Stress, Hyperreactivity, and Health

Sharon Ann Plowman

The linkage of stress with illness and disease pervades everyday life. For example, Arthur Ashe was recently honored by *Sports Illustrated* (Moore, 1992) as the Sportsman of the Year. The article, describing Ashe’s selection and the trials and tribulations he has endured, said in part:

Although Ashe had a family history of heart disease . . . it was exceedingly unusual for a highly conditioned six-foot, 150 pound professional athlete to have a heart attack at 36. So he has often been asked whether the feelings he penned up over the years might not have congealed into occluding deposits in his coronary arteries. Might his control, his defining grace have come at the cost of his health? (p. 23)

Similarly, in the *Sports Illustrated* cover story on Jim Valvano and his battle with cancer (Smith, 1993) Valvano is quoted as saying,

Every season I had bronchitis, bad colds; twice I had pneumonia. The night we won the NCAA, I was sick as a dog. . . . I wouldn’t rest. I’d just pop the antibiotics and keep going. Who knows? Maybe I put my body in a position to get this. I’ve been reading books about cancer. They say it often occurs if your immune system is lowered and then you have a trauma. (p. 19)

The trauma, or really traumas, to which he was referring included allegations of wrongdoing in the North Carolina State basketball program, the subsequent NCAA investigation, charges of point shaving, and being forced to resign from his coaching position.

These isolated cases are reinforced by the perceptions of millions of ordinary citizens. In 1985 the National Center for Health Statistics (NCHS) included a Health Promotion and Disease Prevention Questionnaire (HPDPQ) as part of the National Health Interview Survey (NHIS). The survey was completed by a sample of civilian, noninstitutionalized individuals 18 years of age and older that amounted to approximately 78 million males (M) and 88 million females (F). Roughly half of the respondents reported experiencing “a lot” (M = 17.8%; F = 22.5%) or a “moderate amount” (M = 31.7%; F = 30.5%) of stress in the previous 2 weeks. In response to the question, “In the past year how much effect has stress had on your health?” 38% of the men and 49% of the women reported “some” or “a lot.” The perceptions were consistent in that those individuals who reported higher levels of stress

Sharon Ann Plowman is with the Department of Physical Education at Northern Illinois University, DeKalb, IL 60115.
in the previous 2 weeks also reported a greater effect on health. One unexpected finding was that those 65 years of age or older were less likely (11%) to report that stress had "a lot" of effect on their health than were younger responders (19%) (Silverman, Eichler, & Williams, 1987).

The questions regarding stress were included in the NHIS because one of the 1990 Objectives for the Nation required this information (Silverman et al., 1987). The Healthy People 2000 (U.S. Department of Health and Human Services, 1991) objective, as stated in the Journal of School Health, in this area is more ambitious. To improve mental health and prevent mental disorders, by the year 2000 the goal is to "reduce to less than 35 percent the proportion of people aged 18 and older who experienced adverse health effect from stress within the past year" ("Healthy People 2000," 1991, p. 319). This gives governmental sanction to the linkage between stress and at least mental health.

The American Psychiatric Association has also legitimized the concept of stress-related illness by including some specific conditions in its classification system, the Diagnostic and Statistical Manual (Eliashof & Streltzer, 1992).

Finally, sanction has been given in yet another way by the courts in workers' compensation claims. In 1979, 5% of workers' compensation claims were "stress" claims. By 1985 this number had risen to 15%. The estimated cost is $66 to $150 billion a year or 2–5% of the gross national product (Eliashof & Streltzer, 1992; Lahey, 1989). The case of a Colorado fire fighter is typical:

The Colorado Supreme Court reversed the findings of a Workers' Compensation referee who said a fire fighter's death was not caused by "an injury or occupational disease arising out of and in the course of employment." The fire fighter died from an irregular heart rhythm caused by a pre-existing heart condition, mitral value prolapse and job related mental stress. The referee had found that the main cause of stress in the fire fighter's life were failure to receive a promotion, rejections of proposals made to his superiors, tension from lack of communication with his superiors and disagreement with management philosophy. The Colorado high court said that stress is a disease in its own right and can be implicated in many other diseases and disabilities. . . . The widow was awarded death benefits. (Lahey, 1989, p. 53)

Despite this formidable amount of public, legal, and professional opinion, many within the medical and scientific communities remain unconvinced that the linkage between stress (particularly psychosocial) and illness has been unequivocally substantiated. How then can stress, however defined, cause illness or disease, and what evidence is available to support or refute a cause–effect relationship?

The model depicting how stress and illness may be related is neither well defined nor universally agreed upon, but it may approximate that presented in Figure 1 (Baum, Davidson, Singer, & Street, 1987; Franks, 1983/1984; Marmot & Madge, 1987; Pasternak, 1991; Rice, 1992; Selye, 1983; Steptoe, 1991). This model indicates that the interaction is not a simple stimulus (stress)–response (illness) relationship, but is impacted by modulators and mechanisms of the response itself.

