Stress, Reactivity, and Cardiovascular Disease
Proceedings of the Working Conference
Stress, Reactivity, and Cardiovascular Disease

Proceedings of the Working Conference

Co-Sponsored by
The National Heart, Lung, and Blood Institute
and
The University of Pittsburgh
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The University of Pittsburgh
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FOREWORD

During the past few years, there has been increasing interest in investigating the variability as well as the consistency of cardiovascular parameters. The traditional measurements of, for example, blood pressure, heart rate, total systemic resistance and cardiac output have attempted to identify the "true" value of the measurement under consideration by eliminating sources of variance. Innovations such as exercise stress testing, salt-loading, and glucose tolerance tests, however, have demonstrated the value of assessing the range of these parameters, particularly under standardized laboratory conditions.

Advances in measurement technology now permit continuous noninvasive monitoring of cardiovascular parameters under both laboratory and naturalistic conditions. New techniques have enhanced capabilities to follow the subtle variations of, for example, neurohormonal patterning in response to various forms and levels of environmental/behavioral challenge. Recent interest in "coronary prone" behavior has stimulated extensive research on the relationship of biomedical and behavioral factors to the development of coronary heart disease. Using standardized laboratory challenge conditions, investigators have identified individuals with hyperresponsive cardiovascular patterns as potentially more vulnerable to disease, particularly coronary heart disease. Additionally, preliminary evidence suggests that the deleterious effects of tobacco, salt, caffeine and similar substances may synergistically interact with environmental stressors in such individuals.

Given the extensive interest generated by the initial studies of "reactivity", the conference was planned to accomplish the following objectives:

1. To assess the state of science in the following areas:
   a) stress and cardiovascular/neuroendocrine reactivity;
b) the relationship of stress-induced hyperreactivity to cardiovascular disease, particularly coronary heart disease;
c) the interactive effects of environmental stress and smoking, caffeine, salt and similar substances on cardiovascular reactivity.

2. To examine the theoretical and conceptual bases for these studies.

3. To establish standards and criteria for laboratory stressors.

4. To develop consensus on the most pertinent physiological/biochemical variables to be studied.

5. To establish standards of measurement/instrumentation.

6. To establish criteria for "hypo" and "hyperresponders."

7. To establish standards for determining the effects of "mediators," e.g., exercise, relaxation training, etc.

This area of investigation promises a better understanding of the linkage of stress and heart disease along with the related physiological mechanisms underlying this relationship. It will also provide critical information on the putative synergistic effect of various substances (e.g., salt, caffeine, alcohol) on cardiovascular function, in the presence of environmental stressors. Thus, this conference attempted to establish consensus among key investigators in the field on issues of theory, design measurement, and instrumentation pertinent to understanding the role of cardiovascular and neuroendocrine reactivity in the development of cardiovascular disease. After examining the current theory and research in this area, the participants reviewed, analyzed, and prioritized the most relevant biological, psychological and behavioral parameters to be studied and
the most appropriate methods to accomplish this. This information will serve as a coordinating guideline for researchers in minimizing duplication as well as enhancing the quality of studies being considered in this exciting area of investigation.

The task of planning a conference of this magnitude and scope can only be fully appreciated by those who have experienced the joy and frustrations of such an activity. Beginning with the recognition of the need for such a conference by the cosponsors, a conference planning committee of Drs. Theodore Dembroski, Bonita Falkner, Katrina Johnson, Peter Kaufmann, Stephen Manuck and Redford Williams was formed to develop a format and agenda responsive to the key issues facing the scientific community in this emerging area of research endeavor. As the "science" plan took shape, the administrative and logistic team, headed by Ms. Betty Lou Melani, and including Ms. Carol Holbay, Ms. Lori Liller, Ms. Margaret Malloy, Ms. Debra Reichbaum, Ms. Laurie Sparky, and Ms. June Walker coordinated both the preparations and the support required during the conference. After the conference scientific editing was provided by Ms. Anne Borsuch, and preparing the proceedings for publication was handled by Dr. Judith Graeff.

A final note of appreciation--to the participants themselves, whose pursuit of scientific excellence both in their own work and the conference itself, has resulted in this thought-provoking document, which should provide the scientific community with new standards and guidelines in this exciting new area.

S.M.W.
K.A.M.
T.D.
STATUS OF AND PROSPECTS FOR STRESS, REACTIVITY, AND CARDIOVASCULAR DISEASE: THEMES FROM THE NHLBI-UNIVERSITY OF PITTSBURGH WORKING CONFERENCE

K. A. Matthews, S.M. Weiss and T. Detre

In April 1984, a distinguished group of 67 biomedical and behavioral scientists from the NIH, major U.S. universities, Sweden, and the USSR gathered in Olgebay Park, West Virginia, for a working conference jointly sponsored by National Heart, Lung, and Blood Institute and the University of Pittsburgh, Western Psychiatric Institute and Clinic, School of Medicine, and Graduate School of Public Health. The objectives of the conference were to assess the state of science regarding the relationships among stress, reactivity, and cardiovascular diseases; to evaluate the theoretical and conceptual bases of work in the area; and to identify the most pertinent variables to be studied, including the physiological indices of reactivity, types of stressors which induce reactivity, and the mediators and modifiers of stress-induced reactivity.

To accomplish these objectives, all the participants reviewed relevant articles (numbering over 1,000 journal pages) prior to the conference, attended plenary sessions and developed recommendations in small task groups throughout the 3-day meeting. During the first working session of the task groups, the conferees discussed the theoretical issues, rationale, and measurement strategies regarding stressors and reactivity in six areas: 1) hemodynamic and electrophysiological measures of reactivity, led by Neil Schneiderman and Thomas Pickering; 2) biochemical measures of reactivity, led by Robert McDonald and David Goldstein; 3) psychological markers and correlates of reactivity, led by B. Kent Houston and Craig Ewart; 4) demographic and familial markers and correlates of reactivity, led by Laurence Watkins and Richard Rose; 5) environmental elicitors of reactivity primarily physical in nature, led by James Buell and Wallace McCrory; and 6) environmental elicitors of reactivity primarily psychological in nature, led by David Krantz and Rena Wing.

During the next set of task group sessions, the conferees reviewed and evaluated the theoretical issues, potential mechanisms of action, and
measurement strategies regarding the stimulators and modulators of reactivity to physical and psychological stressors. They met in the following seven groups: 1) caffeine, led by David Shapiro and James Henry; 2) nicotine, led by Leonard Epstein and J. Alan Herd; 3) salt and glucose, led by Bonita Falkner and Kathleen Light; 4) alcohol, led by Robert Levenson and Benjamin Natelson; 5) exercise, led by Bruce Alpert and Joel Dimsdale; 6) relaxation therapies, led by Margaret Chesney and Rolf Jacob; 7) pharmacologic agents, led by Alvin Shapiro and Clarence Grim. In all, 13 task group reports were developed on the above topics.

Plenary sessions highlighted significant scientific areas through brief presentations on stress and reactivity (Redford Williams); reactivity, hyperreactivity and cardiovascular disease (Stephen Manuck), and the implications of the reactivity hypotheses for atherosclerosis (Thomas Clarkson), hypertension (Stevo Julius), and coronary heart disease (J. Alan Herd). Theodore Dembroski briefly reviewed the evidence on stress-reactivity stimulators (e.g., caffeine, nicotine, salt) while Richard Surwit performed a similar task with stress-reactivity inhibitors (e.g., exercise, behavioral therapies, pharmacologic agents, alcohol). All of these activities were orchestrated by the conference chair, Thomas Detre, while Karen Matthews and Stephen Weiss served as the conference organizers.

The major themes and research directions emerging from the conference deliberations will be the focus of this summary chapter.

Definition and Assessment of Reactivity

Most task groups discussed what is meant by the term, reactivity. The common element in the definitions considers reactivity as the deviation from a comparison or control value resulting from a response to a discrete environmental stimulus. The environmental stimulus can be one that is primarily physical or psychological in nature, e.g., strenuous exercise or performing a boring task. According to this definition then, variability of a physiological parameter measured throughout the day, e.g., casual blood pressure readings, would not precisely measure reactivity unless the
environmental stimuli to which the individual is responding are specified. Similarly, lability of resting pressure on successive occasions would not measure reactivity unless a discrete environmental elicitor is known. This is not to say that measures of variability or lability are unimportant or uninteresting for human physiology or pathogenesis of cardiovascular disease. Rather, that reactivity is a term reserved for those situations in which a clear environmental stimulus is apparent.

The conference participants emphasized the complexity of the concept of reactivity in their deliberations. Two different, but not necessarily incompatible models of reactivity nicely illustrate this complexity. One model posits that stress-induced measures, e.g., of blood pressure, are more representative of levels of blood pressure throughout daily events than are resting measures. Manuck labels this model "steady state" (see article this volume) because persons who exhibit this type of reactivity are consistently at levels throughout the day approximating the stress-induced levels obtained in the laboratory and the atypical values are the resting ones. Another model of reactivity assumes that persons display transient peaks of blood pressure throughout the day and that the laboratory-induced levels are good measures of the peaks, but not of the daily mean levels of pressure. It is important to note that both of these models may accurately describe the physiological patterns of subgroups of the population.

The notion of levels of stressors and reactivity also illustrates the complexity of the reactivity concept. At a rudimentary level are the specific stressors and responses, e.g., serial subtraction and epinephrine levels. At another level are the classes or systems involved in the stimulus and response parameters, e.g., mental effort and sympathomedullary system. At still another level is how the central nervous system perceives the stressor and orchestrates the appropriate response to that stressor. This list of levels of organization of reactivity is obviously not exhaustive, but does illustrate the importance of considering numerous ways of assessing reactivity.
The conference participants discussed several interesting assessment issues. One is the appropriate control value to compare to the response value. The participants expressed some concern about the "traditional" way that reactivity measures are taken: control values are measured during a rest period prior to the experimental procedure or prior to the day's events and are statistically adjusted for in analyses of the response values. This procedure does not take into account that persons' uncertainties about the experimental session may inflate the control values and, more problematic, that individual differences in the persons' appraisals of the upcoming experience may differentially inflate the control values.

The conferees suggested several ways to avoid these anticipatory effects on baseline values. The simplest method is to obtain a resting level after the stressors have been administered, e.g., during the last 10 minutes of a 30 minute resting period. An alternative procedure is to have the subject return to the laboratory on a second occasion for baseline measures, knowing that no additional experimental procedures are involved. A final method is to use ambulatory monitoring of measures selected because they were taken during a maximally relaxing period in the course of the day. Each of these methods has certain advantages and disadvantages and should be selected according to the overall purpose of the investigation.

A related assessment issue is how to describe reactivity values: absolute levels or change scores or percentage change scores. Although no consensus about the most suitable measures emerged at the conference, participants agreed that sufficient data should be available to allow the reader to compute all those values.

Variying Roles of Reactivity in Cardiovascular Diseases

A theme which emerged from the conference deliberations is that reactivity may vary in importance and in the role it plays in the etiology and course of atherosclerosis, coronary heart disease, sudden death, and hypertension. For example, Clarkson offered an intriguing hypothesis at the conference concerning the mechanisms that might link reactivity to atherosclerosis.
The predominant model of the atherogenic process is the endothelial injury model offered initially by Ross and Glomset and amended by Schwartz. That is, repeated injury to the endothelial lining of the artery wall is thought to lead to accelerated cell death, which, in turn, alters the permeability of the cell membrane to lipoproteins. The altered permeability permits the influx of LDL cholesterol into the cell and the consequent acceleration of atherosclerotic plaque deposits. Clarkson suggested that the repeated transient elevations of blood pressure in the individual reactive to environmental stress may be an important factor in mechanically promoting endothelial injury and in preventing normal healing of these lesions.

Obrist offered a different model for the role of reactivity in hypertension. Briefly, he proposed that episodic increases in cardiac output, elicited by behavioral changes which require active coping and entail beta-adrenergic activation, promote elevated resistance in the peripheral vasculature over time. These increases in peripheral resistance occur as a function of resulting structural changes in the arterioles or via intrinsic homeostatic processes which act to prevent an over-perfusion of body tissues (autoregulation). Furthermore, the autoregulation mechanism may be particularly relevant because a markedly increased cardiac output will supply oxygen levels above that demanded by the cell tissues during the behavioral challenge.

It should be emphasized that the above hypotheses have not been confirmed. In fact, Julius and some of the other conferees took exception to the hypothesis that reactivity plays an etiologic role in hypertension. In part, this is because of differences in the interpretation of the data showing that mild hypertensives are not necessarily more variable or labile in casual blood pressure measures; the failure to show that hypertensives are more reactive to physical stressors in some studies; and the absence of any population-based longitudinal data showing that reactive normotensives become hypertensive. Nonetheless, these hypotheses nicely illustrate that reactivity may not play a single etiologic role and that it may vary in its importance for the specific diagnoses of cardiovascular disease.
Another way to view the varying roles of reactivity in disease is to consider how stress-induced reactivity may serve as a precursor, correlate, and consequence of cardiovascular diseases. Using hypertension as an example, it has been argued that stress-induced elevations in blood pressure are a precursor of hypertension (see Falkner; Manuck & Krantz, this issue). It has also been noted that normotensive offspring of hypertensive parents, who are at elevated risk to develop subsequent hypertension, exhibit elevations in blood pressure or heart rate in response to stressors (see Rose, this issue). In a sense, stress-induced reactivity can be considered a correlate or marker of risk for hypertension, while not necessarily being a cause of subsequent hypertension. Finally, many secondary adjustments arise from hypertension, such as changes in cardiac performance, decreased baroreceptor sensitivity, structural changes in resistance vessels, and information processing ability (Folkow, 1983; Shapiro, Miller, King et al., 1982). It is feasible that some of these secondary adjustments inhibit or exacerbate stress-induced reactivity as they compensate for an individual's elevated blood pressure.

Stressors as Elicitors of Reactivity

The conference discussion concerning which stressors elicit reactivity highlighted one of the fascinating, but imprecise aspects of any scientific inquiry concerned with stress. The participants acknowledged that the level of stress which individuals experience in response to a given environmental event is crucial for determining the impact of that event and that substantial individual differences exist in how the event might be appraised. In consequence, the impact of some of the psychological as well as physical stressors may vary substantially across experiments according to how the stressors are presented. For example, those experiments in which a physical stressor, like the cold pressor, is presented as a challenge (e.g., adverse sensations to be overcome) vs. those experiments in which it is presented as a diagnostic test, should yield important differences between experiments in the willingness to tolerate the cold pressor test and in perceived stressfulness of the test. This example also
points out the arbitrariness of separating stressors into those that are "psychological" and those that are "physical."

Another theme that emerged during the conference was that stressors can be grouped not only according to the level and duration of stress experienced by individuals but also according to the pattern of physiologic response which the stressors elicit (see Williams, this issue). One way to slice the physiologic pie is to distinguish those tasks which elicit increases in cardiac output and muscle vasodilation from those which elicit increases in total peripheral resistance and muscle vasoconstriction. Another way to slice the pie is to distinguish those tasks which elicit elevations of catecholamines and cortisol from those which elicit elevations only in catecholamines. As a taxonomy of laboratory tasks develops, categorization of tasks according to their physiologic effects will contribute to knowledge of human physiology and to future investigations of the pathogenic effects of stress-induced reactivity.

The conference participants discussed in several different ways the relationship between a person's responses to laboratory stressors and to "field" or "real life" stressors. One way was from an assessment perspective; that is, do laboratory-induced levels generalize to levels achieved throughout the course of the day? Can they serve as a stand-in for levels taken during a naturally occurring stressor? There are minimal data concerning this issue (see Manuck & Krantz, this proceeding). A more theoretical way concerned models of reactivity. Laboratory-induced levels are typically acute measures, whereas levels induced by naturally occurring stressors are a mixture of chronic and acute responses to stressors. Thus, there may be important modifiers of reactivity to natural stressors due to prolonged and/or repeated exposure to the stressors that may not play a role in determining reactivity to laboratory stressors. A final concern was the frequency with which individuals are exposed to naturally occurring stressors which elicit responses similar to those elicited by laboratory stressors. Although individuals may respond similarly to a laboratory and naturally occurring stressor, if the individuals do not sufficiently often experience the naturally occurring stressor, then laboratory measures may not be informative.
Variables Affecting Reactivity

Conference participants agreed that specific psychological and sociodemographic variables are related to reactivity and that population differences in risk for cardiovascular diseases might be explained in part by population differences in reactivity. Among the most promising predictors of reactivity are Type A behavior, hostility, anger, sex, age, and family history of hypertension (Frankenhaeuser, 1983; Houston, 1983; Matthews, 1982; Matthews & Rakackzy, in press). Racial and ethnic differences in reactivity are currently unknown, but are under investigation in several NHLBI funded projects.

The conferees also thought that certain substances and health behaviors might impact on reactivity. Consumption of caffeine, salt, sugar, and alcohol; smoking; pharmacologic agents; and modes of coping with stress may influence reactivity, although it is unclear whether the effects are additive with the exposure to stress or synergistic (interactive) with the exposure to stress. An illustration of this point comes from the study by Dembroski and colleagues described in this issue. In their study, exposure to a stressful task and smoking had additive effects in determining elevations in blood pressure and heart rate, relative to a control condition. A synergistic model would predict a geometric increase in physiologic change, relative to a control condition.

Several of the "substance" task groups made a similar point. That is, although individuals tend to engage in more than one of the above health behaviors, e.g., both smoke and drink alcohol (see Istvan & Matarazzo, 1984), little is known about their interactive effects since they are typically studied in isolation in laboratory studies.

It was also noted that many of these substance/health behaviors may have a particularly deleterious effect in persons with a genetic/familial predisposition for cardiovascular disease.
Directions for Future Research

Because stress-induced reactivity has not been established as a risk factor for cardiovascular disease, the conference participants expressed considerable enthusiasm for the types of studies that would be a prelude to a population-based epidemiological study testing the association of reactivity and subsequent disease. They suggested that parametric studies on the stressors appropriate for specific ethnic, racial, sex, and age groups and evaluated for their reliability or reproducibility and validity or generalizability would be crucial. Clinical studies should be conducted on the physiologic parameters most important and feasible to measure on a large scale. Specific attention to the behavioral and physiological adjustments to certain substances/health behaviors would be useful for cleaning up the noise in measuring stress-induced reactivity, and more importantly, for understanding reactivity in the context of normal, daily living patterns where people do eat, smoke, and drink at the same time.

Animal studies ongoing simultaneously with human studies were thought to be particularly valuable because of the level of control allowed and of the possibilities for studies that would not be feasible in humans. Parametric studies of substance ingestion, studies which include continuous invasive measurement, and selective breeding of genetically predisposed individuals are examples of studies which would not be feasible in humans, but would be very informative for understanding human physiology and potential mechanisms involved in cardiovascular diseases. Given that suitable animal models for studying atherosclerosis and hypertension have been developed, it is most reasonable to pursue studies on the interactions of behavior and substance ingestion or genetic susceptibility to disease. Indeed, work on the behavioral determinants of atherosclerosis by Kaplan, Manuck, and Clarkson in the cynomolgus monkey and of hypertension by Anderson, Henry, and others in the dog and rat has been most fruitful for understanding disease processes.

In conclusion, exciting times are ahead in the area of stress-induced reactivity and cardiovascular disease. There are many hypotheses to be
tested and much parametric research to be accomplished. Whether or not individual differences in stress-induced reactivity will prove to be a risk factor for any of the cardiovascular diseases, research in this area will reveal important information about the exquisite adjustments between the behavioral and physiological systems and hone in on the important processes in determining the etiology and course of cardiovascular disease. We hope that the conference and the volume it produces facilitate addressing important research issues in this area.
WELCOMING REMARKS
WELCOMING REMARKS

T. Detre

It is a great pleasure and privilege to welcome you in the name of the National Heart, Lung, and Blood Institute and the University of Pittsburgh to what promises to be an exciting conference. Two of our deans, Dr. Raymond Seltser, Graduate School of Public Health, and Dr. Donald Leon, School of Medicine, will in fact, actively participate in our proceedings. I want to extend our special welcome to our colleagues from Sweden and the Soviet Union, who will be working with us over the next several days. And work we will. Dr. Stephen Weiss and Dr. Karen Matthews, despite my best efforts to the contrary, have insisted on putting us away in this beautiful but certainly isolated setting to ensure complete protection from all distracting entertainment.

Perhaps they were right. The time available is short and the agenda is very substantive. The methodological problems involved in examining the relationship of stress to cardiovascular disorders are exceedingly difficult. We have been lamenting for years about the promiscuous use of the word stress. We often fail to differentiate between situations that are rather prosaic ordinary life events and those which involve a tour de force. Moreover, many of our experimental stress paradigms are acute. While such studies provide valuable insights about conditions that can cause a temporary change in cardiovascular functioning, the data obtained cannot be generalized to conditions involving chronic stress. Missing also is a clear appreciation that the different types of stressors may have different effects, depending on the stage of the disorder we are studying. I suspect that we also err by looking at risk factors, disregarding their biologic context. Just how significant a risk factor or a constellation of risk factors is, however, will vary depending on the age and sex of the subjects and stage of the disorder. Accordingly, age and sex of the organism and the stage of disorder will also determine the potential effectiveness of an intervention aimed to reduce one or more risk factors regardless whether the type of intervention is "biologic," as may be the
case with low cholesterol diet, or "psychological," as may be the case when some form of relaxation therapy is administered.

Sometimes our frustration tolerance seems to be low. We have in the past, put aside potentially valuable experimental paradigms because we were unable to find measurable biologic correlates. Yet it is quite possible that nothing was wrong with the experimental paradigms; what we lacked was either an appreciation of the often peculiar temporal relationship between stress and biologic response, a method that was sensitive enough, or we were looking at the wrong biologic system in our search for a measurable response.

We have become increasingly aware that genetic and constitutional factors always set the ceiling for the level of functioning the organism is able to achieve. In evaluating our treatments, especially when their effect is modest, however, we tend to forget that whatever we do is limited by this ceiling.

Lastly, and perhaps most importantly, all of us are aware that our investigative efforts aimed to delineate the mechanism by which stress is biologically transcribed are still in their infancy. Yet it is precisely this focus which must receive high priority in the coming years.

Because the questions are so many and the challenges facing us so complex, the National Heart, Lung, and Blood Institute decided that this meeting should not follow the traditional format of a consensus conference but should be devoted instead to elicit your creative ideas, bringing forth recommendations that will allow behavioral medicine to take the next giant step forward. I wish you well in your endeavor, and, once again, our warmest welcome.
STRESS AND REACTIVITY

R. B. Williams, Jr.

We are interested in the question of stress and reactivity because certain psychological characteristics, such as Type A behavior (1) and hostility (2), have been shown to predispose persons to increased risk of cardiovascular disease. An implicit assumption (the "reactivity hypothesis") fueling our concern with stress and reactivity is that persons with such characteristics as Type A and hostility experience degrees of cardiovascular and neuroendocrine reactivity to everyday environmental events (stressors) that are at least partly responsible for the increased disease incidence observed when persons with these characteristics are followed in prospective longitudinal studies.

Before we can even begin to speculate regarding the role of reactivity in pathogenesis, however, it is first necessary to provide a theoretical framework upon which to base our speculations. What is meant by reactivity? Do all environmental stressors cause the same kind of reactivity? Do all individuals respond to the same environmental stressors with the same reactivity? If we can draw upon empirical research in the stress field to pose acceptable answers to questions such as these, then it will be possible to proceed in a more systematic, informed and reasoned fashion to design the studies necessary to elucidate pathogenic mechanisms underlying the relationships between certain psychological characteristics and cardiovascular disease.

In this presentation I shall present a model outlining the critical classes of variables we must study to gain an understanding of how environmental events are translated into patterns of cardiovascular and neuroendocrine response which could play a role in pathogenesis. I shall review the experimental evidence supporting the existence of two qualitatively distinct response patterns (which, for descriptive purposes, I shall designate pattern 1 and pattern 2) in humans and animals, along with observations about the kinds of environmental stimuli which appear
specifically to elicit those patterns. A consideration of brain mechanisms responsible for mediating these response patterns will next serve to buttress the argument for their existence, as well as add to our understanding of classes of environmental stimuli critical for their elicitation.

The organization of this talk as I have just outlined was not chosen without some thought on my part. When it comes to defining those types of environmental stimuli which elicit specific patterns of physiological response, there is room for much controversy. The process of naming psychosocial phenomena often leads among scientists to what may be termed "label narcissism": we all love our own labels for things far more than the labels others might choose. In what follows I hope to present first evidence supporting the objectively evident existence of two patterns of physiological response under conditions that might be described as stressful. If we can agree on at least the broad outlines of those patterns, then perhaps we can enter a dialogue in which, together, we attempt to characterize the circumstances which elicit either pattern. If we can avoid the "name debate," perhaps it will be easier to get on with the work of understanding the role of reactivity in the pathogenesis of cardiovascular disease.

A Theoretical Model

In figure 1 is illustrated my version of the "biopsychosocial" model. While I make no claims that it is better than others' attempts at graphic representation of how environmental events are transduced into physiological responses (reactivity) that could play a role in causing cardiovascular disease, it does illustrate several principles that I feel we must take into account if we are ever to understand the role of reactivity in cardiovascular disease.

First, and most relevant to the focus of this talk, the model shows that the "motor messages" sent by the brain to the body's organs following the perception of some environmental event occur in organized patterns, rather than as isolated responses, and that these patterns involve all three of
the motor effector systems available for the brain's communication with the body--the somatomotor nerves, the autonomic nerves and the neuroendocrine system. This principle has been most cogently enunciated by the English physiologist S.M. Hilton, who suggests:

"that a new approach may be made by starting from the view that the central nervous system is organized to produce not single, isolated variables, but integrated patterns of response. Any variable which can be described or measured independently is actually a component of several such patterns....In this system, the repertoire of patterned responses (may be) very small." (3, p. 214)

Based on this reasoning, then, I suggest that broad classes of environmental events may produce a relatively small number of integrated patterns of response involving the three motor effector systems. This means that rather than studying only one or two physiologic parameters, we should study as many parameters as possible, so to identify more reliably patterns of response. If we can identify and agree on the nature of some of these patterns, it might then be possible to characterize the critical types of environmental stimulation which elicit them.

As the model also indicates, the brain's interpretation and transduction of environmental events into patterns of motor messages can be modulated by the personality of the individual as well as his/her genetic makeup. Thus the model reminds us that different personalities--e.g., those producing Type A and Type B behavior--can result in differences in the patterned response to the same environmental stimulus situation. It also calls our attention to the fact that certain genetic characteristics--e.g., those also responsible for increased predisposition to essential hypertension--can also influence what happens in the motor outflow tracts following any stimulus.

The above sequence of events--environmental event, interpretation by the brain and transduction into patterns of motor messages, modulation by the personality and genes, and effects of motor messages on target organs--occurs on a more or less acute basis within a limited time span, although such acute effects can be sustained as long as the organism is involved with the given environmental stimulus. The model also suggests, however, that we be mindful of certain other processes which occur over
longer, more chronic time periods. First, the personality is the result of developmental processes, beginning at birth and extending into adulthood, which involve the interaction of the genetic predispositions of the individual with his/her environment. A second chronic process involves the cumulative effect of repeated elicitations of the various patterns of response across the life span. If extensive and intensive enough, the "reactivity hypothesis" holds, these repeated responses could, over time, lead to pathophysiological changes resulting in the development of cardiovascular disease.

For the remainder of this presentation, I shall review some experimental data which suggest the existence of two qualitatively distinct patterns of response. This will be followed by a consideration of the means by which the brain produces these patterns, and by some observations regarding the types of environmental stimuli which elicit them.

Two Patterns of Physiologic Response

Paul Obrist has called our attention to the importance of motor activity and the skeletal musculature in determining patterns of response. (4) It follows from this observation that responses of the skeletal muscle vasculature might furnish important clues regarding basic response patterns. The skeletal muscle circulation is one of the most interesting in the body, receiving anywhere from 15-20 percent of the cardiac output at rest up to 85 percent under conditions of heavy work or stress. It is the only vascular bed that has neural and neuroendocrine mechanisms which permit it to exhibit both active vasodilatation and active vasoconstriction. For these reasons and because it supports the functions of motor activity so important for life itself, the skeletal muscle vascular bed deserves our attention as we try to identify the basic physiologic response patterns.

In studies with humans, a number of investigators have used the relatively simple but reliable method of venous occlusion plethysmography (5) to study skeletal muscle hemodynamics under various experimental conditions. Representative of one group of these studies was the demonstration by Brod and colleagues (6) of an active vasodilatation in the forearm skeletal
musculature during performance of mental arithmetic with harassment. The similarity of this skeletal muscle hemodynamic response in humans to that seen with stimulation of the hypothalamic "defense" area in animals (7) has led to the conclusion that under conditions where "fight or flight" behavior is an appropriate response, active skeletal muscle vasodilatation is a key aspect of the integrated response (3). Thus it seems reasonable to suggest that skeletal muscle vasodilatation may be a valid "marker" of one important response pattern with relevance for the role of reactivity in cardiovascular disease. For the time being, let us refer to this pattern as pattern 1. Of course, the model presented earlier leads us to recognize that the skeletal muscle vasodilatation is only one ingredient of pattern 1. Indeed, in their pioneering study, Brod and coworkers (6) were able to demonstrate that at the same time the muscle vasodilatation was occurring, vasoconstriction was also occurring in the skin, kidney and gastrointestinal tract of their subjects, and it follows as well that the neuroendocrine system is also participating in pattern 1.

But what of the other pattern, "pattern 2," that I promised to describe in this presentation? Based on observations of diastolic blood pressure increases during personal interviews (8), my colleagues and I studied the muscle hemodynamic response to mental arithmetic, a sensory intake task and a personal interview (9,10). During mental arithmetic performance we found, as had many others, an increase in forearm blood flow and a decrease in forearm vascular resistance, indicating active skeletal muscle vasodilatation. In contrast, during the sensory intake task we found that forearm vascular resistance showed a significant increase, indicating an active skeletal muscle vasoconstriction. The muscle hemodynamic response to the personal interview provided further clues regarding motoric behaviors associated with muscle vasoconstriction: among those subjects who avoided attending to the interviewer, forearm vascular resistance fell, while among those who attended closely to the interviewer, an increase in forearm vascular resistance was observed.

Thus, it appears, in addition to the skeletal muscle vasodilatation observed during defense behavioral activations, there is a second, qualitatively distinct pattern of muscle hemodynamic response which can be
elicitated, one characterized by active vasoconstriction. As with pattern 1, for the time being let us refer to this second pattern, characterized by active skeletal muscle vasoconstriction, as pattern 2. Similarly, if it is truly a marker of one of the integrated patterns of response to which Hilton referred, it should also be possible to demonstrate characteristic neuroendocrine responses accompanying the muscle vasoconstriction.

The suggestion that we need to be concerned with two basic response patterns, pattern 1 with muscle vasodilatation as a marker, and pattern 2 with muscle vasoconstriction as a marker, is also based on an extensive body of animal research. Anderson and Brady (11) cite research in dogs which leads them to conclude that behavioral states (e.g., shock avoidance) associated with activation of the skeletal-motor system lead to pressor responses mediated by increased cardiac output in the face of decreased peripheral resistance; while behavioral inhibition (e.g., during preavoidance) of the skeletal-motor system leads to increased blood pressure which is mediated solely by increases in total peripheral resistance. Based on observations of skeletal muscle vasoconstriction during alert observation of another cat and vasodilatation during attack, Zanchetti (12) also suggested the existence of a dual cardiovascular response pattern subserving emotional behavior:

"...one type (skeletal muscle vasoconstriction) being the usual companion of immobile confrontation of the preparatory stage, the other type (skeletal muscle vasodilatation) being characteristic of emotional movement (the classical 'defense pattern')."

Given that the existence of the qualitatively distinct skeletal muscle hemodynamic response patterns of vasodilatation and vasoconstriction which appear to characterize two general response patterns--pattern 1 and pattern 2--has been demonstrated in numerous experimental studies employing a diverse array of environmental stimuli in both humans and animals, our research group recently undertook a study (13) to characterize the neuroendocrine components of pattern 1 and pattern 2. Another purpose was to evaluate the effect of personality-related characteristics (Type A behavior pattern) and genetic factors (family history of cardiovascular disease) on the expression of the two response patterns.
To elicit pattern 1, we had 31 undergraduate males perform a mental arithmetic task with a prize to the best performer; and to elicit pattern 2, we had these same subjects perform a choice reaction time task. The tasks were presented in counterbalanced order on two separate occasions, at the same time of day, with a 1-week interval between the two experimental sessions. Hemodynamic measures taken during a 20-minute baseline period followed by a 20-minute task period included heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure and forearm blood flow (FBF); forearm vascular resistance (FVR) was calculated as the mean blood pressure divided by the FBF. In addition, a Cormed continuous exfusion pump was used to obtain integrated venous blood samples throughout the baseline and task periods. The plasma was spun down and frozen to be subsequently assayed for norepinephrine, epinephrine, cortisol, prolactin, growth hormone and testosterone.

