full circle can be found in the most recent Joint National Committee report, in which once again diuretics are recommended as the sole first-line approach to treatment (Chobanian et al., 2003).

Findings from JNC-7 were strongly influenced by the findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest randomized drug comparison trial conducted to date. ALLHAT involved the direct comparison of alpha-blockers, ACE inhibitors, calcium channel blockers, and diuretics in over 40,000 hypertensive patients (ALLHAT Officers, 2002). In this study, clinical disease outcomes (stroke and coronary heart disease) of hypertensive patients treated with these antihypertensive agents were tracked over a five-year period. Unfortunately, due to an increased rate of congestive heart failure detected among patients receiving alpha-blockers, that arm of the study was discontinued early (ALLHAT Officers, 2000). Although this decision resulted in lower adoption rates of alpha-blockers for treating hypertension, it is likely they still can be used safely. Kaplan (2002) suggests that the increased congestive heart failure observed among patients taking alpha-blockers may have been a by-product of the study design, in which known hypertensive patients were withdrawn from antihypertensive medications at the time of enrollment in the study and randomized to the various drug class groups. Accordingly, Kaplan argues that making a switch from a diuretic (which many patients were likely taking prior to enrollment) to an alpha-blocker could result in increased rates of observed congestive heart failure.

Results from ALLHAT study participants in the remaining three groups revealed that patients in the diuretic group had a lower incidence of congestive heart failure and stroke than patients in the ACE inhibitor group. There were no group differences, however, in episodes of fatal or nonfatal coronary heart disease or cardiac-related mortality.

Largely on the basis of the findings from this trial, the JNC-7 recommended thiazide diuretics as the preferred choice for initial antihypertensive intervention (Chobanian et al., 2003). As one might imagine, this conclusion has met with considerable controversy. Weber (2003), for example, claimed that the ALLHAT research design was methodologically flawed. Indeed, the design of the study permitted adding a second antihypertensive agent if blood pressure control was not established with the assigned study drug, as long as the second agent was not another study drug. Because beta-blockers were the most likely candidate to be prescribed in these cases, he wondered whether ALLHAT really showed that the combination of a beta-blocker and a diuretic was simply a combination superior to either the ACE inhibitor/beta-blocker or calcium channel blocker/beta-blocker combinations.

Laragh and Sealey (2003) also criticized the ALLHAT investigation for failing to consider individual differences in renin status in determining optimal treatment matches between study participants and class of medications. According to Laragh's perspective (1983), optimal antihypertensive therapy among high-renin hypertensives would involve different pharmacologic agents from those used among low-renin hypertensives. Rather than conclude that diuretics should be the preferred initial antihypertensive agent, as suggested by ALLHAT, Laragh and Sealey preferred continuation of the 'tailored therapy' approach based upon efforts to identify individual difference variables, like renin status, that might help predict which patient characteristics are associated with optimal treatment outcomes for each medication. These conclusions also correspond more directly with the recommendations for selecting an appropriate antihypertensive agent issued by the World Health Organization and International Society of Hypertension (Guidelines Committee, 2003).

Although the debate over which antihypertensive agent should be considered for a first-line intervention will most likely spawn additional controversy, it has been established that several individual differences exist that are related to optimal blood pressure control with antihypertensive therapy. For example, blacks have been shown to exhibit greater reductions in blood pressure with calcium channel blockers than either ACE inhibitors or beta-blockers (Saunders et al., 1990). Older patients also have been reported to respond better to calcium

channel blockers than beta-blockers, but younger patients respond better to either ACE inhibitors or beta-blockers than calcium channel blockers or diuretics (Morgan, Anderson, and MacInnis, 2001). These findings pertaining to age corroborate the existence of hyperkinetic hypertension in young hypertensives and the more volume-mediated hypertension among older hypertensives (Laragh, 1983). Despite the utility of considering these constitutional factors when selecting an appropriate therapeutic agent, they predict optimal treatment outcomes only in approximately half of the hypertensive patients being treated with antihypertensive medications (Materson et al., 1993).

Several comorbid medical conditions also direct the physician in choosing an appropriate antihypertensive medication. For example, use of beta-blockers is contraindicated in patients with asthma, and heart failure patients should not be prescribed calcium channel blockers (Kaplan, 2002). Likewise, because use of diuretics can create complications for patients with diabetes or gout, these agents should be used sparingly in these cases.

Several hypertensive specialists have advocated a physiological approach to selecting an appropriate antihypertensive agent. As mentioned above, Laragh (1983) has supported categorization of hypertensive patients into high-renin (hyperkinetic) and low-renin (volume-dependent) hypertensives. According to this model, adrenergic-inhibiting drugs would provide an optimal blood pressure–reducing effect for the high-renin subtype and diuretics would provide an optimal blood pressure–reducing effect for the low-renin subtype. Efforts to predict treatment response using plasma renin profiling, however, have revealed only weak effects, and only for some antihypertensive agents (ACE inhibitors; Dickerson et al., 1999). Despite the appeal of this approach, it has been infrequently adopted in clinical settings.

There is also some suggestion that consideration of an individual's hemodynamic profile may be important when selecting an appropriate antihypertensive agent. Patients whose elevated blood pressure is maintained by increased cardiac output would presumably respond better to antihypertensive agents that reduce cardiac output than patients whose elevated blood pressure is maintained by increased peripheral resistance. It is well known, for example, that diuretics, ACE

inhibitors, alpha-blockers, and calcium channel blockers reduce blood pressure by lowering total peripheral resistance, and beta-blockers reduce blood pressure by reducing cardiac output (Lund-Johansen, 1983). Accordingly, then, beta-blockers would be optimal first-line agents for hypertensive patients with elevated cardiac output, and diuretics, alpha-blockers, and vasodilators would be appropriate choices for hypertensive patients with elevated peripheral resistance (Messerli, 1987). A recent report from Taler and colleagues (2002) has demonstrated the utility of this hemodynamic profiling strategy using impedance cardiography in selecting antihypertensive agents for treating resistant hypertension. In contrast to a 33 percent success rate for controlling resistant hypertensive patients' blood pressures with treatment by a hypertensive specialist, a 56 percent success rate was observed in the group in which medications were selected via hemodynamic management. Although there has been a paucity of research examining this unique method for selecting appropriate antihypertensive therapies, it appears to hold promise for optimizing treatment outcomes among resistant hypertensive patients.

One final strategy that has been recommended for selecting antihypertensive agents involves conducting a sequential crossover trial with various medications for each individual patient (Dickerson et al., 1999). In this approach, regular blood pressure assessments are made while patients are administered one-month trials with each of the following medications: ACE inhibitor, beta-blocker, calcium channel blocker, and diuretic. Observing the blood pressure responses to each pharmacologic agent, the physician can easily select the optimum agent without resorting to assessing plasma renin activity or hemodynamic factors. Despite the advantage of this approach for selecting the best first-line antihypertensive agent, however, it is used infrequently. Currently, the process of selecting the optimal initial medication typically involves consideration of age and race of the patient and any coexisting medical conditions.

Adherence to Antihypertensive Therapy

Prescribing an optimal antihypertensive agent is of little value if the patient is not going to take the medication. As we observed with Frank-

lin, blood pressure control was difficult to achieve because he discontinued taking his medication. His case is not that unusual. It has been estimated that over half of the patients being treated for essential hypertension do not take their medications as prescribed (Haynes, Taylor, and Sackett, 1983). In a survey of Medicaid recipients with essential hypertension, only about one-third were taking their antihypertensive medication after one year of treatment, even though health care was provided free of charge (McCombs et al., 1994). As in Franklin's case, many hypertensive patients discontinue taking their prescriptive medications due to their side effects, which are often more uncomfortable than the relatively unnoticeable condition of hypertension itself. Indeed, research indicates that adherence is improved among newer angiotensin receptor blockers, because they are well tolerated with relatively few side effects (Bloom, 1998). Another factor that leads to nonadherence is the patient's adoption of an acute disease model, which involves the belief that one takes blood pressure–controlling medication only until one's "blood pressure is better" (Shapiro, 1996). Cost can also be a problem for many patients with diagnoses of hypertension. Given that hypertension has a higher incidence in lower socioeconomic populations, many patients simply lack the financial resources, including health insurance coverage, to pay for their medications.

Shapiro (1996) also cited complexity of the medical regimen and the patients' daily schedules as factors that resulted in increased nonadherence. For example, patients tend to be more adherent with antihypertensive drugs that need to be taken only once a day (Sica, 1994), and patients with varying daily schedules are apt to be less adherent than those with regular daily schedules. It has also been demonstrated that patients for whom the initial antihypertensive therapy was successful in achieving blood pressure control were more adherent than patients who required trials of several medications before the optimal treatment regimen was identified (Caro et al., 1999). From this perspective, it is important for the physician to select the best drug for initial antihypertensive therapy in order to maximize patient adherence. Finally, Shapiro also noted gender differences in adherence; females were reported to be more adherent than males.

From the research conducted on nonadherence to medical treatments, it is clear that Franklin exhibits many characteristics of patients

who do not adhere to their prescribed therapy. Not only is Franklin a male, but he reported significant side effects associated with the medication that was chosen (a diuretic), a belief that he did not have to take his medication when he was not feeling stressed, and an unpredictable, varying daily schedule in his occupation as a firefighter. Furthermore, Franklin did not discuss his nonadherence with his physician, suggesting that improvements in adherence were not likely. Given the problems with nonadherence that he was experiencing, just what could Franklin or his physician have done to improve regulation of his blood pressure?

It is important to note that relying on clinical judgment of the physician and patient education have both been shown to be insufficient for improving adherence to antihypertensive therapy (Haynes et al., 1983). Simply put, health-care providers must take more active roles in assessing and monitoring patient adherence in order for such adherence to increase, consequently resulting in improvements in blood pressure control. Strategies that have merit include increasing the frequency of clinic appointments, contacting patients who have likely dropped out of treatment, establishing strategies to obtain blood pressure measures at home or work (like workplace visits or the ambulatory monitoring of blood pressure), devising reinforcement programs for adhering to the treatment plan, and developing self-management programs (Polefrone et al., 1987). Even pill counts, accessing pharmacy records, and biochemical assays can be used if the physician suspects problems with adherence (Dunbar-Jacob, Dwyer, and Dunning, 1991). In an analysis of various methods for improving adherence, Kirscht, Kirscht, and Rosenstock (1981) found that both contact with a nurse via phone calls and instruction of a support person regarding the importance of taking antihypertensive medications as prescribed resulted in adherence ratings of over 90 percent.

Non-Pharmacologic Treatment and Prevention of Hypertension

Given the wealth of data supporting a role for various lifestyle factors in the etiology of essential hypertension, it is not surprising that a number of non-pharmacologic, behavioral interventions have also

been examined with respect to obtaining and maintaining blood pressure control among hypertensives as well as among communities at large. The importance of lifestyle factors was highlighted in the JNC-7 Report (Chobanian et al., 2003), which stated "adoption of healthy lifestyles by all persons is critical for the prevention of high blood pressure and is an indispensable part of the management of those with hypertension" (p. 1216). Accordingly, it is recommended that hypertensive patients maintain an optimal body weight, consume a diet low in sodium ($<$ 2.4 g per day) and high in potassium and calcium, exercise regularly most days of the week, and consume no more than one alcoholic beverage per day (Chobanian et al., 2003). Although several non-pharmacologic interventions significantly lower blood pressure by themselves, they also can be useful adjunctive therapies associated with antihypertensive medications. For example, Shapiro et al. (1997) showed that when a non-pharmacologic cognitive-behavioral intervention was combined with standard drug treatments for high blood pressure, lower dosages of medications were required to achieve satisfactory control.