To begin, the stress stimulus may vary. It may be acute or chronic, and each of these can be behavioral, psychological, social, physical, or pathological. The stress stimulus, in turn, is imposed upon a complex unique organism (Baum et al., 1987). Characteristics of that organism (e.g., personality traits, appraisal skills, coping resources, vulnerabilities, risk factors, and behavioral predispositions) determine how the stress is received. The idea of predisposing vulnerabilities continues to be utilized to explain why some individuals become ill when presented with a particular stressor and others do not and why susceptible individuals, when
Figure 1 — Model of the possible relationships and modulators between stress and illness. Based on information from Baum, Davidson, Singer, and Street (1987); Franks (1983/1984); Marmot and Madge (1987); Pasternak (1991); Rice (1992); Selye (1983); and Steptoe (1991).
presented with similar stresses, develop different illnesses. Vulnerabilities include genetic makeup, health status, nutritional state, physical fitness, preexisting pathologies, and stress load (Pasternak, 1991; Rice, 1992; Steptoe, 1991). The response to stress occurs on at least two generalized levels. One is affective (as in anxiety, depression or negativity), cognitive, and behavioral; the other is psychophysiological (Baum et al., 1987; Steptoe, 1991).

Current theory emphasizes two major physiological pathways in the stress-response system (Chrousos & Gold, 1992). The first is the hypothalamic (corticotropin releasing hormone [CRH])-pituitary-adrenal axis. The second is the locus-ceruleus-norepinephrine autonomic (sympathetic) nervous system component. The locus-ceruleus is located in the brain stem and is anatomically and functionally connected to the hypothalamic system. Details of the actions and interactions of these pathways are presented elsewhere in this series of papers (Dishman, 1994) and will be dealt with only briefly here.

It has been suggested that a coordinated series of physiological and behavioral responses that are adaptive and advantageous to the organism in the short term are mediated by these two pathways. These adaptations include such behavioral changes as increased arousal, cognition, vigilance, focused attention, and appropriate aggression accompanied by suppression of feeding and reproductive behavior. The corresponding physiological changes appear to be aimed at a conservation of energy by directing oxygen and nutrients to the central nervous system and stressed body sites thereby increasing cardiovascular tone, blood pressure, heart rate, respiratory rate, gluconeogenesis, and lipolysis in conjunction with suppression of growth, reproductive, and inflammatory/immune responses. These responses occur relatively quickly and in the short term appear to be beneficial to the organism in its attempt to adjust homeostasis and survive.

Chronic excessive response may not be so benign. For example, hypervigilance can become insomnia, and suppression of feeding, anorexia. The chronic effect of cortisol, in particular, is a litany of potential problems that include elevated triglyceride and cholesterol levels, increased sodium and decreased myocardial potassium retention (leading to ion imbalances), increased blood volume, and sensitivity of the arteries to catecholamines. The catecholamines released in acute stress situations, in turn, increase free fatty acids and cholesterol, reduce the threshold of ventricular fibrillation, elevate blood pressure (and the shear force on arterial walls), and increase platelet adhesiveness and aggregation (Eliot, 1987; Sime & McKinney, 1988). These changes form a possible mechanism for the development of hypertension, atherosclerosis, and clinical heart disease. The catecholamine and lipid changes have been documented, for example, in response to race-car driving (which was viewed as an aggressive emotional stress situation) (Taggart & Carruthers, 1971), and in students following periods of exam stress (Francis, 1979).

The level of response mediated by the central nervous system (i.e., the reactivity) is thought to be particularly important in the prediction and determination of the health consequences of stress. Reactivity probably exists on a continuum ranging from low (hyposensitive or hyporeactive) through normal to high (hypersensitive or hyperreactive). Thus, the relationship between the dose of stress and the reaction is mediated by the level of reactivity of the individual. Individuals who are either hypo- or hyperreactive probably have less margin for error in achieving an appropriate or optimal stress response. Those who are hyporeactive may be more prone to illnesses such as seasonal affective disorder, obesity, and chronic fatigue syndrome or to inflammatory diseases such as rheumatoid arthritis. Those who are hyperreactive may be more susceptible to conditions such as anorexia nervosa, melancholic depression, or chronic excessive exercise. Thus, there is a great interest in determining reactivity to stress. One difficulty with this area of research is the uncertainty as to whether reactions to acute bouts of varying types of stress is a state or trait characteristic, and if so, how acute reactivity transfers to chronic reactivity (Chrousos & Gold, 1992; Pasternak, 1991).
The health consequences themselves also form a continuum. The best possible outcome is an enhancement of health. Adaptation to repeated exposure of the stress of physical exercise undertaken in appropriate dosages (i.e., training) is the prime example of health enhancement (Franks, 1983/1984; Pasternak, 1991). Another desirable outcome may be that health simply is not affected one way or another (Marmot & Madge, 1987).

An outcome that could be either positive or negative (though it is most frequently negative) is the possibility of influencing health through alterations in health-related behaviors or practices. Following stressful life events, individuals have shown increases in substance abuse, alcohol consumption, dietary fat intake, dietary simple sugar intake, and cigarette smoking (Baum et al., 1987; Serxner, Catalano, Dooley, & Mishra, 1991; Steptoe, 1991). Likewise, individuals may pay more or less attention to body symptoms. At one extreme this is manifested by being completely preoccupied with symptoms that may or may not be real, constantly complaining about them, and seeking medical attention that may or may not be needed. At the other extreme there is a denial of physical signs and symptoms, false assurance of feeling well, and refusal to seek medical attention for even potentially life-threatening symptoms. Finally, the occurrence of emotionally expressive behavior can actually bring on an illness. Crying-induced asthma brought on during stress-related episodes of emotional disturbance is such an illness behavior (Steptoe, 1991).