The main results of interest are shown in figure 2. During mental arithmetic performance, a significant increase in FBF and a significant decrease in FVR were observed, indicating the expected skeletal muscle vasodilatation. With respect to neuroendocrine responses, there were highly significant increases in prolactin (not shown), norepinephrine, epinephrine and cortisol, while testosterone changed not at all. With the exception of prolactin, all three hormones which showed a significant increase showed significantly larger increases in Type A than in Type B subjects.

During reaction time performance, the pattern of responses was quite different. Overall, there was no change in FVR, a result largely accounted for by the failure of the Type A subjects to show the expected increase, which was observed in the Type B subjects. While norepinephrine showed a significant increase overall, the Type A and B subjects did not differ. In contrast to mental arithmetic, where epinephrine and cortisol were quite responsive, during the reaction time task these two hormones showed no change. Also in contrast to mental arithmetic, where testosterone was unresponsive, during reaction time performance a significant overall increase in testosterone was observed, and that of the Type A subjects was significantly greater than in the Type B subjects.
It was not surprising that epinephrine and cortisol increases were observed as components of pattern 1. Henry (14) has concluded on the basis of an extensive review of the stress literature that cortisol and epinephrine are released under conditions where the classical fight/flight response is activated, and at least one widely accepted situation where the muscle vasodilatation which is the critical marker for pattern 1 is observed is the defense reaction, or fight/flight response. Thus, our findings suggest that, along with the muscle vasodilatation, increased secretion of epinephrine and cortisol are also components of the pattern 1 response.

The increased testosterone response during the reaction time task is not as easy to interpret at the present time, although there are some intriguing clues as to why this hormone should be secreted under conditions requiring males to attend closely to environmental stimuli. In general, the stress literature suggests that with the exceptions of male sexual behavior and male-male dominance confrontations, the usual effect of stress on testosterone levels is to decrease them (15). There are animal studies, however, which suggest that administration of exogenous testosterone has the effect of increasing persistence in a task, as well as a focusing and narrowing of attention (16). Whatever else two males engaged in a dominance confrontation may be doing, they are certainly paying very close attention to one another. Thus, our finding of increased testosterone secretion during an experimental condition requiring close observation of environmental stimuli may be reflecting this hormone's function as a "vigilance hormone." Though it will be important to replicate this finding in further studies, our confidence that the testosterone response we observed is real is bolstered by the observation of Zumoff and coworkers (16) that Type A men excrete more testosterone glucuronide in urine during working but not nocturnal hours in comparison to Type B men.

If our findings are replicated, it would suggest that, in addition to the association of epinephrine and cortisol with pattern 1, a reliable neuroendocrine component of pattern 2 is increased testosterone secretion. Thus, it appears that the principle of integrated patterns of autonomic and neuroendocrine response that is part of the model shown in figure 1 has been supported by the study described above. Not only have qualitatively
distinct skeletal muscle hemodynamic components of two patterns been widely observed; qualitatively distinct patterns of neuroendocrine response have also been observed in association with experimental conditions known to elicit the muscle hemodynamic components.

In addition, there is evidence for the participation, also as suggested in the model, of personality factors in modulating the expression of patterns 1 and 2: Type A males showed greater secretion of cortisol and epinephrine during the condition known to elicit pattern 1, and greater secretion of testosterone during the condition used to elicit pattern 2. Finally, the role of the genes in modulating expression of patterns 1 and 2 also finds some support in the findings of the study cited. Among those subjects with a positive family history of hypertension, the Type A subjects showed a larger cortisol and DBP response to the reaction time task; while among those with a negative family history, the Type A subjects' cortisol and DBP responses were either smaller or not different from those of the Type B subjects.

It would be unwise, of course, to accept as final truth the interpretations I offer here for the findings of a single study involving such a small number of subjects. Replications are clearly needed. I have described these findings in detail, however, because they illustrate the principles advanced at the beginning of my presentation. First, physiologic responses to environmental stimuli occur in patterns; and we found discrete patterns of cardiovascular and neuroendocrine response to two different types of experimental conditions, as shown in figure 2. Second, whatever the ultimate number of such patterns that are found, there is much evidence for two patterns, one characterized by muscle vasoconstriction--pattern 2; and we found that when we used conditions shown in prior studies to elicit pattern 1 and pattern 2, not only the muscle hemodynamic but also the neuroendocrine responses were qualitatively different. The model also suggests that personality and genetic factors may modulate the brain's transduction of environmental situations into patterns of motor messages; and both Type A behavior pattern and family history of hypertension were found to affect and interact in affecting the responses observed. Thus, although more work will be required to be sure the specific details are
correct, the evidence from the study I have described is in strong accord with the principles which underly the model I have presented today.

Further support for the importance of what I have chosen to call pattern 1 and pattern 2 is to be gleaned from neurophysiological studies in animals relating to brain areas where stimulation leads to increased or decreased peripheral resistance due to muscle vasoconstriction or vasodilatation.

How (and When) Does the Brain Produce Pattern 1 and Pattern 2?

Electrical stimulation of points in the premotor cortex, the amygdala, the mesencephalic tegmentum and the central gray matter of the anesthetized cat have long been known to result in a pattern of cardiovascular adjustment characterized by increased cardiac output, vasodilatation in skeletal muscle and vasoconstriction in skin and viscera; moreover, stimulation of these same points in the awake animal results in motoric behavior indistinguishable from that seen during naturally occurring defense reactions (18). Stimulation of the hypothalamic defense areas in the monkey has also been shown to result in increased plasma corticosteroid levels (19). Thus, there is ample evidence that mammalian brains contain sites capable of producing the integrated pattern of cardiovascular and neuroendocrine response which our study (13) suggests is characteristic of pattern 1 in humans.

With respect to brain mechanisms responsible for the production of pattern 2, the evidence is much less extensive. I am indebted to James Henry, therefore, for calling to my attention a most interesting study by Stock and coworkers (20). In awake cats, stimulation of the basal amygdala resulted in a motoric behavior typical of the defence reaction which was associated with tachycardia and increased aortic blood flow measured distal to the renal arteries (and thus probably due to muscle vasodilatation in areas fed by the iliac arteries). This behavioral and cardiovascular response pattern, of course, is identical to that I just described relating to brain areas mediating pattern 1.
When the central amygdala is stimulated, however, a quite different pattern of responses is observed. Motorically the animal is alert and activated, but the ears are not flattened and the head is not retracted as with stimulation of the basal amygdala. This pattern was described as more similar to attack behavior. The cardiovascular response also differed from that seen with stimulation of the basal amygdala: instead of the decreased peripheral resistance secondary to muscle vasodilatation seen with stimulation of the basal amygdala, stimulation of the central amygdala led to a pressor response associated with increased peripheral resistance probably mediated by vasoconstriction in the iliac vascular bed.

While the basal amygdala appears associated with behavioral and cardiovascular adjustments characteristic of pattern 1, the central amygdala appears to be at least one brain area capable of producing behavioral and cardiovascular responses more characteristic of what I have been calling pattern 2. The case for the role of these two amygdaloid complexes in mediating the full blown expression of pattern 1 and pattern 2 as described in the preceding section will be greatly strengthened if further study shows stimulation of the basal amygdala to result in increased plasma epinephrine and cortisol and stimulation of the central amygdala to result in increased plasma testosterone.

Recent theorizing by Floyd Bloom and coworkers (21) about the functions of the locus ceruleus (LC) may provide additional insights regarding brain systems responsible for mediating the elicitation by environmental stimuli of the pattern 2 response. The LC is a collection of adrenergic cell bodies located near the wall of the fourth ventricle at the level of the pons. It is known to supply most of the noradrenergic (NE) innervation to the entire cerebral cortex and cerebellum and much of the noradrenergic innervation of the hypothalamus.

Based on their exhaustive review of the literature pertaining to the anatomic projections, physiology and function of the LC-NE system, Bloom and colleagues conclude that this system "acts at many target sites to somehow enhance the reliability and efficiency of feature extraction from sensory input" (21, p. 899). Among the lines of evidence cited in drawing
this conclusion: 1) in monkey, LC-NE discharge increases with orientation toward a syringe filled with a favored drinking solution; 2) in rat, behaviors associated with decreased vigilance--e.g., grooming--result in reduced LC-NE discharge; and 3) in both rat and monkey the most intense activity in LC-NE neurons was observed at times when "surveillance of the external environment (i.e., vigilance) is suddenly and dramatically increased" (21, p. 873). The interpretation given these findings is worth quoting:

"Thus it would appear that LC-NE neurons vary their spontaneous activity in relation to vigilance levels. Increased vigilance, as during spontaneous or sensory-evoked arousal or during orientation to an unexpected or preferred stimulus, is associated with tonically enhanced LC-NE discharge, whereas decreased levels of vigilance, as during sleep, grooming or consumption behaviors, correspond to periods of diminished activity in the LC." (21, p. 873)

Given the apparent involvement of the LC in vigilance behaviors, and the association of stimulation of the central amygdala with increased vigilance and increased peripheral resistance, it is noteworthy, therefore, that an LC projection to the central amygdala has been described (22). These observations suggest that the LC-NE system may play an important role in mediating the motoric and physiological manifestations of pattern 2, when that pattern is elicited by environmental stimulation. Supportive of such an hypothesis is the observation that NE neurons originating in the LC are responsible for peripheral sympathetic nerve response of two rats to shock induced fighting, but not the adrenal medullary response to footshocks when administered to one rat (23).

While much of the evidence cited above is circumstantial, it does make the rather strong case that plausible brain mechanisms do exist whereby the behavioral and physiologic manifestations of pattern 1 and pattern 2, as I have described can be produced. In addition, this evidence contains some clues as to the specific types of environmental situations which elicit these two response patterns.

Finally, this evidence highlights the important principle suggested by the model in figure 1, that motoric behaviors (such as fight/flight or tonic immobility) do not themselves "cause" autonomic and neuroendocrine responses. Rather, it appears that along with autonomic and neuroendocrine
responses, the motoric behaviors are but a third component of the integrated patterns of response which result from the brain's interpretation and transduction of environmental events.

What are the Adequate Stimuli for Patterns 1 and 2?

I have saved the hardest for last. To draw firm conclusions regarding the nature of effective stimuli for eliciting patterns 1 and 2 is hard because so much of the research upon which we must base answers to this question is fragmented and incomplete. This is because a single study to answer this question would have to sample many physiologic parameters in many types of subjects under many types of conditions. And that is just the easy part; the hard part is that they must be the right parameters in the right types of subjects under the right conditions. The sheer logistic task of finding enough body surface for the electrodes, strain gauges, transducers and intravenous and, possibly, intraarterial needles that would be required makes it unlikely that the ideal study in this area will ever be done.

Nevertheless, the extensive research that has been done contains many clues, and it may be possible to begin to answer this question by recalling the experimental conditions, in both human and animal studies, that have been found to elicit one or another response component of pattern 1 and pattern 2.

With respect to pattern 1, the following have been reported to elicit muscle vasodilatation, epinephrine and cortisol responses or both: 1) situations which elicit fight/flight or defense behavior, such as mental arithmetic with harassment (6); 2) mental work, such as mental arithmetic without harassment (9) or word association testing (24); 3) active, effortful coping, such as shock avoidance in humans (4) and animals (11); and 4) uncontrollable aversive stimulus situations (25).

I am sure I have inadvertently left out other, potentially important examples of experimental behavioral challenges which have been reported to elicit one or more components of what I have called pattern 1. Nevertheless, the cited examples do contain some common elements.
Certainly, situations that induce fear or anxiety appear capable of eliciting pattern 1, and the muscle vasodilatation, increased cardiac output and associated neuroendocrine components would appear adaptive--i.e., they might confer some survival advantage--when the effectiveness of fight or flight behavior might determine whether the organism lives or dies.

But why would simple mental work also elicit pattern 1? I have no ready answer, but would like to speculate that perhaps mental work, thinking, if you will, evolved from the motor functions of the brain. If so, then it is possible that intense "mental" effort activates the same motor systems in the brain that subserve intense "motor" effort. If so, this linkage, possibly a vestigial one, would explain why and how hard mental work produces the same physiologic response pattern as hard physical work. This linkage may not be vestigial, however, in that the neuroendocrine components of pattern 1--e.g., epinephrine and ACTH--may actually facilitate such aspects of thinking as cortical activation and memory consolidation.

What are the conditions which have been reported to elicit pattern 2? Again, while surely incomplete, the following list contains some representative examples of studies in which muscle vasoconstriction (either directly measured or inferred from other measures), testosterone secretion, or both have been observed: 1) passive coping, as in watching a pornographic movie (4); 2) sensory intake, as in reading words projected upside down and out of focus (9); 3) alert immobility, as during a preavoidance period in the dog (11); 4) vigilant observation of another animal who appears about to attack (12); 5) male-male dominance confrontations (15); and 6) under some conditions, shock-induced fighting in the rat (23).

As with those conditions which have been reported to elicit elements of the pattern 1 response, there are also common threads which seem to tie together those conditions cited above as eliciting the pattern 2 response. Whether under emotionally arousing conditions (e.g., male-male confrontation and shock-induced fighting) or under relatively nonarousing
conditions which appear to elicit pattern 2 responding have in common the element of attentive observation of some aspect of the environment.

To paraphrase Paul Obrist (4), so much in science is rediscovery. Beginning well over two decades ago, the Laceys (26) were calling our attention to the importance of mental work and sensory intake as two classes of behavior which are associated with different patterns of somatic and physiologic responses. To the extent that pattern 1 and pattern 2, as I have described, are ultimately recognized as valid ways of conceptualizing reactivity, and to the extent that mental work and sensory intake are at least among the key behaviors eliciting pattern 1 and pattern 2, respectively, the Laceys deserve much credit for calling our attention to these phenomena. In any event, I should like to give them much credit for informing my thinking on these matters.

How Do Pattern 1 and Pattern 2 Lead to Cardiovascular Disease?

By now I suspect you feel there is more than enough to think about without having to ponder how this all relates to the etiology and pathogenesis of cardiovascular disease. I agree! Therefore, I shall leave it to others to confront this thorny question. My own thoughts on this issue are presented elsewhere (27). Beyond that, I can only leave it as an exercise for you to draw your own conclusions as to implications of what I have said for causal mechanisms.

Summary and Conclusions

Reactivity might be understood as a process whereby the brain interprets environmental events and, based on the outcome of that interpretation, sends a pattern of somatomotor, autonomic and neuroendocrine "motor messages" to target organs in the body. This transduction process is modulated by the past history (as reflected in the personality) and genetic make up of the individual. There may be only a limited number of patterns of response associated with psychosocial (as opposed to physical stimuli, such as exercise, diving, and digesting a meal) stimuli. I have
described two such patterns today, along with possible mechanisms whereby they are produced by the brain.

I have tried in this presentation to summarize what to some may be a bewildering array of complex data. No doubt I have made inferential leaps with which some may justly quarrel. I hope that I have brought some order to the complexity, and that where I may have erred, you will at least be stimulated to ponder what I have said and collect the data necessary to set it right.

For those who might like a summary of the key points made herein regarding patterns 1 and 2, I offer for your perusal table 1. I welcome efforts to correct the errors and, especially, efforts to fill in the gaps.

REFERENCES


FIGURE 1. Theoretical model illustrating how personality factors, environmental events and genes interact via the brain's transduction to produce integrated patterns of physiologic response.
FIGURE 2. Patterns of physiologic response observed during reaction time task performance and mental arithmetic performance. (Adapted from 13).
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<th>CHARACTERISTICS</th>
<th>PATTERN 1</th>
<th>PATTERN 2</th>
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<td>Increased (&quot;fight/flight&quot;)</td>
<td>Decreased (but alert)</td>
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<td>Cardiovascular</td>
<td>Muscle vasodilatation</td>
<td>Muscle vasoconstriction</td>
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<td></td>
<td>Increased cardiac output</td>
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<td>Neuroendocrine</td>
<td>Increased epinephrine, cortisol and prolactin</td>
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<td>Effective eliciting stimuli</td>
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IMPLICATIONS FOR ATEROGENESIS

Thomas B. Clarkson

The kinds of implications that cardiovascular reactivity may have for aterogenesis have been a matter of concern to us for the past several years, and we have done much thinking about it, both from a behavioral and a pathogenesis point of view. For the past two or three decades one of the most puzzling problems to those of us in atherosclerosis research has been to understand why some individuals with heavy loads of the traditional risk factors are relatively spared from atherosclerosis while other individuals lacking such heavy loads of traditional risk factors may be markedly affected with atherosclerosis. Research workers concerned with the plasma lipoproteins have attempted to understand this paradox by studying the relative atherogenecity of various lipoprotein particles. With all of their efforts and all of their major advances, however, they are able tonly to explain about half of the variability in the extent and severity of atherosclerosis. Attempts to understand explanations for this other half of variability in the extensiveness of atherosclerosis represent one of the most important of the research areas in our field.

On the basis of the work by Henry McGill and his colleagues, both with the International Atherosclerosis Project and the New Orleans Community Pathology Project, we now understand that atherosclerosis begins in childhood. It is believed that the childhood lesions of atherosclerosis are fatty streaks, and that during the years following puberty fatty streaks are slowly transformed into fibromuscular plaques. Many believe that sometime between the teenage years and early adulthood years the amount of atherosclerosis that a person will ultimately develop is already determined. The fibromuscular plaques of atherosclerosis tend to remain quiescent in most individuals till sometime between age 45 and 65 years, at which time the plaques may become complicated and lead to the clinical disorders of myocardial infarction, stroke, gangrene of the extremities, or to abdominal aorta aneurysms. The natural history of atherosclerosis as I have explained it is what happens to the average North American. There is considerable variability in the rate in which these events progress, and as
I have indicated, some of the factors that determine those rates are understood and many are not.

Some studies, such as those conducted in Oslo, have attempted to relate adult plasma cholesterol concentrations to the extent and severity of coronary artery atherosclerosis determined at autopsy among human patients. While the association between plasma cholesterol concentration and the extensiveness of coronary artery atherosclerosis is statistically significant (with correlation coefficients usually around \( r = 0.4 \)), many individuals with moderately elevated plasma cholesterol concentrations have little or no coronary artery atherosclerosis and other individuals have extensive coronary artery atherosclerosis. Such variation in susceptibility is clearly evident at plasma cholesterol concentrations of 280 to 320 mg/dl and remains evident even at plasma cholesterol concentrations exceeding 400 mg/dl.

We have made a large attempt to determine and to understand the differences among nonhuman primates with elevations of the traditional risk factors in extensiveness of coronary artery atherosclerosis. It is clear to us that the macaques, both rhesus and cynomolgus macaques, resemble human primates very closely in this poor association between coronary artery lesions and the traditional risk factors. The association between lesion extent and elevated low density lipoprotein cholesterol concentrations, or with lowered high density lipoprotein cholesterol concentrations, is of a low order as is seen in human beings. Like the people of Oslo and elsewhere, there are individuals with elevated plasma cholesterol concentrations that have minimal coronary artery atherosclerosis while others have large lesions, and conversely there are monkeys with low plasma lipids that may have extensive lesions. Much of our recent research has been to determine the extent to which psychosocial factors may provide an explanation for this previously unexplained variability.

In our pursuit of psychosocial influences on atherogenesis of nonhuman primates, I am deeply indebted to my colleagues, Dr. Jay Kaplan and Steve Manuck for providing outstanding leadership in behavioral medicine, and I hope along the way that I have been able to provide them with some better
understanding about the pathogenesis of atherosclerosis. In our earlier experiments we utilized cynomolgus macaques and examined the question of whether social stability and social instability influence the extensiveness of coronary artery disease in these animals. We found a major interaction between social environment and the personality type of the animals. Dominant animals, for example, in a socially stable environment were found to have lessened coronary atherosclerosis; on the other hand, equally dominant monkeys in socially unstable conditions were found to have exacerbated coronary atherosclerosis.

We have also examined the question of whether cardiovascular reactivity affects atherogenesis in cynomolgus macaques. We used heart rate reactivity in response to a stressful situation as an indication of the animal's own level of reactivity. Animals were evaluated after consuming an atherogenic diet and before necropsy, and reactivity was related to the amount of coronary artery atherosclerosis. We found that high responders had considerable coronary atherosclerosis, low responders had minimal lesions, and moderate responders had moderate amounts of coronary atherosclerosis. We now believe that our data suggest to us that a fairly large component of this unexplained variability can be explained on the basis of reactivity. We now believe that the challenge for us and for others is to understand how this effect is mediated.

Russell Ross and John Glomset of the University of Washington reintroduced in 1976 a very old hypothesis about the pathogenesis of atherosclerosis in which it was speculated that "arterial injury" was important in lesion initiation and in the progression of lesions. Based on work at many other institutions and particularly the contributions of Dr. Steve Schwartz at the University of Washington, we now have a fairly clear view of the role of arterial injury in atherogenesis. When the arterial endothelium is injured, cells die and are replaced by a process that has come to be known as nondenuding desquamation. The process is one in which endothelial cells die and without leaving an area of desquamation are squeezed out into the circulation by the replication of cells immediately adjacent to them. We believe that there is strong emerging evidence that reactivity is having its action on atherogenesis by way of endothelial injury and the many
things that endothelial injury does in hastening the progression of atherosclerosis.

The exact way in which reactivity injures the endothelium is not known, but it now seems clear that one of the most injurious things to the endothelium is transient increases in blood pressure. My colleague, Eugene Hirsh, from Cleveland has shown that fighting rats have marked elevations in their endothelial cell death rate, and his results along with other studies done by John Guyton and his colleagues have provided additional evidence of endothelial injury among rats exposed to a conditioned avoidance program.

Approaches to studying endothelial injury and endothelial cell turnover rates have improved greatly in recent years. The approach that we use in our laboratory was taught to me by my good friend, Steve Schwartz, from Seattle. Before an animal is necropsied, radioactive thymidine is given so all the endothelium cells that are replicating will take the label, and if you fix the artery properly, coat it with photographic emulsion, and then examine it under a scanning electron microscope, you can see the radioactive nuclei and by calculating the proportion of endothelial cells in the surface of an artery that are replicating, the endothelial cell turnover rate can be determined, and that is directly comparable to the rate in which endothelial cells are dying. The endothelium of arteries is ordinarily a very stable piece of tissue, having a half-life of 7 or 8 years. When you injure the arterial endothelium with things like transient increases in blood pressure that occur with periods of intense psychosocial stress, endothelial cells can turn over in a matter of days.

Based on our current understanding of reactivity and our understanding of the role of endothelial injury in the pathogenesis of atherosclerosis, a reasonable working hypothesis can be set forth. That working hypothesis would be that cardiovascular reactivity, probably by way of transient elevations in blood pressure injures the endothelium. With injured endothelium there is increased permeability of the artery wall to the plasma lipoproteins, there are newly generated endothelial cells, which by liberation of various factors can cause multiplication of the smooth muscle cells beneath it with disturbed lipid metabolism and lipid accumulation in
those intimal smooth muscle cells. I think it is a very exciting time ahead, in that we are now able to look at cellular events in animals with defined psychological pertubations. I am looking forward to a rewarding association between behavioral scientists and atherosclerosis research workers in unraveling some of these exciting problems.
It is well established that behavioral stimuli often evoke substantial responses of the autonomic and neuroendocrine systems, and that the magnitude of such responses varies significantly among individuals. The latter observation, regarding individual differences in psychophysiologic reactivity, reflects a topic of longstanding interest in the investigation of psychosomatic disorders. This interest has grown appreciably in recent years, particularly in relation to cardiovascular and catecholamine reactions to psychological stressors. Indeed, it has been proposed that an exaggerated physiologic responsivity to behavioral challenges may be implicated in the development or clinical expression of major cardiovascular disorders, such as coronary heart disease (CHD) and essential hypertension (1-4). Also, several plausible hypotheses for a reactivity-disease link have now been advanced, and much indirect—but suggestive—data collected. In this regard, the purpose of the present paper is to summarize pathogenetic hypotheses relating individual differences in acute psychophysiologic reactivity to CHD and hypertension, and to review briefly available data relevant to such associations.

General Considerations

It may first be useful to discuss the concept of psychophysiologic reactivity as it may be associated with cardiovascular disease. Most epidemiologic associations are based on assessment of the "casual" or resting levels of suspected risk variables (e.g., clinical evaluations of blood pressure). Measurement of psychophysiologic reactivity, however, involves the assessment of changes in physiologic parameters which occur when individuals are exposed to behavioral or psychological challenges. Since the magnitude of such changes usually cannot be inferred from resting (baseline) levels of these variables, reactivity measurements often contribute unique information on the physiologic functioning of the individual. It has been hypothesized further that, insofar as acute
reactions observed in the laboratory also reflect responses to challenges encountered in daily life, evaluation of psychophysiologic reactivity may provide additional—and perhaps more useful—indicators of pathophysiologic processes than do measurements recorded under resting or casual conditions (2).

A critical question underlying the value of acute measures of reactivity concerns the extent to which laboratory-based measurements generalize to nonlaboratory settings. That is, do individual differences in cardiovascular and/or neuroendocrine responses to standardized test stimuli predict responsivity to naturally occurring stressors? Unfortunately, this question has not yet been addressed in any detail, either empirically or conceptually. However, such generalization could occur in a number of different ways. One possibility is that persons who show exaggerated physiologic responses to laboratory stressors (so-called "hyperreactors") exhibit similarly exaggerated reactions to events occurring in day-to-day activities, whereas individuals who show little reactivity in the laboratory ("hyporeactors") may, in life, experience small or only moderate physiologic reactions to stress. Thus, daily life for the hyperreactor may be accompanied by repeated episodes, or occurrences, of acute physiologic arousal which resemble in their magnitude responses exhibited in the laboratory.

This lab-life relationship—which we will call the "recurrent activation model"—is illustrated in the stylized drawing in figure 1. In the upper and lower panels of this figure are depicted a prototypic hyper- and hyporeactor. For illustrative purposes, heart rate is listed on the ordinate as the physiologic parameter of interest, though any other response measure (i.e., blood pressure, plasma epinephrine or norepinephrine) could be placed in its stead. Note that "real life" in these two individuals is occasioned by repeated episodes of physiologic reactivity which are similar to their corresponding responses in the laboratory. Although reactions seen out of the laboratory will vary in magnitude, depending on the nature of the precipitating stimulus or environmental event, by this model the ordered relationship between individuals is retained.
Recurrent activation is perhaps the most commonly held hypothesis regarding the generalization of individual differences in psychophysiologic reactivity. It is also based, in part, on the assumption that baseline values recorded in the laboratory reflect a common or usual state of organism. Hence, it follows that daily challenges outside the laboratory will precipitate repeated, transient episodes of reactivity (i.e., acute changes from baseline).

It is possible, however, that baseline, or resting measurements represent the more anomalous states of the organism and are observable in a laboratory setting only due to investigators' exceptional efforts to establish a rested condition in their subjects and a relatively stimulus-free environment. Of course, these values still have meaning as baseline measurements, since they indicate what the subject's physiologic state tends to be in the absence of notable behavioral stimuli. Yet, this state might occur quite infrequently during the preponderance of waking hours, when individuals may be continually engaged in significant activities (e.g., work demands) and interactions with other people.

Seen in this context, measurement of a reactive state of the individual in the laboratory might be achieved more easily than baseline evaluations, since the former only requires providing a life-like behavioral challenge. In turn, this reactive state (as suggested above) may also reflect the condition most frequently experienced in daily life. If so, measurement of psychophysiologic reactivity in the laboratory will be more predictive of physiologic states prevailing throughout the waking, active hours of the day than it is of transient episodes of acute arousal. This relationship is illustrated in figure 2 and labelled the "prevailing state model."

These two formulations--recurrent activation and prevailing states--are probably oversimplifications, and some combination or neither may reflect the true generalization of laboratory assessed reactivity. Yet to evaluate reactivity-disease relationships, it is critical to determine how psychophysiologic reactivity finds expression in the lives of individuals; after all, it is during the course of daily activities--and not in the laboratory--that cardiovascular disorders develop. The nature of this
generalization from laboratory to life is important, too, for the types of associations we may wish to explore in relating the reactivity construct to disease endpoints. Pathogenetic formulations hypothesizing relatively persistent states of sympathetic arousal (e.g., Esler et al. [5]), for example, are generally more compatible with a prevailing state model than with notions of generalization based on recurrent and transient activation.

In the preceding paragraphs, we have focused on one issue that illustrates the assumptions of hypotheses implicating idiosyncratic autonomic and neuroendocrine responses in the pathophysiology of cardiovascular disease. Of course, there are many other such issues, including the stability over time (or reproducibility) or individual differences in reactivity, the importance of situational or task influences on the measurement of psychophysiologic responses, influences of subject characteristics (e.g., age, gender, coping styles) on responsivity, and the applicability of common test protocols to various population-based epidemiologic investigations. While substantive consideration of these additional matters is beyond the scope of this paper, an extensive discussion of methodologic and conceptual issues relevant to the study of psychophysiologic reactivity can be found in a recent review by Krantz and Manuck (2). In the remainder of the present paper we will consider, more specifically, the relationship of individual differences in behaviorally induced physiologic reactivity to risk for coronary artery atherosclerosis, CHD and essential hypertension.

Behavioral Factors in CHD

In addition to the standard risk factors for coronary disease (viz., hypercholesterolemia, arterial hypertension, cigarette smoking), psychosocial factors have also been implicated in the pathogenesis of CHD. While there is currently some uncertainty regarding the consistency of reported epidemiologic associations (6), the so-called Type A, or coronary-prone behavior pattern, has figured most prominently among the many psychosocial variables that have been investigated (7). Briefly, the Type A pattern is characterized by extremes of competitiveness, a chronic sense of time urgency, and easily evoked hostility. A contrasting Type B
pattern is defined as the relative absence of these attributes, and consists of a different style of coping with challenge. Regarding the Type A-B construct, a variety of studies--most notably, the Western Collaborative Group Study (8)--have provided evidence that Type A individuals are more likely than Type Bs to develop clinical CHD. Of the various Type A characteristics, moreover, recent studies suggest that aggressiveness, or a high "potential for hostility," may be especially important (9-11). Some, though not all, investigators have also demonstrated relationships between these behavioral characteristics (e.g., Type A, hostility) and coronary artery atherosclerosis, as revealed on angiographic examination (e.g., 10-13).

It is commonly thought that behavioral factors influence the development of CHD through the cardiovascular or endocrine correlates of sympathetic-adrenal-medullary and pituitary-adrenal-cortical activity. One proposed mechanism is that repeated physiologic reactions involving excessive heart rate and/or pressor responses to behavioral stressors promote arterial injury through hemodynamic forces such as turbulence and sheer stress (14). Alternatively, biochemical sources of injury may follow from an increased output of certain endocrine substances, such as catecholamines and corticosteroids, which may exert toxic influences on the coronary arteries. Additionally, increased levels of circulating catecholamines may affect coronary atherogenesis in an indirect manner, as through influences on platelet aggregation and on the mobilization of serum lipids (3,15). Data indicating that acute behavioral stressors can lower thresholds for ventricular fibrillation suggest, further, that disruption of the central nervous control of the heart may be implicated in the initiation of arrhythmic activity, hence potentially, precipitation of sudden cardiac death (3). (Comprehensive discussions of possible mechanisms mediating behavioral influences in CHD can be found in a number of recently published reviews [e.g., 3,4,15]).

Psychophysiologic Reactivity in CHD

If the foregoing physiologic mechanisms (i.e., sympathetic and adrenal-cortical activity) contribute to coronary artery disease or its
clinical sequellae, this contribution would presumably be greatest among individuals exhibiting the most pronounced psychophysiologic responsivity (i.e., hyperreactors). What is the evidence, then, that individual differences in behaviorally induced autonomic and neuroendocrine reactivity are associated with CHD? In addressing this question, several types of evidence can be marshalled: 1) data obtained from appropriate animal models, 2) findings of both prospective and case-control investigations involving human subjects, and finally, 3) results of experimental studies examining the physiologic correlates of coronary-prone behaviors.

With respect to animal models, there is currently one published study of specific relevance (14). In this investigation, cynomolgus monkeys fed a moderately atherogenic diet for 22 months were identified as either "high" or "low" heart rate reactive animals, based on their responses to a standard laboratory stressor (threat of capture). Following necropsy, the high heart rate reactive animals were found to have developed nearly twice the coronary atherosclerosis of their low heart rate reactive counterparts. Interestingly, high heart rate reactors were also those animals which had exhibited the greatest aggressive tendencies during social interactions with other monkeys, a finding which is consistent with recent evidence (noted above) relating to behavioral precursors of CHD in human beings (9-11).