Prevention Programs

In contrast to pharmacologic interventions that are used primarily with essential hypertensive patients, prevention efforts have largely focused on non-pharmacologic community-based programs. In establishing guidelines for the prevention of hypertension, the Joint World Health Organization/International Society of Hypertension Meeting (1992) identified several targeted goals for preventing hypertension worldwide, including weight control, increased physical exercise and potassium intake, reduction in alcohol and sodium consumption, consumption of a prudent diet, and reduction in psychosocial stress. According to these guidelines, incidence of essential hypertension would be considerably reduced if individuals would engage in these lifestyle changes. In fact, population-based studies have shown decreased incidence of hypertension when several of these lifestyle factors are changed (National High Blood Pressure Education Program Working Group, 1993). In particular, there is compelling evidence that

weight loss, reduced sodium and alcohol consumption, and increased exercise among communities has a significant impact on average blood pressures and incidence of essential hypertension. Likewise, these same interventions conducted on children have been shown useful in preventing blood pressure problems later in life (Strong et al., 1992).

Although several excellent prevention studies have been conducted, a classic prevention study aimed at blood pressure control was the Stanford Five-City Project (Fortmann et al., 1990). In this prevention trial, two cities were exposed to a community-based program to improve hypertension awareness and to engage in lifestyle behaviors aimed at lowering risk for blood pressure problems, including an emphasis on losing weight, reducing sodium intake, and increasing exercise. After five years, blood pressures of inhabitants in the two treatment cities decreased by 7.4/5.0 and 5.5/3.7 mm Hg for both SBP and DBP respectively. Although these reductions in blood pressure are not as large as typically seen in intervention studies, they are quite remarkable when one considers the fact that they represent community blood pressure averages. Keeping in mind that data supporting the nonpharmacologic interventions presented below have also been derived from prevention programs, let us examine evidence supporting each approach.

Lifestyle Interventions

Given the important link between obesity and risk for essential hypertension, a number of lifestyle modification programs have focused primarily on regaining normal body weight. One only needs to peruse best-selling book lists or examine the lead stories in popular monthly magazines to know that there are dozens of strategies proposed for losing weight, ranging from use of dietary supplements to appetite suppressants, and from daily exercise programs to various forms of surgery. Regardless of the strategies proposed, body weight is basically a function of the number of calories ingested and the number of calories expended on a daily basis. Therefore, most effective weight loss programs focus on some combination of reducing caloric intake (altered diet) and increasing the number of calories expended (exercise). In the fol-

lowing section, weight loss strategies in general are first considered, followed by specific dietary and exercise strategies for lowering blood pressure.

Weight Reduction

Weight reduction stands out as one of the foremost behavioral interventions for lowering blood pressure. It is well known that even relatively minor reductions in weight can be associated with significant reductions in blood pressure (Trials of Hypertension Prevention Collaborative Research Group, 1997). In an early review of blood pressure control achieved via weight loss, Hovell (1982) reported that for every 2.2 lbs (or 1 kg) of weight lost, DBP was decreased by 1 mm Hg. These findings have been corroborated in more recent reviews of randomized clinical trials examining the relation between weight loss and blood pressure reduction (Blumenthal et al., 2002; Neter et al., 2003). Although studies generally report that a 1 mm Hg reduction in blood pressure is associated with each kg of weight lost, there have been some studies that show even greater reductions in blood pressure associated with each kg of weight lost. For example, Stamler et al. (1980) reported reductions of 2.5 mm Hg SBP and 1.8 mm Hg DBP for each kg of weight lost. The manner in which an obese patient loses weight does not appear to affect the extent of blood pressure reduction, as comparable reductions in blood pressure have been observed among obese patients using appetite suppressants (Stunkard, Wilcoxin-Craighead, and O'Brien, 1980) and among those placed on very low calorie diets (Tuck et al., 1981). However, because long-term maintenance of weight loss is poor for individuals using appetite suppressants or very low calorie diets, they are often not the best strategies to use for controlling blood pressure.

For obese or overweight hypertensive patients, weight loss has been reported to result in blood pressure reductions comparable to many antihypertensive medications (Blumenthal et al., 2002). In a meta-analysis of clinical effectiveness of a variety of blood pressure–lowering interventions, Linden and Chambers (1994) reported that weight reduction appears to be comparable to antihypertensive medications for lowering SBP, but resulted in slightly lower reductions in DBP than antihypertensive medications. Although it is often difficult to achieve significant reductions in weight, the evidence shows that it

can be a very effective intervention for both lowering blood pressure and preventing onset of hypertension.

The effectiveness of weight loss has also been shown to be superior to other non-pharmacologic interventions aimed at preventing hypertension. Data from over 2000 participants in the first phase of the Trials of Hypertension Prevention (TOHP) study showed that while weight loss and sodium reduction were associated with significant reductions of both SBP and DBP after 18 months, stress management or dietary supplements with calcium, potassium, magnesium, or fish oil failed to exhibit any demonstrable reduction in blood pressure (Whelton et al., 1997). In the second phase of this large-scale trial, both weight loss and sodium reduction were shown to reduce incidence of essential hypertension over a three-to-four-year follow-up period when compared with a usual care control group (Trials of Hypertension Collaborative Research Group, 1997). Therefore, weight loss has been shown to be an effective strategy both for lowering blood pressures of hypertensive patients and for preventing onset of high blood pressure problems among high-risk persons.

Although it is well established that weight loss is associated with reductions in blood pressure, it is less clear through which mechanisms weight loss exerts its effect. Numerous physiological alterations occur as the body returns to normal weight levels, and many of these changes influence factors regulating blood pressure shown in Figure 1.2. For example, Kaplan (2002) cites evidence of diminished sympathetic nervous system activity following weight loss, as baroreflex functioning normalizes (Grassi et al., 1998), as well as increased release of nitric oxide in the vasculature that occurs with weight loss (Perticone et al., 2001). Additionally, because high renin activity prior to treatment has been associated with larger blood pressure reductions following weight loss than low renin activity (Blaufox et al., 1992), a broad array of physiological factors appears to be involved in the blood pressure–lowering effect of weight loss.

Sodium Restriction

Because of the known relation between sodium and high blood pressure, moderation of salt ingestion has also been examined as a non-pharmacologic intervention for treating and preventing hypertension.

Low sodium diets were actually highly recommended methods for treating hypertension prior to the discovery and use of diuretics (Kempner, 1948). Like weight loss programs, interventions aimed at reducing sodium intake to below the recommended 2.4 g (or 6 g NaCl, 100 mmol) per day level have been shown to be associated with reductions in blood pressure (Cutler, Follman, and Alexander, 1997; Midgley et al., 1996) as well as reductions in hypertensive target organ pathology and cardiovascular mortality (Kaplan, 2002; Law, 1997). Although variability in the magnitude of reduced blood pressure is associated with the extent of sodium restriction (individuals who restrict sodium the most exhibit the greatest reductions in blood pressure), hypertensive patients can typically achieve SBP reductions between 3 and 6 mm Hg and somewhat smaller DBP reductions according to these reviews. Even greater blood pressure reductions have been observed with sodium restriction interventions used on older adults (Midgely et al., 1996). As mentioned above, sodium restriction was also associated with significant blood pressure reductions as well as decreased incidence of diagnosis of essential hypertension in a prevention trial of high-risk individuals (Trials of Hypertension Collaborative Research Group, 1997), although the overall efficacy of sodium restriction on blood pressure was somewhat less than that observed for weight loss programs.

Although sodium restriction interventions have been associated with decreases in blood pressure, the magnitude of average blood pressure reductions among hypertensive patients is lower than that observed with either pharmacologic or weight loss treatment approaches (Linden and Chambers, 1994). Nevertheless, sodium restriction enhances the effect of most pharmacologic interventions (Kaplan, 2002), suggesting that blood pressure regulation can be more easily achieved with lower doses of antihypertensive therapy. Sullivan (1991) contends that part of the reason for the slightly less impressive treatment outcomes associated with sodium restriction interventions is due to variation in salt sensitivity. According to this perspective, salt-sensitive hypertensives are expected to respond to salt-restricting diets with substantially greater blood pressure reductions than salt-resistant hypertensives. In fact, there is some evidence to suggest that salt-sensitive hypertensives do indeed exhibit greater reductions in blood pressure

following salt restriction than salt-resistant hypertensives (Chrysant et al., 1997; West et al., 1999). However, because standardized laboratory procedures are not yet available to measure salt sensitivity reliably and this hypothesis has not been widely studied, Kaplan (2002) simply recommends uniform sodium restriction guidelines with appropriate blood pressure monitoring for all hypertensive patients.

The physiological mechanisms through which sodium restriction exerts its antihypertensive effect are still not well understood. From the assumption that sodium restriction influences kidney regulation of blood and fluid volume, it could be hypothesized that the reduction in blood pressure observed with sodium restriction is largely due to diminished cardiac output. Indeed, reductions in blood pressure observed with sodium restriction have been shown to be associated with reduced cardiac output, and no change in peripheral resistance (Omvik and Lund-Johansen, 1986). However, because black and older patients respond quite favorably to sodium restriction interventions and are known to exhibit blood pressure elevations due to increased total peripheral resistance rather than cardiac output, there are certain to be other mechanisms at work in lowering blood pressure during sodium restriction. For example, Kaplan (2002) cites evidence that low-salt diets improve arterial distensibility (Avolio et al., 1986) as well as modulate beta-adrenergic responsiveness (Feldman, 1992), each representing additional mechanisms that may improve blood pressure regulation.

Potassium Supplementation

In many studies of the effect of dietary interventions on lowering blood pressure, sodium restriction was accomplished in conjunction with potassium supplementation (Wing et al., 1984), and disentangling their effects proved impossible. Simply put, elimination of high-sodium foods was more easily accomplished when potassium-rich fruits and vegetables were added. However, in order to address the influence of their independent effects on blood pressure regulation, more recent efforts have employed diets that altered the specific electrolytes of interest. Whelton et al. (1997) conducted a meta-analysis of 33 randomized controlled trials employing potassium supplements to determine whether any blood pressure–reducing effect was associated with potassium supplementation alone. Overall, their analysis revealed

a reduction of roughly 3 mm Hg SBP and 2 mm Hg DBP for the oral potassium agents, although a somewhat better treatment response was observed among black participants. The blood pressure–reducing effect of potassium was greatest among individuals consuming high levels of sodium, indicating that potassium supplementation may work by countering the effects of high levels of dietary sodium. Congruent with findings indicating that sodium restriction interventions result in blood pressure reductions primarily among salt-sensitive hypertensives, data on potassium supplementation have also shown an antihypertensive effect primarily among salt-sensitive hypertensives (West et al., 1999). Based upon this evidence, it appears that potassium supplementation alone is less effective as a blood pressure–lowering intervention than either pharmacologic interventions or the non-pharmacologic interventions focusing on weight loss or sodium restriction (Linden and Chambers, 1994).