Closely linked to changes in illness behavior are changes in predisposing and/or risk factors for disease. Depending on the length of time and amount of change in health behavior, risk factors may or may not be impacted. For example, increased dietary fat ingestion would be expected ultimately to elevate cholesterol level, which, if high enough, is acknowledged as a risk factor for coronary heart disease (CHD), and an avoidance of medical attention for years would increase the risk of cancer going undetected in the early stages (Marmot & Madge, 1987; Steptoe, 1991). These behavioral alterations can also affect exposure to illness-producing conditions. For example, an increase in substance abuse might involve the sharing of needles, thus increasing the risk of exposure to AIDS (Baum et al., 1987). Similarly, exposure to traumatic events and posttraumatic stress disorder is more frequent among substance abusers than in the general population (Cottler, Compton, Mager, Spitznagel, & Janca, 1992).

Additionally, stress could bring about changes in organ systems that might, in turn, affect system responses to subsequent stress and increase the risk of future disease. This appears to happen to an organism’s ability to avoid and fight off pathogens. The thymus, the primary organ of the immune system, may be particularly susceptible (Baum et al., 1987).

Another possibility is that stress impacts the course or stability of an existing illness. While theoretically this, like health behavior changes, could be positive or negative (slowing down or speeding up the disease process) it is most likely to be negative. Difficulty in stabilizing blood glucose levels in a diabetic patient under stress, increasing the level of inflammation in rheumatoid arthritis, or the exacerbation of symptoms in those suffering from Crohn’s (gastrointestinal) disease are examples (Baum et al., 1987; Garrett, Brantley, Jones, & McKnight, 1991; Steptoe, 1991).

Alternatively, stress could have a direct physical effect, leading to an acute or chronic clinical crisis. The precipitation of myocardial ischemia, ventricular arrhythmias, and myocardial infarction are cases in point.

Finally, stress might result in death. The evidence here is primarily in the form of case study reports, but they abound in both medical and popular literature. Eliot, Buell, and Dembroski (1982) cite the example of Dr. John Hunter, a pioneer in cardiovascular pathology and medicine. Hunter linked his own attacks of angina with his outbursts of anger, and predicted that his life was dependent on anyone who was able to make him angry. True to his self-diagnosis in 1793, after arguing violently at a faculty meeting, he “fell down dead” (p. 204).
Given the wide variety of possible linkages between stress and health/illness, it is no wonder that stress has been implicated in the etiology of numerous diseases. Some workers in the field even go so far as to declare that no illness is completely free from the influence of stress (Pasternak, 1991; Selye, 1983). Table 1 presents a partial listing of those diseases or conditions for which stress has been implicated by theoretical or experimental evidence.

Because it is impossible to deal with all of the health conditions on the list, the cardiovascular area will be singled out for an in-depth appraisal of the experimental evidence. Furthermore, the discussion will be delimited to the psychophysiological response factor of reactivity. In this context reactivity is defined as the change in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), stroke volume (SV), cardiac output (Q), total peripheral resistance (TPR), or catecholamines/cortisol from baseline or control levels that results from exposure to a specific stress.

Evidence for the relationship between stress and health/illness and reactivity can be divided into three categories:

1. Studies designed to determine the physiological effects of stress on animal models. These studies are particularly valuable because animals (primarily rats) can be bred to be genetically prone to certain conditions, such as hypertension or diabetes.
2. Laboratory studies of humans exposed to mild stressors with or without considering individual characteristics.
3. Field studies of humans exposed to the events of daily life, including job demands, with or without considering individual characteristics.

The human studies are often of the case–control design, wherein individuals with diagnosed health problems (the cases) are compared with those free of that particular health problem (the controls).

**Reactivity and Hypertension**

Hypertension is both a risk factor for CHD and a disease condition in its own right. It is generally agreed that stress causes a response in blood pressure and in the other components of the cardiovascular system and that “normal” blood pressure varies from moment to moment throughout the day (Brody et al., 1987; Dunstan, 1987; Reis & Ledoux, 1987). Although this latter fact may seem trivial, it is the source of one concern for those working in this area. Laboratory or clinical studies typically establish a normal resting level for blood pressure at the time of the experiment and then determine the reactivity to the cold pressor test, Stroop color test, mental arithmetic, personalized speech, or some other structured task. The change from baseline is taken as the reactivity. Another school of thought contends that ambulatory blood pressure recordings more closely approximate real-life situations and an individual’s true blood pressure reactivity. Although variability itself may be important, the difficulty here is that the stresses to which the subjects are exposed during daily life are not then standardized, nor can responses be separated as to physical or psychological cause (Manuck, Kasprowicz, & Muldoon, 1990; Morales-Ballejo, Eliot, Boone, & Hughes, 1988; Pickering, 1987; Pickering & Gerin, 1990; Turjanmaa, Tuomisto, Frederickson, Kalli, & Uusitalo, 1991).