There is also one published prospective study bearing on the reactivity-CHD relationship in humans (16). In this study, it was found that the magnitude of subjects' diastolic blood pressure responses to cold immersion (the cold pressor test) was associated significantly with development of CHD following a 23-year followup. Indeed, the prediction of subsequent disease from subjects' diastolic reactivity to the cold pressor test in this investigation exceeded associations based on many of the more traditional risk factors.

A few retrospective, or case-control, studies contrasting the psychophysiological responses of persons with and without CHD have also been reported (e.g., 17-22). Most of these investigations demonstrate a heightened reactivity to laboratory stressors--usually, increased blood
pressure responses—in patients with histories of angina or previous infarction, when these subjects are compared with noncoronary patient samples or nonpatient controls. The experimental tasks employed have generally involved either interpersonal challenge (e.g., the structured interview for Type A assessment) or relatively demanding tests of subjects' cognitive abilities (e.g., mental arithmetic, Raven's progressive matrices). However, a number of these studies may be faulted on methodologic grounds, such as failure to control for the medication status of coronary patients and for the presence of other chronic disorders known to affect vascular responses (e.g., essential hypertension). Also, virtually no association between behaviorally elicited cardiovascular reactivity and extent of coronary atherosclerosis is reported in one recent study of patients undergoing diagnostic angiography (19). Overall, then, case-control studies provide suggestive evidence, yet findings reported in this literature are not entirely consistent and the studies themselves are few in number and of variable quality.

As noted, a final source of data concerns the autonomic and neuroendocrine response characteristics of persons at behavioral risk for CHD—that is, Type A individuals. This line of investigation is encouraged by the observation that influences of Type A behavior on CHD have been largely independent of the concomitant effects of other major risk factors, such as serum cholesterol, hypertension, smoking and age (6). There are now approximately 40 published studies comparing the physiologic responses of Type A and Type B subjects to diverse psychological and physical stressors. Subjects employed in these investigations range from children, adolescents and college students, to working class and professional adults, and coronary disease patients. In about 70 percent of studies, Type A subjects are found to exhibit larger increases in blood pressure, heart rate and plasma catecholamines and/or cortisol, relative to Type Bs, when exposed to appropriately stressful laboratory tasks. These effects are seen most consistently where subjects are faced with threat of failure, harassment, or competitive task demands, during interpersonal interactions, and when instructional sets are designed to assure high levels of task involvement (2).
Still, several well-conducted studies fail to replicate associations between Type A behavior and indices of reactivity. In this regard, differing methods of assessing the Type A pattern seem to be of some importance; this is especially true of adult samples, where response differences between Type A and B subjects have emerged most frequently in studies employing the interview technique for Type A evaluation, rather than more commonly used questionnaires (17). Other factors, such as the presence or absence of a family history of cardiovascular disease, various demographic variables, and the gender-appropriateness of experimental tasks, also appear to modulate Type A-reactivity associations (23, 24), and may account, in part for inconsistencies in this literature. Nonetheless, it is reasonable to conclude from existing findings that Type A individuals do experience somewhat greater autonomic and neuroendocrine responses than their noncoronary-prone, Type B counterparts, at least when encountering some types of laboratory stimuli. (Several comprehensive reviews of this literature have been published recently [25-28].)

Psychophysiological Reactivity in Hypertension

In addition to the preceding literature relating to CHD, there is also a long history of research on the psychophysiological correlates of essential hypertension. Hypertensive patients, for example, have often been found to exhibit larger blood pressure and/or heart rate responses to common laboratory stressors than normotensive controls. Such differences have been observed during experimentally elicited emotions of fear and anger (29), during conflict-laden interviews (30), on performance of frustrating cognitive tasks (e.g., 31-33), and, somewhat inconsistently, during the cold pressor test (33). More recent evidence suggests that this increased reactivity among hypertensive individuals depends, in part, on the nature of eliciting stimuli. Steptoe, Melville and Ross (34) report, for instance, that hypertensive subjects showed greater pressor responses than normotensives during tasks requiring active coping (such as video games and the Stroop color-word interference task), but not during passive exposure to a disturbing film. Drummond (35) also reports that hypertensive patients exhibited greater elevations in systolic and diastolic blood pressure under mental arithmetic, but not during the cold pressor test, in
comparison with normotensive controls. The passive aspect of the cold pressor test may account as well for inconsistent findings among the many investigations which have employed this stimulus alone (e.g., 33,36,37). Finally, Sullivan, Procci, DeQuattro et al. (38) report that among patients with primary hypertension, heightened systolic reactions to stress were observed only in subjects who also scored highest on psychometric indices of anxiety and anger.

Another literature examines the psychophysiologic response characteristics of normotensive individuals who differ by the presence or absence of a family history of essential hypertension. In common with hypertensive patients, offspring of hypertensives also exhibit increased blood pressure and heart rate responses to laboratory stressors (e.g., 39-42). Here, too, situational variables and subjects' emotional reactions play an important role in eliciting an increased reactivity to behavioral stimuli. For example, Hastrup et al. (4) compared the physiologic responses of sons of hypertensive and normotensive parents to shock avoidance and cold pressor tests (i.e., active and passive coping tasks). This study revealed appreciable group differences in heart rate and systolic pressor responses, but only during the avoidance task. In addition, Manuck, Proietti, Rader and Polefrone (43) report that while heart rate elevations during mental arithmetic were significantly larger in persons having hypertensive parents, this relationship emerged only among subjects experiencing the greatest anxiety and/or anger while performing the experimental task. Taken together, the foregoing findings suggest that hypertensives and persons at familial risk for hypertension possess a heightened cardiovascular response potential, but express this underlying hyperreactivity in relation to situational demands or to concomitant affective responses.

Implications for Hypertension

As in CHD, it is yet unclear what relevance transient episodes of acute cardiovascular arousal, such as those observed in the laboratory, have for an understanding of essential hypertension. However, several possibilities have been suggested. First, in persons who are hypertensive, large pressor
responses to behavioral challenges may be of some significance clinically, since these reactions are superimposed upon an already elevated arterial pressure. If occurring frequently, for example, such responses might accelerate development of vascular and end-organ complications, and in persons with existing coronary disease, lead to increased risk of acute, clinical events (e.g., angina pectoris, myocardial infarction) (44-46). Particularly relevant in this respect are observations by Devereux, Pickering, Harshfield et al. (47) that ambulatory blood pressure assessments during work stress correlated more highly with left ventricular hypertrophy in hypertensive patients than did blood pressure measurements obtained in the clinic or during more quiescent hours of the day. As described previously, moreover, there is evidence from recent animal work that individual differences in cardiovascular response to behavioral stressors are implicated in the development of coronary and cerebral artery atherosclerosis in cynomolgus monkeys (14,48); interestingly, this association was found, in the carotid arteries, only among animals whose systolic blood pressures fell at the upper end of the normal distribution.

Perhaps most controversial is the hypothesis that hypertension may arise from the repeated elicitation of large cardiovascular responses to psychological stressors. In this regard, Obrist (49) has suggested that the markedly increased cardiac output exhibited under stress by highly reactive individuals may, with sufficient time, lead to increased resistance in the peripheral vasculature through structural changes in the arterioles (e.g., smooth muscle hypertrophy) (50) or by intrinsic autoregulatory processes acting to prevent an overperfusion of body tissues (e.g., 51). Obrist appears to favor the autoregulatory mechanism since, in many behavioral situations, an elevated cardiac output will supply $O_2$ levels beyond concurrent metabolic demands (52,53). It should be noted, however, that autoregulation, as a transitional mechanism between the borderline and established phases of hypertension, is itself controversial. For example, it has been suggested that since cardiac output and $O_2$ consumption are often elevated among borderline hypertensives, the increased output is not in disproportion to metabolic demand (e.g., 54). In rebuttal though, Obrist and colleagues (55) note that: (a) such findings are usually found in studies of resting state hemodynamics, where
stress-induced sympathetic, myocardial influences are minimal; and (b) the arteriovenous $O_2$ content difference (i.e., relative $O_2$ extraction) may be reduced even in persons exhibiting an increased cardiac output and higher $O_2$ consumption (56,57).

Recently, Julius and colleagues (58) proposed a second model of psychophysiologic influences in hypertension. Julius suggests that certain well-established behavioral characteristics--such as sociability, sensitivity and submissiveness--generate "...a near permanent state of enhanced alertness" (59). This heightened vigilance is accompanied by disruption, or alteration, of centrally integrated cardiovascular autonomic tone. The initial consequence of this autonomic alteration is, in part, an increased sympathetic drive on the heart, with concomitantly elevated cardiac output. Julius hypothesizes, further, that continued sympathetic stimulation in these individuals leads ultimately to down regulation of adrenergic receptors in the heart, and possibly myocardial structural changes, which then result in decreased cardiac responsiveness and lowered (or normalized) cardiac output. At the same time, development of hypertrophic resistance vessels, with altered wall-to-lumen ratios, may lead to an increased vascular responsiveness (and hence, increased resistance).

Julius' model differs from that of Obrist in at least three respects. First, the altered cardiovascular autonomic regulation suggested by Julius requires a relatively persistent sympathetic discharge. In contrast, Obrist's model presumes that the cardiovascular hyperreactivity of persons susceptible to hypertension is manifested in daily life as repeated episodes of acute and transient sympathetic arousal. Julius' proposal is compatible with a reactivity hypothesis, then, only to the extent that lab-to-life generalization of reactivity resembles what was earlier termed the prevailing state model--that is, where a heightened cardiovascular reactivity observed in the laboratory is most predictive, in daily life, of physiologic states prevailing during the preponderance of waking and active hours. A second distinction is that Julius proposes that the autonomic characteristics of borderline hypertensives are a reflection of specific behavioral attributes of these individuals. Obrist's hypothesis suggests
that behavioral events act as stimuli for the expression of an increased sympathetic reactivity, but does not assume that this hyperreactivity is also behavioral in origin. Finally, unlike Obrist, Julius' model does not invoke autoregulation in accounting for the transition from borderline to established phases of hypertension.

In both of these models, autonomic influences (with or without a behavioral correlate) are seen as a "triggering" mechanism in the pathogenesis of hypertension. Although von Eiff (60) has reported a correlation between the magnitude of blood pressure elevations seen during mental arithmetic and subsequent rises in children's casual blood pressures, there are yet no studies of a longitudinal nature following prehypertensive individuals through the development of borderline and established hypertension. Hence, prospective data supporting a reactivity-hypertension progression are currently lacking in this literature.

Of course, another possibility is that the apparent hyperresponsivity of hypertensives and of persons at risk for hypertension is not a participant in the sequence of events leading to essential hypertension. A common central nervous system disruption of autonomic control over the heart and vasculature, for example, may account for both the greater cardiovascular reactivity of hypertensive patients and their elevated blood pressures. In this case, a hyperreactivity to psychosocial stimuli in normotensive individuals might be predictive of later hypertension, but play no direct or causal role in development of the hypertensive condition.

Finally, a last avenue of speculation pertaining to psychophysiologic factors in hypertension is suggested by Light, Koepke, Obrist and Willis (61). Light and colleagues propose that autonomic mechanisms may contribute to hypertension through disruption of the regulation of blood volume and the control of blood pressure by the kidneys. This hypothesis is consonant with Guyton's notions concerning the importance of the kidneys in any long-term regulation of arterial pressure. Moreover, recent evidence suggests that behavioral stressors can exert substantial influences on renal functioning. For instance, Grignolo, Koepke and Obrist (61) reported that shock avoidance induces significant sodium and fluid
retention in dogs, especially among those animals exhibiting the greatest heart rate elevations during avoidance procedures. Sodium retention in this animal model is apparently a result of increased reabsorption of sodium in the renal tubules and reflects sympathetic influences on renal nerve activity. That these observations may have specific relevance for human studies is indicated by findings of Light et al. (61), who report that laboratory tasks involving competitive challenge similarly elicited decreased sodium and fluid excretion in many normotensive, young adult males. Yet, interestingly, these effects occurred only in individuals who (a) showed the greatest heart rate reactivity to the experimental task; and (b) had either borderline systolic hypertension or a familial predisposition to hypertension. In addition, these effects persisted well after termination of the experimental stressor, where they were accompanied also by marginal elevations in blood pressure (63). Thus, heart rate reactivity—as an individual differences variable—appears to be associated with a decreased excretion of sodium and fluid, which appears specifically under stress, and then only in persons who are at heightened risk for hypertension.

Conclusions

It has been hypothesized that physiologic reactivity to behavioral stressors may be implicated in the pathogenesis of CHD and essential hypertension. At present, many aspects of the construct of individual differences in reactivity remain incompletely understood, such as the manner in which laboratory-assessed reactivity may generalize to nonlaboratory settings. Nevertheless, speculation that such reactivity reflects a pathogenic process—or is a marker for correlated pathogenic processes—receives some support from epidemiologic evidence that behavioral factors play a significant role in cardiovascular disease. Several sources of data relevant to hypotheses invoking reactivity in the development of CHD and hypertension have also been reported, although such hypothesis-testing research is still in its early stages. To review briefly, in relation to coronary disease there is currently one study based on an animal model associating behaviorally elicited heart rate reactivity with severity of coronary artery atherosclerosis, and one prospective study
employing human subjects in which diastolic responsivity to the cold pressor test was found predictive of subsequent CHD. Available case-control studies provide positive, but mixed results, and vary widely in methodologic rigor. Finally, the majority of studies examining psychophysiologic correlates of the Type A pattern have found a moderate relationship between Type A behavior and physiologic responses to a variety of laboratory stressors. However, Type A-reactivity associations seem partially dependent on the particular Type A assessment technique employed, and may vary significantly with differences in situational parameters and sample characteristics. With respect to essential hypertension, it has been found in numerous investigations that hypertensive patients show larger cardiovascular reactions to common laboratory stressors than do normotensive control subjects, and similar differences have emerged in comparisons of individuals with and without family histories of hypertension. In addition, persons at risk for hypertension who also exhibit the greatest cardiac responses to stress appear to show an anomalous retention of sodium and fluid when exposed to significant behavioral challenges.

Still, there is little evidence that a physiologic hyperresponsivity to behavioral stimuli contributes appreciably to the etiology of CHD or essential hypertension, nor have many attempts been made to establish such direct reactivity-disease links by either experimental or epidemiologic investigation. As a result, the types of evidence that would most clearly implicate autonomic and neuroendocrine reactivity as risk variables remain to be collected. Hence, we believe it is premature to regard reactivity as a proven or established risk factor. We would also caution against extrapolation from early research studies to the clinical use of psychophysiologic assessment techniques in relation to cardiovascular disease. On the other hand, the preponderance of available evidence, while largely indirect, is consistent with such relationships, and testable hypotheses have been proposed. Moreover, current data in this area provide ample justification for continued, if not more vigorous, exploration of psychophysiologic factors and of their possible role in mediating behavioral influences in CHD and hypertension.
REFERENCES:


FIGURE 1. Stylized figure depicting the generalization to nonlaboratory settings of individual differences in laboratory-assessed heart rate reactivity, as predicted by the "recurrent activation model." The upper and lower panels illustrate responses of a prototypic hyper- and hyporeactor, respectively. Depicted on the left (Lab) are subjects' heart rate responses to a standardized behavioral stimulus (or stressor) in the laboratory. Illustrated on the right (Life) are the predicted heart rate responses of these individuals to naturally occurring events in daily life. (See text.)
FIGURE 2. Stylized figure depicting the generalization to nonlaboratory settings of individual differences in laboratory-assessed heart rate reactivity, as predicted by the "prevailing state model." Figure legend is the same as the described under figure 1 above. (See text.)
IMPLICATIONS FOR HYPERTENSION

S. Julius

My task here is to share with you some difficulties that I have in extrapolating from some studies of reactivity in patients with hypertension to the pathophysiology of hypertension. I intend to provide you with this evidence and my evaluation of it as a basis for discussion. Let me preface this by saying that I am a firm believer that the autonomic nervous system and behavior have an important role in hypertension. Where I have great difficulties is what is the mechanism, how does it happen? and whether there is evidence for the notion that repeated pressor episodes lead to established hypertension.

I take it as a fact of life that blood pressure variability to mental stress is increased in borderline hypertension and prehypertension. People in this audience have demonstrated that over and over again. Take any group of patients with a family history of hypertension or with borderline hypertension who are presumably on their way towards hypertension, expose them to various mental stressors, and their blood pressure responses will be excessive. There is no doubt in my mind that Dr. Falkner, Dr. Obrist, Dr. Nestl, all those investigators who have studied mental stresses are right (1-3). Where I have difficulties is whether that represents the mechanism by which the hypertension develops. That is to say, does hypertension develop as a process of summation of these repeated pressor episodes? I should also define "hypertension." For the purpose of this presentation, hypertension is defined as a disease that is progressive, gets worse over time, is self-sustaining and if untreated, eventually causes serious target organ damage. That is the nature of human essential hypertension.

As I have indicated, the responsiveness to mental stress in borderline hypertension is increased. The next logical question that has to be asked is whether overall blood pressure reactivity is increased in borderline hypertension or is it only related to mental stress? Is hypertension a disease of the regulation of the blood pressure, and are blood pressure
responses abnormal to numerous other stimuli? In my assessment and beyond any doubt, borderline hypertension is not a disease of the regulation of blood pressure. Responses to exercise, responses to volume expansion, responses to isometric exercise, and responses to tilt are all normal in the majority of patients with borderline hypertension (4,5,6). Only one area, and that is the responsiveness to mental stress, is associated with hyperreactivity. It follows then that we have to ask whether mental stresses we see in the laboratory are the ones that also prevail in everyday life, or whether other factors that influence blood pressure variability are prevailing. In other words, is blood pressure variability increased in patients with borderline hypertension? The evidence is that blood pressure variability in borderline hypertension is normal and that the variability increases with advancing hypertension (7).

I would like now to discuss whether pressure episodes can predict future hypertension. This would be expected if hypertension develops as a result of summation of pressor episodes and if the pressor episodes in the laboratory are representative of future blood pressure trends. Though there is some new evidence on the possible predictive role of exercise and cold pressor testing, it is still my firm belief that laboratory stressors do not predict the future development of hypertension. The cold pressor test was proposed to predict hypertension by Dr. Hines in the Mayo Clinic many years ago, but in the number of prospective studies which have emerged since then, it has not shown to bear any relevance to hypertension. A recent report from the Mayo Clinic, which speaks to the contrary, has been accompanied by an editorial rebuttal on methodological grounds (8).

Similarly, a recent Israeli report that exercise responses predict future hypertension has to be taken with a grain of salt (9). These investigators have demonstrated that blood pressure levels during exercise predict better future hypertension than resting blood pressure levels do. There is nothing about blood pressure reactivity in that study, it is based on achieved blood pressure levels in an open-ended exercise paradigm. It is conceivable that exercise overcomes the variability of blood pressure taken in the physician's office and that the predictive power therefore of exercise blood pressures is stronger. However, it does not mean that they
are hyperresponsive. In fact, the variability of blood pressure may be decreased at the exercise point which is the one that predicts. This study has to be compared with the landmark study of Dr. Carolyn Thomas which found no predictive value to exercise for future hypertension in a very carefully followed-up group of medical students at Johns Hopkins (10).

The next logical question is whether a typical personality pattern presumably with excessive blood pressure variability predicts future hypertension. I know of two studies of personality that promise to follow their individuals prospectively. One is by Dr. Carolyn Thomas and was based on originally observed Rorschach tests in young people (11). On followup the original differences in the Rorschach scores did not predict the development of hypertension. There was also a study by Harris and Soklow which showed that borderline hypertensives in a behavioral role-playing setting were hyperreactive (12). They were followed up in a later report for the stability of the behavioral traits, but no data were given about their blood pressures in the second study (13).

I would also like to be provocative by pointing out the value judgment that enters into our thinking. Ask anyone, especially those who were jogging this morning, whether exercise is very good for health. On the other hand, the defense reaction is bad for you, yet, physiologically, they are rather similar. In both there is a mild increase of cardiac output and blood pressure. Defense reaction, in fact, is an exercise for lazy people. You get yourself ready to exercise without doing it. So, maybe armchair exercises are healthy. Our accepted position is that the defense reaction is deleterious to health and this may be right, but as any value judgment, it also may be wrong.

Now let me review the animal evidence about neurogenic hypertension. I will limit myself to experiments whose purpose was to raise pressure, and by summation of pressor episodes to cause hypertension. I will not review such studies as, for example, Dr. Henry's where hypertension was created by social stress but there was no evidence that this occurred through repetition of pressor episodes or through increased blood pressure variability. What I want to discuss is the simple proposition whether
repeated pressor episodes lead to hypertension. There are only two studies that I know of where a direct stimulation of the central nervous system was used to produce pressor episodes and induce hypertension. Folkow and Rubenstein produced mild hypertension by electrodes implanted in the defense area in the brain but the condition was reversible after 12 to 13 weeks when the stimulation stopped (14). Upon restimulation there was a very fast increase of blood pressure towards those high levels, however, again, the hypertension was not self-sustaining. Dr. Leyard and his colleagues stimulated stellate ganglia in dogs (15) and produced mild hypertension after seven days. In that short period of time the blood pressure elevation was reversible.

Another group of studies utilizes removal of baroreceptor inhibition to cause blood pressure variability and thereby create hypertension. With this method, it is not possible to cause severe, sustained hypertension. Particularly revealing is a report from Dr. Reis' laboratory that raises a very interesting question whether central nervous control of blood pressure variability may be regulated separately from the control of blood pressure level. Here is a quote from their paper: "Rats have been deafferented in the A2 areas of the brain, kept for 11 months and six of them had exceedingly labile blood pressure. Standard deviation of their blood pressure variability was 15 mm compared to 4 mm in others. They never developed hypertension. In fact, their blood pressure was decreased."(16) It is possible, I propose, that mechanisms regulating blood pressure variability and mechanisms regulating tonic sympathetic control of the blood pressure are very different, one from the other.

To finish the overview of animal experiments, let me also mention that it has been impossible to create sustained hypertension by operant conditioning of primates. Please keep in mind that we are talking about progressive and self-sustained hypertension. Why are investigators who clip the renal artery able to produce fulminant hypertension and we, believers in the important role of the nervous system, have such difficulties getting blood pressure to go up even a little? A recent report by Anderson et al. showing that sodium loading is conducive to blood
pressure elevation with operant conditioning, is encouraging but even in his study hypertension was mild and fully reversible (17).

Now, back to human studies. There is an underlying notion to all of them. If blood pressure reactivity is increased in the laboratory, it is likely that in real life the variability is increased and that repeated pressor episodes eventually will lead to hypertension. Increased blood pressure reactivity to stress has been particularly well demonstrated in patients with borderline hypertension. It is therefore appropriate to ask whether, in this early phase of hypertension, spontaneous blood pressure variability is increased. The truth is that blood pressure variability increases with blood pressure level (18). It is lowest in normotensives, it is almost unchanged in borderlines, and it becomes more prominent as hypertension becomes more serious. If we are right, that the variability causes hypertension, then there should be a variable phase first, and a stable phase later. However, the truth is just the opposite. Borderlines, who in old times used to be called labile, have a more stable blood pressure than those with so-called stable hypertension whose blood pressure is, in fact, labile.

Even if blood pressure variability were elevated in borderline hypertension, we must ask the next logical question. Does blood pressure variability predict hypertension or its complications? The Framingham evidence would indicate that an occasional peak of blood pressure is not important and what counts is the average blood pressure reading (19). Soklow's paper also suggests it is the average blood pressure, not the five highest or the five lowest blood pressure readings, that predict cardiovascular damage (20). Let me define this variability. There is no doubt in my mind that when you look at the differences between home blood pressures and the blood pressure in the physician's office, borderline hypertensives always have larger differences. They are excitable in the physician's office, but this is not a generalized phenomenon since the overall variability over 24 hours is not increased. I read Dr. Pickering's and Dr. Devreaux's paper as saying that blood pressure at work is important for future prognosis but not for its variability (21). That is to say, blood pressure at work was higher but not more variable.
If it is not blood pressure variability, what could it be? Dr. Obrist proposes that increases of cardiac output and not blood pressure are important via the so-called autoregulation mechanism. Let me shortly discuss autoregulation. For those who are not familiar with hemodynamics let's reiterate that flow is a linear function of pressure. Whenever pressure increases, flow increases. However, the amount to which flow increases depends on the size of the blood vessel. In a large vessel, small increases in pressure cause a large increase in flow. In a vessel that has a narrow caliber, the pressure must be substantially increased in order to elicit a small increase in flow. Change in vascular resistance by changing vessel caliber is an effective way to regulate the flow.

Dr. Guyton postulates a priority in the body in which flow is the regulated variable whereas pressure and resistance are the adjusted variables (22). The body will maintain a steady baseline flow and adjust pressure and resistance to maintain a desirable level of flow. For the whole body, the total flow is represented as cardiac output. What is the desired cardiac output which the body tends to autoregulate? Physiologists accept that the purpose of autoregulation is to maintain an optimal flow in relation to the metabolic demands of the tissue. If flow exceeds metabolic demand, then vascular resistance increases. This lowers the flow, and the final result is a normal flow but a higher pressure. In the body, total metabolic needs for all tissues are reflected as oxygen consumption. Let us therefore remember that autoregulation should happen only if cardiac output exceeds the oxygen needs of the body. We looked into this back in 1968 and before us, Dr. Johansson and Dr. Sannerstedt did the same (4-6). We all found that oxygen consumption in borderline hypertension is increased. From the graphs it can be seen that patients with borderline hypertension do have a higher cardiac output but also have a higher oxygen consumption. Consequently, I fail to see the stimulus for autoregulation. There is no overperfusion.

The other notion about stress-induced salt retention as a cause of hypertension is a very appealing one but it must not be oversimplified. It should be kept in mind that nobody has shown volume expansion in any type of hypertension; in fact, the blood volume in human borderline hypertension
is substantially decreased (23). If sodium retention plays a role, it probably does not translate into a simple volume expansion leading to overperfusion and thereby setting into motion the autoregulatory process. It must be much more complex.

In conclusion, let me state my belief that blood pressure reactivity and variability are legitimate and very important areas of inquiry into human physiology. I am glad that this conference will define the topic and stimulate better research in the field. I also firmly believe that reactivity to mental stress is increased in hypertension. However, I fail to see this increased reactivity and the ensuing blood pressure variability as the mechanism for the development of hypertension. It is quite likely that tonic and phasic control of cardiovascular sympathetic discharge may be separate phenomena. Consequently, I expect that reactivity studies will improve our knowledge about blood pressure reactivity which is important, but they will not necessarily contribute to our understanding of physiologic mechanisms that lead to hypertension. I do not believe that hypertension develops as a simple summation of pressor episodes. Studies on the relationship of tonic control of sympathetic discharge to mental phenomena may be desirable and mechanistically useful.

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IMPLICATIONS FOR CORONARY HEART DISEASE

J. Alan Herd

Atherosclerosis is a process in which lipids are deposited in the arterial wall. Through some process not well understood, endothelial cells are lifted from the lining of the artery and lipids gain access to the intima. In response to the altered intimal composition, vascular smooth muscle cells move into the arterial intima and proliferate. Lipids accumulate in the smooth muscle cells and produce lipid streaks. Later, lipids, fibrous tissue, and other proteoglycan materials are deposited in the extracellular space. Chronic inflammatory cell proliferation, hemorrhage, necrosis, and calcification occur at later stages. Although lipid infiltration into the arterial wall is an important part of atherogenesis, the formation of the atheromatous plaque is initiated by the proliferation of vascular smooth muscle cells. Thus, the pathophysiological mechanisms promoting the primary proliferative process of vascular smooth muscles may be critical for the development of coronary artery disease.

Studies by several investigators have demonstrated that smooth muscle cells do not proliferate in culture except in the presence of blood serum (Ross et al. 1974). Ross et al. (Ross and Gromset, 1973) reported that serum lipoproteins were necessary for optimal cell growth in culture. In addition, these authors (Ross et al. 1974) demonstrated that addition of platelets and calcium to platelet-poor plasma increased the activity of plasma serum in promoting the proliferation of arterial smooth muscle cells in culture. As shown in figure 1, five percent dialyzed plasma serum had little or no effect on proliferation of arterial smooth muscle cells unless the serum was allowed to clot in the presence of platelets. In these experiments, equal numbers of smooth muscle cells were added to culture dishes and incubated in medium containing one percent serum. After seven days, the dishes were separated into four groups. One group was incubated in serum-free medium. The remaining groups were incubated in a medium containing five percent dialyzed serum from whole blood containing platelets, five percent dialyzed plasma serum exposed during the process to
platelets, and five percent dialyzed plasma serum in which no platelets were present. Results demonstrated that much of the growth-promoting activity of dialyzed serum was directly or indirectly derived from platelets. These experiments further illustrate the importance of humoral factors in promoting proliferation of vascular smooth muscle cells.

Acceleration of atherosclerosis occurs under the influence of many risk factors. One with both clinical and epidemiologic evidence linking it to atherosclerosis is elevated levels of insulin in blood. Patients with atherosclerosis frequently have abnormalities in glucose tolerance (Stout, Bierman and Brunzell 1975), and many have elevated insulin responses to oral glucose compared to control subjects without evidence of vascular disease (Stout 1981). In addition, elevated levels of plasma insulin increase the risk of myocardial infarction and coronary heart disease mortality in middle-aged men without overt signs of diabetes or atherosclerosis. These observations suggest that insulin influences development of atherosclerosis, and elevated plasma levels increase risk for coronary heart disease.

Neurohumoral risk factors provide a lead for exploring behavioral influences on coronary heart disease. Neuroendocrines, including epinephrine, norepinephrine, and cortisol, influence the interaction of insulin with several metabolic processes. Clinical and epidemiologic evidence relates plasma levels of cortisol to lipid metabolism and severity of coronary artery disease. These effects may be mediated by effects of insulin sensitivity, both through aggravating hyperlipoproteinemia and promoting the basic process of atherogenesis. Thus, the behavioral and physiological influences on neuroendocrine factors which affect insulin sensitivity warrant further discussion.

Cortisol and Atherosclerosis

Troxler (Troxler et al. 1977) has the opportunity to study the association of plasma cortisol and coronary atherosclerosis in young male aircrew of the United States Air Force. Coronary angiography was part of the clinical
evaluation carried out because of medical conditions or electrocardiographic findings that could preclude flying duty. Plasma cortisol, serum cholesterol, triglycerides, percent body fat, blood pressure, age, smoking habits, and coronary angiograms were measured on 71 men. As part of this evaluation, a standard 2-hour oral glucose tolerance test was administered between 8 a.m. and 10 a.m. A portion of each glucose tolerance test plasma specimen was analyzed for cortisol concentration. Coronary angiograms were scored on a scale of 0-6 according to amount of obstruction observed in the right and left coronary arteries. Forty-eight percent of the subjects showed no evidence of coronary artery disease, 20 percent showed mild disease, and 32 percent showed moderate to severe obstruction of the coronary arteries. Significant correlation between elevated serial morning plasma cortisol and moderate to severe coronary atherosclerosis was found. In relation to other risk factors, plasma cortisol was second only to serum cholesterol as a discriminator in that population. In addition, a high degree of correlation was found between levels of cortisol and levels of both cholesterol and triglycerides. Cortisol may have had a direct effect on cholesterol metabolism and an indirect effect on triglycerides through its influence on the interaction of insulin in lipid metabolic processes.

Insulin and Atherosclerosis

Epidemiologic studies have demonstrated a relation between plasma insulin levels and the incidence of myocardial infarction and coronary heart disease mortality in middle-age men (Ducimetiere, Eschwege, Papoz, Richard, Claude and Rosselin 1980). Ducimetiere et al. measured serum cholesterol, serum triglycerides, systolic blood pressure, body weight and height as well as recorded history of cigarette smoking. In addition, they measured plasma glucose and plasma insulin levels before, and 2 hours after a 75 g oral glucose load. The population was 7,246 nondiabetic working men aged 43-54 years who were initially free from heart disease and were followed for 63 months on the average. They demonstrated that the fasting plasma insulin level and the fasting insulin-glucose ratio were positively associated with risk for myocardial infarction and coronary heart disease mortality independent of all the other factors (figure 2).
They concluded that high insulin levels constitute an independent risk factor for coronary heart disease complications in middle-age nondiabetic men.