Findings from studies examining the effect of potassium supplementation on blood pressure of normotensive volunteers have typically shown only very small effects on blood pressure. In the TOHP trial of non-pharmacologic interventions among individuals at risk for developing hypertension, potassium supplementation was associated only with a significant 1.8 mm Hg reduction in DBP, and had no effect on SBP (Whelton et al., 1995). Likewise, Sacks et al. (1998) reported a small blood pressure reduction (<2 mm Hg) associated with potassium supplementation among normotensive women with low potassium intakes.

As is the case with sodium restriction, mechanisms associated with blood pressure reductions observed with potassium supplementation are unknown. As adequate amounts of potassium are needed for proper functioning of vascular smooth muscle cells and nerves, and renal functioning, it is likely that a number of physiological mechanisms are involved in the blood pressure–reducing properties of potassium supplementation.

Calcium Supplementation

The majority of empirical studies examining dietary interventions for treating essential hypertension have involved sodium restriction or potassium supplementation. However, several studies have attempted

to determine whether calcium supplementation results in lowered blood pressures, but they generally suffer from the same problems as many of the early studies of potassium supplementation (for example, failure to control for concomitant changes in other electrolytes). In a meta-analysis of 42 randomized controlled trials of interventions that included calcium supplementation, Griffith et al. (1999) found an average SBP reduction of 1.4 mm Hg and an average DBP reduction of 0.8 mm Hg, relatively unimpressive results. In their analysis comparing efficacy of various types of antihypertensive therapies, Linden and Chambers (1994) also reported negligible effects of calcium supplementation on blood pressure change. Likewise, findings from the TOHP trial with individuals at risk for hypertension showed no beneficial effect of calcium supplementation on levels of blood pressure (Yamamoto et al., 1995). Given the relative lack of support for calcium supplementation, it is not considered an effective non-pharmacologic intervention for essential hypertension, except perhaps in rare cases where a patient exhibits low serum calcium.

Magnesium Supplementation

Compared with the number of studies examining the relation between the other electrolytes and blood pressure, there are relatively few examining the relation between magnesium supplementation and reductions in blood pressure. In fact, their number is inadequate to even conduct a meta-analysis. In a small sample of hypertensive patients, Kawano et al. (1998) reported an average 2.5 mm Hg reduction in ambulatory SBP and an average 1.4 mm Hg reduction in ambulatory DBP with magnesium supplementation. Studies employing magnesium supplementation on normotensive women (Sacks et al., 1998) and persons at risk for hypertension in the TOHP study (Yamamoto et al., 1995), however, found no effect of magnesium supplementation on blood pressure. Like calcium supplementation, magnesium supplementation appears to be beneficial only among patients with identified magnesium deficiencies.

Dietary Programs Involving Multiple Factors

Although dietary supplements of potassium, calcium, or magnesium can be easily administered and tested using pills, the optimal nutri-

tional plan would involve simply consuming a regular diet comprised of an adequate supply of each of these electrolytes. Although dietary manipulations present a problem for determining which specific dietary parameter (electrolytes, fats, fiber, or vitamins) is associated with reductions in blood pressure, they represent a more ecologically valid strategy for examining how these interventions might work best in real life. This is particularly true for prevention programs, where it is unlikely that entire populations will be requested to take oral supplements of potassium, calcium, or magnesium. Because a single food item can contain multiple electrolytes that might influence blood pressure regulation, it is apparent that some of the control experimenters had in the majority of randomized clinical trials is sacrificed with this type of work. Nevertheless, comparisons of broad dietary practices that affect multiple nutritional factors have been conducted, and several have been shown to be related to reductions in blood pressure. For example, hypertensives consuming vegetarian diets have been shown to exhibit lower blood pressures than meat-eating hypertensives (Margetts et al., 1986). Obviously, there are several differences between vegetarian and non-vegetarian diets regarding nutritional parameters, and efforts to identify the primary source of the blood pressure–lowering effect have been unsuccessful.

One of the more impressive controlled trials of dietary practices and hypertension is the Dietary Approaches to Stop Hypertension (DASH) trial (Appel et al., 1997). In the DASH trial, mild hypertensive patients were assigned to a usual diet control condition, a condition assigned to increase fruits and vegetables, or a third condition receiving both assignments to increase fruits and vegetables *and* reduce fat intake. Although significant reductions in blood pressure occurred among participants in the increase fruits and vegetables condition, the combined increase fruits and vegetables/decrease fats group exhibited more than twice the reduction in blood pressure seen with the increase fruits and vegetables alone condition. Among some participants in the DASH trial, the magnitude of blood pressure reduction was comparable to the typical effects of antihypertensive medications (Sacks et al., 2001). These impressive findings pertaining to the importance of a low-fat, high-fiber diet for controlling blood pressure led to their in-

clusion among general lifestyle modifications used to treat hypertension in JNC-7 (Chobanian et al., 2003).

Omega-3 Fatty Acid Supplementation

Based upon a few studies linking consumption of omega-3 polyunsaturated fatty acids, commonly found in fish, to lower blood pressure, several studies have examined whether diets supplemented with fish oil would lead to reductions in blood pressure. In a meta-analytic review of these studies, Appel et al. (1993) reported that use of fish oil supplements resulted in approximately a 4 mm Hg reduction in blood pressure. In combination with weight loss, fish oil supplements have been shown to result in reductions as high as 13 mm Hg (Bao et al., 1998). Although not commonly recommended for lowering blood pressure, omega-3 fatty acid supplementation appears to hold promise for reducing blood pressure, at least in combination with other antihypertensive therapies.

Caffeine Restriction

Because the relation between caffeine use and incidence of hypertension is equivocal, lesser attention has been paid to caffeine restriction as a recommended non-pharmacologic intervention for reducing high blood pressure. In general, if caffeine increases ambulatory blood pressure among hypertensive patients, Kaplan (2002) advises patients to consider switching to decaffeinated beverages. Additional clinical trials are needed in order to make any further recommendations regarding caffeine restriction as a method for lowering blood pressure.

Alcohol Restriction

As observed in Chapter 6, alcohol consumption represents a unique lifestyle factor that appears to exhibit differential effects on risk for hypertension and magnitude of cardiovascular response to stress. Although incidence of essential hypertension increases with chronic alcohol use, its acute effects are to attenuate blood pressure responses to stress. Despite its unique characteristics, alcohol restriction has been examined as an intervention strategy for lowering blood pressure. In a meta-analytic review of 15 randomized controlled trials examining pro-

grams to reduce alcohol consumption, Xin et al. (2001) reported that reductions in alcohol consumption were associated with diminished blood pressures. SBP was reduced by an average of 3.3 mm Hg and DBP was reduced by an average of 2 mm Hg in these studies. In contrast, in a recent controlled trial, Cushman et al. (1998) reported no impact on blood pressure with moderate alcohol restriction; however, participants in this study were not heavy drinkers. Although alcohol restriction is associated with reductions in blood pressure, the magnitude of this effect is far smaller than blood pressure reductions observed for pharmacologic interventions as well as other behavioral interventions like weight loss. In summary, lifestyle recommendations from the JNC-7 associated with alcohol consumption include consuming no more than two drinks per day for males and one drink per day for females (Chobanian et al., 2003).

Increased Physical Activity

Up until now, we have primarily discussed interventions that have focused on the dietary or consumption end of weight regulation. As stated above, any effective weight loss program involves both regulating caloric intake *and* increasing caloric expenditure. Certainly, consideration of physical activity is critical for interventions aimed at losing weight as well as those aimed at lowering blood pressure. The primary method for increasing caloric expenditure is to increase the duration of time each day spent in activities that require more calories (exercise). Additionally, a regular physical exercise program prevents the reduction in metabolic rate that occurs with very low calorie dieting (Donahoe et al., 1984), enabling a dieter's body to burn off more calories. Therefore, a well-constructed exercise program involving both aerobic and muscle-strengthening exercises is an important part of calorie expenditure in successful weight loss programs. Let's examine the effect of increasing activity through physical exercise upon blood pressure.

Kelley and McClellan (1994) conducted a meta-analysis of nine randomized controlled trials comparing lower-extremity exercise interventions (walking, jogging, or cycling) with control groups and found a significant reduction in blood pressure with aerobic exercise. SBPs were reduced by 7 mm Hg and DBPs were reduced by 6 mm

Hg. Linden and Chambers (1994) reported even greater reductions in blood pressure in their analysis of the literature, approximating the magnitude of blood pressure reductions observed in studies employing antihypertensive medications. However, conclusions from more recent reviews of the literature have tended to be more conservative (Blumenthal et al., 2002; Kelley and Kelley, 2000; Whelton et al., 2002), focusing on many methodological problems associated with this body of literature that limit making definitive statements. For example, many studies employing exercise interventions failed to use appropriate no-treatment control conditions, and often participants were not randomized into treatment conditions. Estimates of blood pressure reductions associated with various forms of exercise revealed in more recent meta-analyses (Kelley and Kelley, 2000; Whelton et al., 2002) were much lower, approximating 3 mm Hg for both SBP and DBP.

As with weight loss and sodium restriction interventions, a multitude of physiological effects occur as an individual engages in an exercise program, and it is difficult to determine which mechanism is responsible for the blood pressure–lowering effect of physical activity and exercise. Kaplan (2002) cites several possibilities, including improved sympathetic nervous system regulation of blood pressure via baroreceptor reflex sensitivity (Grassi et al., 1994), improved vascular flexibility (Tanaka et al., 2000), and increased release of nitric oxide (DeSouza et al., 2000), all of which have been shown to occur via exercise.

Psychological Approaches to Blood Pressure Reduction

Early psychological interventions aimed at lowering blood pressure were based primarily on the observations of psychoanalytic practitioners who focused on treating the unique personality conditions under which hypertension occurred (Alexander, 1939; Ayman, 1933). For example, if hypertension was associated with unconscious hostile urges and dependency needs, as hypothesized by Alexander, then psychoanalysis aimed at resolving these conflicts should result in reductions in blood pressure. Although there have been reports of hypertensive patients showing marked reductions in blood pressure with supportive or psychoanalytic therapies (Moses, Daniels, and Nickerson, 1956; Reiser

et al., 1951), these studies were not adequately controlled and improvements in blood pressure status were achieved only in some patients.

Because of the perceived importance of the sympathetic nervous system in the etiology of essential hypertension, the vast majority of studies examining psychological interventions aimed at lowering blood pressure have focused on interventions that were thought to alter sympathetic nervous system functioning. These include studies employing various relaxation and meditation strategies as well as more direct methods of physiological control obtained via biofeedback. The most recent psychological intervention efforts have added cognitive behavioral stress management components to the more commonly used relaxation strategies to optimize stress-reducing components of these psychological interventions. Let's examine each of these types of psychological intervention and supporting empirical work.

Muscle Relaxation Strategies

Although relaxation and meditation strategies have been used for centuries, they were introduced to the scientific and medical community through the work of Jacobson (1939). According to Jacobson, reductions in muscle tension, through intensive training in progressive muscle relaxation, resulted in a generalized lowered state of arousal, including reductions in blood pressure. Basically, progressive relaxation training involves the tensing and relaxing of each of the major muscle groups of the trainee in a standard sequence with the aim of releasing residual muscle tension within each consecutive muscle group.