Exactly what constitutes hyperreactivity is not fully agreed upon either. Some studies use a fixed value, such as a blood pressure increase of 20 mmHg, as being hyperreactive. Other studies simply divide their subject population into high and low reactors by taking a given number from the top and bottom of the distribution, disregarding actual values. Morales-
Table 1  Diseases for Which a Dysregulation of the Stress Response Has Been Implicated

<table>
<thead>
<tr>
<th>Disease</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Chrousos &amp; Gold, 1992; Wand &amp; Dobs, 1991</td>
</tr>
<tr>
<td>Amenorrhea, reproductive dysfunction, menopausal symptoms, premenstrual syndrome</td>
<td>Harlow &amp; Matanoski, 1991; Kaye et al., 1987; Rabin et al., 1990; Rivier, Rivier, &amp; Vale, 1986; Swartzmann, Edelberg, &amp; Kemmann, 1990</td>
</tr>
<tr>
<td>Anorexia, bulimia</td>
<td>Chrousos &amp; Gold, 1992; Gold, Gwirtsman, et al., 1986; Turpin &amp; Lader, 1986</td>
</tr>
<tr>
<td>Anxiety, panic disorder</td>
<td>Gold, Pigott, Kling, Kalogeros, &amp; Chrousos, 1988</td>
</tr>
<tr>
<td>Arthritis (Oseo- and Rheumatoid)</td>
<td>Anderson, Bradley, Young, McDaniel, &amp; Wise, 1985; Thomason, Brantley, Jones, Dyer, &amp; Morris, 1992</td>
</tr>
<tr>
<td>Cancer</td>
<td>Justice, 1985; Sklar &amp; Anisman, 1981</td>
</tr>
<tr>
<td>Cardiovascular disease, cerebrovascular accidents</td>
<td>Krantz &amp; Manuck, 1984; Steptoe, 1981</td>
</tr>
<tr>
<td>Chronic excessive exercise</td>
<td>Luger et al., 1987</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>Chrousos &amp; Gold, 1992</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Gold, Loriaux, et al., 1986</td>
</tr>
<tr>
<td>Depression, attempted suicide</td>
<td>Gold, Goodwin, &amp; Chrousos, 1988a; 1988b; Paykel, 1976</td>
</tr>
<tr>
<td>Gastrointestinal ulcers, colitis, Chron’s disease</td>
<td>Craig &amp; Brown, 1984; Garret, Brantley, Jones, &amp; McKnight, 1991; Salim, 1987</td>
</tr>
<tr>
<td>Grave’s disease, hypothyroidism</td>
<td>Chrousos &amp; Gold, 1992</td>
</tr>
<tr>
<td>Headaches, migraines</td>
<td>Hovanitz &amp; Wander, 1990; Sorbi &amp; Tellegen, 1988</td>
</tr>
<tr>
<td>Herpes virus infections, mononucleosis</td>
<td>Kiecolt-Glaser, Speicher, Holliday, &amp; Glaser, 1984</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Heine &amp; Weiss, 1987; Krantz &amp; Manuck, 1984; Light, 1987; Shapiro, 1978</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Chrousos &amp; Gold, 1992</td>
</tr>
<tr>
<td>Low back pain</td>
<td>Bigos et al., 1991; Frymoyer et al., 1980; Heliövaara, 1989; Kopelman et al., 1988</td>
</tr>
<tr>
<td>Obesity</td>
<td>Chrousos &amp; Gold, 1992</td>
</tr>
<tr>
<td>Respiratory infections, common cold</td>
<td>Cohen, Tyrrell, &amp; Smith, 1991; Graham, Douglas, &amp; Ryan, 1986</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Day, 1981; Turpin &amp; Lader, 1986</td>
</tr>
<tr>
<td>Seasonal affective disorder</td>
<td>Chrousos &amp; Gold, 1992</td>
</tr>
</tbody>
</table>
Ballejo et al. (1988) described a continuum of reactivity to mental stress as being made up of five overlapping levels or categories. Category 0 represented "low normal," whose peaks are 130/80 mmHg (mean blood pressure [MBP] = 97 mmHg). Category 1 represents "high normal" reactivity, between 130/80 and 140/90 mmHg (MBP = 97–107 mmHg). Category 2 is considered "borderline" reactivity (160/95 mmHg; MBP = 107–117). Category 3 is "moderate" reactivity (180/100 mmHg; MBP = 117–127 mmHg) and Category 4 is severe (≥200/150 mmHg; MBP > 127 mmHg). Those individuals who are normal or borderline at rest but have exaggerated responses are labeled "hot reactors" and are the ones for which there is the greatest concern.

At least six relationships are possible to explain a link between reactivity and hypertension and/or CHD (Light, Dolan, Davis, & Sherwood, 1992; Manuck et al., 1990; Pickering & Gerin, 1990; see Figure 2). Hyperreactivity:

1. Potentiate vascular and target-end organ complications of already present hypertension. This presupposes that both borderline and essential hypertensives are hyperreactors.
2. Be a marker for increased risk of hypertension due to its association with another, as yet unidentified, factor, which is truly pathogenic, whereas high reactivity itself has no direct role.
3. Play a direct causal role in the pathogenic process without requiring the presence of or interaction with another pathological variable.
4. Directly contribute to the pathological process, but only if exposure to life stressors (economic factors, occupational strain, social support, daily hassles, life events) of sufficient intensity and consistency occurs.
5. Contribute to the pathogenic process by modifying the influence of another unknown pathogenic factor.

There is, of course, no known reason why these possible relationships need to be viewed as mutually exclusive. Nor is there any reason to assume that hypereactivity has to be a solo cause of hypertension, although this is the proof that is often sought. Hypertension is undoubtedly a polygenic multifactorial disease.