**Metabolic Effects of Cortisol and Epinephrine**

It has been known for some time that glucocorticoid excess prolongs the removal of glucose during a glucose tolerance test in normal humans (Fajans and Conn 1954). Also, hypersecretion of adrenal cortical hormones in Cushing's disease has a diabetogenic effect. However, the mechanism whereby glucocorticoids may influence removal of glucose from blood is poorly understood. Shamoon et al. (Shamoon, Soman and Sherwin 1980) examined the influence of cortisol on glucose metabolism during continuous infusion of cortisol during a period of five hours. Normal adult men and women were studied after consuming a standard carbohydrate diet and fasting overnight before observations were made. The effect of cortisol infusion on plasma glucose and glucose kinetics in the normal human subjects is illustrated in figure 3. Infusion of cortisol increased levels of glucose in plasma without influencing rates of glucose production. Removal of glucose from blood was reduced which resulted in cortisol-induced hyperglycemia. These effects of cortisol on glucose metabolism occurred in the absence of significant changes in plasma or glucagon concentrations. Concomitant effects on fatty acid and amino acid metabolism suggested that cortisol interfered with the cellular action of insulin.

**Behavioral Influences on Cortisol and Epinephrine**

Many investigators have reported results of experiments concerning behavioral influences on physiological processes. The majority of studies performed have demonstrated effects on cardiovascular function. In particular, changes in heart rate and blood pressure have been studied under a variety of behavioral conditions. Other investigators have studied behavioral influences on neuroendocrine processes. In general, psychological factors have been shown to influence secretion of cortisol, epinephrine, and norepinephrine. Although the psychological characteristics of experimental conditions used to test behavioral
influences are not well-defined, some general characteristics of situations influencing secretion of cortisol and epinephrine can be stated.

One characteristic of situations provoking increased secretion of cortisol is novelty of an experimental situation. Davis et al. (Davis, Gass and Bassett 1981) tested normal young men under a graded exercise tolerance test procedure. One group of subjects was experienced with exercise testing and the other group had no previous experience with the procedure. The subjects in both groups had similar capacities for physical work. No significant relationship could be demonstrated between maximal oxygen uptake, venous lactate concentrations, Borg ratings of perceived exercise, or serum cortisol responses during exercise. However, the post exercise increase in serum cortisol levels was greater in the naive subjects. Serum cortisol increased 59 percent in the experienced subjects and 138 percent in the naive subjects. The authors concluded that novelty was the major determinant in the increased cortisol response in naive subjects compared to experienced subjects. Furthermore, this cortisol response bore little relationship to maximal oxygen uptake, heart rate, or venous lactate concentrations. Apparently, the magnitude of response observed in cortisol concentrations was influenced more by psychological factors than the physiological effects of exercise.

**Improving Insulin Action on Metabolic Processes**

Conditions which interfere with the influence of insulin on metabolic processes are said to increase insulin resistance. When insulin resistance was first defined, it was measured by determining the rate of insulin-glucose uptake in patients with non-insulin-dependent diabetes mellitus or patients with severe obesity. The inference that insulin action was reduced was obtained by measuring the effects of insulin injected intravenously on levels of glucose in plasma or by combining administration of glucose and insulin intravenously and measuring plasma glucose concentrations during the next 60 minutes (Reaven 1983).

Ultimately, an important manifestation of insulin resistance is elevated levels of glucose in plasma, levels that are higher than would be expected
in proportion to concentrations or insulin in plasma. A useful indicator of the average blood sugar concentration in an individual over a period of several weeks is the concentration of hemoglobin Alc. This form of hemoglobin is present in red blood cells of normal subjects in a proportion of up to 5 percent of the total concentration of hemoglobin. In patients with diabetes mellitus and elevated plasma levels of glucose, concentrations of hemoglobin Alc may rise to 15 percent. Since hemoglobin synthesis is a slow and nearly irreversible reaction in red cells, the level of hemoglobin Alc reflects concentrations of glucose at the time the red blood cell was formed. Because red blood cells remain in the circulation for approximately 120 days, it takes several weeks for the concentration of hemoglobin Alc to reflect abrupt changes in levels of glucose in blood. Thus, measurement of hemoglobin Alc gives an objective assessment of the average concentration of glucose over long periods of time (Koenig and Cerami 1980).

Improving insulin sensitivity can be achieved through several therapeutic measures. The effect of physical training on insulin production in obesity has been demonstrated by Bjorntorp et al. (Bjorntorp, de Jounge, Sjostrom and Sullivan 1970). These investigators studied obese patients during a physical training program which increased maximal oxygen uptake and increased muscle strength. Body weight actually increased during the training program due primarily to an increase in body fat. A normal glucose tolerance test performed before and after the training program showed no change in blood glucose values. However, there was a substantial reduction in the concentrations of insulin in plasma following administration of glucose. Authors interpreted results of these studies as indicating an increased insulin sensitivity of tissues. Since body fat mass was not decreased, the effect of physical training on insulin sensitivity apparently occurred independently of any change of adipose tissue function.

Summary

The pathophysiological mechanisms contributing to coronary heart disease include a mix of genetic factors, traditional risk factors, and behavioral
influences. The behavioral influences may be mediated as much through neuroendocrine factors as through effects on cardiovascular functions. Plasma levels of cortisol are related to lipid metabolism and their effects on lipid metabolism may be mediated by effects on insulin sensitivity causing hyperinsulinemia. High circulating levels of insulin would be expected to promote atherogenesis by direct effects on vascular smooth muscle proliferation and elevating circulating levels of triglycerides and low density lipoproteins. Evaluation of this link between behavioral factors and atherogenesis might be aided by measurements of hemoglobin Alc, measurements of insulin receptor concentration and affinity in red blood cells and monocytes, and the measurement of insulin to glucose ratios in plasma.

The behavioral influences on neuroendocrine factors apparently involve specific psychological factors. In particular, new situations and tasks that exceed perception of self-competence or elicit intense, sustained efforts to cope with tasks enhance neuroendocrine responses. However, further research is necessary to determine the psychological characteristics of situations eliciting exaggerated neuroendocrine responses.

Corrective measures include physiological and behavioral approaches. The physiological influences of physical inactivity and obesity can be overcome by the appropriate corrective measures. The influences of behavior pattern, psychosocial factors, and conditioning might best be corrected by cognitive restructuring, relaxation training, and, where necessary, isolation of individuals from provocative situations.

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FIGURE 1. Response of arterial smooth muscle to platelet factors in plasma serum. Equal numbers \((3 \times 10^4)\) of primate arterial smooth muscle cells were added to a large series of 35-mm petri dishes and incubated in medium containing 1% serum pooled from several Macaca nemestrina. After 7 days (arrow) the dishes were separated into four groups. One group was incubated in serum-free medium. The remaining groups were incubated in medium containing: 5% dialyzed serum from whole blood containing 3.95 \(\times\) 10^5 platelets per ml; 5% dialyzed plasma serum which had been exposed during the process of recalcification and serum formation to an equivalent number of platelets, derived from the same pool of blood; 5% dialyzed plasma serum in which no platelets were present during the process of serum formation. This experiment demonstrates that 5% dialyzed plasma serum has little or no proliferative effect unless allowed to clot in the presence of platelets.
FIGURE 2. Mean annual incidence of CHD complications according to quintiles of fasting (0) and 2 h after glucose load (2) plasma insulin/glucose ratios (I/G). Quintiles limits are defined as follows:

I/G mU/g: 6, 7-9, 10-12, 13-17, 18;
I/G mU/g: 16, 17-24, 25-34, 35-53, 54.

Comparison of observed and expected number of events among quintiles (chi-square test)
FIGURE 3. The effect of cortisol infusion on plasma glucose and glucose kinetics in normal humans.
TASK GROUP REPORTS ON REACTIVITY
HEMODYNAMIC AND ELECTROPHYSIOLOGICAL MEASURES OF REACTIVITY

Group Leaders: Neil Schneiderman and Thomas Pickering

Group Members: David Anderson, Jack Dawson, J. Richard Jennings, Donald Leon, Shirley Mueller, Paul Obrist, Orville Smith, Igor Shkhvatsabaya

This task group defined reactivity as the physiological changes of an organism from a specified control level in response to a particular set of stimulus conditions. Factors that may influence the pattern, magnitude and/or duration of these adjustments include the individual's perception of the stimulus, behavioral response style (e.g., personality), emotional state, genetic background, physical status, and past history. Because the same measures and measurement strategies may not be equally appropriate for investigation relationships between biobehavioral factors and different disease states such as hypertension, coronary artery disease and sudden cardiac death, the task group declined to rank order a list of physiologic measures as being uniformly important to the study of individual differences in reactivity. Instead, the task group decided to address a number of issues that were deemed to be important.

The first issue addressed involved the selection of response measures. Since the physiologic adjustments of an organism consist of an integrated pattern of responses, the task group felt that it is important to select judiciously a sufficient number of response measures to allow for the response pattern and its variation to be identified. Thus, it is often desirable to assess blood pressure (BP), the electrocardiogram, cardiac output, peripheral resistance, flow in different vascular beds, as well as the status of the heart and coronary arteries. Alternative methods for making these determinations, the basis for choosing among them, and current technological limitations of the available procedures were discussed.

A second set of issues considered by the task group dealt with the methods required to evaluate the CNS, autonomic, and hormonal regulation of the relevant hemodynamic and electrophysiologic measures as well as the procedures that can be used to evaluate cardiovascular regulation in terms
of (a) parasympathetic vs. sympathetic nervous system activity, (b) alpha vs. beta adrenergic activity, (c) patterning of autonomic responses and (d) CNS vs. afferent vs. efferent functioning.

The third issue discussed by the group involved the identification of animal models that seem best developed for relating stress and reactivity to cardiovascular disease.

A fourth set of issues involved the specification and implications of using different control levels in assessing the responses to particular stimulus conditions.

Selection of Response Measures

Blood Pressure

Blood pressure (BP) is a potentially important measure of cardiovascular reactivity for both hypertension and coronary artery disease, although evidence linking acute changes of BP with long-term consequences for either disease is very limited. Invasive measures of BP remain as the "gold standard", and any noninvasive technique should be validated against invasive BP. Nevertheless, there are potential problems with invasive techniques; e.g., the frequency response of the recording system, and differences in the pressure wave form depending on the recording site. Apart from accuracy, the other advantage of the invasive technique is the ability to detect transient changes, which may often be missed by the intermittent noninvasive techniques.

Auscultatory techniques, based either on use of the stethoscope or Korotkoff sound microphones, are the best established noninvasive method, and form the basis for virtually all the epidemiologic data relating to hypertension and its consequences. A large number of automatic recorders are now available using Korotkoff sound microphones, but many of them have not been satisfactorily validated. It is essential that when automatic recorders are used they are calibrated for each subject, either with a stethoscope or display of the Korotkoff sounds. Errors inherent in the
method are related to inappropriate match between the size of the cuff and the diameter of the arm, improper placement of the microphone, and movement artifact. Ideally, such recorders should also be calibrated for detecting change of pressure as well as the basal value.

When stethoscope or Korotkoff sound microphones are used, the person making the blood pressure measurements needs to be trained to make accurate, reliable measurements. Where more than one observer is being used in a study, it is important to assess interobserver reliability. Standardized training programs (e.g., Indiana University School of Nursing) and high quality videotapes for training assessments are available.

Oscillometric methods are also popular. These can reliably detect systolic and mean arterial pressure in the majority of subjects but cannot detect diastolic pressure. Methods combining Korotkoff sound detection and oscillometry offer promise for the future.

Another invasive technique which has been advocated is the measurement of pulse transit time, either using the R wave to radial pulse interval or the interval between brachial and radial pulse. While this technique has the advantage of not requiring a cuff and therefore offers the possibility of continual beat-to-beat measurement, correlation between changes of pressure and changes of transit time have been disappointing, and it is unlikely that the measure will find widespread application.

There have been isolated reports of other promising noninvasive techniques, including Doppler methods, but so far these have not found wide acceptance.

A method for detecting beat-to-beat changes of BP is obviously desirable for reactivity studies. Cuff based methods take no more than one reading every 30 seconds, with the exception of the cuff tracking method, which can track changes over periods of up to two minutes. The cuff tracking method, however, gives a somewhat damped measurement, and very acute changes may be underestimated.
Ambulatory monitoring of BP can now be carried out using both invasive and noninvasive techniques with acceptable accuracy in the majority of subjects. Between 100 and 200 readings per 24 hours can be obtained with the noninvasive techniques, compared with 100,000 readings per 24 hours with invasive measurements. The advantages of ambulatory monitoring are that variability in real life can be studied, although since the environmental conditions are often relatively uncontrolled, BP reactivity to a specific stimulus may be less easy to quantify. Laboratory studies have the advantage of enabling the experimental conditions to be very precisely controlled, so that between-subject comparisons can be made, but their relevance to real life changes has not so far been well established. Laboratory and ambulatory studies should be regarded as being complementary to each other.

Electrocardiogram

The electrocardiogram continues to be a dominant measure in both cardiologic and biobehavioral applications. Technical guidelines are readily available (American Heart Association) for clinical electrocardiography, and specific guidance on the use of heart rate is also available (Psychophysiology, 1981). A heart rate measure has been used almost universally in studies of stress and cardiovascular reactivity. Recent interest has been in a more complete approach using other aspects of the electrocardiogram.

**Heart rate.** Heart rate has been measured either tonically, i.e., by counting beats over time frames of a minute or more; or phasically, i.e., by measuring the rate or interbeat interval of each heart beat during a condition of interest. Choice of tonic or phasic measurement depends on whether the effect under study is suspected of exerting persistent or transient influences on heart rate. Particularly in the case of phasic measurement, the investigator should be aware of the inherent variability of heart rate; e.g., due to respiratory heart rate interactions. Statistically, i.e., averaging or manipulative control may be required to isolate the response of interest. Expression of phasic changes such as heart rate or interbeat interval may alter the interpretation of results
since these indices are related as reciprocals rather than linearly. In normal adult data the differences due to the measure chosen are not major, but certain statistical properties are maintained if heart rate per second or interbeat interval per beat are used as metrics.

Physiologically heart rate is controlled by both sympathetic and parasympathetic systems. The relative degree of control varies with species; e.g., vagal-parasympathetic control is dominant in humans. In any average case, neural interpretations of heart rate change cannot be made from heart rate alone given the complexity of its control.

Ambulatory monitoring of the electrocardiogram is well developed. Clinical applications focus on arrhythmia and qualitative changes but heart rate changes to natural events may be of interest to behavioral medicine. Systems that monitor only heart rate can be obtained much more cheaply than systems designed to detect EKG abnormalities.

Features of the electrocardiogram. Electrocardiogram morphology in resting and exercise conditions is of great importance to cardiology. Features that change with stimulation are those of primary interest for the biobehavioral scientist. Chief among these is the depression of the ST segment, which is associated clinically with myocardial ischemia. Depression of 0.1 mV (1 mm) or more is thought significant and has been demonstrated in response to psychological stimulation. The timing of the waves of the electrocardiogram has also proven useful. For example, the Q-T interval reflects the length of electrical systole and by itself and in relation to phonocardiogram signals has been a correlate of clinically significant events. Finally, the amplitude of the T wave has been proposed as an index of sympathetic tone. Routine use of this index must, however, await further validation given potential problems that have been noted.

Measures of electrical stability. Electrical instability of the myocardium is thought to be an important feature of cardiac sudden death. Assessment of cardiac arrhythmias in response to psychophysiological and neurophysiological manipulation provides an important tool for exploring this problem. Adequate examination requires multilead electrocardiography
and an appreciation of commonly encountered arrhythmias--particularly ventricular ectopy. A more invasive technique is to stimulate the heart electrically varying timing and stimulation parameters. The threshold at which repetitive extrasystoles occur provides an index of electrical instability. The ability similarly to modify sinus node excitability by the timing and intensity of discrete psychological stimuli is also noted as possibly relevant to the assessment of electrical stability. Finally, the capability of pacing heart rate in animal and in some human studies is noted as a powerful technique to determine whether observed effects are due solely to rate changes rather than extrinsic factors.

Assessment of Cardiac Performance

Before addressing the matter of the utility of various measures of cardiac performance in the study of the effects of stress and reactivity, several issues must be acknowledged. The first among these is that there are numerous precise and reliable invasive methods which can be used in humans, and even more technologically advanced methods for application in laboratory animals. However, in order to obtain valid data regarding stress and reactivity in humans, the methods employed should be easy, painless and technologically simple. Thus, the emphasis, at least for humans, must be on noninvasive techniques that have been precisely established to be accurate and reproducible.

Contractility. The systolic time interval measure (PEP/LVET) is a reliable method for estimating changes in left ventricular performance. Simultaneous measurements of left ventricular isometric contraction time, stroke volume and external systolic time intervals have established the validity of the methods. Cardiac apex motion, when calibrated, provides a reliable and useful adjunct to systolic time intervals for the assessment of left ventricular performance. However, it must be emphasized that this statement applies to the calibrated apex cardiogram and not to the commonplace and usual methods of recording apex motion.

Under laboratory conditions, measures of maximal rate of left ventricular pressure development (dP/dT Max) are also very useful methods of
performance assessment in individuals subjected to acute hemodynamic changes. Percentage changes in dP/dT Max under the same experimental conditions can be compared, one subject to another, with considerable reliability.

Measurement of changes in mean rate of circumferential fiber length shortening is also a good method for estimating changes in contractility. This method was originally based on angiographic images and was considered to be reliable. With recent improvements in m-mode echocardiographic technology, it is now possible to obtain similar information from this noninvasive procedure. However, as with many noninvasive techniques, it must be recognized that great skill on the part of the observer is required to assure that this method is used in a standardized and reproducible fashion.

Cardiac output. There are several reliable methods for measuring cardiac output. These include the classical Fick method, indicator dilution methods and periaortic electromagnetic flow meters. Thermodilution, when carefully and precisely performed, correlates well with high quality dye dilution measures and offers a bit more flexibility pertaining to subject posture and activity. However, it must be recognized that changing subject posture and activity make it more difficult to perform the test precisely. Thermodilution has the advantage of not requiring blood withdrawal, which might constitute another variable in a series of observations.

In animals, an electromagnetic flow meter offers numerous advantages, but it is not to be employed in behaving humans. There are several imaging methods for measuring stroke volume. Contrast left ventricular angiography and, to a lesser extent, nuclide imaging appear to be good methods, but with obvious limitations.

All in all, however, stroke volume is most easily measured by dividing dye dilution cardiac output by heart rate.

Impedance cardiography is enjoying a renewal of interest and some investigators have shown it to be a reliable technique. More work is now
under way to establish and overcome pitfalls in this method. Assuming continual progress, impedance cardiography will be useful and will offer the advantage of determining systolic time intervals simultaneously.

Bidirectional Doppler studies across the ascending aorta appear to offer promise of the technique being a useful noninvasive method for measuring stroke volume.

Interestingly enough, combining end expiratory CO\textsubscript{2} and CO\textsubscript{2} rebreathing may offer a good method of noninvasively estimating cardiac output.

**Rate-pressure product.** Even though pressure-rate product measurements seem to correlate well with myocardial oxygen demand, this is true only under certain experimental conditions. In contrast, under some pharmacologic conditions, the factors that influence pressure-rate product vary considerably. The use of the pressure-rate product measure was established for dynamic exercise. When applied to other situations (i.e., isometric exercise), the results are not necessarily comparable with those of dynamic exercise in terms of effect upon the myocardium. Thus, this double product of heart rate and systolic BP has some value in assessing oxygen demand under at least some circumstances, but its use with regard to the study of stress and reactivity needs to be approached with caution.

**Assessment of Venous Circulation**

Venous volume, venous tone and the status of the splanchnic pool are very difficult to measure, even in the experimental animal. Shifts of venous volume towards the heart under conditions of stress and similar data would likely be helpful in understanding the cardiovascular response. Using venous occlusion plethysmography and measures of venous pressure simultaneously, however, it is possible to obtain venous compliance curves and concomitant expressions of capacitance or tone.

**Measurement of Flow**

**Coronary blood flow.** There is no satisfactory noninvasive technique for
humans for measuring coronary flow, and invasive measurements have generally been confined to the cardiac catheterisation laboratory. Various isotope techniques have been described which are based on intra-arterial injection of isotope with external counting. For the foreseeable future, behavioral studies involving measurements of coronary flow are likely to be confined to animal studies.

Coronary flow measurements during normal behaviors are currently restricted to invasive procedures on experimental animals. This may be approached with either electromagnetic (EM) or Doppler flow techniques. The pros and cons for selecting the techniques to use are the same as for measuring other regional flows; i.e., the use of the EM technique necessitates the additional implantation of an occluder in order to determine flow zero. This means a more extensive dissection of this critical artery from the surrounding myocardium, whereas the Doppler system suffers from potential variability depending upon which portion of the blood flow velocity profile is being sampled; also the choice of a directional Doppler system is possibly important because of the tendency to have reverse flow at low heart rates. In either case the simultaneous implantation of a coronary sinus catheter for sampling venous blood for determination of metabolic activity of the myocardium would be essential for discriminating neural from intrinsic (metabolic) regulatory factors.

Venous occlusion plethysmography. The use of venous occlusion plethysmography to measure arterial inflow to a limb has been a useful basis for tests in humans. Criticism has centered around the reproducibility of the technique and the interpretation of the results. Therefore, documentation of the following parameters must be made when this technique is used:

1. The technician must be able to reproduce the same results within the same day and from day to day.

2. Interpretation of the record must be confirmed by an independent blind observer.
3. The mercury strain gauge must be verified as sensitive by periodically using an artificial arm and perfusion pump to assure that the absolute flow is the same as a recorded flow.

It must be recognized that the baseline vascular resistance measured using this technique is affected by many factors including temperature, sympathetic tone, and circulating vasoactive substances. Therefore, in any experiment measuring baseline vascular resistance these factors must be controlled.

When maximal dilation is produced by ischemia and minimal vascular resistance is measured using plethysmography, maximal dilation must be confirmed by hand exercise on top of ischemia.

A possible alternative to venous occlusion plethysmography which is now being used, is impedance plethysmography.

**Cutaneous blood flow.** Cutaneous blood flow is an important index related to thermoregulation and the response of the sympathetic system to central events. Available techniques are Xenon clearance, venous occlusion of the finger, skin temperature impedance and photoelectric technique. No one technique is of value for every application. Flow per se is probably best measured by clearance and occlusion techniques although these techniques do not provide beat-by-beat measures. Skin temperature is also a relatively slowly responding and indirect index of cutaneous flow. Impedance and photo techniques provide beat-by-beat measures, but it is unclear whether these are measures of flow. All measures except the clearance technique have been shown to be responsive to psychologic manipulation. An alternative measure of cutaneous vascular responsivity would be to measure the distensibility of the cutaneous vascular bed by computing pulse wave velocity between an arterial and peripheral site.

**Renal blood flow.** Renal flow measure in the animal model may be particularly important because of the continued implication of the kidney in both secondary and essential hypertension. The renal bed is exquisitely responsive to both direct neural and hormonal influences and thereby serves
as a sensitive indicator of the influence of behavioral and psychological variables.

Renal flow measurements in real time are essential because the speed of the neural responses is within two seconds of the initial stimulus and is over within five seconds. This means that invasive flow measuring techniques are required. Either electromagnetic or Doppler approaches may be used; with the EM being bulkier and requiring one occluder but the Doppler being less accurate.

**Labeled microspheres to measure distribution of flow.** Labeled microspheres are a reliable and good indicator of regional blood flow. The major advantage of labeled microspheres is that the technique allows multiple measurements over time. In addition, the technique can be used in both the awake and anesthetized animal. Because the animal must be sacrificed at the end of the experiment, the technique obviously cannot be used in humans. There are several important factors that must be considered when using this technique:

1. The microsphere injection should be into the left atrium or a vascular compartment that allows good mixing of labeled microspheres.

2. There must be verification that the microspheres are not shunted. Fifteen micron diameter microspheres are ideal for measurement of muscle blood flow.

**Methods to Assess Control of the Circulation**

Invasive and noninvasive hemodynamic electrophysiologic measurements provide reliable cardiovascular indices that are helpful in determining nervous system regulation. Sympathetic and parasympathetic activity can both be assessed by observations of relevant indices (e.g., PEP/LVET as an index of beta-adrenergic drive on the heart; heart rate variance, reflex changes to various maneuvers or responses to pharmacologic manipulations and blockade as an index of parasympathetic tone).
Increased parasympathetic activity is noted by both increased vagal tone and release of inhibition. Increased vagal tone is assessed by measurement of R-R interval differences influenced by respiratory maneuvers; i.e., valsalva maneuver, single breath and six breath per minute techniques. Control levels manifested by severe bradycardia, muted heart rate responses to standing, lack of an increase in heart rate to increased BP or cardiac contractility associated with a vasodilatory task (discordant response) and decreased heart rate response after release of heightened sympathetic tone (after withdrawal of hand from ice after cold pressor task and release of grip after isometrics) are also mediated by increased vagal tone. Increased vagal tone is accompanied by increased release of vagal inhibition which is manifested by increased heart rate with standing, with tasks performed, and with tilt table maneuvers.

Loss of vagal tone is the first manifestation of neuropathy in diabetes mellitus, followed by complete denervation when sympathetic involvement occurs. Sequential determinations of R-R response and heart rate assessments during respiratory maneuvers enable investigators to evaluate these processes.

Increased sympathetic activity is manifested by increased resting heart rate, increased heart rate variability with respiration and increased BP, heart rate (HR), total systemic resistance (TSR), cardiac output (CO), and contractility with task performance. Abnormal sympathetic activity can produce increased BP-TSR or HR-CO with standing.

It should be noted that increased sympathetic activity can lead either to increased or decreased total systemic resistance, depending upon whether muscle vasodilation occurs. Thus, one form of increased sympathetic nervous system activity is associated with active (beta-adrenergic mediated) vasodilation in skeletal muscle and is usually accompanied by decreased TSR. The TSR can increase, however, if the alpha-adrenergic mediation of vasoconstriction in other vascular beds is sufficiently great as to overshadow the effects of the muscle vasodilation. Another form of sympathetic reactivity is associated with an absence of muscle vasodilation; in this situation TSR increases.
The alpha adrenergic response includes increases in systolic and diastolic BP and TSR. Increased beta-adrenergic activity produces an increase in systolic BP, HR, CO, and cardiac contractility.

An increase in central arousal is noted by additional patterns of response which may be superimposed on the preceding patterns demonstrated by (a) lack of habituation with absence of return of the measures to baseline after a proper post-task rest period or (b) sustained increase in reactivity measures throughout the task. Increased delta values indicate high or "hot" reactivity. Therefore, the response can be abnormal in three ways: 1) hypertension during casual BP readings, 2) high cardiovascular increase on a task without the individual being hypertensive (manifest with an alpha and/or beta hemodynamic pattern), and/or 3) lack of habituation within or between tasks.

Lack of arousal needs further assessment. This phenomenon may reflect a dysautonomic response or in normal individuals it may reflect a lack of engagement or a withdrawal of attention from the experimental situation.

Indirect measures of cardiac contractility as an index of beta adrenergic activity include PEP/LVET and Q-T/Q-S2 ratios and indices from echocardiographic and impedance cardiographic techniques. Baroreceptor reflex gain is assessed by the valsalva maneuver, passive head up tilt, phenylephrine injection and neck suction techniques.

Neck suction. An alternative to pharmacological and other manipulations (e.g., valsalva maneuver) in evaluating baroreceptor gain is neck suction. Dwain Eckberg at the Medical College of Virginia has developed the necessary equipment and detailed the methodology in several publications. It involves creating a brief (less than 1 second) negative pressure around the neck coincident with the time when the pulse wave would be maximally stretching the carotid baroreceptors. Its effects are additive to that of the pulse pressure. The advantage of the technique is that it can be used frequently and under a variety of circumstances. Thus, one can evaluate gain as a function of conditions and tasks, and in relation to HR reactivity or levels of HR. One limitation is that it can only be used to
evaluate baroreceptor influences on HR (R-R interval) and not BP, unless the BP is measured continuously as with invasive or direct recordings.

The efferent vagal pathway to the heart is assessed by observing the effects of atropine on heart rate. Efferent sympathetic pathway or end organ response is assessed by tyramine or norepinephrine effects upon systolic BP.

Central and peripheral receptor functions can be assessed by drug intervention. Drugs are also useful in the assessment of abnormal responses; i.e., by diminishing excessive central sympathetic outflow as well as by blocking opposing responses. Blocking of beta-adrenergic or vagal responses selectively enables investigators to assess the stimulus-response relationships of the unopposed system.

Psychopharmacologic agents can modulate central sympathetic tone. Decreased central sympathetic tone can be enhanced by blocking reuptake of norepinephrine, e.g., with maprotiline (Ludromil). Increased sympathetic tone is dampened by blocking the reuptake of serotonin, e.g., with trazodone (Desyrel). The increased arousal response can also be blunted by benzodiazopines or similar sedatives.

Central alpha-two agonists decrease peripheral sympathetic effects. Predominantly by decreasing TSR. Mild sedation is a beneficial side effect which may decrease the hyperarousal response. Peripheral alpha-one blockade decreased TSR by vasodilation.

Beta-adrenergic blocking agents, which are lipid soluble, cross the brain barrier and have central influences that enhance their effects. Cardioselective beta blockers preserve peripheral vasodilation and avoid accentuation of TSR, which is enhanced by noncardioselective agents.

Animal Models

Among the available models of experimental cardiovascular pathology, several appear to be particularly appropriate for studies of stress and
reactivity. These may be differentiated in terms of genetically vulnerable and nonvulnerable models. The former include a) the spontaneously hypertensive rat, which has been shown to be "hyperreactive" to stimulation, not only in terms of BP and HR response, but also in terms of renal functions, b) the SHR-WKY cross-bred rat (Lawler) which responds to sustained conflict with a permanent element of BP not observed in normotensive controls exposed to the same stimuli, c) the salt sensitive rat of Dahl, which is also hyperresponsive to stress, as shown by Friedman and others. A similarly useful model now exists for heart failure, which has been shown to be prematurely induced by stress in the cardiomyopathic hamster.

Among the nongenetically susceptible animal models are a) psychosocial stress models, and b) aversive conditioning models. The psychosocial model of Henry and colleagues involves crowding and aggressive confrontations of adult mice reared in isolation, and has been shown to be associated with a number of chronic physiological alterations. More recently, the work of Manuck, Kaplan, and Clarkson has extended the psychosocial stress model, in combination with cholesterol diet, to studies of coronary atherosclerosis in primates. Aversive conditioning models include Anderson's studies of the development of hypertension in dogs exposed to a combination of avoidance conditioning schedules and increased salt intake. Dog and monkey models, because of their size, seem especially well-suited for hemodynamic studies.

The relevance of laboratory measurements to comparisons of cardiovascular adaptations under naturalistic conditions remains an empirical matter. The use of telemetry of pressure and flow variables from experimental animals in the social situation has been achieved by Von Citters, Franklin and others and is currently being reviewed with modifications and improvements in the pressure measurements for a collaborative US-USSR program on Primate Social Behavior and Hypertension.

Importance. A rank order of the key variables that deserve measurement in animal models might be:
1. Arterial pressure (with heart rate)
2. Cardiac output (with total peripheral resistance)
3. Renal blood flow
4. Coronary blood flow
5. Skeletal muscle flow
6. Metabolic studies (water, electrolyte balance)
7. Measures of sympathetic and parasympathetic control would be desirable.

Measurement strategy. There seems to be no noninvasive measure of BP that is as accurate as that provided by use of the chronically indwelling catheter. Cardiac output and regional flows are best measured by Electromagnetic or Doppler flow probes. The observation of pressures and flows over extended time periods necessitates the use of a computer for data reduction and analysis.

Control Levels

It is well documented that "resting" levels of cardiovascular function vary appreciably within and among individuals considered to be free of any cardiovascular disease such as young adult humans who commonly comprise the volunteer subject population of many basic research efforts evaluating hemodynamics. In part, this variability of resting levels appears to be the result of the novelty of and individuals' uncertainties about the laboratory situation. This creates a problem, particularly in those individuals who have elevated "resting" levels since it can cause an underestimation of the differences in levels found during various laboratory or even naturalistic stressors. That is to say, individual differences tend to be minimized. This has been demonstrated to be the case when resting levels are obtained once the individual is acclimated to the situation and has experienced the stressors.

One traditional method used to resolve the influence of baseline differences is statistically to correct for initial resting levels. However, this disregards the possibility that the effects of the situation may well be additive to those of the experimental stressors or tasks.
There are three ways to minimize these situational-anticipatory effects on baselines. The simplest method is to obtain a resting level after the experimental stressors have been administered, i.e., during the last 10 minutes of a 30-minute resting period. This is not only the simplest method, but it has the advantage of controlling the influence of nonlaboratory circumstances such as events of the day on baseline. The limitations of this method are that with some people these nonlaboratory influences may not dissipate during this followup resting period nor will the effects of the laboratory stressors.