Initial reports of progressive muscle relaxation training were very positive, with SBP reductions ranging from 11 to 13.6 mm Hg and DBP reductions ranging from 4.9 to 12.6 mm Hg (Brauer et al., 1979; Southam et al., 1982; Taylor et al., 1977). Both Jacob, Kraemer, and Agras (1977) and Eisenberg et al. (1993) reported that the magnitude of the observed blood pressure response to treatment with relaxation therapy was significantly predicted by the patient's initial blood pressure; not surprisingly, patients with the highest pre-treatment blood pressures improved the most with relaxation therapies. Furthermore, substantial treatment effects were more likely to be observed among studies that assessed blood pressure on only a single occasion at pre-treatment (Eisenberg et al., 1993). For studies that conducted a more

thorough assessment of blood pressure at pre-treatment, blood pressure reductions in response to relaxation interventions were much smaller (2.3 mm Hg reductions in SBP and 1 mm Hg reductions in DBP). Although more recent studies have confirmed the blood pressure–lowering effect of relaxation training in clinic settings, these promising treatment effects have also failed to generalize to nonclinic or work settings (Agras et al., 1987; Chesney et al., 1987). Furthermore, findings from the Hypertension Intervention Pooling Project (Kaufmann et al., 1988), a data base comprised of data from twelve different intervention studies, revealed essentially no change in SBP and only a 2 mm Hg reduction in DBP associated with relaxation interventions. Therefore, although the initial results for relaxation treatments were compelling, causing them to be mentioned as possible treatment options in the Joint National Committee recommendations for treating essential hypertension (Joint National Committee, 1988), the inability to demonstrate generalized treatment effects led to a less prominent role for them.

Meditation Strategies

In contrast to the focus on relaxing muscles in the somatic nervous system, meditation strategies involve directing concentration on a mental image, word, or phrase. Like muscle relaxation strategies, meditation strategies have been used for centuries within various philosophical and religious practices. Benson (1975) is largely responsible for formalizing a meditation strategy and employing it with hypertensive patients. In Benson's technique, called the respiratory-one method, patients are instructed simply to concentrate on their regular breathing pattern and reciting the word "one" with each exhalation. Transcendental meditation represents another variation of this technique; it involves concentration on a designated mantra rather than the breathing-related stimuli of the respiratory-one method. Like the research on progressive muscle relaxation, the initial work by Benson et al. (1974) revealed impressive reductions in blood pressure, but subsequent research has resulted in less impressive outcomes (Goldstein et al., 1982; Surwit, Shapiro, and Good, 1978). Many of the same limitations that applied to studies of progressive relaxation training also apply to studies on meditation, including findings that the greatest blood pressure

reductions are observed among patients with the highest initial blood pressures (Jacob et al., 1977). In Eisenberg et al.'s (1993) meta-analysis of non-pharmacologic interventions, meditation fares a little better than progressive muscle relaxation with respect to SBP reduction, but yielded no significant change in DBP reduction.

Schneider and colleagues (1992) have explored the utility of transcendental meditation for lowering blood pressure and reported it results in greater blood pressure reductions than other behavioral interventions like progressive muscle relaxation. In particular, transcendental meditation has been shown to be particularly effective with older African American hypertensives (Schneider et al., 1995). In a study examining the hemodynamic processes underlying the observed reductions in blood pressure associated with regular practice of transcendental meditation, Barnes et al. (1999) reported that the blood pressure reductions were associated with reductions in total peripheral resistance rather than cardiac output. Because blacks and older hypertensives have been shown to exhibit increased blood pressure due to increased peripheral resistance, it appears that transcendental meditation may be a particularly useful strategy for controlling blood pressure among older black individuals. However, because strategies employed in transcendental meditation are quite similar to those used with other forms of meditation (respiratory-one method), it is quite likely that the beneficial effect of meditation is not specific to transcendental meditation.

Biofeedback of Cardiovascular Parameters

Biofeedback is the process of bringing information pertaining to typically undetectable physiological states into awareness for the purposes of gaining instrumental control over them. As blood pressure level represents a physiological state that is largely undetected by the individual, efforts at exerting control over blood pressure, by either increasing or decreasing it, require that information about blood pressure level be provided to the individual continuously so that he or she can learn which behavioral responses are associated with its increases and decreases. With extensive training, then, hypertensive patients could presumably learn to regulate their own blood pressure levels based upon the information gleaned through biofeedback.

Direct Blood Pressure Feedback. Initial efforts at employing biofeedback interventions with essential hypertensive patients focused on the provision of blood pressure information from the occluding cuff. However, due to the intermittent nature of gathering blood pressure information via the Riva-Rocci method, a new procedure, known as the constant cuff method, had to be established to provide more regular estimates of blood pressure information to the patient. Basically, the constant cuff method involves inflating the occluding cuff above SBP and gradually decreasing air pressure until the first Korotkoff sound is detected (SBP level). Cuff pressure is then maintained at this level for about a minute, and the patient is instructed to make the Korotkoff sounds disappear, resulting in a reduction in blood pressure. Air pressure is then released for a brief rest period, and the procedure is repeated as the SBP criterion is lowered with each consecutive trial.

Several early studies conducted using the constant cuff feedback paradigm with essential hypertensive patients revealed impressive reductions in SBP with training (Benson et al., 1971; Blanchard, Young, and Hayes, 1975; Kristt and Engel, 1975). For example, Benson et al. reported that five of seven patients were able to lower SBP by 16.5 mm Hg using the constant cuff feedback procedure, and an average reduction in SBP of 23.7 mm Hg was observed among four patients in the study by Blanchard and colleagues. Kristt and Engel reported that blood pressure reductions that were noted with biofeedback training could be observed at least three months after completion of training, indicating that the blood pressure–lowering effect of biofeedback generalized beyond the training setting. It should be noted that none of these early reports were well controlled and each included only a few hypertensive patients. Like empirical work on both progressive muscle relaxation and meditation, subsequent investigations of the direct constant cuff feedback procedure employing more sophisticated designs and larger samples yielded less impressive results (Goldstein et al., 1982; Surwit et al., 1978). In fact, Surwit et al. found no evidence for any blood pressure reduction with biofeedback. In Eisenberg et al.'s (1993) meta-analysis of biofeedback interventions, any significant effect observed among biofeedback interventions was associated with the fact that less than credible control groups were used for purposes of comparison in these studies. Furthermore, significant treatment out-

comes were observed only among studies in which pre-treatment and post-treatment measures of blood pressure employed single blood pressure determinations.

Part of the difficulty in employing the constant cuff method for providing blood pressure feedback to the patient pertains to the intermittent nature of the procedure itself and potential discomfort associated with having an occluding cuff tightly situated on the arm for extended periods of time. Researchers began to examine other physiological parameters that could be measured continuously without discomfort. Heart rate, of course, would be such a parameter, but changes in heart rate that can be achieved with heart rate feedback are often not accompanied by changes in blood pressure (Larkin, Manuck, and Kasprowicz, 1990), rendering heart rate feedback an ineffective tool for reducing blood pressure. Other parameters have proved more useful in this regard, in particular, pulse transit time, finger temperature, and continuous measures of blood pressure using the vascular unloading technique.

Pulse Transit Time Feedback. In a few studies, Steptoe (1977; 1978) examined whether pulse transit time feedback could be used to assist in lowering blood pressure. As indicated in Chapter 2, pulse transit time is inversely correlated with blood pressure, so reductions in blood pressure would be associated with lengthening pulse transit time. In these studies, Steptoe demonstrated that pulse transit time could be altered with feedback, and that groups receiving feedback presumably lowered blood pressure more than no-feedback control groups who were instructed to lower blood pressure. Additionally, persons receiving pulse transit time feedback were better at maintaining their lowered blood pressures during a reaction time task than individuals who participated in relaxation training (Steptoe, 1978). However, due to the uncertainty of pulse transit time as a proxy for blood pressure, very little additional work has been done using pulse transit time feedback. Additionally, it has been demonstrated to lower blood pressures among essential hypertensive patients only as part of a multi-component intervention that included relaxation training (Buby, Elfner, and May, 1990).

Thermal Feedback. In contrast to pulse transit time feedback, thermal biofeedback has been more richly investigated. From evidence that fingertip temperature is a good indicator of blood flow into the

capillaries, it is known that peripheral vasoconstriction associated with high blood pressure leads to reductions in fingertip temperature. Conversely, vasodilation results in increased blood flow into the fingertips as well as increased temperature.

Initial reports demonstrating blood pressure reductions among essential hypertensive patients were quite promising (Blanchard et al., 1984; Fahrion et al., 1986), even though these trials were conducted on patients already taking antihypertensive medications. Fahrion et al., for example, reported that 58 percent of medicated patients were able to discontinue taking blood pressure medication and 35 percent were able to reduce dosage of their antihypertensive medications following treatment with thermal biofeedback. Average SBP reductions were about 15 mm Hg and average DBP reductions were about 10 mm Hg. In a subsequent trial comparing thermal biofeedback to progressive muscle relaxation training, Blanchard et al. (1986) found that thermal biofeedback was superior to progressive muscle relaxation training in lowering blood pressure as well as maintaining reduced blood pressures over a year after discontinuing antihypertensive medications. In more recent controlled trials, thermal biofeedback, like other non-pharmacologic interventions, has failed to demonstrate its efficacy for lowering blood pressure (Blanchard et al., 1996), perhaps suggesting that treatment effects do not hold up when compared with credible control conditions.

Continuous Blood Pressure Feedback. With the advent and regular use of continuous blood pressure monitoring via the vascular unloading principle (Peñaz, 1973), direct blood pressure feedback can be provided without the complications associated with the constant cuff method. Although not many studies have employed this instrumentation, it has been shown to be useful in training participants to increase or decrease blood pressure (Elbert et al., 1992). Interestingly, in this study, biofeedback-trained reductions in blood pressure were associated with activation of baroreceptors and dampened cortical activity. Analysis of the timing of these learned responses confirmed that reductions in both blood pressure and cortical inhibition resulted from baroreceptor activation. Although this study was not conducted on hypertensive patients, the findings provide some support for Dworkin's (1991) hypothesis that blood pressures can be altered through instrumental conditioning.

Hunyor et al. (1997) conducted a study comparing continuous blood pressure feedback with a placebo feedback condition to determine whether blood pressure could be lowered among essential hypertensive patients. In this study, although some of the hypertensive patients could lower SBP, a comparable number of patients in the placebo group were equally successful at lowering blood pressure, suggesting that the reductions in blood pressure were not due to the feedback provided. From these preliminary efforts, it seems that outcomes associated with continuous blood pressure monitoring are similar to those from studies using the constant cuff method for provision of feedback.

Combination Stress Management Programs

Given that no single psychological intervention has received uniform empirical support for its use in treating essential hypertension, several investigators have attempted to assemble interventions that consist of multiple stress management components (for example, meditation with biofeedback or relaxation-assisted biofeedback). Foremost among these efforts is the non-pharmacologic treatment program built upon the central features of yoga by Patel (1973; 1975), which includes training in relaxation, meditation, and biofeedback of skin conductance. In these studies, substantial reductions in both SBP (greater than 20 mm Hg) and DBP (14 mm Hg) were observed among hypertensive patients. Similarly, Johnston et al.'s (1993) intervention included various forms of relaxation and meditation; in contrast to Patel's work, however, Johnston et al. reported no significant reduction in blood pressure among hypertensives in their treatment condition. Consistent with the findings from Patel's laboratory, Ward, Swan, and Chesney (1987) conducted a meta-analysis and concluded that multiple component interventions for reducing blood pressure were better than single method interventions. These findings were corroborated by the subsequent meta-analysis conducted by Eisenberg et al. (1993). In contrast, Linden and Chambers (1994) found no added benefit for multiple treatment components in their meta-analysis of the literature on non-pharmacologic interventions for lowering blood pressure. It would seem then that the relative efficacy of combination approaches, in contrast to single method approaches, has yet to be determined.