As stated, if frequent hypereactivity hastens the development of vascular and end-organ complications, then it would be anticipated that individuals who are hypertensive would also be hyperreactive. There is a general trend to support this linkage, but agreement is not universal (Brody et al., 1987; Drummond, 1983; Drummond, 1985; Herd et al., 1987; Light, 1987; Manheim, Jern, Pilhall, Hansson, & Jern, 1992; Manuck et al., 1990; Rüddel, Langewitz, Schächinger, Schmieder, & Schutte, 1988; Shapiro, 1978). In addition, reactivity may change from day to day, although it has been shown to be reasonably stable in the few studies that have investigated this issue (Glass, Lake, Contrada, Kehoe, & Erlanger, 1983; Manuck et al., 1990; Pickering & Gerin, 1990; Schulte, Neus, & von Eiff, 1981).

One exception to this trend may be age. SBP and norepinephrine (NE) reactivity have been shown to increase with age. HR and DBP have been shown to be inconsistent, decreasing in some studies and increasing in others, whereas epinephrine reactivity seems not to vary between young and old (Barnes, Raskind, Gumbrecht, & Halter, 1982; Saab, Matthews, Stoney, & McDonald, 1989; Steptoe, Moses, & Edwards, 1990; Uchino, Kiecolt-Glaser, & Cacioppo, 1992). The evidence is largely cross-sectional, and longitudinal descriptions are needed.

In an analysis of studies involving behavioral tasks, Pickering and Gerin (1990) concluded (a) that increased reactivity is more characteristic of established, rather than borderline, hypertension; (b) that increased reactivity in hypertensives is more apparent in SBP, rather
Frequent hyperreactivity hastens development of vascular and end-organ complications; hypertensives/CHD patients are hyperreactors.

Hyperreactivity is a risk marker for hypertension/CHD

Hyperreactivity over time is a direct cause of hypertension/CHD

The impact of hyperreactivity varies with individual vulnerability and stress load

Hyperreactivity acts synergistically with some other pathological factor to bring about hypertension/CHD

Hyperreactivity and cardiovascular diseases are in no way related

Figure 2 — Model of six possible relationships between hyperreactivity and essential hypertension and/or coronary heart disease.

than in HR; (c) that there are insufficient data to support the belief that increased reactivity is seen with active, but not passive, coping; and (d) that there are also insufficient data to support the view that increased reactivity is more characteristic of behavioral, rather than physical, tasks. In both cases in which insufficient data is noted, the trend is in the suggested direction.

A meta-analysis by Fredrickson and Matthews (1990) concluded that essential hypertensives exhibit exaggerated blood pressure responses to active, passive, and cold pressor stresses but that borderline hypertensives exhibit exaggerated reactivity (SBP, DBP, and HR) mainly to active stressors.
Can stress cause essential hypertension in hyperreactive individuals either directly or acting synergistically with some other factors? Animal studies "have provided direct evidence that environmental demand can play a causal role in the development of hypertension" (Light, 1987, p. 1-68). Much of this evidence has come from genetically manipulated rats (spontaneously hypertensive rats [SHRs]). Experimental results using these rats have shown that they are hyperreactive to environmental stresses, that this hyperreactivity precedes the development of hypertension, that exposure to aversive stimulation facilitates the development of sustained hypertension, and that removal of such stimulation impedes the development of hypertension (Herd et al., 1987). Another strain of rats has been bred to be either salt sensitive (S) or salt resistant (SR). Both strains remain normotensive in the presence of low sodium intake. The S strain becomes hypertensive in the presence of either high sodium intake or avoidance conditioning, with the elevation in blood pressure being greatest when the two stimuli are combined. Thus, genetic predisposition, diet, and emotional reaction seem to interact synergistically to produce and sustain an increase in arterial blood pressure in laboratory rats (Friedman & Iwai, 1976; Herd et al., 1987).

The evidence in humans for a causal relationship between hyperreactivity and hypertension is neither so clear-cut nor so direct. There is, of course, the indirect, incomplete evidence previously discussed that hypertensives tend to be hyperreactive. This however, even if accepted, does not determine whether the hyperreactivity is a precursor or a consequence of hypertension, just that the two factors are somehow associated. If anything, the fact that established hypertensives show increased reactivity over borderline hypertensives would strengthen the view that hyperreactivity is more a consequence than a cause of hypertension (Pickering & Gerin, 1990).

There is also some evidence that susceptibility may, at least in part, also be a genetic predisposition in humans. Increased reactivity has been found frequently, but not invariably, in response to physical and mental stressors in males and (less consistently) in females with a positive family history of hypertension compared to those with a negative family history. Of course, not everyone with a positive hypertensive family history becomes hypertensive. Other characteristics such as high levels of anger, hostility, or anxiety (negative affectivity), regulation of body sodium, Type A behavior, coping skills, job stress, or stressful life events may be important factors in the expression of genetic susceptibility (Barnett, Hines, Schirger, & Gage, 1963; Diamond, 1982; Eich & Jacobson, 1967; Falkner, Kushner, Onesti, & Angelakos, 1981; Haythornthwaite, Pratley, & Anderson, 1992; Heine & Weiss, 1987; Herd et al., 1987; Jorgensen & Houston, 1989; Lawler, Lacy, Armstead, & Lawler, 1991; Light, 1987; Light, Koepke, Obrist, & Willis, 1983; Manuck, Kaplan, & Clarkson, 1985; Manuck et al., 1990; Matthews, Cottington, Talbott, Kuller, & Siegel, 1987; Pickering & Gerin, 1990; Thomas & Duszynski, 1982; Widgren, Wikstrand, Berglund, & Andersson, 1992).