An alternative procedure is to have the individual return to the laboratory on some second occasion just to relax, knowing full well that no experimental stressors will be used. As a precaution, this second occasion should be scheduled on a day that is relatively routine and when the individual has not taken any substances or is in a condition (e.g., having an infection) that would influence cardiovascular function.

A third method is to use ambulatory monitoring in which occasions are selected in the course of the individual's every day life that are maximally relaxing (not sleep). This can be time consuming and is restricted to the measurement of HR and BP. It offers the advantage of providing HR and BP data over a variety of circumstances including periods of natural relaxation.

RECOMMENDATIONS

Task Group A

A. The task group on hemodynamic and electrophysiological measures defined reactivity as the physiological changes of an organism from a specified control level in response to a particular set of stimulus conditions. Factors influencing the pattern magnitude, and/or duration of these adjustments include:
1. The individual's perception of stimulus
2. Behavioral response style (e.g., personality)
3. Emotional state
4. Genetic background
5. Physical status
6. Past history.

B. The group dealt with four issues:

1. Selection of response measures
2. Methods used to assess neural and hormonal influences controlling circulatory adjustments
3. Animal models
4. Methodological problems in assessing reactivity as a function of different control levels.

C. Selection of Response Measures

Since the physiologic adjustments of an organism consist of an integrated pattern of responses, a sufficient number of responses must be measured to allow the response pattern and its variation to be measured.

1. Blood pressure

   a. Invasive measures of BP remains the "gold standard", and noninvasive techniques should be validated against invasive BP measures.

      (1) Another advantage of invasive BP is that is can detect transient changes.

   b. Ausculatory techniques are the best established noninvasive measures.
c. Oscillometric techniques are reasonably reliable for detecting SBP and MAP, but not DBP.

d. Pulse transit time not recommended.

e. Ambulatory monitoring of BP can be accomplished with reasonable accuracy in many subjects, but great care must be taken in evaluating results.

2. EKG

a. Investigators of phasic HR changes need to be sensitive to the inherent variability of HR due to respiratory-HR interactions.

3. Assessment of cardiac performance

a. Contractility

(1) The systolic time interval measure (PEP/LVET) is a reliable method for estimating changes.

(2) Mean rate of circumferential fiber length shortening is a good index of contractility change.

i. originally based on angiographic date, but recent improvements in M-mode echocardiography makes it possible to make the assessment noninvasively.

b. Cardiac output

(1) Reliable invasive measures include Fick, Dye dilution, thermal dilution, EM flow probe, and contrast left ventricular angiography.
(2) Impedances cardiography techniques are making progress and appear to be reliable in some hands.

(3) Respiratory CO\textsubscript{2} and CO\textsubscript{2} rebreathing offers another noninvasive technique.

4. Flow

a. Coronary flow and renal flow measurements in behaving organisms are currently restricted to invasive procedures in experimental animals (e.g., EM flow and Doppler flow probes).

b. Muscle blood flow by venous occlusion plethysmography is useful but requires considerable care.

c. Distribution of flow can be repeatedly (up to 16 measures) sampled in animals using labeled microspheres.

d. Cutaneous blood flow provides an index of thermoregulation and sympathetic reactivity. Techniques include Xenon clearance, venous occlusion of the finger, and photoelectric techniques.

D. Methods to Assess Control of Circulation

1. Parasympathetic vs. sympathetic tone

a. Heart rate variances or V for parasympathetic tone
b. PEP/LVET or QT/S\textsubscript{2} ratios for sympathetic drive on heart

2. Baroreceptor reflex gain can be assessed by:

a. Plotting R-R interval against SBP after phenylephrine injection
b. Valsalva maneuver
c. SBP decrease and HR increase to tilt
d. Neck suction coincident with maximal stretching or baroreceptors

3. Efferent parasympathetic pathway can be evaluated in terms of HR response to atropine, amyl nitrate, and IV nitroglycerine.

4. Efferent sympathetic pathway can be assessed in terms of SBP responses to tyramine and by selective alpha and beta agonists and antagonists.

5. Recent interest has focused upon central arousal as indicated by a lack of habituation of autonomic indices during or after tasks.

   a. Increased differences in values have been examined as "hot reactors."

   b. Use of alpha-2 agonists, or beta-adrenergic blocking agents that are lipid soluble can be used to assess central sympathetic drive.

E. Animal Models

1. Models

   a. Genetically susceptible animals such as SHR, SHR x WKY cross, salt sensitive rat.

   b. Aversive conditioning models (Anderson) and psychosocial models such as Henry, and Bowman-Gray group.

2. Strategies

   a. No noninvasive measures of BP that are as accurate as cardiac indwelling catheter.
b. CO and regional flow are best measured invasively.

c. Telemetry advances make assessment in free moving animals promising.

F. Control Levels

1. It is necessary to specify control levels when assessing responses to particular conditions.

a. Casual measurement of BP examines BP response to a task, which differs from:

1. Between task baselines (control levels)
2. Resting baseline (control levels)
3. Ambulatory resting
4. Ambulatory active
BIOCHEMICAL MEASURES OF REACTIVITY

Group Leaders: Robert McDonald, David S. Goldstein

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The definition of the baseline value must be considered in interpreting biochemical measures of reactivity. Reference values vary as a function of the time of day, the stage of sleep, or the stage of the menstrual cycle. Given the choice of a very large number of biochemical determinations over these time periods, integrated sampling, or sampling at the same point in time in control and treatment groups, the latter approach seems best. Integrated sampling may eliminate the contribution of time-dependent factors at the expense of loss of sensitivity in detecting acute reactivity-related changes. The investigator needs to decide whether absolute or percent changes provide the more valid measure of reactivity, depending upon what is known about the physiology of the particular system being studied.

The task group considered a three-tiered hierarchy to provide a conceptual framework for reviewing the role of biochemical measures of reactivity. At the lowest tier are the levels themselves of these substances; e.g., catecholamines. At the next tier are the systems that orchestrate these biochemical measures. This series of systems includes the pituitary-adrenocortical axis, the sympathoadrenomedullary system, the system controlling gonadotropins, the cholinergic nervous system, the renin-angiotensin system, and the central neural pathways for neuropeptides. The top tier consists of the individual's patterns of response to environmental stimuli as the person perceives them. Each pattern differentially activates one or more effector systems in a manner which is reproducible for that individual but which may vary among individuals.

Disorders of reactivity may occur at any level of the hierarchy to produce changes in reactivity which are related to the later development of
coronary disease or hypertension. Thus, a Type A individual may have an abnormality in his pattern of response to his perceived environment. A hypertensive may have increased sympathoadrenomedullary activity. A hypernoradrenergic hypertensive may have normal sympathetic outflow and normal behavioral reactivity but ineffective neuronal removal of norepinephrine.

Biochemical variables which may be relevant to the relationship between reactivity and hypertension include norepinephrine, epinephrine, cortisol, testosterone, estrogen, prolactin, growth hormone, dopamine, prostaglandins, neuropeptides, kinins, and renin. Variables possibly related to atherosclerosis include epinephrine, norepinephrine, cortisol, testosterone, estrogen, prostaglandins, neuropeptides, and kinins. Variables possibly related to coronary heart disease (including myocardial infarction) include epinephrine, norepinephrine, cortisol, testosterone, estrogen, the cholinergic nervous system, prostaglandins, neuropeptides, and kinins.

In measuring these substances, usually by radioimmuno- or radioenzymatic procedures, the investigator must consider not only these levels but also the state of specific receptors, translation of receptor occupation into physiological action by the cell, the threshold and gain of the response, the time course of the response, and statistical aspects of the experimental design.

It is virtually impossible to predict on the basis of what is known about steady-state levels which of the above variables actually will prove valid in prospective studies of reactivity. Illustrative of the complexity of this area is the issue about whether dexamethasone suppression testing validly measures depressive reactions that may occur in coronary patients.
The task group proposed and examined a number of psychological variables as possible correlates of reactivity and categorized them into three groups: (1) those that have been found to relate significantly to reactivity, (2) those that have been related to cardiovascular disease (CVD) endpoints but not as yet to reactivity, and (3) those that have not been related to either reactivity or CVD endpoints.

1. Personality Variables That Are Related to Reactivity

**Type A Behavior Pattern**

Type A behavior has been assessed by a Structured Interview (SI) and by various self-report questionnaires, most notably the Jenkins Activity Survey (JAS). Reviews of the literature indicate that Type A measured by either procedure predicts reactivity under certain conditions, namely those of moderate difficulty and moderate incentive. It should be noted that the SI predicts reactivity more consistently than the JAS and, when observed, the differences in reactivity between Type A and Type B subjects are greater when the behavior pattern is measured by the SI.

**Hostility**

Hostility is conceptualized as a complex set of enduring attitudes reflecting "ill-will" and a negative or suspicious view of others. Potential for hostility, a clinical rating derived from speech stylistics and content of responses to the SI, has been found to relate to reactivity in two studies but not in a third. Hostility as measured by the Cook and Medley "Ho" subscale from the MMPI, a scale interpreted to measure cynicism and suspicion, or paranoia, has been studied in conjunction with reactivity
in one study and not found to show a significant relationship. Hostility as measured by the test hostility measure and hostility reported by subjects to minor interpersonal conflicts have been found to relate to reactivity.

Anger

Anger, as assessed by the Spielberger State Anger Scale, has been found to relate to reactivity by Glass et al. and in a study of individuals with a possible family history of hypertension. Anger, as assessed by the Spielberger Trait Anger Scale, has been found to relate to reactivity in normotensive undergraduates independent of family history. In hypertensive workers, anger arousal, as assessed by the Novaco Anger Scale, was found to relate to reactivity defined by the difference between blood pressures assessed in a worksite medical dispensary and those assessed at subjects' actual worksites.

Anger Expression

In contrast to the experience of anger, how it is or is not overtly expressed is of potential importance in studies of reactivity. Reducing frequency of angry verbal interactions between hypertensive patients and their spouses was shown to reduce systolic BP reactivity in a controlled experiment. Hypertensive workers who are high on "Anger-In" as defined by scoring high on the Novaco Anger Scale and low on the Galassi Adult Self Expression (an Assertiveness Scale) were found to have larger differences between medical dispensary and worksite blood pressures than other hypertensives. Overt anger expression in role-play encounters was related to greater pressor responses. In an animal model, in cynomolgus monkeys, heart rate responses to a standard stressor was related to the frequency of aggressive behavior in socially housed groups of animals.

Dominance/Submission

A primary behavioral descriptor of social relationships in nonhuman primates is the asymmetric and transitive dominance hierarchy. It has been
observed that dominant cynomolgus monkeys housed in unstable social conditions develop more severe atherosclerosis than their subordinate counterparts. Dominant monkeys showed greater reactivity as defined by differences in heart rate observed as a function of relative proximity and physical contact (passive affiliation) than subordinates.

**Anxiety**

The relationship between general anxiety, as assessed by self-report scales, and reactivity has been investigated in a number of studies with negative results. Self-report measures of test anxiety have yielded mixed results in relation to reactivity. However, none of these studies controlled for possible underreporting of anxiety by individuals who score high on the Marlowe-Crowne Scale, a measure of defensiveness. Defensive-low anxiety subjects showed heart rate increases over baseline that were comparable to subjects reporting high anxiety, independent of defensiveness.

**Affiliation**

Affiliative behavior, operationalized as body contact, has been found to be associated with lowered heart rate in both human and animal studies.

**Locus of Control**

The evidence on the relationship between locus of control and reactivity is mixed. Two studies suggest a relationship between internal locus of control and reactivity, while a third study suggests that this relationship may be moderated by availability of control.

2. Personality Variables That Are Thought To Be Related to CVD

Variables thought to be associated with the development of CVD but for
which there are no associations with reactivity include depression, neuroticism, status-incongruity, life and job dissatisfaction, and social support and networks. The lack of data on these associations appears to be due to the absence of relevant reports in the literature. Given the potential associations between these variables and CVD, investigation relating these constructs to reactivity may be warranted.

3. Personality Variables That Have Not Been Related to Reactivity or DVD

For a number of personality variables there is little evidence to suggest their association with either reactivity or CVD (e.g., psychoticism, extroversion/introversion, and sex-role orientation); whereas one personality variable has shown some association with a risk factor for coronary heart disease (serum cholesterol), namely field dependence in Type A subjects. With the exception of the latter variable, there appears to be little compelling rationale for investigations involving these variables.

General Considerations and Recommendations

General considerations and recommendations for future research on psychological correlates of reactivity are summarized as follows:

Subject Characteristics

Most data on reactivity have been collected from homogeneous samples—usually involving predominately white, male, college volunteers; or, in case-control studies of essential hypertension (EH) and CHD, carefully matched patient and nonpatient samples. As a result, little is yet known regarding the comparative responsivity of individuals differing in age, gender, ethnicity, and socioeconomic status, although there is a growing literature on Type A behavior and reactivity in children and adolescents. However, the limited data available indirectly suggest that these subject characteristics may influence autonomic reactivity to behavioral stressors.
Age. Sensitivity to pharmacologically induced beta-adrenergic stimulation has been suggested as declining with advancing age. This is a change which may lead elderly individuals to appear less reactive than their younger counterparts on certain response measures such as heart rate. Moreover, due to the interrelatedness of all hemodynamic adjustments, a decreased sensitivity to beta-adrenergic stimulation may result in a somewhat different patterning of cardiovascular responses among older individuals.

Race. We are aware of no published studies explicitly comparing physiologic reactions to psychological stimuli in black versus white subjects. However, it has been suggested that, unlike for whites, essential hypertension in blacks tends to be volume dependent and more often associated with low plasma renin activity. In view of the possibly different physiologic mechanisms underlying much hypertension in blacks, then, it is plausible that behaviorally elicited autonomic and neuroendocrine responsivity in blacks also differs relative to whites. In turn, reactivity may play a different role in the pathogenesis of cardiovascular disorders among blacks.

Sex. With respect to gender, it is commonly observed that BP levels are lower in women than in men until about age 50 to 60, after which BP rises markedly in females, as does the incidence of EH and CHD. In psychophysiologic studies, women also occasionally show a less pronounced cardiovascular and catecholamine responsivity to behavioral stimuli than do men, as noted earlier. Interestingly though, familial risk for EH has been found to potentiate SBP reactivity to a greater extent in females than in males. Others have reported that the HR and BP reactions among women also differ reliably between phases of the menstrual cycle and vary with measured estrogen and progesterone concentrations. Thus, hormonal fluctuations may significantly influence behaviorally induced cardiovascular responses among normally cycling females. At the very least, these findings suggest that psychophysiologic reactivity in women should be assessed with a knowledge of the phase of each subject's menstrual cycle at the time of testing, or preferably, at a common point in the cycles of all participating women.
Thus, there are differences in sex, age, socioeconomic status, and race and ethnicity which need to be taken into account when designing studies and interpreting relationships between personality variables and reactivity. These factors influence the measures selected for tapping the personality variables and also for selecting stressful tasks that are appropriate in terms of the subject's involvement (i.e., matching person and task/situation).

Personality variables and other individual differences may interact with themselves and affect reactivity. For example, hostility as well as family history of CVD may interact with measures of Type A to further potentiate cardiovascular reactivity. This will be particularly important to the extent that epidemiologic evidence supports such an interaction of personality variables to disease outcome.

The failure to find relationships between certain personality variables such as anxiety and physiological reactivity may be due to suppressor variables masking true relationships. For example, scales tapping defensiveness make it possible to uncover a relationship between levels of anxiety and physiological reactivity. Weinberger, Schwartz, and Davidson have devised a system for subclassifying subjects who report low anxiety into two subgroups: persons who correctly label their anxiety as low; persons who incorrectly perceive and/or report that their anxiety is low. The first subgroup shows the predicted low levels of physiological reactivity, while the second subgroup shows high reactivity equal to, if not greater than, subjects reporting high anxiety.

An essential consideration must be the assessment of personality variables using a task or eliciting stimulus, which is appropriate to that personality variable. It must not be assumed that any psychological measure of individual difference will predict cardiovascular reactivity to every situation. The literature on Type A behavior provides a strong example of this interrelationship of variable and situation. Type As are not always more responsive than type Bs. Studies show that only tasks providing a challenge, competition, or threat will differentiate these groups. Stressful stimuli such as the cold pressor test apparently do not
engage the Type A and do not elicit hyperresponsivity. Although the exact qualifications of "type A stimuli," assessed by responsivity, are not known in detail, there is no doubt of the importance of task selection in this field of research.

The same is also true in studies of the cardiovascular responsivity of hostile, angry people. To elicit a response in a hostile person, one who may be suspicious of the motives of others or who feels "people are no damn good," a stimulus must be relevant to this dimension. Harassment, verbal abuse, and unfair treatment are all stimuli relevant to the hostile person and may well yield greater responses.

Not only the task, but the entire situation surrounding the task must be considered. A mental arithmetic task performed for an incentive within a friendly atmosphere may stimulate the competitive Type A but should not affect the hostile subject. Changing the mood of the task by introducing an antagonistic, surly technician may engage the angry subject but may lose the competitive one when the task is no longer an enjoyable challenge.

In summary, it is unlikely that one stimulus will work for all kinds of responsivity. Consideration must be given to the combination of personality variable and task situation; when the goal is to elicit responsivity, to ensure that the stimulus will be relevant to the individual difference under consideration.

It is not advisable to restrain our search for behavioral correlates of reactivity to a concept of reactivity which incorporates only measurement of acute responses to brief laboratory tasks, e.g., cold pressor, reaction time, mental arithmetic. At the same time, we caution against presuming that the behavioral correlates of a laboratory task are also relevant to fluctuations in cardiovascular and neuroendocrine states outside the laboratory. In this regard, it is necessary to begin obtaining measurements in both laboratory and natural settings and to establish the nature of the associations between the two (recurrent activity vs. prevailing state).
In ambulatory measurement there is a need to obtain both behavioral concomitants and the subjective experience of the individual.

Subjects' task appraisals. As noted earlier, physiologic responses to behavioral stressors are critically dependent on the manner in which individuals construe or interpret the stimuli presented to them. This fact poses perhaps the greatest challenge to investigators examining reactivity across a broad range of subject populations. It is unlikely that the level of engagement experienced by a 20-year-old college student when asked to perform difficult problems in mental arithmetic (e.g., serial subtraction by 17s) will be comparable to that of an educationally disadvantaged inner-city youth of the same age. Similarly, the thematic content of an interpersonal challenge (e.g., stress interview) may be more relevant to the experiences of some individuals than of others. These problems point to the need for adjustment, or "tuning" of stimulus attributes to match the characteristics of relevant groups within populations of interest.

In the case of cognitive tasks like mental arithmetic, such adjustment might be achieved by calibration of task demands to the performance capabilities of the individual subject. In other instances, stimulus adjustment may be more difficult, requiring use of a different kind of challenge, rather than varying the relative demands of a common task. This point is illustrated well by MacDougall, Dembroski, and Krantz. These investigators failed to observe differences in the cardiovascular responsivity of Type A and Type B females to laboratory stimuli which had previously elicited differential responses in Type A and B males. When women were instructed to interact verbally with a female confederate, however, subjects' cardiovascular responses did vary as a function of Type A, indicating that a face-to-face interpersonal challenge represented a more appropriate (effective) behavioral stimulus among these young adult women.

In epidemiologic studies, a psychological standardization of stimulus tasks to compensate for the disparate attributes of all socially and demographically distinct subgroups of the population is impracticable, and may on occasion be undesirable if group differences in appraisal are
thought to underlie risk. Nevertheless, measurement of psychophysiological reactivity is unlike assessment of height, weight, blood lipids or other strictly physical parameters, since calibration of stimulus characteristics to particular samples of interest is often a necessary prerequisite for these evaluations.
DEMOGRAPHIC/POPULATION VARIABLES RELATED TO REACTIVITY

Group Leaders: Laurence Watkins, Richard Rose

Group Members: A. Aleksandrov, Katherine Detre, Elaine Eaker, Clarence Grim, George Kaplan, Robert Levenson, Barbara McCann, Richard Surwit, Carl Thoresen

Studies of reactivity and its relationship to cardiovascular disease in different demographic groups are important for the following reasons:

(1) Differences in reactivity among groups may help to explain the associations between group characteristics and the risk of the cardiovascular diseases, coronary heart disease and hypertension.

(2) Demographic characteristics and population group membership may serve as markers for common processes which determine reactivity.

(3) There may be synergistic effects among group membership, reactivity, and exposure to other risk factors; or group membership may act as an effect-modifier for the putative reactivity-cardiovascular disease association.

An alternative formulation of these concepts is to regard reactivity as either a dependent or independent variable. Thus, reactivity may be regarded as a dependent variable partly determined by one or more demographic or population variables. On the other hand, it may be regarded as an independent variable along with population-demographic variables, in studies examining relationships of risk factors to cardiovascular disease.

Because the relationship between reactivity and CVD is unclear, we have chosen to focus on clarifying the relationship of demographic variables to various measures of reactivity. Cardiovascular reactivity results from a complex interaction among end-organ receptor sensitivity, neuroendocrine responsivity, renal function, and central nervous system activation and control. These classes of responses should be assessed independently.
Because of the obvious interaction of cultural variables with responses to standardized stressors, we believe that reactivity should be tested with "physiologic" challenges as far as possible. Where a cognitive challenge is required, it may be advantageous to develop one more neutral than mental arithmetic, for example some nonverbal computer game.

The following population-demographic variables were considered: age, sex, family history, race, ethnicity, and a class of socioeconomic variables including education, income, occupation, social mobility, place of residence, and marital status. In the case of each of these variables, the problem of defining or operationalizing the variable was first addressed. Then, specific additional descriptors which might be important in the study of reactivity were considered, and problem areas for such studies were identified. Finally, the relationship between the variable and CVD was reviewed or considered briefly, and the available evidence on the relationship between the variable and reactivity was collected or examined.

Age

An individual's age is a well-known determinant of the risk of CVD. In industrialized societies, mean blood pressures rise with age. Similarly, the incidence of CHD increases with age in industrialized societies. The relationship of age to the reactivity-blood pressure relationship is complex since cardiovascular regulation probably differs in different developmental phases of essential hypertension (EH). There is evidence that in the early phase, cardiac output is increased, peripheral vascular resistance is normal, and the activity of the renin-angiotensin system may be increased. In established EH in older subjects, cardiac output typically returns to normal, while peripheral resistance is elevated, and activity of the renin-angiotensin system may be normal or even low.

Definition and additional descriptors. While a simple biological or chronological definition of age may appear adequate, there is evidence from a variety of studies that in evaluations of the relationship between age and BP during pre-adult development, account should be taken of such
factors as pubertal development (by the Tanner Scale), bone age, height, weight, and other indices of body mass. It is plausible that reactivity might also be affected by such factors and account should be taken of them in the design of studies.

Association of age with reactivity. We are aware of, but have not examined in detail, a variety of physiologic studies demonstrating age-related diminution of beta-adrenoreceptor mediated cardiovascular responses. For example, in older subjects, peripheral vascular responses to beta-adrenoreceptor stimulation with metoprolol and isoproteronol are diminished. Studies of radioligand binding sites on human mononuclear leukocytes indicate that these changes in beta-adrenoreceptor mediated effects are not due to a change in the number or affinity of the receptors. Instead, in leukocytes of older individuals there is reduced cyclic AMP production following in vitro isoproterenol stimulation. In contrast, alpha I adrenoreceptor mediated vasoconstriction is enhanced and is relatively more prominent in older subjects as beta-adrenoreceptor mediated vasodilatation decreases. It is unknown whether postjunctional alpha II adrenoreceptor mediated vasoconstrictor responses change with age.

Other sources of data which we have not explored include those in which the blood pressure response to venipuncture was recorded in subjects in differing age. In addition, published studies of infants' responses to visual cliff stimulation may be a fruitful source of information on reactivity. A number of studies have demonstrated that reactivity of the renin-aldosterone system and the renal response to sodium loading decreases with age.

Gender

It is known from epidemiologic studies that there is a 10 to 20 year lag in occurrence of myocardial infarction and sudden death among women as compared to men. While the incidence of angina pectoris is less frequent in women prior to the age of 65, it is the most common presenting symptom of CHD in women. Angina pectoris also has a better prognosis in women prior to age 65 than in older women.
Cross-sectional studies have demonstrated that systolic and diastolic blood pressure (SBP, DBP) levels are higher in men than in women until menopause, when the levels in women surpass those of men of the same age. Longitudinal data show a steady increase of SBP and DBP with age among men and women, and blood pressures in men are consistently higher than in women. The difference between the longitudinal and the cross-sectional data may be due to differential mortality of men with elevated blood pressures.

Evidence for a gender differential in reactivity. Only a few studies have examined gender differences and similarities in cardiac and neuroendocrine responsiveness to various stressors. In addition, there is a paucity of information on variation of physiological reactivity with the menstrual cycle, menopausal status, hormonal therapy and oral contraceptive use.

However, from the studies that have examined both females and males, a certain consistency in results emerges and further systematic study is warranted. The research of Frankenhaeuser, VonWright, et al. demonstrates that important gender differences exist in neuroendocrine responses in male and female university students. During rest and relaxation, differences in catecholamine excretion of males and females are slight, but in challenging performance situations consistent differences appear. For stress induces by intelligence testing, a color-word conflict task and venipuncture, females show a lack of adrenaline increase, while there is a significant rise in males. The same researchers also looked at a "real-life" stress situation (a 6-hour examination for matriculating from high school): they found that females did increase their adrenaline secretion to a significant degree but that the rise was significantly higher for males. It is important to note that females did not perform less efficiently than males on any of the above tests; however, self-reports showed males had increased feelings of success and confidence while females reported feelings of discomfort and failure.

Similarities in adrenaline excretion have been found in males and females when the social role is similar. For example, women in "nontraditional" roles tend to respond to achievement demands by increase in adrenaline.
secretion which is similar in degree to that of males. Women engineering students, bus drivers, and lawyers show similar adrenaline excretion to males in responses to a cognitive-conflict task.

Shapiro and Miller have found that among mild hypertensives women perform mental tasks with lower speed and accuracy compared to men at the same level of BP. These effects are diminished after administration of antihypertensive medications.

MacDougall, Dembroski and Krantz have found that women who exhibit Type A behavior show larger hemodynamic responses than Type B women but the situations that evoke such responses may be very different for females and males.

Additional Descriptors. Although research on gender differences and hyperreactivity have examined and controlled some physiological characteristics that may be related both to reactivity and to sex differences (e.g., relative weight), it would also be important to examine cigarette smoking, alcohol intake, education and physical activity.

Problems. Overall, it appears that women are less physiologically reactive than men. However, some evidence suggests that as women move into more male-dominated occupations and responsibilities their degree of reactivity may increase.

Research is needed over the life cycle to unravel these interesting but complicated differences. For example, are girls socialized in ways that protect them from hyperreactive responses or are the differences entirely biological? Do women who enter the more "nontraditional" roles lose a "learned coping response" or are the differences biologically determined? More research is needed on differential gender responses to similar stimuli, with special attention to the meaning of the stimuli, involvement in the task, interpretation of threat, expectations of success and failure, etc. Are women whose reactivity responses are similar to those of men at increased risk of CHD? In addition, special attention should be paid to various issues related to the study of reactivity in women. For example,
how does physiological reactivity differ in prepubescent and pubertal adolescents? Is there variation in reactivity over the menstrual cycle? What is the response to endogenous or exogenous hormones? Does estrogen replacement therapy in postmenopausal women have any effect? Variation over the life cycle is important and comparisons should be made between pre- and postmenopausal women. The cause of cessation of menses (i.e., natural vs. surgical) may be an important confounding factor.

Other variables that should be ascertained in comparative studies include age, education, occupation, social support, feelings of distress during tasks, family history of heart disease and hypertension, marital status, parity, smoking history, drugs, personality variables. Without these, comparisons could be confounded.

**Family History**

A familial history of EH or CHD has long been identified as a risk factor for the development of these disease outcomes. At least a quarter of a century ago, EH was shown by the work of Pickering, Platt, Miall, and others to exhibit significant familial aggregation. Since the 1930s, clinicians have recognized that ischemic heart disease clustered in families.

In recent literature, psychophysiological responses have been assessed in normotensive individuals at elevated risk for EH or CHD by virtue of a positive parental history of these disease outcomes.

**Definition.** In recent studies, family history has been defined as reported, and less often as documented, history of disease in one or both parents. Questionnaire reports of familial medical history are commonly used to form groups of prehypertensive or pre-CHD individuals who, presumably, differ in risk. Thus, many recent studies contrast psychophysiological reactivity in familial or genetic groups vs. control groups according to positive or negative parental disease history.
Additional descriptors. Investigators often categorize a child as "at risk" if one or both parents are reported to have either EH or CHD. Some investigators have attempted to quantify the risk according to whether neither, one, or both parents—or extended family members—are affected.

Problems. There is a potential problem of bias if individuals are classified as being at risk for disease outcomes on the basis of positive parental history. Neither EH nor CHD exhibits a simple, lineal pattern of transmission from parent to offspring; both diseases are multifactorial in etiology. Some proportion of cases of EH and CHD must occur "sporadically" despite negative family history. The issue is whether inferences drawn from the study of "familial" cases can be generalized to the larger population of prehypertension or pre-CHD individuals.

Practical problems. It has become fashionable to define family history on the basis of offspring report—particularly in studies of college-age samples. There is a significant limitation in this definition of convenience: many adolescents and young adults lack adequate information on the medical status of their parents. Parental reports of EH are typically documented in a physician's records, but only if the parent reports antihypertensive treatment. The mere report "I have been told that I have high blood pressure by my doctor" is not sufficient. Further, parental report of normotension must, we believe, be documented by direct measurement of parental BP by trained observers using appropriate measurement techniques. The classification of parents for CHD is even more difficult, because no simple yet sensitive measurement of CHD is available.

Studies of at-risk children may encounter subtle problems arising from illegitimacy or adoption. In data collected from volunteer families in Indiana, the frequency of nonpaternity was significant and population frequency of nonpaternity may, in some instances, be greater.

An alternative high-risk research strategy may be useful in some applications. Discordance for EH among monozygotic twins during early and mid-adulthood suggests the strategy of studying the normotensive identical co-twin of hypertensives. The co-twins could be studied over time to
evaluate psychophysiological reactivity during the early developmental stages of EH. The identical co-twins of EH cases offer a truly "high risk" sample for investigation.

Association of Family History with EH/CHD

The familial aggregation of EH and CHD is well-known. Significant heritability has been demonstrated in classic twin and adoption studies of casual BP levels and in twin studies of EH and CHD. The collaborative VA Twin Studies in the United States are among the most recent of these.

Relationship of Family History to Reactivity

In recent years, a number of investigators have compared normotensive individuals allocated into "positive" and "negative" family history groups according to parental medical history. Representative studies include those by Remington et al. and Falkner et al. Remington et al. studied offspring of probands attending a hypertension clinic. BP was observed in response to a series of stressors. The finding was that baseline BP was elevated in those with a positive family history, but stress reactivity did not differentiate the two groups. Falkner et al. reported increased BP and HR reactivity (exaggerated responses of longer duration) to 10 minutes of paced mental arithmetic among at-risk adolescents with positive family histories than among those with negative family histories. In a subsequent study, the same investigators showed that normotensive adolescents who were above the 90th percentile of the BP distribution and who had a positive family history of EH and increased HR and BP reactivity at baseline, were significantly more likely to develop fixed EH during a 41-month followup. Lawler and Allen reported that during two laboratory tasks, 11- to 13-year-old children with a positive parental history of EH or CHD exhibited greater cardiovascular reactivity than did controls. Manuck tested college-age subjects who were differentiated by parental medical history; increased SBP responses characterized the at-risk subjects during isometric hand grip and cognitive challenges. Baseline HR was also elevated in the positive family history group. When classified into high vs. low HR reactors, the high HR reactors with a positive family history had higher BP
levels at baseline. No association of family history and baseline BP was observed among the low HR reactor subjects. Jorgensen studied reactivity to the Stroop test, serial subtraction and shock avoidance and reported that subjects with a positive family history exhibited greater BP responses and greater stereotyping to each of the three stressors.

More direct evidence of a genetic influence on cardiovascular reactivity to laboratory stress has been reported by Rose, Grim and Miller in a study of normotensive twins and pairs of singleton strangers, drawn from the same population. Blood pressure and HR were assessed during five stressors presented under computer control. The twins and paired singletons were tested concurrently in separate, adjacent rooms. Preliminary analyses of the twin data reveal significant genetic variance in BP responses to the stressors. Casual pressures of the twins, taken immediately before the stress protocol began, indicate significant effects of genes, gender, age, and familial risk. The interactions of these variables were evaluated in a hierarchical multiple regression analysis: genetic effects and influences of family history remained significant after account was taken of the association of casual BP with weight. In addition, physiologic and biochemical responses to sodium loading and depletion have revealed clear-cut genetic influences on plasma renin activity, aldosterone and norepinephrine as well as urinary norepinephrine and sodium excretors.