Individualized Cognitive Behavioral Stress Management Programs

Based upon a more comprehensive understanding of the cognitive, physiological, and behavioral responses to stress, recent efforts at developing stress management programs have extended beyond those interventions that primarily operated on the physiological arousal system. In other words, both cognitive and behavioral response patterns to stress have been recently incorporated into the types of stress management programs being used with essential hypertensive patients. Linden and Chambers (1994) referred to this relatively new breed of programs as individualized stress management programs, due to their focus on individual factors involved in the stress response. As such, although one element of an individualized stress management program may be labeled cognitive therapy, the exact nature of the thoughts targeted in this approach depends upon the unique cognitive responses of a given individual. Likewise, although anger management may represent a component of one of these individualized stress management programs, one patient may be trained to become more assertive while another patient may be trained to tone down his aggressiveness. In their meta-analysis of non-pharmacologic interventions for lowering blood pressure, Linden and Chambers reported that these individualized approaches fared much better in lowering blood pressures than either single method or multi-component stress management techniques. Because of the promise these programs showed, the Canadian Hypertension Society recommended such programs for patients who live stressful lives or have stressful jobs (Spence et al., 1999). To support these conclusions, Linden, Lenz, and Con (2001) conducted a randomized controlled trial of the individualized stress management approach on the ambulatory blood pressures of 60 hypertensive patients. In this study, the combination of interventions included autogenic training, biofeedback, cognitive therapy, anxiety management, and Type A behavior modification. Congruent with expectations, patients receiving the individualized treatment approach exhibited significant reductions in both ambulatory SBP and DBP in comparison to persons in a no-treatment control condition. Furthermore, when the control patients were subsequently treated with the same individualized approach, they too exhibited comparable reductions in ambulatory SBP and DBP.

Anger Management Training. Because of the literature linking problems in anger expression with hypertension, many of these individualized intervention programs have incorporated anger management training. These programs are generally structured around cognitive-behavioral approaches to reducing intensity of anger as well as improving anger expression (Larkin and Zayfert, 1996a). Many of these intervention trials employing anger management training have been shown to be associated with significant reductions in blood pressure among hypertensive patients (Achmon et al., 1989; Bosley and Allen, 1989; Larkin and Zayfert, 1996b) or significant reductions in taking antihypertensive medications (Lehnert et al., 1987). Comparable reductions in blood pressure have been reported using a similar anger management training program with high-hostile cardiac patients (Davidson et al., 1999). In contrast, data from the TOHP trial conducted on persons at high risk for hypertension showed no benefit for an individualized stress management program consisting of relaxation training, cognitive strategies, time management, anger management, and general problem-solving (Batey et al., 2000), suggesting that such approaches may be less beneficial as prevention programs.

Physiological Mechanisms Associated with Blood Pressure Reductions Observed with Non-Pharmacologic Interventions

Because of the complexity of factors associated with blood pressure regulation, numerous physiological mechanisms have been proposed as being involved in the reduction of blood pressure observed with non-pharmacologic interventions for essential hypertension. As with the pharmacologic interventions, it is likely that different mechanisms are involved in blood pressure reduction associated with distinct non-pharmacologic interventions. As such, the physiological mechanisms associated with blood pressure control following weight loss (for example, increased insulin sensitivity or decreased vascular resistance) may be quite different from the mechanisms associated with blood pressure control following stress management interventions (for example, reduced sympathetic nervous system activation; Blumenthal et al., 2002). Reduced sympathetic nervous system activity, however, has been hypothesized to be associated with blood pressure reductions among all

forms of non-pharmacologic intervention (Blumenthal et al., 2002). Let's examine the evidence supporting this hypothesis.

In contrast to those of dietary, weight loss, or exercise interventions for lowering blood pressure, the efficacy of psychological interventions must involve the nervous system in some way. After all, stress management involves cortical activity in learning the particular procedure, adhering to regular practice, and enhancing motivational factors responsible for its long-term efficacy. Johnston (1991) suggested several mechanisms through which stress management resulted in lower blood pressures, including a reduction in catecholamines and other stress hormones, the promotion of a better quality of life less affected by emotional distress, and the reduction in cardiovascular response to stress. Although he presented some evidence to support each of these mechanisms' effectiveness in lowering blood pressure, there was no clear picture regarding how psychological interventions lead to reduced blood pressures. For example, while some studies have reported that psychological interventions resulted in reductions in cardiovascular responses to stress (Blanchard, McCoy, Wittrock, et al., 1988; Ewart et al., 1984; Patel, 1975), others have failed to show any reduction in cardiovascular reactivity to stress following treatment (Blanchard, McCoy, McAffrey, et al., 1988; Larkin, Knowlton, and D'Alessandri, 1990). Jacob and Chesney (1986) reviewed the literature examining the effect of psychological interventions aimed at reducing cardiovascular response to stress and concluded that evidence that these interventions altered indices of cardiovascular reactivity was lacking. Actually, it is not that surprising that many of these stress management procedures have failed to show attenuations in cardiovascular reactivity to stress. Most psychological interventions include training in relaxation in a quiet room to optimize reduced physiological arousal. In contrast, presenting the patient with stressful stimuli during an assessment of cardiovascular reactivity requires that the patient generalize his or her skills at lowering physiological arousal from a relatively quiet environment to a stressful situation. Given that most stress management training programs do not conduct training in real-life stress situations, it is unlikely that such a transfer of training can be demonstrated satisfactorily. In fact, studies that have conducted stress management training during stressful situa-

tions have typically shown greater reductions in cardiovascular reactivity to stress following training than studies that have conducted more traditional forms of training in a quiet environment (Bentham and Glaros, 1982). Larkin and Zayfert (1996b), interestingly, reported that cardiovascular reactions to confrontation were decreased in hypertensives following training in anger management, but cardiovascular reactivity to other non-anger-eliciting stressors remained unaffected by the training. Therefore, cardiovascular reactions to stress appear to be affected by psychological interventions, as long as the intervention being used permits training during stress presentations.

Although the hypothesis that stress management exhibits its antihypertensive effect through the sympathetic nervous system has not been firmly established, many clinicians assume that hypertensive patients experiencing life stress would be good candidates for stress management approaches. This follows from the logic that if a hypertensive patient is obese, weight loss efforts would provide an optimal approach for controlling blood pressure, if a hypertensive patient consumes too much salt, then sodium restriction approaches would prove optimal, and if a hypertensive patient displays an exaggerated sympathetic nervous system activation to stress, then stress management approaches may prove useful. Although this approach appears logical and is appealing due to its simplicity, there is little evidence to support it. Although a few studies have reported better treatment outcomes among patients with elevated parameters of sympathetic nervous system arousal (Cottier, Shapiro, and Julius, 1984; McGrady and Higgins, 1989), many other studies have failed to demonstrate any association between pre-treatment measures of sympathetic nervous system activation and blood pressure control with stress management procedures (Blanchard et al., 1989; Larkin, Knowlton, and D'Alessandri, 1990). In sum, there is very little evidence to suggest that blood pressure reductions that occur with psychological interventions are due to a reduction in the magnitude of stress-elicited cardiovascular responses.

Given the apparent failure to link treatment outcome with reductions in sympathetic nervous system activation, investigators have turned to examining the relation between other cognitive or motivational factors that have been traditionally important to consider in psychotherapy research in general. Foremost among these variables is

the influence of expectancy. Simply put, patients who expect to achieve blood pressure reductions with psychological interventions would be hypothesized to exhibit the greatest reductions in blood pressure with training. There is evidence that this indeed is true. For example, Agras, Horne, and Taylor (1982) demonstrated that patients undergoing relaxation training who were informed that they should expect to experience immediate reductions in blood pressure exhibited an average 17 mm Hg reduction in SBP following three training sessions compared to an average 2.4 mm Hg reduction in SBP among a control group receiving the same intervention but told that the effects would be delayed. Wittrock, Blanchard, and McCoy (1988) reported that patients who expected to lower blood pressure through a thermal biofeedback intervention exhibited greater reductions than those patients with lower expectations. Interestingly, these same findings pertaining to expectancy were not observed among patients undergoing relaxation training; rather for these patients, those that reported experiencing the greatest depth of relaxation during training showed the greatest reductions in blood pressure.

Congruent with findings on the role of expectancy in reducing blood pressures with psychological interventions, there is evidence that blood pressure can be reduced by sheer suggestion. For example, in a classic study by Chasis et al. (1956), hypertensive patients were provided reassurance and the rationale that their blood pressure problems would be treated with a novel, effective treatment, a 'therapeutic electron gun.' Exposure to treatment sessions with this device resulted in average reductions of 20 mm Hg SBP and 14 mm Hg DBP, even though the rationale behind the treatment was entirely fabricated. In a review of the literature on placebo effects associated with blood pressure treatments, Shapiro (1996) cited evidence that simple instructions to alter blood pressure, presented within the context of a believable rationale, resulted in significant reductions that were comparable to the magnitude of blood pressure reductions observed among most types of non-pharmacologic interventions. Obviously, these findings have implications for research as well as for the clinical management of hypertension. Regarding research, because of these known placebo effects, it is important to implement experimental designs that permit examination of efficacy of treatment effects above and beyond that of the blood

pressure reduction associated with the placebo effect. Unfortunately, credible placebos are difficult to devise when using non-pharmacologic interventions, and blinding procedures are simply impossible to use when patients need to practice the specific intervention strategies that their care-providers have taught them on a regular basis in order for them to work. Regarding clinical practice, it seems obvious that our knowledge of the substantial placebo effects would strongly incline clinicians to focus on optimizing this effect to obtain the best blood pressure reductions possible by providing sufficient reassurance to patients and conveying the expectation that the treatment will work for them. Acknowledging the importance of the doctor–patient relationship in optimizing treatment outcomes, JNC-7 (Chobanian et al., 2003) highlights these suggestions as well for both pharmacologic and non-pharmacologic interventions.

Social Support Interventions to Reduce Blood Pressure

Because low social support has been strongly associated with increased incidence of essential hypertension and increased cardiovascular reactivity to stress, as reported in Chapter 7 (pp. 246–248), interventions aimed at altering access to and perception of social support have been tested among hypertensive patients. Uchino et al. (1996) reviewed 14 studies that measured blood pressures among either normotensive or hypertensive individuals before and after interventions aimed at increasing social support. Presumably, if social support was related to lower blood pressures, interventions of this type would be hypothesized to result in reductions in blood pressure. Although findings from intervention studies of normotensives were mixed, a meta-analysis of intervention studies that was done on intervention trials employing essential hypertensive patients yielded a significant effect, with family-based social support interventions resulting in blood pressure reductions. Most of these interventions targeted the involvement of family members in the treatment process and instructed them to take an active role in treating the patient's blood pressure problem, including reinforcing treatment compliance and assisting in monitoring the patient's blood pressure. Although these findings further support the hypothesis that reduced social support is linked to an increased inci-

dence of essential hypertension, they also indicate that social interventions represent an important component of the management of high blood pressure.