There is also some evidence from prospective studies that hyperreactivity at one point in life can predict the development of essential hypertension later in life. A compilation of prospective studies completed in the last 30 years is presented in Table 2. Despite the wide variation in the number of subjects, subject characteristics, years of follow-up, measures of reactivity, and stressor applied, a promising, albeit not overwhelming, pattern is apparent. Reservation must be expressed based on some of the weaknesses of the studies. In some cases the percentage of reactive subjects developing hypertension is small (Barnett et al., 1963; Borghi, Costa, Boschi, Mussi, & Ambrosioni, 1986; Dlin, Hanne, Silverberg, & Bar-Or, 1983), in others the established baseline must be questioned (Eich & Jacobsen, 1967; Wood, Sheps, Elveback, & Schirger, 1984), and in still others, the influence of baseline borderline hypertension or positive family history cannot be separated from reactivity (Borghi et al., 1986; Falkner et al., 1981) or is unknown.

The study by Light et al. (1992) was specifically designed to eliminate the weaknesses of previous studies. They found that initially normotensive high reactors showed higher SBP,
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. subjects</th>
<th>Years follow-up</th>
<th>Stress</th>
<th>Reactivity predictive of subsequent hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett, Hines, Schirger, &amp; Gage, 1963</td>
<td>207 (40 hyperreactors)</td>
<td>27</td>
<td>Cold pressor</td>
<td>Yes, (10% vs. 0%) hyper- vs. normal reactors</td>
</tr>
<tr>
<td>Harlan, Osborn, &amp; Graybiel, 1964</td>
<td>385 Navy pilots</td>
<td>18</td>
<td>Cold pressor</td>
<td>No</td>
</tr>
<tr>
<td>Eich &amp; Jacobsen, 1967</td>
<td>73 medical students</td>
<td>9–10</td>
<td>Cold pressor</td>
<td>No, but also no aging increase so probably Type II error</td>
</tr>
<tr>
<td>Thomas &amp; Duszynski, 1982</td>
<td>1,185 medical students</td>
<td>&lt;36</td>
<td>Cold pressor</td>
<td>No, in original analysis Yes, in later analysis (Menkes et al.) Yes, (71% vs. 19%)</td>
</tr>
<tr>
<td>Wood, Sheps, Elveback, &amp; Shirger, 1984</td>
<td>142 children (same subjects as Barnett et. al)</td>
<td>45</td>
<td>Cold pressor baseline = 2 tests, 27 years apart</td>
<td>Yes, (71% vs. 19%)</td>
</tr>
<tr>
<td>Wilson &amp; Mayer, 1981</td>
<td>3,820 males &amp; females</td>
<td>~3</td>
<td>Treadmill exercise</td>
<td>Yes, (21% vs. 9%)</td>
</tr>
<tr>
<td>Dlin, Hanne, Silverberg, &amp; Bar-Or, 1983</td>
<td>75 males</td>
<td>5.8</td>
<td>Submaximal cycling exercise</td>
<td>Yes, (10.6% vs. 0%)</td>
</tr>
<tr>
<td>Reference</td>
<td>No. subjects</td>
<td>Years follow-up</td>
<td>Stress</td>
<td>Reactivity predictive of subsequent hypertension</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Sparrow, Rosner, Vokonas, &amp; Weiss, 1986</td>
<td>1,564 males</td>
<td>6.6</td>
<td>Orthostasis (supine-sitting SBP)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mann, Craig, &amp; Raferty, 1985</td>
<td>137 patients</td>
<td>2</td>
<td>Ambulatory &amp; clinical BP &gt; clinical BP</td>
<td>Yes</td>
</tr>
<tr>
<td>Parker et al., 1987</td>
<td>226 children</td>
<td>2</td>
<td>Orthostasis handgrip exercise, cold pressor</td>
<td>Yes, future BP + tracking low or high</td>
</tr>
<tr>
<td>Menkes et al., 1989</td>
<td>910 male medical students</td>
<td>20–36</td>
<td>Cold pressor</td>
<td>Yes, (6.7% vs. 2.4%) most pronounced if &lt; 45 years old</td>
</tr>
<tr>
<td>Falkner, Onesti, &amp; Hamstra, 1981</td>
<td>80 borderline hypertensive teens</td>
<td>5</td>
<td>Mental arithmetic</td>
<td>Yes, 67% borderline to established</td>
</tr>
<tr>
<td>Borghi, Costa, Boschi, Mossi, &amp; Ambrosioni, 1986</td>
<td>44 young adults</td>
<td>5</td>
<td>Mental arithmetic + sodium sensitivity</td>
<td>Yes, 20% borderline to established</td>
</tr>
<tr>
<td>Light, Dolan, Davis, &amp; Sherwood, 1992</td>
<td>51</td>
<td>10–15</td>
<td>Ambulatory BP, behavioral tasks, speech, mental arithmetic</td>
<td>Yes, higher BP but not hypertension; age &lt; 36 years at follow-up</td>
</tr>
</tbody>
</table>
DBP, and HR levels 10 to 15 years later (by both ambulatory and clinical testing) than did low reactors whose baseline values had not differed before. This suggests that blood pressure levels of the high reactors increased more than did the low reactors' blood pressure over the intervening years. Furthermore, they showed by multiple regression analysis that SBP, DBP, and HR reactivity improved prediction of follow-up blood pressure when added to equations already incorporating standard risk factors, baseline blood pressures, and parental history of hypertension. These were patterns of higher blood pressure, however, not necessarily the attainment of clinical hypertension. It should be pointed out, though, that even at follow-up these subjects were only 29 to 36 years of age. Future hypertension could still occur. Although Light et al. felt that their results strengthened the viabilities of the "reactivity hypothesis," they pointed out that the nature of the relationship remains to be clarified.