These twin studies are complemented by studies in normotensive first-degree relatives of hypertensive subjects attending Indiana University Hypertension Clinic. Grim et al. have reported that in contrast to normotensive subjects without a family history of hypertension, those with a positive family history had greater baseline blood pressure, plasma renin activity and a decreased ability to excrete sodium, but no difference in plasma or urinary norepinephrine was evident.

Race/Ethnicity

Race may be an important variable in studies of reactivity. In the United States, there are distinct racial differences in the prevalence and incidence of hypertension and CHD. The prevalence of hypertension in black
adults is about twice that observed in white adults, though it is significant that in national samples mean blood pressures are no different in blacks and whites until about age 25. Coronary disease mortality in black men is slightly less than that observed in white men, while coronary mortality in black women exceeds that observed in white women. In a small number of prospective epidemiologic studies, the incidence of coronary disease in black men was significantly less than that observed in white men, and in the only study which included black women, their mortality rates exceeded those of white women, a difference in accord with the national data.

It should be noted that the predisposition to develop hypertension does not appear to be a characteristic common to black people everywhere. Epidemiologic studies in rural areas of Tanzania and the Gambia have detected populations with a prevalence of hypertension as low as 2 percent by WHO criteria. In urban settings in Nigeria and Ghana there is an appreciably higher prevalence of hypertension, as high as 25 percent. However, comparisons of mean BP levels in rural Ghana and rural Georgia reveal consistently higher pressures in United States subjects (15-20 mm Hg differences for systolic pressure and 10-15 mm Hg differences for diastolic pressure) among black adults over a wide spectrum of age. In Durban, South Africa, the age-adjusted prevalence of hypertension is the same in black and white males. In the Caribbean, despite similarities of racial origin and cultural background among black populations, there are marked variations in the prevalence of hypertension—as low as 14 percent in a St. Lucian village and as high as 33 percent in urban areas of Trinidad.

In those developing African and Caribbean countries from which data on coronary disease incidence or mortality are available, the rates are one or two orders of magnitude less than those observed in industrialized countries. It is probable that different distributions of the standard risk factors account for these mortality differences, though it is also likely that socioeconomic and cultural factors account for different risk factor distributions.
Definitions. Studies of the relationships between disease and race have typically utilized self-reports of racial identification, though it should be noted that in Caribbean settings, studies comparing individuals of African and Indian ancestry have required that three or four grandparents be identified by individuals as being of common ancestry in order for a subject to be regarded as either African or Indian. Others are considered mixed. Race should not be regarded in studies of CVD and reactivity as a proxy for genetic constitution. With regard to black/white comparisons in the United States, because of differences in disease risk, this category is useful. However, it should be regarded as a measure of exposure to certain common experiences rather than as a genetic marker. In this regard, it may be more important to identify characteristics of an individual's educational opportunities, social experiences, socioeconomic attainment, psychological resources, and styles of coping with behavioral stressors. This would take explicit account of the sociohistorical context and of cultural characteristics of cohorts of individuals whose life experiences are being examined. A corollary of this is that if genetic inferences are to be made from racial comparisons, investigators should make explicit use of genetic markers in the pursuit of these investigations or employ twin or other familial studies.

Ethnicity is not coterminous with racial heritage. Within the field of sociology, there is dispute concerning the definition of ethnicity and a current controversy concerns its identification with culture-specific behavior or cultural awareness. However, in epidemiologic studies, interviews may be used to ascertain the individual's perception of his cultural heritage, cultural identification (self-concept) and cultural practices (including food consumption, language, membership in organizations, and social networks).

It should be noted that studies of men of Japanese ancestry in Hawaii and California have yielded conflicting evidence concerning the relationship of ethnicity (specifically cultural identification) and the incidence and prevalence of CHD.
Relationship of race/ethnicity to reactivity. The only available evidence concerning racial influences on reactivity is derived from the studies of Alpert et al. on BP responsiveness in black and white adolescents to the stress of treadmill exercise. These investigators observed that peak exercise BPs were higher in black females ages 6 to 15 years when account was taken of both age and body surface area. The investigators suggested that systemic vascular resistance might differ in these populations during exercise. In contrast, the reactivity of the renin-aldosterone system appears to be lower in black than white normotensive subjects and this racial difference increases with age. In hypertensive subjects the reaction of the renin system is likewise markedly blunted in blacks. In their recent review, Krantz and Manuck cited no other studies of racial differences in cardiovascular reactivity.

Socioeconomic Variables

Socioeconomic class has been found to be inversely related to coronary disease mortality and incidence and to BP prevalence and incidence in a variety of studies. Coronary disease has also been related to job characteristics in a number of Swedish studies. In addition, the incidence of hypertension has been related to engaging in a high stress occupation. Examinations of coronary mortality by geographic location have revealed marked state-to-state variation in American studies. Thus, there is evidence that socioeconomic status and variables customarily employed to define it, including occupation, income, education, and place of residence, are related to the prevalence and incidence of cardiovascular disease.

Occupation. Studies of the relationship between occupation and CVD suggest that account should be taken of white collar versus blue collar occupational stratification. In addition, there is evidence that the nature of the occupation as a marker for an amalgam of physical and emotional stressors may be an important variable in studies of the relationship between occupation and coronary disease. The work of Karasek et al. has indicated that factors such as monotony, repetitiveness, and degree of control over occupational activities may affect CVD risk. Some investigators have classified individuals according to job titles and have
utilized measures of stress implied by these titles. It should be noted, however, that the normative data underlying this job classification system are not ideal.

Classification of individuals by occupation is but a proxy for a certain life experience and exposure. Information on an individual's most recent occupation may provide normative data to the exclusion of a history of job exposure. It may be necessary to take account of a history of occupational mobility in studies of cardiovascular reactivity. It is even possible that reactivity may influence an individual's choice of occupation.

Income. Evaluation of income, like that of occupation, is also fraught with difficulty. It may be adequate to rely on self-report of income, but the choice must be made among family income, individual income, number of family members supported and source of income (self-employed vs. salary) in examining this variable.

Education. "Years of education" is a simple measure of educational attainment. However, the influence of education on reactivity may be age-cohort specific and may vary within racial-ethnic groups.

Place of residence. Place of residence, urban/rural, or classified by a census tract, may be a marker for a number of socioenvironmental indices. In addition, urban/rural differences may account for variations in access to and utilization of medical care, which may confound disease associations in prospective studies.

Evidence relating reactivity to socioeconomic variables. There is a paucity of research specifically examining the relationship between cardiovascular reactivity and socioeconomic variables. Evidence from the Lipid Research Clinics study suggests that education level may be weakly related to systolic blood pressure responses (SBPR) to treadmill exercise. Criqui, et al. assessed SBPR to treadmill exercise following 3, 6, and 9 minutes of exercise. Systolic blood pressure responses at 9 minutes of exercise were inversely related to educational level among females ages 20-49 years, but not in men, nor in women 50 years of age or older.
The relationship of occupational level to cardiovascular reactivity has been assessed in two studies employing 12-minute quiz interview. Schiffe et al. found that subjects with angina who were classified as executives showed greater heart rate and SBPR to the quiz than subjects with angina who were classified as nonexecutives. In addition, S-T segment depression was more frequent and of greater magnitude in executives (with and without angina). Sime et al. found that in age-matched subjects, SBPR were greater in executives than nonexecutives.

We found no studies specifically examining the relationship between measures of SES and reactivity. However, Corse et al. used the Hollingshead Two Factor Index of Social Position to match subjects according to socioeconomic status in a comparison of cardiovascular reactivity differences in subjects with and without a history of CHD.

In summary, few studies have actually been conducted to assess specifically the relationship of socioeconomic variables to cardiovascular reactivity. However, the investigations cited suggest that the inclusion of socioeconomic variables in such studies, particularly large-scale epidemiological studies, is warranted to assess further their impact on reactivity.

CONCLUSION

The data suggest that a parsimonious choice of population-demographic variables should be made in studies of stress-reactivity and CVD. The influence of age, sex and family history should be examined explicitly. Studies of familial reactivity are most likely to yield information on genetic variation. The same cannot be said of studies comparing racial groups. Studies which employ racial comparisons should take account of sociocultural variables similar to those which might be important in gender comparisons.
TASK GROUP REPORTS ON STRESSORS
PHYSICAL STRESSORS

Group Leaders: James Buell and Wallace McCrory

Group Members: Bruce Alpert, Leonard Epstein, J. Alan Herd, Rolf Jacob, Peter Kaufmann, Robert Miller, Kristina Orth-Gomer, David Shapiro, Jim L. Shields

The task of the group was to develop standards and guidelines in the area of physical stressors.

It was the consensus opinion of the group that suitable physical stressors must include the following:

a. The physical stressor must be quantifiable in terms of the specifics of conducting the procedure.

b. There should be a characteristic physiologic response pattern which is known to occur as the normal response style.

c. The technique should be reproducible in individual labs.

d. There should be a stability of response to the stressor in the absence of intervention.

e. There should be dose response capability, that is, the intensity of stressor can be graded.

f. The technique should be ethical and acceptable both to subjects and investigator.

g. The procedure should be affordable.

h. The test should be unitary, that is, a singular maneuver rather than an admixture of physical stressors, such as heart, noise pollution, and humidity in combination.
i. The technique should be time defined, i.e., acute of X intensity and duration versus chronic response.

j. The task should be plausible, that is, having real-world relevancy. Those maneuvers as contrived laboratory procedures which have no counterpart or validation in the real world as documented by ambulatory or field monitoring should be excluded.

The following stress maneuvers were considered potentially useful and meeting these criteria in studying cardiovascular reactivity and its relationship to CVD.

Exercise stress tests. These are of two varieties: a) Dynamic large muscle exercise is the premier measure of fitness as defined by estimates of maximal aerobic power. The electrocardiographic and physiologic response patterns are predictors of CVD which is extant in terms of ischemic STT response, chronotropic inadequacy, and the inability to mount a reasonable blood pressure level under exercise stress. Vehicles for performing exercise include treadmill, a field step test by Balke and bicycle ergometry. Exercise of large muscle groups in this way elicits neuroendocrine and electrophysiologic manifestations. There are metabolic consequences which are well established and it is desirable to acquire physiologic data during multiple stages. The Bruce protocol was recommended as the standard for treadmill testing in normals. Where possible, maximal treadmill tests are preferable over submaximal tasks; however, in healthy populations, heart rate response can be extrapolated in submaximal tests to a maximal level, yielding an expression of relative aerobic fitness.

b) Isometric stress testing incorporates a large body of literature and is usually accomplished using a hand grip dynamometer. It is recommended that the task be standardized by requesting the subject to perform 50 percent of a previously performed maximum voluntary contraction and to persist in the endeavor for 2 minutes. A variety of cardiovascular metabolic responses may be monitored during this test.
Cold pressor test. The cold pressor test has been used by Ansel Keyes in one study as a response predictor of coronary disease. It is predominantly an alpha-mediated and vasoconstrictive response when uncontaminated by cortical influences. It is recommended that the water temperature be 1°C to 3°C and that the hand be inserted to the wrist or above and maintained for a period of 60 seconds at which time BP should be taken. In addition, the instructions to the subject should be given in a nonthreatening and nonchallenging manner. As with exercise stress tests, cooperation and motivational factors may be important in coloring physiologic responses.

Postural maneuvers. Physiologic responses to change in posture from supine to standing provide a means of testing the integrity and appropriateness of cardiovascular regulation. Blood pressure, heart rate, and various metabolic responses have been reported in health and disease and this maneuver changes preload on the left ventricle as well as requiring an exquisite coordination of autonomic responses to maintain BP in the face of decreased venous return when assuming the erect position. It is advocated as a screen for preexisting disease or disautonomic states, which by definition would confound the area of reactivity research. Responses to postural changes as a predictor of CVD are unknown. It is recommended that the subject remain supine at rest for 20 minutes, and then assume the upright position for 10 minutes with physiologic measurements being taken immediately prior to standing and at 1- to 2-minute intervals for 10 minutes in the erect position. Minimum observation should be BP and pulse rate; however, a variety of physiologic and metabolic measurables can be obtained during this maneuver.

Noise. In the European literature, noise has been related to hypertension and there are also many reports on the hemodynamics and patterns of responsiveness to noise in health and disease. Because of absence of expertise in this area, the task group considered that while potentially useful, there is a need to review the European literature, methodology, findings, applicability to reaction and the like. In addition, of course, effects are somewhat dependent upon subjective factors, such as level of hearing.
Physical factors. Ambient temperature stress was discussed and considered potentially useful in terms of heart conservation or dissipation responses. However, only specific laboratories equipped with excellent temperature control systems would be capable of carrying out this research. On the other hand, it was recognized that ambient temperature does influence physiology and its response and it was therefore advocated that investigators be assured that their experiments are carried out in a comfortable ambient temperature, considered to be approximately 72°F - 76°F.

Manipulation of time and its influence upon circadian rhythms were also discussed; however, the task group did not feel that manipulations of this sort were suitable for general application. On the other hand, it is well-known that jet lag, etc. influence physiology profoundly and it was therefore advocated that time of day and natural circadian rhythms of test subjects be standardized and stated during investigations.

Finally, the task group considered areas involving autonomic maneuvers, such as hyperventilation, baroreceptor stimulation, and a variety of pharmacologic blocking and stimulating maneuvers. These clearly are important in dissecting out patterns and mechanisms of reactivity but they are largely within the province of certain specialized laboratories and centers possessing the necessary qualified investigators and equipment to carry out these sorts of small, focused investigations.
PSYCHOLOGICAL STRESSORS PRODUCING REACTIVITY

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The concern of this task group was to describe and evaluate psychological stressors used in studies of physiologic reactivity.

For the purposes of discussion, psychological stressors were defined as tasks which elicit a physiologic response by virtue of information processing or appraisal by the subject. It is recognized that physical stressors, such as pain, noise, or thermal stimuli, may contain psychological components. Indeed, it is difficult to imagine a stimulus situation which would not involve some appraisal or interpretation by the subject. For example, when the cold pressor task is presented under high, rather than low, challenge instructions, cardiovascular reactivity to the stimulus can be greatly enhanced. However, our major concern is with situations in which the psychological features of the task are the primary elicitors of reactivity.

Tasks Utilized as Psychological Stressors

Psychological stressors that have been utilized in laboratory studies of reactivity include the following:

- Mental arithmetic
- Reaction time tasks (shock-avoidance; competitive reaction times)
- Cognitive problems (Raven's matrices, anagrams, Stroop color word)
- Video games
- Simulated public speaking
- Certain medical and surgical procedures
- Vigilance tasks (ranging from very low demand tasks that are monotonous (under load); to tasks involving modest demands for attention (sensory intake tasks); to tasks which overload the subject.)

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Many of these tasks involve a mental challenge and are the most commonly used in the psychological stressor literature, in part because they evoke large responses and in part because task administration can be easily standardized.

Other tasks are not as easy to standardize and produce less predictable physiological responses. Included are:

- Interpersonal games (cooperation-competition)
- Role playing tasks
- Interviews such as the Type A-B Structured Interview

Though sometimes difficult to standardize, these tasks are still valuable because they may mirror responses to real-life interpersonal interactions.

**Determinants of Response Intensity**

The amount of reactivity to the aforementioned tasks may be increased or decreased by varying task instructions or task characteristics along the following dimensions:

- Incentives (positive and negative)
- Predictability
- Controllability (ability to modify the outcome, such as the delivery of shocks)
- Harassment/frustration
- Difficulty of task (level of challenge)
- Duration of task
- Engagement/involvement
- Pacing (deadlines)
- Novelty
- Effort exerted
- Presence of others (e.g., social facilitation or observer evaluation)
- Affective tone (anger, fear, excitement)
These dimensions are not meant to imply mutually exclusive categories. They are, instead, characteristics which have been shown by a variety of investigators to be capable of modifying the physiologic response to the tasks. These "intensity modifiers" could be applied to other stimulus situations and may be particularly important in modifying the responses to real-life style.

**Dimensionalizing Stimulus Tasks According to Patterns of Responses Elicited**

Evidence suggests that stereotypically different patterns of physiologic responses are produced by tasks with different behavioral demands (termed "situational stereotypy"). At least two types of response patterns could be identified that might be relevant to studies of cardiovascular disease: 1) those eliciting predominantly beta-adrenergic responses ("type I") with associated increases in heart rate, cardiac output and muscle vasodilation, 2) those eliciting minimal or no changes in cardiac output or HR, but typified by increases in total peripheral resistance (TPR) ("type II"), and 3) those causing a "mixed" pattern consisting of increased HR, CO, as well as TPR. It should be noted that while these patterns have been defined by cardiovascular features, they are associated with a wide range of neuroendocrine responses which are also worthy of investigation (e.g., epinephrine, norepinephrine, cortisol), because they may be involved in deleterious effects these patterns may have. Both of these patterns could be involved in pathogenesis or instead, could be markers of pathogenic processes.

To the extent that these seem to be major patterns of physiologic responses, investigators should be aware of the kinds and intensity of patterns elicited by various stressors. Tasks involving active coping, mental effort, conflict, competition, unpredictability, and stimuli inducing anger and distress are most likely to elicit the "type I" response. The effects of controllability on this response seem to be mediated by effort and fear. In addition, conditions such as effort and distress may mediate the involvement of cortisol responses in the "type I" pattern. With regard to the TPR (or "type II") response, this seems to be confined to tasks involving quiet attentiveness to the environment.
There may also be differences between chronic and acute responses; and to the extent that these responses are chronic, there may be changes in end-organ response patterns (e.g., beta-receptor function) which are worthy of study. In view of the fact that for "type I" responses, vascular responses and neuroendocrine responses are the major observed variables, factors such as body posture may interact with obtained measurements and should be controlled and noted. Also, when nonhomogeneous populations are involved, there may be differences in receptor responsiveness, and therefore patterns of responses elicited are worthy of study using agents such as pharmacologic agonists.

Generalization to Naturalistic Settings

An important question is now psychologically induced physiologic reactivity observed in laboratory settings is related to physiologic response in the natural environment during normal daily activities. Confirmation that hyperreactivity in response to a laboratory maneuver is predictive of hyperreactivity to conceptually similar situations in everyday life would enhance confidence that laboratory-derived data have meaningful implications for characterizing what is typical of individuals. During the past decade technology has evolved that permits automatic ambulatory determinations of BP and HR responses at regular intervals during the day or even for 24-hour periods. Ambulatory-derived data of this sort have the potential to yield useful information regarding what is normal BP outside the clinic, and whether abnormal reactions observed in the laboratory occur frequently in the natural environment.

With new capabilities for ambulatory monitoring of cardiovascular function--especially HR and BP--there are opportunities for observing reactivity during naturalistic conditions, which are inevitably less controlled than laboratory experimental conditions. Measures of urinary hormone excretion (e.g., as used by Marianne Frankenhaeuser's group in Sweden) provide another important means of physiologic measurement in naturalistic settings. Therefore, it is necessary to impose some organizing structure on what otherwise would be merely a temporal sequence of readings over a 24-hour period. Since BP responses presumably are
affected by individual confrontations with stressors varying in intensity and quality, we recommend that the subject keep a brief diary which describes circumstances at the time of each recording in terms of certain important dimensions. In addition, it would be quite helpful in analyzing pressor responses recorded automatically via ambulatory monitoring instruments to know the following sorts of facts: Was the subject smoking? Ingesting caffeine or alcohol? Interacting with other persons? In this regard, during such recordings, care must be taken to specify: What was the person's level of physical activity? What was the person's affective state (tense, nervous, irritated, angry, time-pressured)? and Were other people present?

The value of such a diary is suggested by preliminary findings from studies of ambulatory monitoring indicating that heart rate increases are most associated with physical activity, that DBP increases are most associated with interpersonal interaction, and that SBP increases are most associated with harassment or stress. Such findings from ambulatory monitoring will likely have implications for the laboratory researcher who would hope to generalize from the lab to naturalistic settings involving interpersonal interaction or harassment.

Clearly, a major problem in generalizing to naturalistic settings is the complexity of the variables operating on the subject to produce the observable responses. To simplify this problem somewhat, several investigations have noted the relationships between occupation and CVD risk level and/or level or reactivity produced of: job demand and overload, degree of match of person and job, pacing of work, degree of task irrelevant interference, discrepancy between task demands and available coping resources, and frequency of job adjustments (i.e., temporal, geographic, etc.).

In addition to paying close attention to the context in which stressors occur, investigators should also measure subjects' sociopsychological states that are likely to affect stress reactivity and tolerance. Some important person-variables include: trait anxiety, level of subjective distress, level of ongoing (role related) stresses, life event changes
(with due consideration to their number, valence, controllability, predispositions to anger and hostility, coping styles, and amicability and use of social supports). In contrast with level of trait anxiety and hostility, which have been directly related to certain measures of cardiovascular reactivity, these other-person variables have been shown to mediate self-reported stress level and responses. As such, therefore, work is needed to evaluate the role of these variables in CHD, EH and their sequelae.

Utility of Animal Models in Studying Psychological Stressors

Another method for studying organisms in the natural environment is through the use of animal models, and it is feasible to utilize animal models of CVD. Several of these models have demonstrated pathophysiological similarities to those shown by human beings and also exhibit behavioral and physiological response characteristics analogous to those observed in human models of cardiovascular reactivity and behavioral hyperresponsivity. The major advantages of animal models include the ability: 1) to monitor invasively disease processes and endpoints, 2) to conduct long-term studies allowing observation of the development of the disorders, and 3) to control more rigidly the experimental environment (including diet and the delivery of stressors).

A number of animal models have been used traditionally in studies of CVD. Each model has its particular strengths and applications. Thus, rats and mice, by virtue of their small size and low cost, are relatively easy to use and have been particularly useful in investigations of individual differences in reactivity and in studies of aggressive interaction. Dogs have been employed in psychophysiological studies of cardiovascular hyperresponsivity and have also been used to evaluate renal response to stressors. Finally, monkeys have been used for many years in studies of cardiovascular responsiveness and have recently been shown to provide a good model for the study of individual differences in reactivity and the role of these differences in the pathogenesis of atherosclerosis. The complexity of their social interaction patterns makes monkeys especially attractive for modeling the complex interaction between
environmental-individual characteristic interactions which seem to typify human existence.

It is worth describing in additional detail some of the ways in which monkeys, in particular, provide opportunities for studying the form and possible pathogenic consequences of physiologic responses to relevant psychological/social challenges. For example, many species of monkeys predictably form hierarchies of aggressive dominance and networks of affiliation and mutual social support. Naturalistic challenges to these animals can involve manipulations such as social group reorganization, introduction of strangers to established social groups, and introduction and removal of females to groups of males. Moreover, it seems possible to determine with appropriate techniques (e.g., radiotelemetry) the extent to which physiologic responses characteristic of controlled test situations are generalized to the same animals under a more normal set of living conditions (i.e., interactions taking place within normally constituted social groupings). It may be that animal models in general, and nonhuman primates in particular, offer excellent opportunities for describing general laws underlying reactivity phenomena through comparative clinical studies.

Methodological Issues

Selection of stressors. A number of theoretical and methodological issues should guide the selection of psychological stressors. Obviously, tests used in the laboratory should be reliable (i.e., have high test-retest correlation) and valid (i.e., measure what they claim to measure). In addition, it is recommended that behavioral tests of cardiovascular reactivity be:

(1) Replicable in different laboratories, too much research is laboratory-specific;
(2) Capable of producing sizeable physiological responses and a wide range of individual variability in response;
(3) Quantifiable and manipulable on the critical dimensions which are believed to provoke cardiovascular and neuroendocrine responses;
(4) Repeatable without producing substantial adaptation to responses or learning;
(5) Generalizable to life outside the laboratory (i.e., whenever possible, they should possess external validity);
(6) Selected strategically to test specific hypotheses about pathophysiology; and
(7) As culture-free as possible, i.e., should be valid when applied to as wide a range of population (ages, sexes, ethnic groups) as possible. An exception to this is when individual differences in reactivity that are group specific might not be desirable to eliminate since they may reflect differences in disease risk.

Selection of response variables. Epidemiological studies suggest that certain conditions, which may loosely be described as being psychologically stressful, can increase the probability of a variety of medically adverse outcomes rather than having a specific type of stress produce a specific type of pathology. However, this may be the result of the heterogeneity of the stress condition. Unfortunately, the disease-specific orientation of the National Institutes of Health has tended not to encourage studies concentrating on specific types of pathology, and this may be an inefficient research strategy. Whenever possible, laboratory or prospective studies should look at mechanisms (e.g., neurophysiological, endocrine and immunological) and at endpoints (e.g., cardiovascular, gastrointestinal and oncological) that are relevant to a variety of illnesses.

Measurement methodology

In studies of reactivity, it is essential to specify how baseline measures are determined, and ideally to approximate true conditions of minimal stress. Relatively few minutes of rest in a strange laboratory environment with the anticipation of unfamiliar procedures may be quite stressful, and differentially so for different subjects. Furthermore, baseline scores, as well as percentage or absolute increase, must be reported for each subject to give the reader a complete picture.
Statistical procedures for psychological stressor research. In addition, multivariate statistical techniques, which are suitable for the analysis of large, complex organized systems of variables, should be applied when sample sizes are adequate. Too often the statistical tools employed and the numbers of individuals studied are not equal to the level of complexity of the response system studied. In this regard, factor analysis is useful for determining the linear components of a response system and of the organization of the responses. Multivariate analysis of variance can indicate whether two or more groups of subjects differ on one or more components (linear dimensions) of an entire system of response variables. Discriminant function analysis can indicate the linear composites of variables which reliably discriminate two or more groups of subjects. Canonical correlation analysis can be used to discover linear composites of highly intercorrelated; i.e., it can indicate the independent channels of linkage or influence interconnecting two complex systems of variables.

Experiments in which multiple tests or tasks are administered to many subjects in order to elicit multiple cardiovascular and neuroendocrine responses may be suitable for analysis by means of three-mode factor analysis. This analysis yields factors or components for each domain of observation (i.e., factors for tests, for subjects, and for responses), as well as a table of coefficients (core matrix) showing the interrelationships among the three sets of factors. This powerful technique has not been applied to cardiovascular stress data.

The cardiovascular stress research area has remained isolated from important advances in the development of methodologies for the analysis of complex response systems. This isolation has given the research area a haphazard, piecemeal quality. Methodology should be suitable for the level of complexity of the phenomena themselves.

The task group further endorsed, where necessary, a research strategy aimed at determining the reliability, stability, and lab-life generality of various tasks employed in studies of reactivity induced by specific psychological tasks.
PRESENTATION
STRESS-SUBSTANCE INTERACTION AND REACTIVITY

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Despite recent declines in cardiovascular-related deaths, cardiovascular diseases remain the leading causes of morbidity and mortality in most industrialized societies (1). Many worldwide prospective and retrospective studies generally have uncovered two separate categories of factors that are predictive of the incidence and prevalence of coronary heart disease (CHD).

Risk Factors

The first category includes the so-called traditional risk factors such as elevations in serum cholesterol, blood pressure and cigarette smoking frequency (2-7). Various dietary and consumatory habits, amount of physical exercise, and failure to maintain hypotensive therapy are all behaviors that have been implicated either theoretically or empirically in one form or another in elevations of the classic risk factors. Although the relationship between traditional risk factors and CHD morbidity and mortality remains very important, the variance in CHD manifestations left unexplained by these factors has promoted a broadened search for additional pathways that may participate in atherogenesis and the pathophysiology of CHD. Here, the expanded search has resulted in a second separate category of risk factors that generally is related to the concepts of stress and coronary-prone behaviors.

A variety of stress-related factors has been examined for association with CHD, including such diverse attributes as anxiety, neuroticism, depression, social-occupational mobility, status incongruity, job freedom, occupational demand and Type A coronary-prone behavior pattern.
Risk Factors and Reactivity

An increasingly promising and productive approach to both the classic and stress-related risk factors is based on the belief that both categories can operate in concert to accelerate the atherosclerotic process and/or participate in precipitating a clinical event. From this perspective, risk factors can operate in both static (e.g., clinic determinations of levels of cholesterol, blood pressure, and self-report of average smoking behavior) and in a dynamic manner (e.g., stress-induced levels of cholesterol, blood pressure, and cigarette smoking). At the outset, it should be made clear that dynamic reactions of classic risk factors in response to behavioral challenge are associated with a host of complex physiologic processes involving the central nervous system (CNS), autonomic nervous system (ANS), and associated mechanical and neuroendocrine activity (9,10).

Cigarette Smoking and Reactivity in Men

A particularly relevant example of how behavioral factors can affect cardiovascular reactions to one of the major risk factors is demonstrated by our recent research on cigarette smoking. Despite the fact that many smokers increase consumption of cigarettes before, during, and after bouts of acute stress, most research concerned with the effects of smoking on cardiovascular and neuroendocrine responses have investigated smoking in a relaxed state, usually with the subject in a recumbent posture (11,12). The few studies that have attempted to investigate how cigarette smoking and stress may combine to affect physiologic response either used passive stressors, inadequate designs, or incomplete and inappropriate measures (13-17). Much smoking occurs during daily activity in which active coping is required by the demands of the environment, e.g., on the job. Since stress-related active coping alone is associated with increased ANS activity, and since the effects of nicotine alone operate in a generally similar fashion to stimulate sympathetic and parasympathetic ganglia, we reasoned that the combined effects of stress and cigarette smoking would interact to produce larger cardiovascular responses than either stress alone or smoking alone (18).
A 2x2 factorial design was used to evaluate the latter hypothesis in which the variables were smoking vs. sham smoking (unlighted cigarette), and stress (videogame) vs. no stress (relaxation), respectively. All subjects were young male smokers (n=51) who first were monitored for 1 hour during which no smoking was permitted. A 10-minute baseline period followed, which established that experimental groups were statistically homogeneous with regard to resting HR and BP values. Afterwards all subjects were challenged (stressed) with a "test of eye-hand coordination" involving a moderately difficult videogame (Atari Breakout). The initial test game was utilized for three reasons. First, to confirm that the experimental groups were homogeneous with respect to challenge-induced hemodynamic activity; second, to record initial performance skill for playing the game; and, third, to assess challenge-induced physiologic response in order to test the proposition that hyperreactivity to psychological challenge might be related to hyperreactivity induced by cigarette smoking. Randomly assigned subjects then either smoked or sham smoked a cigarette and afterwards either relaxed or again played the videogame (stress) under instructions to improve performance.

Results revealed that the condition of sham smoke/relax had virtually no effect on cardiovascular reactions, whereas the conditions of smoking/relaxing and sham smoking/stress produced similar increases in blood pressure (BP mean $\Delta=15/9$ mm Hg) and heart rate (HR mean $\Delta=15$ BPM). In sharp contrast, subjects who smoked and then engaged in the videogame (stress) evidenced about twice the magnitude of BP and HR increases relative to the smoke alone and stress alone groups. In fact, the Rate Pressure Product Index (a rough index of myocardial $O_2$ consumption) suggested a synergistic effect that reflected levels of increase beyond the additive effects. A second major finding of the study revealed a significant correlation between BP response to the initial game (i.e., before any cigarette smoking) and BP response to simply smoking a cigarette followed by relaxation. In other words, subjects who were "hot" reactors to psychological challenge tended to be "hot" reactors to the effects of cigarette smoking alone.
Since both stress alone and smoking alone have a demonstrable impact on ANS activity, it seems clear that the combination has much more pronounced effects on cardiac function and arteriolar tone with associated increases in HR, stroke volume, BP, and vascular resistance. These and related hormonal activity can affect thrombotic occlusion, myocardial oxygen depletion (aggravated even more by enhanced carbon monoxide levels) (9-11) and increased vulnerability to a variety of arrhythmias. All of these processes are almost certainly more significantly affected in the "hot" relative to the "cold" reactor, which suggests why some smokers may be at higher risk than other smokers. Of course, a prospective study is needed to address the issue, but from a physiological perspective, stress-related smoking is likely to increase risk for a CHD event, especially in those with advanced underlying atherosclerosis and, in this regard, the hyperreactor is likely to be at highest risk of all during and after such activity. Finally, it is conceivable that the stress-smoking interaction may produce transient performance decrements in complex psychomotor activity. The stress/smoking group showed a decrement in performance relative to the initial test game whereas the stress/sham smoking group actually showed performance enhancement.

Cigarette Smoking and Reactivity in Women

In the above study all participants were young, white males. Cigarette smoking is also a potent risk factor for CHD and sudden cardiac death in women (19,20). Yet, surprisingly little is known about physiologic response to cigarette smoking in women due to the use of primarily male subjects in such research and where women have been included, analysis of sex differences has not been reported (21). There is ample reason to study stress-smoking effects on women because evidence suggests that women may respond with less physiologic response to stress than their male counterparts (22). Certainly, to our knowledge, there have been no adequately controlled studies of how cigarette smoking and stress combine to affect cardiovascular reactions of women. Consequently, we have very recently conducted a
study similar to that described above in which young women subjects
were recruited as participants (Dembroski & MacDougal, unpublished
data).