Summary

There are many effective strategies known to lower blood pressure among patients with essential hypertension. In general, more substantial reductions in blood pressure can be achieved by using pharmacologic interventions in contrast to non-pharmacologic interventions, although several non-pharmacologic interventions (weight loss, sodium restriction, and individualized stress management programs) have also been shown to reliably result in reductions in blood pressure.

Several pharmacologic agents, which presumably function through different mechanisms that affect blood pressure regulation, have been shown to be excellent choices for treating essential hypertension, including diuretics, adrenergic inhibiting agents, and vasodilators. Diuretics exert their blood pressure–lowering effect by altering fluid retention orchestrated by the kidneys, adrenergic-inhibiting drugs decrease sympathetic nervous system activation of the circulatory system, and vasodilators operate directly on the blood vessels in the vasculature. Although there are a few known predictors of treatment outcome associated with each of these categories of medications (for example, age and ethnicity), each type of medication has been shown to reduce blood pressure and the cardiovascular complications associated with high blood pressure.

Prescription patterns for the various antihypertensive agents have changed over the years. Because diuretics were some of the first medications shown to elicit blood pressure–reducing effects, they were often chosen as first-line treatment agents and used as the standard of comparison for testing newer antihypertensive agents. Stepped-care approaches to treating hypertension were advocated, which involved using diuretics as the first-line agent for treating hypertension, followed by use of beta-blockers if adequate reductions in blood pressure were not observed with diuretics, and finally, with the addition of vasodilators. With the discovery of newer antihypertensive medications with fewer side effects, prescriptive patterns shifted to more of a 'tai-

lored' therapy approach (Poulter, 1991). This approach involved selecting the appropriate antihypertensive agent based upon unique aspects of the patient's blood pressure regulation problem. Accordingly, hypertensive patients hypothesized to exhibit high blood pressure due to excessive sympathetic nervous system activation would be prescribed adrenergic-inhibiting medications as first-line treatment agents. Most recently, largely based upon findings from the ALLHAT trial (ALLHAT Officers, 2002), recommendations for prescribing blood pressure–reducing drugs have shifted back toward an emphasis upon the use of diuretics as first-line agents (Chobanian et al., 2003). Although these recommendations have been met with considerable controversy due to the methodological problems associated with the ALLHAT trial (Laragh and Sealey, 2003; Weber, 2003), prescriptions for diuretics have again risen (Kaplan, 2002). It is safe to conclude that uniform agreement among physicians regarding choice of antihypertensive agents has not been obtained, nor is it likely to emerge in the near future.

Even though several pharmacologic agents are known to reduce blood pressure, they will not exert their treatment effect if the patient does not take the medication as prescribed. This was clearly the case with Franklin. Many patient and physician factors have been shown to influence whether a patient is going to adhere to the prescribed treatment regimen. Although the patient's gender, level of trust in his or her physician, and capacity to understand treatment instructions represent patient variables that are known to alter adherence, there are several factors associated with adherence that are under the control of the physician. For example, the physician must be able to educate the patient regarding the importance of taking blood pressure medication, even when the patient is feeling good or unstressed. The physician can also consider selecting antihypertensive agents that can be dosed so that taking medication fits into the patient's daily schedule easily. Furthermore, because of the demonstrated placebo effects associated with all forms of antihypertensive therapy, it is the physician's job to provide a solid rationale for the treatment choice to enhance the patient's belief in the intervention. Obviously, if the physician informs that patient only that he or she has high blood pressure and should take a pill the physician is going to prescribe, therapeutic outcome as well as adherence to what may be a perfectly suitable intervention will be minimal.

Decades of research have been conducted on various non-pharmacologic interventions for reducing blood pressure. Lifestyle interventions have included programs aimed at weight loss, sodium restriction, restriction of alcohol and caffeine use, increased exercise, increasing consumption of low fat/high fiber diet, and potassium, calcium, magnesium, or fish oil supplementation. Although almost all of these interventions have been associated with reductions in blood pressure, the magnitude of reductions observed is less than that achieved with antihypertensive medications. Weight loss and sodium restriction stand out as interventions that may exhibit comparable reductions in blood pressure to those seen with pharmacologic agents for selected patients like obese or salt-sensitive patients. In contrast to pharmacologic interventions, these lifestyle change programs have also been shown to be quite successful in lowering blood pressure and risk for development of essential hypertension in community-based prevention trials.

Several psychological interventions have also been examined regarding their efficacy at lowering blood pressure, including training in relaxation, meditation, or biofeedback. Like lifestyle modification programs, each of these interventions has been shown to result in lower blood pressure, but not comparable to the extent observed with use of antihypertensive medications. Furthermore, although these psychological interventions have resulted in reductions in blood pressure in clinic treatment settings, they often fail to demonstrate generalization of treatment effects to real-life settings. More recent findings using individualized stress management programs for treating essential hypertension, particularly those that include training in anger management, have been shown to result in somewhat better reductions in blood pressures than single-method psychological interventions. However, additional work is needed using these interventions before definitive conclusions can be drawn.

Finally, social support interventions constitute a third type of non-pharmacologic intervention aimed at lowering blood pressures. Although there is not a substantial body of literature examining these social support interventions, those that have been reported have shown promise in achieving lowered blood pressures. Certainly, the support that a patient receives from his or her physician is critical in developing an effective intervention program for reducing blood pressure.

Although many different pharmacologic and non-pharmacologic interventions have been employed to reduce blood pressure among hypertensive patients, the mechanisms responsible for resulting in the observed reductions in blood pressure are far from clear. Even among interventions where the mechanism responsible for the treatment effect appears obvious (beta-blockers lower blood pressure by reducing sympathetic nervous system response action on the heart), solid evidence is lacking. In fact, more often than not, it appears that interventions, both pharmacologic and non-pharmacologic, involve multiple blood pressure regulatory mechanisms. A significant amount of attention has been given to cardiovascular reactivity to stress as a mechanism involved in mediating the stress–hypertension relation. As such, one might expect certain interventions aimed at lowering blood pressure might exert their effect by eliciting reduced cardiovascular reactions to stress. For example, it could be hypothesized that treatment of essential hypertension with adrenergic-inhibiting drugs or via psychological interventions like relaxation, meditation, and biofeedback might result in reductions in cardiovascular reactivity to stress and consequently lower casual blood pressure levels. Despite the apparent logic contained within this hypothesis, there is simply no evidence to support it. Although some individuals who are treated with these interventions that presumably target sympathetic nervous system involvement in regulating blood pressure may indeed experience reductions in cardiovascular response to stress, this effect is certainly not observed among all patients participating in these intervention trials. Furthermore, the magnitude of reduced cardiovascular reactivity to stress observed with blood pressure–reducing treatments has not been shown to be related to the magnitude of blood pressure reductions observed among treatment participants. These findings confirm that reductions in blood pressure that occur with most interventions discussed in this chapter are most likely the result of complex alterations in blood pressure regulation that involve the kidney, heart, brain, and vasculature.

Because Franklin was dissatisfied with taking antihypertensive medication, he volunteered to participate in an individualized cognitive behavioral stress management program aimed at improving anger management and expression (Larkin and Zayfert, 1996a). As described

previously, Franklin exhibited a somewhat aggressive style of anger expression during a behavioral role-play assessment, even though he reported no problems with experiencing and expressing anger on standardized measures of anger expression. Most notably, Franklin exhibited very poor eye contact during these role-play assessments, in relation to both normotensive control participants and other hypertensive patients. Although his overall ratings of assertiveness during post-treatment role-plays showed very little change with treatment, two changes were noticed. First, he more than doubled his average duration of eye contact during confrontation scenes, from an average of 15 seconds to 32 seconds. Second, his ratings of anger experience and expression on Spielberger's State-Trait Anger Expression Inventory increased to slightly elevated ranges. Although increased anger and anger expression would not necessarily be associated with a positive treatment outcome for a patient with Franklin's predilection toward aggressive interchanges, they may reflect a greater awareness on his part regarding his anger control problems and less defensiveness in completing self-report questionnaires of this type. Although Franklin still had room to improve in learning how to express his anger constructively, he had taken some important steps in the right direction during the six-week training experience. It should also be noted that Franklin's blood pressure declined from 145/99 mm Hg at pre-treatment to 136/92 at post-treatment, indicating that these slight changes in anger management style and awareness of anger management style were associated with reductions in blood pressure comparable to the magnitude of blood pressure reductions observed in other studies employing individualized stress management approaches (Linden et al., 2001). Interestingly, among all behavioral parameters measured in Franklin's cohort of study participants, only improvement in eye contact was correlated with magnitude of blood pressure change observed among patients receiving anger management training (Larkin and Zayfert, 1995). Patients who increased their eye contact the most during the role-play assessment following the intervention exhibited the greatest reductions in both SBP and DBP. Although it is unclear why improved eye contact during confrontation is associated with reductions in blood pressure, Franklin's response profile is certainly congruent with these findings. It could be hypothesized that improved eye contact may

be associated with an improved ability to listen to the messages delivered by study confederates during these staged encounters and to develop a better understanding of their position. Alternately, the improved eye contact could be associated with the perception that a more effective response was delivered. A third possibility might be that patients detected some aspect of social support in the confederate and perceived him or her as less threatening. Future experimental work will need to elaborate on the unique association between eye contact and blood pressure, and the potential mechanisms linking them.

9

Conclusions and Future Directions

Just what should be done with a patient like Franklin? Although his case may appear quite complicated, involving multiple etiologic factors including exposure to a stressful job, a genetic propensity for developing hypertension, and an array of lifestyle factors that may increase his risk, it is really a fairly typical case of essential hypertension. Most individuals with hypertension are exposed to some degree of environmental stress and exhibit a wide range of lifestyle behaviors that may be linked to increased risk for developing it. However, these characteristics are common among most normotensive individuals as well. Therefore, it is quite difficult to ascertain which etiologic factors are operative in a single case of essential hypertension. In particular, because psychological stress has been inconsistently defined and measured throughout decades of research and theorizing, answers to questions concerning the relation between stress and hypertension have been even more elusive than an understanding of the links between hypertension and etiologic factors for which there are uniformly accepted measurement strategies like weight or sodium consumption. Given some of the unique problems associated with examining the linkage between stress and hypertension, let's return to the question represent-

ing the primary purpose of this book: does stress cause essential hypertension?

Does Stress Cause Essential Hypertension?

The evidence examined in this book shows that there is indeed an association between stress and essential hypertension. As initially depicted in Figure 4.1, exposure to environmental stressors represented the stimulus in this model, and onset of the underlying pathology associated with hypertension represented the consequence. Based upon empirical evidence presented in Chapter 4, stressful life events, engaging in high-strain jobs, and even living in stressful industrialized nations have each been related to higher blood pressures. Findings linking stress to hypertension have also been strongly supported by animal research that has consistently shown that animals exposed to a variety of stressful environments exhibit higher blood pressures than animals in less stressful environments. Yet, despite these commonly observed associations, demonstrating a causal role for stress in the etiology of hypertension requires much more evidence than what is currently available. Because most research designs employed to examine the stress–hypertension relation in humans are correlational in nature, causality cannot be inferred. Furthermore, given the ethical problems associated with conducting truly experimental work to make these sorts of claims, it is possible that arriving at a definitive conclusion may be a long way off. It is simply impossible to expose designated groups of humans to stressful conditions to determine whether they establish high blood pressure. Justifiably, in the absence of experimental work on humans, we are left with making inferences from correlational research.