In summary, there is currently no compelling evidence to support a direct, solo causal role for hyperreactivity in the development of hypertension in humans, but there is indirect evidence that hyperreactivity may play some, as yet unspecified, role. The evidence does seem to support that fact that reactivity may be a marker for increased risk of high (or at least higher) blood pressure (Brody et al., 1987; Folkow, 1987; Light et al., 1992; Manuck et al., 1990; Morales-Ballejo et al., 1988). The objective of studying risk and hyperreactivity is that, ultimately, psychophysiological stress tests or even closer appraisal of blood pressure responses to exercise tests could be useful, cost-effective clinical tools to aid in the identification and management of those at risk for hypertension (Parker et al., 1987). Further research is needed that will utilize more comprehensive assessments of reactivity, determine whether central or peripheral mechanisms underlie hyperreactivity and exactly what they are to various stressors, utilize animal models in direct cause-and-effect studies, and include other possible risk factors in human prospective studies (Manuck et al., 1990).

Reactivity and Coronary (Ischemic) Heart Disease

The role of stress as a risk factor in the pathogenesis of CHD is the topic of a vast array of conflicting studies. Interest is high because the traditional biomedical risk factors (cigarette smoking, high cholesterol, hypertension, diabetes mellitus, and family history of heart disease without considering the newly acknowledged sedentary lifestyle) account for only approximately 50% of the variance in extent, severity, and incidence of CHD and fail to predict many, if not most, new cases (Eliot, 1987; Eliot et al., 1982; Krantz & Raisen, 1988). The hope is that some factor or combination of factors in the psychological domain will improve this predictability.

At least three distinct lines of psychological research have evolved. The first concentrates on psychosocial factors such as the impact of life events, chronic stress, daily hassles, socioeconomic status, social support, spousal behavior, and occupational stress (unemployment, job demands, job autonomy, and job satisfaction) (Krantz & Raisen, 1988). Broadly generalizing, studies utilizing the life-events methodology have been inconclusive, and the impact of the aforementioned factors in CHD development have, in large measure, been dependent on the perception and meaning of the factors to the individuals involved. This, of course, does not mean that these factors are unimportant. They are, however, not the focus of this paper.

The second line of research is psychobehavioral and is directed primarily at understanding the Type A behavior pattern (TABP). The 1981 National Institutes of Health's Review Panel on Coronary Prone Behavior and Coronary Heart Disease (Review Panel, 1981) concluded that global TABP is associated with increased risk of clinically apparent CHD greater than or equal to that imposed by age, hypertension, hypercholesteremia, and cigarette smoking.

The third line of research centers on psychophysiological reactivity (Krantz & Manuck, 1984). As with hypertension, this topic, including the interaction of TABP and hyperreactivity,
will be emphasized here. The primary hypothesis is that cardiovascular and endocrine hyperactivity play a direct role in the development of the clinical manifestations of CHD. Of course, any of the other models presented in Figure 2 are also feasible. The suspected route for direct causation is that hyperreactivity (alone or in combination with other factors such as diet) leads to atherosclerosis. When atherosclerosis (a symptomless condition) progresses to the point where coronary occlusion occurs, the clinical manifestations of ischemia, angina pectoris, electrocardiographic (ECG) dysrhythmia, myocardial infarction, or sudden death become apparent (Manuck et al., 1987). If hyperreactivity is the link, and TABP truly a risk factor, then it would be expected that Type As would be more reactive than Type Bs.

Krantz and Manuck (1984) reviewed 37 studies that had compared reactivity responses of Type A and B subjects to a variety of stressors. Seventy percent \( (n = 26) \) of the studies reported greater reactivity in Type A subjects than in Type B subjects. The subjects varied in age (children, adolescents, adults), occupation, and health status. The other 11 studies reported either no differences in reactivity or, least frequently, greater reactivity in Type B subjects than in Type A subjects. These 11 studies were judged as having more methodological problems than those in the first group. The authors concluded “that globally defined Type A... is correlated, perhaps only moderately or weakly, with physiological hyperreactivity in certain laboratory paradigms” (Krantz & Manuck, p. 441). Krantz and Raisen (1988) reasserted this conclusion, and it appears to be equally valid in 1993.

In view of this rather modest endorsement of global Type A hyperreactivity, it should come as no surprise that other studies have shown that a variety of individual and situational characteristics relate more strongly to physiological reactivity than does global TABP, especially since the assessment tool used to determine TABP may make a difference in the results obtained. For example, it appears (a) that Type A males respond more to stressors that they perceive as challenging than to stressors viewed as nonchallenging or noncompetitive, (b) that Type A males who rate higher on potential for hostility tend to perceive greater challenges in a situation than do low potential for hostility subjects and, hence, react more strongly, and (c) that regardless of behavior ratings (A or B) females in “traditional” roles show less reactivity than do males to the same stressors, whereas females in “career oriented nontraditional” roles approximate the male reaction. It has been suggested that this more “economical” female response may be one reason why “traditional” females suffer from fewer cardiovascular problems than do males and “career” women.