Young women who were smokers (n=43) were treated similarly to their
male counterparts in the stress-smoking study described above. The
exceptions were that after the initial test game, those in the stress
condition (videogame) were offered the opportunity of winning an
additional $10 for superior performance (to enhance challenge) and the
women played the game for at least 12 minutes after smoking/sham
smoking one cigarette. All groups were statistically homogeneous both
with respect to baseline values and challenge-induced physiologic
response to the initial test game prior to any smoking manipulation.
Results revealed similar interactive effects of stress-smoking
manipulation. Results revealed similar interactive effects of stress
smoking in women to those observed in men. For example, during 8-12
minutes after sham smoke/relax, subjects were slightly below baseline
(e.g., mean Δ SBP = 0.7 mm Hg). In other words, pretending to smoke had
virtually no impact on BP during subsequent relaxation. Subjects in
the sham smoke/stress condition were similar in BP response to those
in the smoke/relax condition (e.g., mean Δ SBP = 6.6 and 5.5 mm Hg,
respectively). In sharp contrast, 8-12 minutes after smoking a
cigarette, subjects in the smoke/stress (videogame) condition still
showed substantial and sustained increases in cardiovascular response
(e.g., mean Δ SBP = 22.1 mm Hg). Similar results were obtained for DBP
and HR over the same time frame. These results clearly suggest that
the stress/smoking combination is at least additive and may very well
go beyond to produce synergistic effects.

In order to determine whether the smoke/stress interaction would occur
in response to a different kind of challenge, one apparently more
relevant to women (23), the women were subsequently subjected to the
Rosenman Type A Structured Interview. Following a 5-minute recovery
period, subjects either once again sham smoked or smoked a cigarette.
Afterwards, a woman experimenter administered the SI in a mildly to
moderately challenging manner while cardiovascular reactions were
monitored. Again, pronounced and sustained differences between the groups were obtained over the entire course of the 12-15 minute interview. For example, HR reactions among those women who had smoked prior to the interview were consistently five to six times higher than in those who had sham smoked. In addition, as was the case with the males, "hot" reactivity to the initial test game was correlated with "hot" reactivity to cigarette smoking alone while relaxing. A new finding in this study was that amount of cigarettes typically smoked in a day, "hot" reactivity to the initial test game, and hostility scores were all significantly intercorrelated. The finding is in accord with results obtained in two previous studies of women (23), in which high hostility scores were characteristic of women who smoke and women who responded with "hot" physiologic reactions to psychological challenge.

In summary, the findings reviewed here clearly indicate that very complex relationships are present, involving classic risk factors, stress, personality attributes, consumatory behaviors, and physiologic reactivity. Moreover, the observation that many consumatory behaviors covary; e.g., cigarette smoking, caffeine, and alcohol, and that each can affect cardiovascular reactions to challenge (24,25) makes it clear that sorting out individual and interactive effects is a complex challenge for future research. Even more difficult will be identification of CNS, ANS and related mechanical and neuroendocrine processes operating during interactive effects as well as gaining a precise understanding of how such processes are related to pathophysiological mechanisms in atherogenesis and clinical CHD. At the very least, new findings in this arena offer more evidence of the importance of primary and secondary prevention programs. In designing such programs, one might well consider that the two separate categories of risk factors described at the outset of this paper are not so separate after all.
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TASK GROUP REPORTS ON STIMULATORS
PSYCHOLOGICAL STRESSORS PRODUCING REACTIVITY—CAFFEINE

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Caffeine is the most widely used psychotropic agent, yet there is insufficient research on its relation to cardiovascular reactivity and cardiovascular disease. The studies that exist are provocative, but there is as yet no real consensus on the role of caffeine.

Caffeine as a Risk Factor

Recent studies from various laboratories have indicated that caffeine may intensify the effects of acute psychological stress in human subjects. This added stimulation of an already aroused sympathetic adrenal medullary system is paralleled in chronic studies of psychologically stressed animals by increases in plasma renin and corticosterone as well as increased myocardial damage and an accelerated mortality. Epidemiological observations in various countries have established increased plasma cholesterol levels and suggest increased rates of coronary heart disease associated with caffeine use. However, there is uncertainty because smoking usually accompanies caffeine consumption. There is need for a fresh look at the role that caffeine may play independent of nicotine and carbon monoxide in the hypertension and heart disease of the chronically aroused psychosocially stressed organism.

Caffeine and Cardiovascular Reactivity

It is clear that caffeine has significant cardiovascular effects that are mediated through arousal of the CNS. This has been suggested in recent research showing combined effects of caffeine and mental stress on BP and other functions. This research indicates a greater BP response in individuals with a family history of hypertension, although this effect has not been confirmed. The BP effects appear to be comparable in caffeine as
well as noncaffeine users. At present, the data on humans indicate that the caffeine and stress effects combine in an additive fashion. The data from animal studies, in contrast, suggest that caffeine may intensify physiological effects in association with chronic stressful life conditions. Whether these effects are relevant to hypertension is unknown.

Adenosine Model of Caffeine's Action

An explanation of the mediation of caffeine's effects on the cardiovascular system, both at rest and under stressful conditions, is available in recent neuropharmacological research. Caffeine appears to bind competitively at adenosine receptors within the CNS. The normal action of these receptors is presynaptic inhibition of activity in nerve fibers normally associated with the sympathetic nervous system expression of responses to stress. Blockade of these inhibitory receptors would accentuate sympathetic activity both at rest and more importantly, during stress. This model of caffeine's action has not gained complete acceptance. The model, however, can explain most of the pharmacological effects of the drug on resting subjects and suggests that caffeine's influence will be even greater during stress.

Methodological Issues

1. In double-blind studies of the acute effects of caffeine, attention should be given to the method of administration and appropriate placebo. Because of individual differences in absorption and possible adverse effects, the caffeine should be dissolved in water or some other liquid rather than given in a capsule. The somewhat bitter taste of caffeine and the nonbitter taste of the placebo should be made equivalent or the taste of substances could be masked by quinidine or cherry syrup. If it is desirable to include the influence of stimulus or other characteristics of coffee, then decaffeinated coffee should be used.

2. Variable doses of caffeine should be used, e.g., 100 to 300 mg.
3. In experiments on cardiovascular reactivity, use of caffeine and individual differences in caffeine usage may be a source of error variance. To reduce this variance, prior caffeine use should be controlled as much as possible, and information on caffeine usage should be obtained.

4. In planning the duration of studies of the acute effects of caffeine consideration should be given to the fact that the half-life of caffeine is at least 4-6 hours.

5. Caffeine is present in varying amounts of coffee, chocolate, soft drinks, cocoa, and medications. In evaluating caffeine use, detailed diaries may be useful to quantify this variable.

SOME RECOMMENDATIONS

1. Human psychophysiological stress research has looked primarily at BP and heart rate changes. Current research suggests that forearm blood flow may be a sensitive indicator of the combined effects of caffeine and psychological stress. Other measures related to sympathetic function such as electrodermal activity should be considered. Other EKG indices and measures of EEG or other CNS functions may be useful.

2. Recent studies have examined the combined effects of caffeine and mental arithmetic on cardiovascular responses. Other psychological stressors may uncover whether caffeine and psychological stress interact in a synergistic fashion, e.g., videogames, tasks involving competitive interpersonal interaction. In contrast to these active coping tasks, other tasks such as vigilance or the cold pressor test could be considered.

3. Further study is needed to examine the degree of tolerance and individual differences associated with caffeine use. Repeated laboratory studies of cardiovascular reactivity in caffeine users with and without caffeine abstinence are needed. Sleep electrophysiological studies of tolerance/withdrawal may be helpful.
4. In regard to long-term prospective studies, the evidence at present regarding the role of caffeine as a risk factor for hypertension or coronary artery disease is controversial. There is as yet no compelling basis on which to recommend a large scale clinical study. Human cardiovascular reactivity studies plus animal studies suggest that caffeine may turn out to be an important risk factor--at least, it cannot be eliminated from consideration.
NICOTINE AND REACTIVITY

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Epidemiology

Cigarette smoking. Cigarette smoking has been shown repeatedly to be one of the three most important risk factors for coronary artery disease and heart attack. The degree of risk is proportional to the number of cigarettes smoked per day, per year, with significant increases in risk beyond 15 cigarettes per day over a period of years. When BP is higher than 140/90 mm Hg and serum levels of low density lipoprotein cholesterol are elevated in heavy smokers, the risk is greater than the sum of the individual risks of these three important factors. Interestingly, smoking is not itself directly related to hypertension.

The most significant effect of smoking on plasma lipids is on HDL cholesterol concentrations. These tend to be significantly depressed in smokers compared to nonsmokers or ex-smokers. The effects are observed in men and women (both on and off contraceptive hormones) and some studies have found the effects to be somewhat stronger in women than men. Finally, most studies report a dose response effect on HDLC concentrations.

Most investigators agree that cessation of cigarette smoking causes a reasonably prompt reduction of risk, but it has been difficult to document this statistically. This is true in part because most individuals who quit heavy smoking also take steps to control other coronary risk factors in their lifestyles.

These statements have been validated in the Framingham Study, the MRFIT project, the Whitehall Study and the Oslo Study. However, it is important to recognize that the precise mechanism whereby cigarette smoking induces or accelerates atherosclerosis remains unclear. It might be speculated
that the vasoactive properties of nicotine play a role but with over 4,000 chemical compounds being generated by burning tobacco, such speculation cannot be justified.

**Pharmacology of Cigarette Smoking**

The burning of tobacco results in the liberation of nicotine, carbon monoxide, carbon dioxide, oxides of nitrogen, ammonia and tar. Tar is a mixture of polycyclic aromatic hydrocarbons which, among numerous other compounds, contains the amines that cause bladder and probably cervical cancer. Of the more than 4,000 compounds, nicotine, carbon monoxide and tar are thought to be the most pathogenic. The burning of a single cigarette produces 0.05 to 2.5 mg (average 1.1 mg) of nicotine and 0.5 to 35 mg of tar.

**Chemistry, absorption, distribution.** Nicotine is a natural liquid alkaloid that is highly fat soluble. It is absorbed across mucous membranes in the mouth and across alveolar membranes in the lung. After absorption, nicotine passes directly to all systemic organs including the brain. It is delivered to the brain in proportion to cerebral blood flow and almost all passes the blood brain barrier. Consequently, about 20 percent of absorbed nicotine is delivered directly to the brain within a few seconds after absorption. Concentrations also decrease rapidly by washout and are reduced to less than 50 percent of the peak concentration in 5 minutes and less than 10 percent after 1 hour.

**Actions.** Nicotine has many different actions in many different sites and its effects are also dose dependent. It has the potential for both stimulant and depressant actions.

1. **Peripheral nervous system.** Small doses of nicotine stimulate autonomic ganglia directly and facilitate the transmission of impulses. The major effect of ganglionic stimulation on the cardiovascular system is adrenergic since adrenergic nerves dominate innervation. The major effect of ganglionic stimulation on the GI tract is vagal with increased gastric
secretion and increased gastrointestinal motility. Nicotine also facilitates the release of norepinephrine from adrenergic terminals by potentiating the transmission of impulses through ganglia. Thus, the effects of nicotine in low concentrations would be an enhanced response to adrenergic impulses. When larger doses of nicotine are administered, the central stimulation is followed by blockade of transmission. Doses that cause blockade apparently are much greater than those ordinarily obtained from tobacco smoke.

2. Adrenal. Small doses of nicotine also stimulate release of epinephrine from the adrenal medulla. Release of adrenocortical hormones also is stimulated.

3. Direct releasing effects. Nicotine, in all doses, causes a release of norepinephrine from adrenergic terminals by a direct effect in those terminals. This effect of nicotine is sympathomimetic and can be reduced by alpha- and beta-adrenergic blocking agents.

4. Sensory receptors. Nicotine stimulates many sensory receptors. In particular, it stimulates chemoreceptors of the carotid body and the aortic arch. The results of this stimulation are an enhancement of respiratory and cardiovascular responses to hypoxia.

5. Cardiovascular effects. Nicotine is known to cause acceleration of heart rate and increase in arterial blood pressure. These responses are related to stimulation of cardiac sympathetic nerves, peripheral vasoconstriction, and stimulation of the aortic and carotid bodies and medullary center through chemoreceptors for nicotine which stimulate somatic sensory activity, the central respiratory and vomiting center and which can produce convulsions.

Low doses (less than 1 mg cigarette) of nicotine induce responses on the order of 15 beats per minute increase in heart rate and a 10 mm Hg increase in systolic and diastolic pressure. Higher doses appear to induce progressively less change. These dose response effects are found in both
smokers and nonsmokers in somewhat varying experimental conditions. Interestingly, BP but not heart rate changes commonly observed in laboratory settings after smoking were observed in an ambulatory monitoring study.

Nicotine's sympathetic stimulation of the heart's sinoatrial node and conduction system enhances automaticity, frequency and conductivity. Simultaneous parasympathetic stimulation, which depresses these physiologic parameters, only partially offsets the powerful sympathetic effects. In humans, in distinction to most lower animals, heart rate is controlled largely by parasympathetic stimulation and withdrawal and sympathetic activity comes into play in a secondary sense to accommodate stress and exercise-like activities. Accordingly, when one considers the substantial degree of heart rate increase that occurs when a nonhabituated person smokes a single cigarette, it becomes apparent that sympathetic effects are quite extensive, and, in addition, effects other than those on the sinoatrial node are likely to be involved. Widespread sympathetic stimulation causes vasoconstriction which, in turn, serves to augment venous return to the heart and central blood volume. Heart rate acceleration follows and is mediated through stimulation of volume receptors in the right atrium. This latter mechanism is likely to be at least as important as direct stimulation of the sinoatrial node in causing nicotine's cardioaccelerator effects. Cardiac acceleration increases myocardial oxygen demand directly.

Sympathetic stimulation of myocardium enhances contractility—the rate of individual fiber length shortening. Increases in cardiac diastolic volume resulting from vasoconstriction also provides enhanced end diastolic stretch of individual myocardial fibers and thereby results in increased contractility. Thus, a larger volume of blood is ejected from the heart with each beat with greater velocity. The peripheral manifestation of these can be seen in an increase in central arterial pressure. Cigarette smoking appears to induce increases in cardiac output and reductions in left ventricular ejection times. Not all studies have, however, found decreases in preejection period.
These contractility responses also create a significant increase in myocardial oxygen consumption and demand. In individuals with already impaired coronary blood flow, such oxygen demand increases may not be met and regional ischemia may develop.

Nicotine, through sympathetic stimulation, also causes arterial vasoconstriction. This, when added to the ejection volume-velocity effects, enhances blood pressure elevating mechanisms.

Briefly stated, nicotine has profound cardiovascular effects which increase heart rate and blood pressure and increase myocardial oxygen demand. Tachycardia and blood pressure elevations are but minor manifestations of more complex physiologic effects.

6. Endothelial effects. Administration of nicotine through tobacco smoke or intravenously, increases the rate at which endothelial cells are desquamated. The concentration of desquamated endothelial cells in circulating blood increases rapidly after administration of nicotine.

7. Platelet aggregation. Nicotine increases platelet aggregation and thrombosis formation by several mechanisms. The release of epinephrine increases blood concentrations and enhances platelet aggregation. The direct effect of nicotine on platelets may also alter receptor characteristics. In addition, nicotine inhibits the release of prostaglandin from vascular endothelium and does not affect the platelet release of thromboxane. The end result is an increase in platelet aggregation and thrombosis formation.

8. Lipid metabolism. Cigarette smoking is associated with increased serum levels of LDL and decreased levels of HDL in man. Studies on animal models have not been as clear, particularly among nonhuman primates. For example, Rogers et al. failed to find any significant effect of chronic cigarette consumption either on plasma lipids or on atherosclerosis. Also, Raymond et al. failed to find alterations of plasma lipoproteins among stumptailed monkeys exposed to cigarette smoke. However, in both studies,
plasma lipid concentrations were relatively low (TPC < 200 mg/dl). It may be that diets involving greater amounts of cholesterol and saturated fat would provide results more in accord with those observed in studies of human beings. Also, interactions between behavioral/psychologically induced stress and high fat-high cholesterol diets may provide clearer effects on plasma lipids. In fact, animal models could provide a way to ask questions paralleling those in human studies. In particular these questions could involve tests of the various constituents of cigarette smoke and their effects on the artery.

9. Endocrine effects. In addition to increasing circulating levels of catecholamines, nicotine also increases circulating levels of cortisol, corticosteroids, growth hormones, and prolactin. Nicotine stimulates release of ACTH and probably beta endorphin. It also stimulates pituitary secretions of several trophic hormones. In addition, nicotine apparently reduces hypothalamic concentrations of dopamine and increases concentrations of serotonin. The end result is an increased secretion of prolactin from the pituitary gland.

10. CNS effects. Nicotine excites receptors in the midbrain tegmental neocortical cholinergic pathway. The result is activation of norepinephrine containing cells in locus coeruleus and release of acetylcholine in the cortex. The electrical effects are cortical desynchronization. The EEG excitatory activity is also accompanied by a selective reduction in EMG activity in major muscle groups of the extremities.

11. Electrocortical activity. Nicotine increases the power in theta and alpha wave activity as well as the dominant alpha frequency. In chronic smokers, deprivation of nicotine causes a slower alpha and increased power in theta and alpha frequencies. This pattern in deprivation is similar to the progression from wakefulness to sleep and is accompanied by subjective sense of drowsiness. The administration of nicotine restores electrocortical activity to normal and enhances the ability of the smoker to process information.
12. Cerebral neurochemical effects. This is a controversial subject with many different effects reported in different species. Studies have been made of catecholamine, dopamine, and serotonin in various regions of the brain. No clear picture emerges because of the difficulty in separating acute from chronic effects and in determining the appropriate dose to be administered to specific animal models.

Interactions Between Smoking and Other Risk Factors

Alcohol and smoking. There is strong epidemiologic evidence that tobacco and alcohol consumption are positively correlated in populations with widely diverse demographic characteristics, and this relationship is especially well documented in studies of alcoholics, of whom 90 percent are smokers. Controlled laboratory experiments comparing effects of ethanol given at different dose levels on smoking by nonalcoholic (light social drinkers) versus alcoholic subjects have shown that only alcoholic smokers respond with reliable increases in smoking. Responses of nonalcoholics were variable, with ethanol-induced changes in the rate of smoking behavior related to the average number of alcoholic drinks usually consumed. This suggests that prior history of alcohol use is a determinant of alcohol effects on smoking. Consistent with this is a finding by Henningfield, et al. that effects on smoking of another depressant, pentobarbital, were directly related to the subject's history of sedative use: Pentobarbital suppressed smoking in individuals without histories of sedative abuse while increasing smoking by prior sedative abusers. Repeated drug use may alter drug effects, or variables that lead to repeated drug use might also influence drug effects.

Caffeine and smoking. A number of epidemiologic studies report that tobacco and caffeine use are moderately to strongly correlated. Controlled laboratory experiments have confirmed this association in two studies, while two other experiments by the same group failed to demonstrate an increase in smoking following coffee ingestion. In a well-controlled design that compared placebo, caffeine base, or d-amphetamine sulfate preloads with subjects prior to smoking sessions, Chait and Griffiths found
increases in smoking following d-amphetamine but not after caffeine or the placebo. This suggests that the positive correlation between cigarette smoking and coffee drinking is not produced by a simple pharmacologic effect of caffeine.

Exercise, salt, obesity. Smokers tend to weigh less than nonsmokers. However, cessation of smoking is associated with a return to the average weight of nonsmokers. Interactions between smoking and exercise indicate that physically active subjects are less likely to be cigarette smokers than sedentary subjects.

Type A and smoking. In a number of studies, hostility--one component of Type A--was related both to smoking and degree of coronary atherosclerosis.

Measurement of Smoking

Smoking in reactivity studies can be measured in two ways. First, exposure measures can be used to assess smoker/nonsmoker differences. Such things as carboxyhemoglobin in blood, expired air-carbon monoxide concentrations (CO\textsubscript{a}), urinary cotinine, and salivary or serum thiocyanate provide estimates of short- and long-term exposure to smoking, which are needed to determine smoking/nonsmoking status. These measurements are particularly important for intervention studies in which cessation rates are often exaggerated. In a very general way, exposure measures will provide an estimate of dose-response relationships between amount of smoking and exposure. However, since smokers tend to self-titrate serum nicotine, it is difficult to use exposure measures as estimates of actual smoking behavior. Specifically, smokers of differing nicotine and CO level cigarettes will have similar steady state values of serum nicotine and carboxyhemoglobin.

Second, the act of smoking, or smoking topography should be measured when issues related to acute exposure are studied. Such variables as number of puffs, puff duration, cigarette duration, and, most importantly, integrated puff volume can be measured reliably in laboratory settings. In addition,
new methodology provides for the study of smoking topography in ambulatory populations.

Investigators interested in studying smoking and nicotine relationships need not be restricted to smoking as a method for studying nicotine. For example, nicotine can be delivered intravenously; taken by mouth in gum, pill or liquid form; or taken by aerosol. Since the method of administration may influence the cardiovascular, neuroendocrine and behavioral effects of nicotine, investigators should use IV or aerosol modes of administration when possible.

Since nicotine shows dose-dependent relationships to cardiovascular changes, it is important to measure and, if possible, control nicotine dose.

In addition, smokers show tolerance to smoking over the day, such that continual smoking may produce smaller cardiovascular responses to the same dose of nicotine over time. Investigators must control for previous daily dose in studies in which cardiovascular and neuroendocrine responses are related to nicotine dose. The magnitude of cardiovascular response and rate of recovery are related to nicotine dose. Based on laboratory studies of subjects smoking moderate nicotine content cigarettes, serum nicotine concentrations and pulse rate can remain elevated for at least 2 hours past smoking. A "washout period" of 4 hours is commonly used in the pharmacological studies to reduce effects of tolerance on measured physiological variables. Investigators should realize that these deprivation manipulations, while necessary to study the pharmacologic effects of nicotine, may increase withdrawal in heavy smokers and exaggerate the psychological contributions to behavioral stress reactivity tasks.

Nicotine Regulation

Evidence for nicotine regulation derives from research showing that smokers alter their smoking behavior in predictable ways when nicotine availability
is experimentally manipulated. Preload or substitute doses of nicotine decreased ad libitum smoking; while reducing potential nicotine exposure via brand switching, shorter cigarettes, ventilation, etc., yields increases in smoking rate, puff duration and volume. Studies that measure nicotine in the body (direct exposure measures) suggest, however, that only partial regulation is achieved by these maneuvers, as constant levels are rarely observed. It appears in applied (nonlaboratory) studies that smokers can adjust to somewhat lower levels of nicotine, despite compensatory behavioral adjustments of the kind just noted, without marked cognitive or performance decrements. Research on persons who self-select various tar/nicotine/CO level of cigarettes has shown similar steady state nicotine and CO levels, independent of type of cigarette. Likewise, randomized, controlled switching studies suggest similar CO exposures despite tenfold differences in cigarette yield of CO.

Behavioral Consequences of Smoking

Any effort to understand behavioral/physiological interactions between smoking and cardiovascular changes must address the major behavioral factors that influence smoking. First, nicotine can act as a positive reinforcer, smokers may smoke either to obtain the effects of nicotine or to remove the effects of nicotine withdrawal. Second, smokers may smoke to regulate the level of stimulation. That is, smokers may smoke in a boring, monotonous situation to increase stimulation; similarly, smokers in demanding situations may smoke to reduce their level of stimulation. These central physiological effects may be accompanied by verbal reports of improved mood. Third, smoking may be used to alter performance. In fact, smoking improves performance in simple tasks such as vigilance, but may impair more complex tasks, such as incidental learning.

In terms of cardiovascular responses to cigarette smoking, similar effects may be observed after smoking, independent of whether the behavioral effects are classified as stimulant or relaxant. Nicotine has paradoxical effects in that it is a CNS stimulant and yet is often subjectively relaxing. For example, the same dose of nicotine may act to increase alpha
EEG activity when a subject is aroused, probably as a result of a direct peripheral effect of nicotine as a relaxing agent on muscle, and produces alpha blocking when a subject is very relaxed. In addition, nicotine intake in small or moderate doses seems to focus attention. Finally, the avoidance of withdrawal symptoms may itself be calming and reassuring.

Since persons smoke to regulate affective states and behavioral performances, it may be important to develop hypotheses about how behavioral and pharmacological effects may interact. Many smokers increase smoking behavior before, during, and after periods of stress in order to relax, or modulate affect. Thus, it is important to determine how cigarette smoking and psychological stress combine to affect cardiovascular reactions. Recently, MacDougall and Dembroski showed that smoking/relaxing and sham smoking/stress conditions produced similar increases in BP (12/9) and HR (15 BPM). However, the combination of smoking a cigarette followed by stress induced twice the amount of increase in BP/HR than that produced by smoking alone or stress alone. An additional finding was that reactions to psychological challenge (videogame) following 1 hour deprivation of smoking were significantly correlated with subsequent cardiovascular reactions to smoking and relaxing.

Finally, evidence suggested that the combination of smoking and stress may impair complex psychomotor activity. A followup study by Dembroski and MacDougall with young adult females replicated the findings observed for males, and in addition showed that estimated daily nicotine dose (number of cigarettes smoked daily) was associated with pronounced cardiovascular reactions to psychological challenge following 1 hour of nicotine deprivation. These heart rate results are supported by recent data on smoking by females during mental arithmetic tests. As discussed by MacDougall, Dembroski and colleagues, this largely additive effect is probably due to the fact that the mechanisms by which stress and cigarette smoking affect cardiovascular function are generally similar. Stress increases sympathetic nervous system (SNS) activity, and the active agent in cigarette smoke is nicotine, which stimulates sympathetic and parasympathetic ganglia.
Recommendations

The major question is whether reactivity can assist in identifying smokers who are at risk for developing CHD. Research should assess relationships between a wide variety of behavioral challenges selected for their potential interactive or synergistic effects with smoking on pathophysiological and psychological variables. The effects of smoking patterns and reactivity, as well as interrelationships among reactivity and other behavioral/health/psychological factors as caffeine and alcohol use, exercise, obesity, salt ingestion, hostility and anger-in should be investigated. Likewise it is important to determine whether behavioral mechanisms that relate to reasons for smoking such as mood or performance regulations are related to reactivity. These effects must be looked at as a function of sex, age, race, and stage of disease. Finally, intervention studies that assess the effects of reducing smoking are important to establish whether reactivity can be reduced after cessation.
PSYCHOLOGICAL STRESSORS PRODUCING REACTIVITY--SALT/GLUCOSE

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Glucose-Insulin Related Activity

The increased risk of type I and type II diabetes for atherosclerotic cardiovascular disease is recognized. The relationship of glucose-insulin interaction and cardiovascular reactivity is relatively unexplored and is a potentially productive area to investigate. Relevant data to support this issue emerged from a few experimental and clinical studies that demonstrate interaction of glucose-insulin fluctuation and sympathetic system activity. These interactions result in varying cardiovascular and neurohumoral responses, differ according to fasted/fed state, and are affected by cortisol.

A number of significant issues were raised which warrant further investigation. A primary issue pertinent to all stress reactivity research is to determine whether the level of sympathetic response varies as a function of glucose loaded state (i.e., fed or fasted), and it is recommended that specific studies be performed to address the issue. Furthermore, it is recommended that this fed/fasted condition be standardized in ongoing studies of reactivity.

Another general issue is the question of whether "hot reactors" may have hyperinsulinemia as a factor which contributes to their exaggerated stress reactivity. Specific clinical categories which are relevant and warrant investigation include 1) reactive hypoglycemia, 2) impaired glucose tolerance, 3) obesity, and 4) high cardiovascular reactivity. An investigative approach could involve a two-part assessment which would initially involve monitoring glucose, insulin, cardiovascular parameters, catecholamines, and cortisol response during standardized stress testing.
Subsequently, as a separate challenge, these parameters could be monitored during glucose tolerance testing. The relationships of the responses under the two conditions could be assessed. Finally, the interaction of glucose-insulin on behavioral state or mood changes should be evaluated.

**Salt (Sodium and Potassium)**

The general background justifying the significance of sodium-reactivity interaction includes experimental data on the effects of altering sodium intake. A high sodium intake has been shown to effect changes in sympathetic nervous system function. These changes include decreased circulating catecholamines, increased renal alpha receptor density, and decreased beta receptor density. Other studies which have focused on local vascular responses have demonstrated an increased BP response to infused norepinephrine. Also demonstrated has been an increase in forearm vascular resistance and a decrease in blood flow in subjects identified as salt sensitive.

A few relevant studies in animal models have promoted data on the interaction of behavioral stress and sodium loading. In dogs receiving continuous saline infusion and avoidance stress for 2 weeks, 24-hour BP levels rose. Concurrent with the BP increase, there occurred sodium retention but a water diuresis. Increasing potassium intake attenuated the BP response. In another study, SHR but not WKY rats on a high sodium diet were observed to retain sodium without diuresis during air jet stress. The effect of stress in these animals was a decrease in glomerular filtration rate, and an increase in tubular reabsorption resulting in an increase in sodium retention. Mechanisms to account for these responses have not been fully determined but could include inappropriate sodium retention with increased total peripheral resistance due to altered vascular response to adrenergic activity or sodium and volume retention with increased cardiac output. However, these two possibilities are not mutually exclusive.

Two studies have demonstrated that in humans a reduction in sodium intake attenuates BP response but increases HR response to stress, particularly in
individuals with borderline hypertension or hypertensive parents. The addition of a high potassium intake enhances these responses. The combination of low sodium/high potassium intake has been shown to lower blood volume and alter baroreceptor sensitivity. An investigation of normotensive offspring of hypertensives demonstrated that salt-loading increased baseline BP, increased stress BP and decreased stress HR. Offspring of normotensives showed no changes in stress response following salt loading. Similarly, high risk individuals who are high reactors to stress have been shown to demonstrate stress induced sodium retention.

Further studies of stress induced cardiovascular reactivity are necessary under conditions of sodium loading and of sodium depletion. It is now recognized that in the design of these studies accounting must be made of other cations (Ca++, Mg++, K+).

Design strategies should be developed to address the following issues:

1. Possible racial differences in cardiovascular reactivity at differing levels of sodium balance or loading should be taken into account.

2. The methodology of sodium loading should address temporal factors as well as route of administration (diet vs. tablets vs. infusion).

3. The state of the nervous system at the time of sodium loading may be a determinant of the response (i.e., whether the body excretes or retains the sodium). Thus it is important to evaluate hemodynamic (baseline BP, HR, CO, ambulatory BP, BP variability), neuroendocrine (catecholamine steroids, including aldosterone and renin), and behavioral states (life events) during the salt loading period.

4. Another strategy to evaluate the nervous system under varying levels of sodium loading would involve manipulation of adrenergic activity (pharmacologic agonists/antagonists).
5. A further area to address is the effect of salt on mood or behavior.

6. Another issue which could be relevant in the stress/salt interaction is that of salt appetite. It is conceivable that stress may alter salt appetite in some individuals.
PRESENTATION
Hyperreactivity of the autonomic nervous system has been assumed to be a primary lesion contributing to the development of cardiovascular disease (1,2). Both behavioral and pharmacologic treatments of cardiovascular disease often work by reducing the effects of autonomic nervous system on cardiovascular end organs (2). In this presentation we will briefly review pharmacologic and behavioral interventions which reduce cardiovascular reactivity by dampening the effects of the autonomic nervous system.

**Pharmacologic agents**

Pharmacologic agents which are used to modify cardiovascular reactivity may be classified into four groups: alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, centrally acting agents, adrenergic neuron blocking agents, and calcium channel blockers (3). The generic names of the most common agents in each class are listed in table I.

Alpha-adrenergic blocking agents such as phenoxibenzamine and prazosin typically decrease peripheral resistance by relaxing smooth muscle in the vascular walls. Beta-adrenergic blocking agents are commonly used to reduce cardiac output by blocking the effects of epinephrine on the myocardium. Centrally acting agents such as methyldopa, act by stimulating centers in the central nervous system. Many of these agents have been thought to act on alpha-adrenergic neurons in the tractus solatarius producing an inhibition of peripheral sympathetic activity. A fourth class of agents includes drugs which interfere with chemical mediation at the post ganglionic adrenergic nerve endings. These drugs may deplete stores of the neurotransmitter or prevent their release. Quanethidine is one such agent. During chronic administration, it impairs the release of norepinephrine from peripheral adrenergic neurons (3).
The final class of agents more recently used in the treatment of cardiovascular hyperreactivity is the calcium channel blockers. Nifedipine is one commonly used calcium channel antagonist. It appears to inhibit the transmembrane influx of calcium ions into cardiac muscle and other smooth muscle. This suppresses cardiac or smooth muscle response to sympathetic stimulation (4).