Despite the fact that a definitive statement regarding the causal influence of stress on essential hypertension is premature, several features of the body of literature covered in this book support the possibility that a causal connection between stress and hypertension may eventually be made. First, there is *consistent* evidence linking stress with hypertension. Multiple studies using a variety of methods for measuring stress and blood pressure have revealed an association across numerous populations from different countries. Second, as you were

quickly able to determine from the length of this book, the *magnitude* of this body of literature is substantial. Findings linking stress and hypertension are not just reported across a few studies; literally thousands of studies have been conducted exploring the relation between them. Third, solid *experimental animal research,* in which a causal association between exposure to stress and elevated blood pressure has been confirmed, is congruent with the correlational findings from research on humans. Fourth, *prospective research* linking stress at an earlier point in time with subsequent onset of essential hypertension assists in determining potential causal directions among variables known to be associated with one another. In this type of research, because measures of stress obtained upon entry into the study predict onset of elevated blood pressures or diagnosis of essential hypertension years or even decades later, evidence often presumes that stress leads to hypertension rather than supporting alternate causal models. Fifth, there have been a considerable number of viable *theoretical perspectives* built upon the premise that exposure to stress influences blood pressure, primarily through the sympathetic nervous system (Julius and Esler, 1975; McEwen, 1998). Finally, the presence of *biologically plausible* physiological mechanisms for explaining how a psychological construct like stress results in elevated blood pressure increases one's confidence that a causal relation may be operating. Still, although the presence of each of these features provides additional support for the hypothesis that stress can cause essential hypertension, it is important to remember that definitive conclusions cannot be made without additional experimental work.

Since sufficient experimental support is not yet available to conclude that stress causes hypertension, one can only imagine how this issue might play out in legal hearings concerned with such cases. Imagine for a minute that Franklin decided to file for a workers' compensation claim or work-related disability based upon the assumption that his stressful job resulted in his blood pressure problem, and that he could no longer maintain employment due to his diagnosed elevated arterial pressures. The outcome of such a proceeding would determine whether Franklin should get compensated for his job-related blood pressure problem. Obviously, this sort of proceeding could get rather

ugly, with one side arguing that stress can cause blood pressure problems based on much of the literature presented in this book, and the other side pointing the finger at other potential causal elements associated with the onset of Franklin's hypertension (being overweight or having a family history of hypertension).

Historically, arguments for or against obtaining workers' compensation claims have focused on whether a known cause-and-effect relation existed between a work-related cause and the medical injury effect. For example, if a worker was exposed to a toxic gaseous substance while at work and subsequently developed respiratory problems, it would be essential to demonstrate that a cause-and-effect relation was present. This would be fairly easy to do if other workers exposed to the toxic gas also developed similar respiratory problems and if workers who were not exposed to the toxic gas showed no ill effects. In this case, the presence of the toxic gas can be said to be a 'necessary and sufficient' factor in explaining the worker's respiratory problems. The presence of the gas was 'necessary' to observe respiratory problems among workers, *and* it was 'sufficient,' in that no other factors explained the immediate onset of respiratory problems in this group of workers. In the case of essential hypertension, there are no known 'necessary and sufficient' factors explaining its etiology. For example, in Franklin's case, other firefighters exposed to the same accident did not exhibit chronic elevations in their blood pressures. Therefore, it would be difficult to conclude that exposure to the accident necessarily caused Franklin's elevated blood pressure. Further, given the complex number of variables that may influence the relation between stress and hypertension, it is quickly apparent that exposure to the accident was also not sufficient in explaining why Franklin developed high blood pressure. Based upon these considerations, LaDou, Mulryan, and McCarthy (1980) argued that efforts to obtain workers' compensation for elevated blood pressures presumably linked to job stress should be declined. Not only are there problems in establishing a firm causal link between job stress and essential hypertension, but the expenses associated with policies that would award compensation on anything less than those injuries that fit the 'necessary and sufficient' profile would be insurmountable. Finally, as we know in Franklin's

case, essential hypertension can be treated successfully, and it should not limit most patients' work productivity if the proper steps are made to reduce blood pressure.

What Role Does the Acute Stress Response Play in the Association between Stress and Hypertension?

Through integrating the body of literature linking stress with hypertension and theoretical and empirical work on the effects of stress on the body itself, multiple demographic, constitutional, psychological, and social factors have been associated with increased risk for essential hypertension. Central to the model presented in Figure 4.1 was consideration of the mediating role of the acute stress response, comprised of affective, behavioral, cognitive, and physiological response domains. Although there is little evidence to suggest that hypertensives respond to stress with differential affective responses (namely, anxiety or anger) than normotensives, there is consistent evidence to suggest differential behavioral, cognitive, and physiological responses to stress between hypertensives and normotensives. Hypertensives, for example, have been shown to make less assertive responses to confrontation than normotensives, particularly in the nonverbal domain of eye contact. Regarding acute cognitive responses to stress, hypertensives have been reported to perceive emotionally charged stimuli as less threatening than normotensives. Furthermore, hypertensives have been shown to exhibit higher pain thresholds than normotensives, demonstrating the ability to tolerate pain at much higher intensities. Finally, there is some evidence that hypertensive patients respond to stress with more substantial cardiovascular reactions than normotensives. Comparable findings on young normotensive adults with hypertensive parents indicate that these behavioral, cognitive, and physiological response profiles are likely to precede onset of hypertension rather than occur as a consequence of having high blood pressure. However, prospective evidence linking these components of the acute stress response with subsequent onset of hypertension has been reported consistently only for cardiovascular response to stress. This is not to say that the

other behavioral and cognitive response profiles should not be considered potential mediators of the stress–hypertension relation; rather, prospective trials linking behavioral or cognitive responses to hypertension have yet to be conducted.

Although not all studies examining the relation of cardiovascular reactivity to stress have supported its mediating role in the stress–hypertension relation, the preponderance of evidence suggests that it plays an important role in explaining how a psychological construct like stress leads to tissue pathology associated with elevated blood pressure. There is certainly more evidence positioning cardiovascular response to stress as a mediating factor explaining how stress is linked with onset of hypertension than for any other affective, cognitive, or behavioral variable. Likewise, the magnitude of cardiovascular responses to stress has been shown to be affected by many individual difference variables known to be associated with increased risk for hypertension, including ethnicity, age, sodium consumption, and lack of social support. Therefore, not only is cardiovascular response to stress prospectively associated with onset of essential hypertension, but it is also associated with several individual difference variables known to increase risk for hypertension. Interestingly, both pharmacologic and non-pharmacologic interventions that are known to result in lowered blood pressures have not systematically been demonstrated to alter the magnitude of cardiovascular response to stress. From these findings, it is apparent that while exaggerated cardiovascular reactivity to stress may be associated with increased risk for essential hypertension, it may not represent the only way that stress is etiologically linked to hypertension. Perhaps future empirical work on other acute behavioral (eye contact) or cognitive (emotional defensiveness) responses that hypertensives display in response to stress may help elucidate alternate etiologic pathways.

It remains to be seen whether there is a 'final common pathway' through which stress exerts its blood pressure–elevating influence on the circulatory system. Data available at the present time appear to suggest that such a final common pathway may not exist, and that multiple routes to the condition of essential hypertension may more accurately portray the etiologic map linking stress with hypertension. At present, exaggerated cardiovascular reactivity to stress appears to

represent one of these potential links supported by documented empirical evidence.

The Role of Individual Differences in the Association between Stress and Hypertension

Recognizing that a relation between stress and hypertension exists and that cardiovascular reactivity to stress appears to be an important mediator of that relation, let's turn to the remaining component of the model depicted in Figure 4.1. In contrast to the variables comprising the acute stress response, individual difference factors consist of relatively stable constitutional, lifestyle, psychological, and social factors that influence risk for essential hypertension, possibly through their influence on the magnitude of the acute stress response. Many of these variables, described in detail in Chapters 6 and 7, interact with one another in complex ways to affect both the magnitude and patterning of the acute stress response and the risk for essential hypertension, including age, gender, ethnicity, parental history of hypertension, sodium consumption, hostility, and lack of social support. For example, a middle-aged African American man with hypertensive parents, like Franklin, predictably exhibits a different risk profile for essential hypertension than his African American colleagues with normotensive parents or his Caucasian colleagues with hypertensive parents. Rather than attempting to chart all of the complex interactions among these individual difference variables, it seems more parsimonious to view a given patient's risk for hypertension associated with individual difference factors as his or her overall 'vulnerability' to develop essential hypertension. Under this strategy, a patient's vulnerability to develop essential hypertension increases as the number of pertinent individual difference variables increase. This perspective would certainly be congruent with other diathesis–stress models of pathology (Zubin and Ludwig, 1983) and the model of stress portrayed in Figure 3.4.

Once an individual's vulnerability profile has been identified, steps can be taken to determine whether any of these vulnerability factors can be altered to presumably lower the risk for hypertension onset. Although Franklin cannot alter his age, gender, ethnicity, or parental health history status, he can take action to promote a healthier lifestyle,

express anger more effectively, and engage in positive social interactions. As noted in Chapter 8, Franklin participated in a six-week anger management training program and was able to reduce his blood pressure significantly by learning how to express his anger more effectively. Furthermore, because the anger management training was conducted in small groups, the frequency of positive social interactions in his life increased (at least for six weeks!). Presumably, because Franklin still maintained his job as a firefighter, the blood pressure reduction that was observed resulted from reducing his vulnerability to stress, not from eliminating the sources of environmental stress in his life.

Although many individual difference variables have been shown to influence the stress–hypertension relation, there are several for which the degree of influence on the stress–hypertension relation is unknown, including physical exercise, presence of diabetes and obesity, smoking, and various dietary supplements. It may be that some of these variables exert only a direct influence on risk for hypertension and subsequent cardiovascular disease rather than influencing risk for hypertension associated with stress. Certainly, additional research is warranted in these cases to determine the nature of the causal pathways operating for each individual difference variable. Obviously, even if smoking, diabetes, and obesity turn out not to be involved in the stress–hypertension link, these findings should not thwart our efforts to address the negative health effects associated with them with patients and through community-based public health efforts.

In conclusion, Figure 4.1 outlines a model for depicting the various factors involved in explaining how stress can lead to essential hypertension. It is useful to distinguish variables that potentially mediate the relation between stress and hypertension (acute stress responses) from those that influence the relation by altering vulnerability to stress (individual difference variables). It is also important to recall that several of the relations depicted in Figure 4.1 are bidirectional, as they portray the true complexity of the ways in which these variables interact. Despite the utility of this conceptual model in organizing this incredibly rich literature, it is important to remember that the true application of this model will depend upon the quality of empirical work to be conducted in the years ahead.

Directions for Future Research

Given that the answer to the question proposed in the introduction to this book cannot yet be answered affirmatively, there is clearly a need for additional research into the complexities of the stress–hypertension relation. Through such empirical work we can hope to be able to address the question of whether stress causes hypertension more convincingly in a few years. Let's consider a few areas in which future empirical work looks promising for leading us to this goal.