Of course, there is not universal agreement on these issues, and other traits such as a sense of time urgency, controllability, chronic activation, anger (in and out), person–environment fit, and genetics are being explored. Long-term prospective studies that take situational and individual characteristics into account and that have as their end point clinical cardiovascular pathology are needed (Booth-Kewley & Friedman, 1987; Chesney & Rosenman, 1983; Dembroski, MacDougall, Herd, & Shields, 1979; Diamond, 1982; Glass et al., 1980; Krantz, Lundberg, & Frankenhaeuser, 1987; Shepherd et al., 1987; Stoney, Davis, & Matthews, 1987; Wright, 1988).

The most convincing evidence linking reactivity to cardiovascular pathophysiology, as with hypertension, comes from animal studies. However, even here, the evidence does not extend beyond the development of atherosclerotic lesions to the clinical consequences, probably because of the short time span of the studies and often the necessity of sacrificing the animals to document the lesion results.

Although a number of studies using a variety of animals (mice, rats, pigs, chickens, and monkeys) have shown that a manipulation of social groups interacting with positions of dominance or submission can lead to the development of atherosclerotic lesions, only two studies have looked at the impact of reactivity (Manuck et al., 1987; Schneiderman, 1987). Both of these were conducted on monkeys (cynomolgus macaques). In the first study (Manuck,
Kaplan, & Clarkson, 1983) 22 adult male monkeys that had been fed a moderately atherogenic diet for 22 months were fitted with ECG telemetry, and baseline HR levels were established. The stress imposed was the threat of capture and physical handling. Animals were then divided into high and low reactors based on the HR responses to the stress. Autopsy results showed greater coronary atherosclerosis in the high-reactor group than in the low-reactor group. The second study replicated these results in adult female monkeys (Manuck et al., 1985).

In humans, evidence that directly links hyperactivity to atherosclerosis is nonexistent—although some, but not all, studies have found angiographic evidence of greater disease progression in Type As than Bs (Review Panel, 1981)—and is weak in directly linking hyperactivity to the clinical manifestations of CHD.

High levels of HR, SBP, DBP, rate pressure product (RPP), or catecholamine reactivity have been reported in case control studies of cardiovascular patients that distinguish them from nonpatients or that differentiate between the severity of impairment in terms of wall motion abnormality (Krantz et al., 1991; Rozanski et al., 1988; Rosanski, Krantz, & Bairey, 1991; Zotti, Bettinardi, Soffiantino, Tavazzi, & Steptoe, 1991), S-T segment depression or other ECG dysrhythmia (Reich, DeSilva, Lown, & Murawski, 1981; Schiffer, Hartley, Schulman, & Abelmann, 1976; Specchia et al., 1984; Specchia et al., 1991), left ventricular dysfunction (Bairey, Krantz, & Rozanski, 1990; LaVeau et al., 1989), angina (Sime, Buell, & Eliot, 1980), or platelet activation and aggregation (Grignani et al., 1991). Unfortunately, as with the hyperreactive response of hypertensive patients, there is no way to truly distinguish cause and effect in these studies. It is as feasible that hyperreactivity results from the presence of the abnormalities measured as that the abnormalities in some way resulted from hyperreactivity.

Studies that have attempted to predict recurrences of clinical manifestations in hyper-reactive coronary patients are a somewhat stronger design. Given that ventricular ectopic activity has been implicated in sudden death, Follick et al. (1990) attempted to relate such activity to cardiovascular reactivity. Patients who had already had a myocardial infarction and had exhibited frequent premature ventricular contractions (PVCs) but who had not sustained ventricular tachycardia served as subjects. Cardiovascular reactivity was not found to predict the frequency of PVCs. On the other hand, Manuck, Olsson, Hjemdahl, and Rehnqvist (1992) showed that the degree of reactivity was predictive of reinfarction or cerebrovascular stroke in a different patient group.

Only one prospective study using initially healthy individuals is available, and that was published in 1971. Keys et al. (1971) showed that the response of DBP to the cold pressor test was a significant predictor of future clinical manifestations of cardiovascular disease during 23 years of followup. Diastolic blood pressure reactivity was a stronger predictor than some standard risk factors that were assessed.

In summary, the question of whether stressful experiences, mediated through hyperreactivity, are risk factors for developing atherosclerosis or the clinical manifestations of CHD is even less settled than the link between hyperreactivity and hypertension. As such, this area of inquiry will require even more properly designed studies. There appears to be, however, a belief among most of those working in this area (regardless of whether their own studies have shown a linkage or not) that the topic is worth pursuing. It is widely acknowledged that this area is more complex than initially anticipated but that it is too important to abandon despite the complexity.

**Conclusion and Implications**

We are not at the point where hyperreactivity explains the connection, if any, between stress and health in the cardiovascular system. We are not at the point where reactivity can be used either by physicians and health workers to identify those most vulnerable to stress...
or by physical educators as an item in determining fitness, as has also been alluded to (Gutin, Manos, & Strong, 1992). However, there is sufficient circumstantial evidence to continue pursing the linkage (Krantz & Raisen, 1988). When and if causal or risk factor linkage is determined, early intervention in environmental and behavioral factors will hopefully be valuable in the prevention and diagnosis of disease manifestations.

References