Comprehensive Measurement of Blood Pressure Regulation

The complexity of blood pressure regulation was highlighted in the very first chapter. There is no doubt that a multitude of physiological factors are involved in regulating arterial pressure. These include both physiological mechanisms that are responding directly to the external environment (like sympathetic nervous system response to stress) and those that are responding to changes within the internal environment of the circulatory system (like baroreceptor activation). Blood pressure dysregulation can be caused by events occurring outside of the circulatory system *or* by a systematic counter-regulatory action within the circulatory system itself. Obviously, in order to fully understand blood pressure regulation in response to something like exposure to environmental stress, it would be crucial to measure both the initial response patterns and the consequent compensatory actions. Unfortunately, studies linking stress with hypertension often do a poor job of comprehensively assessing blood pressure regulatory processes. For example, while many studies have measured changes in autonomic nervous system functioning in response to an environmental stressor, they fail to measure simultaneous changes in baroreceptor sensitivity, neuroendocrine release, or altered fluid retention. Future research would clearly benefit by broadening use of assessment strategies to employ multiple measures of the various components of blood pressure regulation as they respond to an environmental stressor. These efforts will provide a more comprehensive understanding of the multiple physiological systems involved in blood pressure regulation, particularly as the system responds to stress.

Broader Application of Ambulatory Measurement of Blood Pressure

Given the rapid advances in ambulatory recording technology that have occurred over the past decade, much has been learned regarding the 24-hour blood pressure profiles of both hypertensive and normotensive patients. In particular, because ambulatory measures of blood pressure are better predictors of target organ pathology and incidence of cardiovascular and cerebrovascular disease than clinic-derived measures, their increased use in clinical settings may also be warranted. Given the surprisingly high prevalence of both isolated clinic hypertensive and isolated clinic normotensive patients seen in clinic settings, it would seem that ambulatory or home blood pressure measurement strategies should be used more regularly. The current reliance on clinic-based blood pressure determinations for assigning diagnoses and formulating treatment plans runs the risk of treating isolated clinic hypertensive patients, who may not need treatment, and failing to treat isolated clinic normotensive patients, who clearly warrant treatment. Research examining methods of detecting these clusters of patients for whom blood pressures in the clinic do not correspond to blood pressures during daily life would certainly be worthwhile. Furthermore, empirical work that examines the behavioral features of these clusters of patients, which might explain why they exhibit such disparate blood pressures in the clinic and during daily life, is needed. Once these features have been elucidated, methods for training these patients to provide more accurate clinic measures could be devised and tested. For example, in a recent study, we identified three patients with isolated clinic hypertension. Because our assessment protocol involved obtaining several hundred blood pressure determinations over a three-week period, all three of these patients exhibited normal blood pressures for the first time ever when they visited their physicians shortly after participating in our assessment protocol. What this suggests is that perhaps the elevated blood pressures of isolated clinic hypertensive patients can be extinguished if blood pressures are taken repeatedly prior to their clinic visits. Obviously, additional research is needed to confirm these observations, but they represent plausible hypotheses aimed at improving the accuracy of clinic-based blood pressure determinations.

Consideration of Hemodynamic Parameters

Although much has been learned regarding blood pressure regulation over the past century, the ability to distinguish elevations in blood pressure that are the result of increased cardiac output from those that are the result of increased peripheral resistance was one of the most important technological advances. Obviously, these measurement strategies enabled Lund-Johansen (1991) to differentiate the largely cardiac-mediated high blood pressure among young hypertensives from the vascular-mediated high blood pressure among older hypertensives. Although not commonly employed in clinic settings, measurement of hemodynamic functioning appears to have some promise in selecting the optimal pharmacologic agent for treating essential hypertension. In this regard, the use of hemodynamic profiling to optimize treatment outcomes warrants additional investigation. If the development of initial treatment plans for controlling hypertension were associated with better outcomes, it is possible that patients could be treated with lower doses of medication, experience fewer side effects, and be more compliant in taking their medication.

With the advent of impedance cardiography, empirical work on cardiovascular reactivity to stress can also explore hemodynamic underpinnings of known relations between cardiovascular reactivity to stress and individual difference variables. Through this sort of work, we already know that males and blacks are more likely to exhibit blood pressure responses to stress that are associated with increases in total peripheral resistance than females and whites. Without this technology, differences in cardiovascular reactivity to stress associated with these demographic variables would have been entirely missed. In addition, changes in hemodynamic responses to stress could also be explored in response to pharmacologic or non-pharmacologic interventions for reducing blood pressure. Very little is known regarding the altered hemodynamic response profile associated with various treatments for hypertension. Even though we know that most interventions that reduce blood pressure do so without resulting in concomitant reductions in blood pressure reactivity to stress, we do not know whether the same null findings apply regarding hemodynamic reactivity to stress. It is possible, for example, that while the overall magni-

tude of blood pressure response to stress is unaffected with treatment, the hemodynamic pattern of the response might change from a theoretically more problematic peripheral resistance response to a cardiac-mediated response. Certainly, additional empirical work examining hemodynamic response differences associated with selected anti-hypertensive treatments is warranted.

Testing Other Models of Allostatic Overload

Depicted in Figure 3.1 are the four distinct types of allostatic overload outlined by McEwen and Stellar (1993). Applying these models to research on stress and hypertension, the bulk of the literature has focused primarily on one type, the increased frequency of stress model. Although a few studies have been conducted using the delayed recovery model (Schuler and O'Brien, 1997), additional empirical work is clearly needed to examine whether recovery from stress, failure to habituate to stress, or an inadequate stress response is associated with problems of blood pressure regulation. One could argue, for instance, that the failure to exhibit any blood pressure response at all during mental stress may be just as problematic as exhibiting an exaggerated cardiovascular response. It will remain for future research to elaborate on whether these other models of allostatic overload have any place in describing the stress–hypertension relation.

Use of Objective Psychological Measures

From the demonstrated defensiveness of some hypertensive patients and the recognized influence that awareness of hypertensive status has upon responses to measures of psychological functioning, it appears that studies of individual difference variables as they relate to essential hypertension may be seriously questioned if they solely rely on self-report questionnaires. Unfortunately, a sizable portion of investigations examining psychological parameters among essential hypertensive patients have employed self-report methods of assessment without obtaining concomitant measures of defensiveness. It is difficult to interpret results from these studies, knowing that some hypertensive patients have been shown to exhibit defensive response styles. Even with Franklin, the ob-

servation that his self-reported measure of anger and anger expression *increased* with anger management treatment was thought to be associated with defensiveness that was evident during the pre-treatment assessment. Naturally, one solution to this problem is to expand the types of assessment strategies used for obtaining information regarding psychological functioning. This can be done by using either role-play or naturalistic assessments as well as querying significant others in the patient's life. In contrast to self-report methods of assessment, these more direct methods of assessing behavioral functioning have often resulted in more consistent data differentiating hypertensive patients from normotensive controls (Fox et al., 1993; Larkin and Zayfert, 2004).

Use of Individualized Patient Assessment in Optimizing Treatment Outcome

For the most part, intervention studies examining both pharmacologic and non-pharmacologic approaches have selected patients on the basis of pre-treatment blood pressure without reference to other constitutional or psychosocial characteristics that may influence treatment outcome. For example, studies of the effect of sodium restriction programs on blood pressure reduction rarely have selected patients on the basis of their sodium sensitivity, and studies of stress management programs on lowering blood pressure have typically used samples of hypertensives without regard to the quality of their pre-treatment stress management skills (like the inclusion of patients already equipped with a broad array of stress management skills). Presumably, for many interventions that are matched with important individual characteristics, outcomes for treatment as well as prevention programs could be enhanced. From this perspective, reductions in blood pressure might not be expected for an obese hypertensive patient participating in a stress management program. Through adoption of a comprehensive assessment of potential factors placing a patient at risk for developing hypertension, a treatment plan could be individually tailored to each patient's unique blood pressure regulation problem. Unfortunately, very little empirical work has examined this approach to matching patients and treatments. Recent work employing individualized stress management programs (Linden et al., 2001) represents one effort in

this direction. In order for us to comprehend fully the various patient characteristics that need to be taken into account in devising an optimal treatment plan, this approach will need to be examined more broadly among the known pharmacologic and non-pharmacologic interventions aimed at reducing blood pressure.

Concluding Remarks

The next decade promises to bring us closer to a more definitive understanding of the link between stress and essential hypertension. It is already certain that the relation between stress and essential hypertension is not simple or direct, and that multiple etiologic factors need to be considered when explaining how a psychological construct like stress can result in the disturbed blood pressure regulation seen in essential hypertension. Optimal assessment strategies aimed at identifying the unique predictors of increased risk for hypertension on a case-by-case basis need to be devised and tested so they may be applied in clinical settings to facilitate the accurate diagnosis of hypertension as well as effective treatment planning. The literature examined in this book suggests that at least some essential hypertensive patients develop blood pressure regulation problems based upon exposure to environmental stressors and the patterning of their associated acute stress responses. Increased efforts should be made to improve identification of these individuals so that lifestyle and psychosocial prevention programs that target the unique behaviors associated with risk for hypertension can be tested and implemented. With this type of data, we will be much closer to being able to state that stress causes essential hypertension.

So, where might that leave us with our patient, Franklin? Although Franklin, in many ways, was a typical hypertensive patient, his case was also unique. In contrast to hundreds of thousands of patients currently being evaluated and treated for essential hypertension, Franklin participated in a few ongoing clinical research projects during which he was provided access to state-of-the-art ambulatory blood pressure monitoring as well as an individually tailored anger management intervention trial. For Franklin, data from the ambulatory blood pressure monitoring period confirmed that he indeed exhibited high blood

pressures throughout the day and most of the night and was not simply showing an isolated clinic hypertensive profile. The monitoring record also yielded information regarding the extreme lability of Franklin's blood pressure and his propensity to exhibit elevated pressures during periods of stress, particularly those involving the experience and expression of anger. Once he reviewed these records, Franklin began to see the seriousness of his blood pressure problem and was motivated to participate more actively in his treatment program. In this regard, ambulatory monitoring of blood pressure was useful in enlisting Franklin's participation in treatment planning and improving his motivation to work with his medical team to regulate his blood pressure better.

As noted in Chapter 8, Franklin's blood pressures declined somewhat following his participation in the anger management training program. Unfortunately, most physicians rely solely on pharmacologic interventions for regulating blood pressure, and the opportunity to participate in this type of intervention trial is not available in most primary care settings. In Franklin's case, this non-pharmacologic approach clearly served as a helpful adjunctive treatment. Certainly, not all patients with essential hypertension would benefit from this type of stress management intervention, but with continued research, it is likely that we will be able to better elucidate the characteristics of patients for whom such an approach would be worthwhile. In this regard, patients like Franklin will be able to lower their blood pressures using lower doses of antihypertensive medications, if any are used at all.

Patients like Franklin deserve health care providers who are fully informed about the latest advances in the assessment, treatment, and prevention of essential hypertension. I hope that the information presented in this book represents one step in this direction. As empirical work continues to accumulate in this area, we hope to see continued exploration of the utility of ambulatory monitoring of blood pressure for ascertaining diagnoses of high blood pressure and monitoring treatment effectiveness, the development of more sensitive measures of vulnerability to stress associated with hypertension, and a greater use of individual difference variables in identifying optimal treatment choices. As we move in this direction, patients like Franklin will be better treated and hypertension will be less of the public health problem that it is today.

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