Although all of these agents are to some degree effective in the treatment of various forms of cardiovascular disease, there is a significant incidence of adverse reactions to many of these drugs (3). For instance, alpha-adrenergic blockers are often reported to produce GI distress and headache while beta-adrenergic blockers are sometimes associated with depression, lack of energy and impotence. Centrally acting agents such as methyldopa have frequently been associated with impotence in males, while adrenergic neuron blocking agents such as reserpine have frequently been sited as causing severe depression. One of the reasons why patients report adverse reactions from pharmacotherapy is that most pharmacologic agents are relatively nonspecific in action. For instance, because of the pervasiveness of alpha- and beta-adrenergic receptors throughout the body, most of the alpha and beta blockers have far reaching effects beyond those targeted in the cardiovascular system. Other agents such as reserpine which have therapeutic effects peripherally, have serious debilitating central nervous system effects. These problems become particularly troublesome when therapy must be chronic as in the treatment of hypertension or angina pectoris. Similarly, the cost/benefit ratio of these treatments becomes questionable when disease is mild such as in borderline hypertension.

Behavioral Techniques

The use of behavioral techniques in the treatment of cardiovascular disease came in part as a response to the quest for alternatives to pharmacotherapy as well as an outgrowth of the development of biofeedback and instrumental conditioning of autonomically mediated responses. Early biofeedback experiments suggested that autonomically intervated responses could be
voluntarily controlled. Furthermore, these experiments suggested that this control could be made to be specific to the target organ being trained. A good example of this early work is a study by Shapiro et al. (5) which demonstrated that palmer skin potential, reflecting pseudomotor activity, could be voluntarily controlled. One group of subjects was given a reward each time a skin potential response occurred; a second group was given the same number of rewards but at times when the response was absent. The first group showed increases in the response rate relative to the second group which showed a response decrement. The fact that the same reward, with instructions held constant, could be used either to enhance or diminish the autonomic response argued strongly that the control was voluntary. Lowering variations in the electrodermal response were found not to be associated with such physiologically related functions as skin conductance, heart rate, and respiration suggesting that this control was relatively specific.

An example of the specificity of biofeedback and conditioning techniques in achieving cardiovascular control was provided by Schwartz (6). He developed an on-line procedure for tracking both phasic and tonic patterns of blood pressure and heart rate in real time and showed that subjects could learn to control patterns of simultaneous changes in both functions. That subjects could learn to some extent, to differentiate heart rate and blood pressure responses emphasized the plasticity of central control of cardiovascular responses. If these biofeedback techniques could indeed produce specific changes in cardiovascular activity, then they could be seen as behavioral analogues to various forms of pharmacotherapy (1).

Several experimental investigations of behavioral control of cardiovascular reactivity led to the suggestion that specific biofeedback techniques would produce more potent attenuation of particular cardiovascular responses than less specific relaxation procedures. One study by the Shapiro group (7) demonstrated that subjects given specific heart rate feedback to decrease their heart rate in response to cold pressor test were significantly more successful than subjects who were instructed to decrease their heart rate without being given specific biofeedback (figure 1). Similarly, Steptoe
demonstrated that pulse transit time feedback was significantly more effective in increasing transit time (a measure related to blood pressure) than relaxation training during which subjects were given a challenging task (see figure 2).

Despite these successful experimental studies demonstrating the specificity of biofeedback techniques in modifying sympathetically mediated responses, clinical trials of biofeedback and relaxation have failed to show that there are any specific advantages for biofeedback techniques over relaxation strategies in treating cardiovascular disease. For example, Surwit et al. (9) reported findings of a controlled group outcome study in which two types of biofeedback training were compared to a form of meditation in the treatment of borderline hypertension. Twenty-four borderline hypertensives served as subjects and were eventually divided into three treatment conditions. All subjects received two 1-hr baseline sessions and eight 1-hr biweekly treatment sessions. The first treatment group received binary feedback for simultaneous reductions of blood pressure and heart rate. The second group received analog feedback for combined forearm and frontalis electromyographic (EMG) activity. The third group received a meditation-relaxation procedure modeled after Benson (10). Six weeks following the last treatment session, all subjects received a 1-hr treatment followup session. The three treatment groups all showed significant reductions in pressure over trials during each session implying that each of the behavioral methods tested was equally effective as a clinical intervention.

Though no clinical advantage could be demonstrated for the "specific" biofeedback techniques, some investigators have reported impressive clinical results in the use of relaxation in a variety of cardiovascular problems. Patel (11) proposed to modify the sympathetic nervous system contribution to hypertension by using skin resistance biofeedback in combination with yoga breathing-relaxation exercises and meditation to treat a group of 20 hypertensive patients. Initial average blood pressure on medication was 160/102 mm Hg. Following 36 half-hour sessions over a 3-month period, average pressure dropped to 134/86 mm Hg. Furthermore, total
drug requirement was reduced by 42 percent. Only four patients failed to demonstrate improvement. These results were replicated in a later study (12) in which increased medical attention and repeated blood pressure measurements were used as a placebo control. After a 12-month followup, the treatment group had an average pressure reduction of 20.4/14.2 mm Hg compared to no change for the controls. Smaller but equally consistent improvements in blood pressure following the application of an abbreviated form of meditation training have been reported by Benson et al. (13) and Stone and Deleo (14). Progressive relaxation training has also been used as an effective therapy for hypertension (e.g., 15).

Another approach to the treatment of hypertension which appears to be promising incorporates the patient's self-monitoring of blood pressure with relaxation strategies. Whereas in many cases certain behavioral techniques such as relaxation can be effectively applied to the treatment of disease without clarification of the relationship of stress to symptom severity, it is always useful to assess the relationship between the symptom and the environment in which the patient lives. As applied to the treatment of hypertension, such an intervention involves frequent monitoring and graphing of blood pressures throughout the day in order to clarify the relationship of environmental stimuli to pressor responses. Relaxation or other behavioral techniques aimed at reducing blood pressure would then be applied to those situations in which blood pressure was most likely to be elevated. The outcome of such an intervention is illustrated in the following case report (1). As shown in figure 3a, this patient showed wide fluctuations in systolic and diastolic blood pressure throughout the day. During weekly sessions, blood pressure graphs were analyzed and the patient was given instructions as to how to change his behavior, including the practice of relaxation, in order to modify his blood pressure. The results of this therapeutic intervention are illustrated in figures 3b, c, and d. As can be seen by the end of 10 weeks, the variability in blood pressure was greatly reduced yielding an essentially normotensive pattern.

Behavioral methods have also been used successfully in the treatment of Raynaud's disease, a vasospastic disorder involving the digits of the upper
and lower extremities. Patients suffering from the disease report experiencing discoloration and sometimes pain in the fingers and toes upon exposure to cold or emotional stress (16). Although there is some debate as to the mechanism of the vasomotor disorder, it is considered to be an example of excessive peripheral vasomotor reactivity (16). In one study by Surwit et al. (17), 30 female patients diagnosed as suffering from idopathic Raynaud's disease were trained to control their digital skin temperature using either autogenic training or a combination of autogenic training and skin temperature biofeedback. All subjects were exposed to an initial cold stress procedure in which they were seated in an experimental chamber while the ambient temperature was slowly dropped from 26°C to 17°C over 72 minutes. Skin temperature and other cardiovascular responses were monitored during the temperature change. This procedure was given to half of the subjects immediately before and immediately following a full month training sequence. The remaining half of the sample was exposed to an additional cold stress challenge prior to treatment as a no treatment. The study results are illustrated in figure 4. Autogenic training and biofeedback combined with autogenic training were equally effective in producing a significant improvement in subjects' ability to maintain digital skin temperature relative to both their initial cold stress as well as the second cold stress given with the no treatment control sample. All treated subjects also reported approximately 50 percent reduction in vasospastic attack frequency. In a subsequent study (18) subjects were given autogenic training, skin temperature feedback, or EMG feedback, as a treatment for Raynaud's disease. Again all three treatments were equally effective in producing a significant attenuation of vasospastic frequency as well as increased resistance to a controlled cold challenge.

Migraine and vascular headache represent another category of cardiovascular disease in which vascular instability has frequently been attributed, in part, to the autonomic nervous system (19). Interest in the application of behavioral techniques to the treatment of migraine can be traced to the early work of Sargeant, Green and Walters (20). These investigators reported that spontaneous recovery from a migraine was correlated with a 10°F increase in digital skin temperature over a 2-minute period. They
reasoned that if spontaneous increases in skin temperature were associated with headache relief, then inducing digital vasodilatation voluntarily may provide a behavioral treatment for migraine. The rationale for this intervention is that increased digital bloodflow is accompanied by decreased adrenergic SNS activity (1,20).

Numerous studies and case reports published between 1972 and the present substantiate the utility of digital skin temperature feedback, autogenic training and teaching patients to warm their hands, in the alleviation of migraine headaches (1). However, as with other disorders, nonspecific relaxation techniques have been shown to be as effective as biofeedback procedures in the treatment of migraine (1). For instance, in one widely cited study, Blanchard et al. (21) applied a controlled group outcome design to test the differential efficacy of temperature biofeedback as compared to progressive muscle relaxation or a waiting list control. Ten subjects were given temperature feedback with autogenic training and 10 subjects were given progressive muscle relaxation training. Both groups were encouraged to practice at home. Ten subjects constituted a waiting list control. Subjects in both the temperature feedback and relaxation condition showed significantly greater decreases in the frequency and intensity of migraine headaches than did the waiting list control. Interestingly, subjects receiving progressive relaxation did slightly better than subjects receiving temperature biofeedback and autogenic training. At a 1-month followup, the gains were maintained in 9 out of 13 in the group receiving temperature feedback and in all the subjects receiving relaxation training.

Neuroendocrine Mechanisms of Relaxation and Biofeedback

Despite the ubiquitous application of relaxation and biofeedback procedures to all sorts of cardiovascular disease, little is known about the neuroendocrine mechanism by which such training affects cardiovascular responsivity. Nevertheless, over the past eight years, a number of studies have appeared in the literature in which the neuroendocrine consequences of relaxation were explored. In 1976, Stone and Deleo (14) reported small but
significant blood pressure reductions (15/10 mm Hg) in 19 patients who practiced a Buddhist relaxation procedure for 6 months. These changes were found to be accompanied by significant reductions in plasma dopamine beta-hydroxalase, a catecholamine metabolite. Furthermore, patients practicing relaxation also showed decreases in furosemide-stimulated plasma reactivity suggesting a decrease of sympathetic tone in the kidney. Davidson et al. (22) trained six patients with surgically implanted tantalum myocardial markers in deep muscle relaxation. Trained subjects demonstrated a decrease in norepinephrine levels as well as indices of myocardial contractility during relaxation as compared to a control state. Mathew et al. (23) examined the neuroendocrine effects of progressive relaxation training and EMG biofeedback in 20 outpatients with migraine headache. After eight sessions of EMG biofeedback-assisted relaxation training, trained subjects were seen to show lower levels of epinephrine, norepinephrine, as well as monoamine oxidase activity compared to untrained controls who also underwent two venepunctures. This same group (24) reported similar findings when they compared the effects of relaxation training in a group of 15 anxious patients and 15 nonneurotic controls who were examined twice without any intervention.

Other investigators have reported contradictory results. Hoffman et al. (25) studied the neuroendocrine effects of the relaxation response (10)--a variation on the meditation procedure--in 19 normal volunteers. In contrast to previous investigations, the effects of venopuncture were more carefully controlled by admitting patients to a clinical research unit 10-12 hours prior to testing, and withdrawing all blood samples via an indwelling intravenous catheter which was inserted 30 minutes before the withdrawal of the first blood sample. Plasma norepinephrine levels were determined while the subject was supine, after 5 minutes of standing, and while the subject was practicing an isometric hand grip. These measurements were repeated before and after half the subjects were trained in the relaxation response. Following training, subjects who practiced relaxation showed significantly higher levels of plasma norepinephrine than subjects who were not trained in relaxation in response to the isometric hand grip. No differences in systolic blood pressure, diastolic blood
pressure or heart rate between the groups were observed. These findings were interpreted as indicating that alpha adrenergic receptors may have been down-regulated in those subjects who practiced relaxation but SNS activity itself increased with relaxation.

Finally, Surwit and Feinglos (26,27) admitted 12 non-insulin-dependent diabetic patients to a clinical research unit for 9 days. All subjects received the glucose tolerance test and an insulin sensitivity test. Half of the subjects were then given 5 days of progressive relaxation and EMG biofeedback training while the other half of the subjects remained in the hospital without training. Glucose tolerance tests and insulin sensitivity tests were then repeated while subjects who learned relaxation practiced their relaxation strategies. All subjects had low levels of catecholamines and there was no significant difference in catecholamine levels between subjects trained in relaxation and controls. As in the Hoffman et al. study, blood samples were withdrawn by an indwelling catheter which had been inserted well before test samples were withdrawn.

The effects of relaxation on adrenocortical responding have also been studied. Jevning et al. (28) reported that plasma cortisol concentrations decreased in long-term practitioners of transcendental meditation (TM) during the practice of relaxation. Similar changes were not found in controls at rest or in controls learning meditation for the first time. These results were contradicted in a report by Michaels et al., in which practiced meditators (TM) and untrained controls were studied while practicing meditation or sitting quietly with their eyes closed. No significant differences in plasma cortisol, plasma renin activity, plasma aldosterone or plasma lactate were found between the two groups. DeGood and Redgate (29) studied the effects of progressive relaxation and EMG biofeedback on plasma cortisol responding in 24 subjects who were characterized as to trait anxiety using the Spielberger State-Trait Anxiety Scale. The 12 participants above the median on initial trait anxiety showed significant reductions in plasma cortisol over eight sessions of relaxation training. In contrast, subjects who scored low in trait anxiety showed no change. Surwit and Feinglos (26,27) also studied the effects of progressive relaxation and EMG feedback on plasma cortisol levels. In
their study previously described, subjects receiving progressive relaxation and EMG biofeedback showed significant decreases in plasma cortisol, pre/post training compared to untreated controls. This change in plasma cortisol was accompanied by a significant improvement in glucose tolerance in treated patients.

The data on the effects on meditation and relaxation procedures on various neuroendocrine parameters appear to be contradictory. The apparent confusion may be due to the considerable methodological difficulties inherent in assessing the neuroendocrine effects of relaxation. At this time, it would be most prudent to withhold judgement as to what neuroendocrine mechanisms mediate the apparent effects of relaxation on cardiovascular reactivity. Nevertheless, it is obvious that if relaxation procedures do influence cardiovascular responding, then some neuroendocrine changes must be taking place. There was suggestion that relaxation may decrease cardiovascular responsivity by decreasing sympathetic activity directly. There is an equal amount of data which suggest that relaxation produces decreased adrenocortical responses as well. Recent evidence suggests that glucocorticoids may play a significant role in cardiovascular reactivity. Several studies have shown that increased levels of glucocorticoids can increase vasomotor responding to catecholamines (e.g. 30,31). Idiopathic Raynaud's disease has also been associated with high levels of plasma cortisol (32). In that glucocorticoids are known to prevent the down-regulation of beta-adrenergic receptors (33) as well as prevent the degradation of catecholamines in the intersynaptic cleft (31), glucocorticoids apparently play an important role in modulating the reactivity of cardiovascular end organs to sympathetic nervous system stimulation. If relaxation techniques really do influence adrenocortical activity, then they would be predicted to have a modulating effect of cardiovascular reactivity even if they do not directly influence the sympathetic nervous system itself.

Summary

Hyperreactivity of the autonomic nervous system has been assumed to be a primary lesion contributing to the development of cardiovascular disease.
Pharmacologic treatments of cardiovascular disease usually operate either by inhibiting sympathetic nervous system activity through central stimulation or by interfering with efferent sympathetic activity at the level of the effector organ, the receptor, or the postganglionic nerve ending. A variety of biofeedback and relaxation techniques has also been demonstrated to reduce cardiovascular responsivity. These techniques have shown to have some degree of clinical efficacy in the treatment of hypertension, peripheral vasomotor disorders and migraine headache. However, the neuroendocrine mechanisms by which these procedures exert their effects are not clearly understood. There is suggestive evidence that biofeedback and relaxation procedures work by reducing the activity of both the sympathetic nervous system as well as the adrenocortical axis.

REFERENCES


27. Surwit, R.S. and Feinglos, M.N. Relaxation induced improvement in glucose tolerance is associated with decreased plasma cortisol. Diabetes Care, 1984, 7, 203-204.


Table I
Pharmacologic Modulators of SNS Activity

I. \( \beta \)-Adrenergic blockers
   A. Phenoxybenzamine
   B. Prazosin
   C. Phentolamine
   D. Tolazoline

II. \( \alpha \)-Adrenergic blockers
   A. Propranolol
   B. Nadolol
   C. Timolol
   D. Metaprolol

III. Centrally acting agents
   A. Clonidine
   B. Methylldopa

IV. Adrenergic neuron blocking agents
   A. Guanethidine
   B. Reserpine

V. Calcium channel blockers
   A. Nifedipine
   B. Verapramil
Fig. 1. Mean heart rate in successive 5-sec periods of the two cold pressor tests. Each point is the mean of nine subjects.

FIGURE 1. Mean heart rate in successive 5-second periods during cold pressor test prior to and following exposure of half the subjects to heart rate feedback. From Victor, R., Mainardi, J.A. and Shapiro, D. Effect of biofeedback and voluntary control procedures on heart rate and perception of pain during the cold pressure test. Psychosomatic Medicine, 1978, 40, 216-225.
ROOM TEMPERATURE (°C)

26° 25° 19° 17°

TASK GROUP REPORTS ON MODULATORS
MODULATION BY EXERCISE

Group Leaders: Bruce Alpert, Joel Dimsdale

Group Members: Jack Dawson, Richard Hughes, Katrina Johnson, Wallace McCrory, Richard Rose, Neil Schneiderman

Premise and Introduction

Does aerobic fitness (AF) modulate reactivity to behavioral stressors? The committed exerciser and, indeed, 96 percent of physicians believe that physical conditioning results in enhanced morale, decreased subjective stress and anxiety, and increased coping resources. Are there any physiological data to support this?

Exercise brings about a number of physiological changes which may well be related to the above belief.

Effects of AF

<table>
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<tr>
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<th>At Rest</th>
<th>Exercise</th>
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<tr>
<td>SBP</td>
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<tr>
<td>DBP</td>
<td>0</td>
<td>0 (no change)</td>
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The traditional measures for cardiovascular reactivity are HR and BP. If AF does indeed modulate HR and BP reactions to behavioral stressors, then one may assume that the lessened reactivity could be related to decreases in transmitter release or to down-regulation of alpha and/or beta receptors. However, before acting on the hypothesis, it is well to consider the nature of the evidence relating AF to decreased stress-induced
reactivity. Rarely has a hypothesis been believed so strongly on the basis of such meager evidence.

Committed exercisers are convinced that their AF has had a beneficial effect on the ability to navigate through life stress with some measure of equanimity. The problem is that many other factors change simultaneously with AF.

1. The AF individual decreases his or her risk profile on variables such as smoking which enhance reactivity.

2. In the process of exercise many individuals change their social behavior. Jogging enhances a social network which, in turn, may be a more relevant modulator of reactivity than the fitness per se.

3. The enthusiasm fostered by fitness programs may lead to decreased stress reactivity by a kind of Harthorne effect.

There is a paucity of published and personally reported data concerning the effects of training (aerobic fitness) on the variables of cardiovascular reactivity. Sinyor et al. studied 15 trained and 15 untrained male university students. The subjects underwent a protocol involving mental arithmetic, a quiz, and the Stroop Color-Word test. Blood sampling was performed for assessment of epi, norepi, cortisol, and prolactin. There were no differences in the delta HR values to the stressors when trained and untrained subjects were compared. There was, however, a significantly faster return to baseline HR values in the trained subjects. No BP values were obtained. There was no significant difference in epi and norepi peak responses, but the norepi peaked earlier in the AF individuals in response to mental arithmetic. The cortisol values were not significantly different. The authors' conclusion was that aerobic training may influence cardiovascular reactivity.

A recently completed study by Lake et al. of 61 subjects, 40 fit and 21 sedentary, 39 Type A and 22 Type B, demonstrated responses to five
challenges. These were: 1) SI, 2) boa constrictor, 3) mental arithmetic, 4) cold pressor, 5) competitive card game. There were no A-B differences seen in response to challenges 2, 3, and 4. During the SI, BP was highest for the As and for the sedentary subjects. There was an interaction between Type A and sedentary behavior such that BP increases were most pronounced for the sedentary A. However, during the card game, the BP response in fit A was greater than in sedentary A, sedentary B, or fit B. The conclusions reached were that tasks vary in their effects on variables of cardiovascular reactivity. The interview may be the prototype for interpersonal challenge; the card game may represent a highly competitive task similar to an athletic event.

Two recent abstracts by Falsetti et al. and by Garber et al. address the issue of reactions to mental stress in trained vs. untrained subjects. Due to the brevity of the abstracts and the apparent lack of controls, the task group could not interpret the results of these studies.

Although not measuring an effect on reactivity per se, Blumenthal et al. have shown an effect of extreme training on Type A interview scoring as assessed by the JAS.

Methodological Considerations

Aerobic fitness can be, and has been, construed as an independent variable (with an interest in its possible effects on reactivity) and as a confounding variable, which can mask the effects of other manipulated variables on reactivity. In a prospective study, subject differences in AF could seriously confound planned manipulations, and it is, therefore, important to match groups on AF at entry into a study. Further, changes in exercise habits should be monitored during followup. Fairly simple assessment of AF may be made; e.g., from results of a step-test, to facilitate subject matching.

As an independent variable, the influence of AF on reactivity may, itself, be confounded by the effects of other group differences. The self-selection processes that lead some adults to engage regularly in
exercise are likely to be predictive of reactivity. "Convenience samples" characterize much of the literature associating jogging with behavioral measures, but such studies are severely limited as a consequence. Matching on age and gender (and perhaps ethnicity) as well as accepted risk factors are clearly requisite in a study that asks whether an exercise program affects reactivity. We assume that many other demographic and personality characteristics may modulate an individual's response to exercise intervention and the effect of such intervention on reactivity.

Further, it is apparent in much of the current literature that has examined AF as an influence on reactivity, investigators have employed a simple pre/post-design with no controls. In so doing, the investigator has no assessment of the effects of retesting per se. At least some psychological tasks widely used in laboratory investigations of cardiovascular reactivity exhibit significant habituation effects on retesting at short intervals; subjects typically exhibit significantly less reactivity on followup. These potentially serious problems of practice effects and/or effects of regression to the mean mandate the use of control groups, appropriately matched on entry into the study but from whom the intervention is withheld. Ideally, such matching should be on a case control basis; that is, the control group should be assigned to a task in which attention is given. Indeed, from a conceptual viewpoint, the ideal design might be a co-twin control, one employing monozygotic twin pairs; but in most applications, this design will be impractical. An alternative may be to employ a cohort reasonably homogenous on many personal and demographic characteristics, randomly allocated into control and intervention subgroups.

One such possible cohort might be found in a group of army recruits at completion of basic training: all individuals would be in a state of excellent AF, and they could be reasonably matched on background variables. Half of the recruits might continue in a state of AF following assignment; while the remaining half, assigned to clerk typist work, would become deconditioned.
In designing studies to assess the effects of aerobic exercise upon cardiovascular reactivity, coping to perceived aversive stimuli in the laboratory setting needs to be appreciated. Protocols should also obtain assessments of reactivity during stressful encounters in more naturalistic settings, such as in the workplace or in the field. Would differences in reactivity best be observed within-subjects, in a longitudinal context where AF level is experimentally manipulated? Would such differences relate to psychological inventories designed to assess coping behavior?

Attention to attitudinal lifestyle differences between aerobically fit and deconditioned or sedentary groups are likewise important in designing a protocol. Risk factors may differ and affect outcome measures. The existing data suggest that a "benefit" of AF with respect to cardiovascular reactivity variables in response to mental stress is shortened hemodynamic recovery time. Given the paucity of data, further inquiry into the relationships between AF and cardiovascular reactivity and their proper positions in our armamentarium of interventions appears warranted.
PSYCHOLOGICAL STRESSORS PRODUCING REACTIVITY—RELAXATION THERAPIES

Groups Leaders: Margaret Chesney and Rolf Jacob

Group Members: B. Kent Houston, Viktor Kramelashvili, Neal Miller, Patrice Saab, Gary Schwartz, Carl Thoresen

Psychological Stress Management Procedures: Modulators of Reactivity

The mandate for this task group was to examine and make recommendations regarding psychological stress management procedures in the modification of stress-induced reactivity. The major psychological stress management procedures are relaxation and biofeedback strategies. However, a number of related stress management procedures are relevant to this review such as training in specific strategies for coping with stress, anxiety management training, and assertiveness or social skills training. These latter approaches have been relatively unexplored with regard to their effects on cardiovascular reactivity and, thus, were not included in the task group deliberations. The theoretical basis for their potential relevance will, however, be discussed in the following section.

Historical and Theoretical Background of Relaxation Techniques

Historically, six general categories of relaxation techniques that historically were developed to help reduce psychological and physiological responses to stress. Each of these categories of techniques has a somewhat different theoretical orientation and therefore has stimulated somewhat different research questions.

Somatic relaxation techniques. These techniques were developed to help reduce cognitive and somatic responses to stress. Meditation techniques, notably TM and Zen, have long been practiced, presumably to help persons take a passive attitude to stimuli in general, including ones' own thoughts and emotions. Progressive muscle relaxation was developed in the 1920s to help people reduce the skeletal muscle components of stress responding, and in the process, reduce autonomic responses influenced directly and/or
indirectly by skeletal muscle control. About the same time, autogenic training was developed to help reduce autonomic reactions to stress (e.g., lower HR and BP) using specific images and attention to specific regions of the body. Yoga techniques clinically combined cognitive and somatic strategies presumably to gain greater mental and physical control. Benson, in the late 1960s, attempted to integrate these different approaches by proposing that a neurophysiological final common pathway, termed the relaxation response, led to generalized decreases in sympathetic tone and possibly generalized increases in parasympathetic; whereas, Davidson and Schwartz proposed that different neurophysiological and psychophysiological processes were involved in different relaxation techniques. The recent book by Woolfolk and Lehrer reviews both the history and current status of these different approaches.

**Biofeedback.** Biofeedback was actively developed in the 1960s by Miller, Kimmel, Shapiro, Lang, Kamiya and others to help subjects gain specific control over selective physiological responses. Concepts of operant conditioning, motor skills learning and cybernetic theory stimulated the growth of this research. Demonstrations of highly selective autonomic and skeletal muscle learning in both lower animals and humans stimulated renewed interest in the cognitive and sometic techniques described above.

**Systematic desensitization.** Drawing on models of classical conditioning (including counter conditioning and extinction), Wolpe proposed in the 1950s that subjective, physiological and behavioral responses to anxiety and anger-provoking stimuli could be reduced with this technique. The systematic desensitization techniques focused on the concept of a hierarchy of weaker to stronger stimulus presentations, which finds a parallel in medicine in the area of desensitization from allergies. Wolpe's work played a major role in the development of behavior therapy as a field.

**Cognitive behavior therapy.** In the 1960s, Lazarus and colleagues proposed that cognitive appraisal of stressful events played a key role in mediating the relationship between potential psychosocial stressors and psychophysiological responses. His early psychological studies manipulating
the mental sets subjects held while watching stressful movies helped lead to the development of modern cognitive behavior therapy techniques for changing people's appraisals of stressful life events.

**Education and information.** In the 1950s, Janis documented that people's responses to and recovery from major life stresses such as surgery, were determined in part by how much knowledge and preparation they had for this event, as well as the degree of control they experienced in these situations. The role that information and perceived control plays in modulating psychophysiological responses to stress has been explored in the classic work of Glass and Singer and is an active area of current research.

**Environmental change.** Most recent in origin has been the development of various assertiveness techniques, social skills training techniques, and social communication techniques to help individuals better deal with and alter stressful environments. Besides helping subjects directly alter or make decisions to remove themselves from specific stressful situations, these techniques presumably increase relaxation by giving people a greater sense of perceived control and self-efficacy.

These six categories of techniques are not exhaustive, since related techniques such as hypnosis and imagery have also played a significant role in the history of relaxation methods. The point of this brief overview is to illustrate how different theories historically stimulated the development of different techniques. Modern theories and research are changing the way we currently conceptualize and integrate these various techniques.

**Efficacy of Psychological Stress Management Procedures for Reducing Reactivity**

A sizeable number of studies with both patients and normal subjects have demonstrated attenuation of various physiological parameters during exposure to and in recovery from laboratory stressors. These stressors have included the cold pressor, exercise, reaction time, actual or
threatened aversive stimuli and mental challenges. Dependent variables have included BP, HR, skin conductance and indirect measures of blood flow. There is a relative paucity of studies examining phasic changes in biochemical variables during stress-induced reactivity as an outcome variable for psychological stress management procedures.

A review of the published reports permits a cautious conclusion that stress management procedures can reduce cardiovascular reactivity and other indices of arousal, although it remains to be seen whether the effects are related to what was intended to be the "active" treatment ingredient rather than to the nonspecific effects derived from instructions or expectations. Furthermore, other studies fail to support this conclusion, underscoring the need for further research in this area. Despite the evidence for attenuation of reactivity, the specific pattern varied across studies. For example, some studies found reductions in one parameter but not in others, and some studies found changes in recovery rate and no attenuation of the amplitude of stress response. Explanations for these discrepant findings are that the studies varied in the specific stress management procedure used, the length and intensity of training, as well as the specific configuration of laboratory stressors and subject populations. For example, reactivity may be particularly attenuated in subjects with elevated levels of or elevated reactivity in the physiological variable studied (e.g., hypertensive patients showing attenuation of BP response).

Another explanation for the discrepant findings is suggested by a pattern across studies indicating that the different stress management procedures are associated with different effects on reactivity. For example, biofeedback may result in more specific attenuation of the feedback parameter than other variables, especially when the effects are tested under stress. Meditation procedures, on the other hand, may tend to increase orienting responses to stressors but still facilitate poststress recovery. Relaxation-based approaches may not always result in attenuation of peak stress response, but still shorten recovery time. Possible mechanisms underlying these effects on reactivity will be discussed in the following section.
Mechanisms by which Psychological Stress Management Procedures May Reduce Cardiovascular Reactivity

The mechanisms by which psychological stress management procedures may reduce cardiovascular reactivity can be arranged in a hierarchy. At one level are the cognitive effects of these procedures, which may change the way stimulus situations are perceived and evaluated. For example, stressors may be appraised by subjects as indicating different levels of opportunity, challenge, or threat. Moreover, cognitive factors such as the subject's confidence that he or she can apply stress management procedures and otherwise cope with the stressor may be a mechanism by which reactivity is reduced. Also, cognitive diversion away or distraction from the stressor may be involved. Stress management procedures may achieve an effect via any of the foregoing cognitive processes and hence influence the degree and quality of the subject's emotional arousal. This arousal, in turn, will be expected to affect cardiovascular reactivity via neurohormonal mechanisms of the brain.

Stress management procedures may also operate by affecting the pattern of visceral and somatic responses to a stressor. For example, these procedures may induce preparation for or execution of a pattern of response to intense motor activity or of vigilance of "freezing." These response patterns may have cardiovascular components "hard-wired" into them in the brain, and/or exert effects mediated by their metabolic consequences. It is probable that further research will discover a number of such response patterns. Psychological stress management procedures could result in subjects responding to stressors with somatic-visceral response patterns involving lower levels of arousal than the response patterns typically elicited by same stressors without treatment.

In addition, psychological stress management procedures may teach subjects a certain amount of direct visceral control (without somatic mediation) over specific cardiovascular responses to environmental stressors. Furthermore, the demonstration by use of biofeedback instruments that subjects have learned either direct or indirect control of a cardiovascular
response may increase their confidence that they can cope and thus have additional effects via cognitive mechanisms. Finally, psychological stress management strategies may also help subjects achieve somatic awareness, which, in turn, may facilitate their maintenance of physiological stability despite the presence of stressors.

The foregoing factors operate via the neurohumoral mechanisms of the brain, including direct sympathetic and parasympathetic innervation of various components of the cardiovascular system and hormones such as adrenaline, noradrenaline, glucocorticoids, mineralocoids, growth hormone, endorphins and enkephalins. These processes and neurohormonal substances may interact and affect various receptors. While the physiological mechanisms for producing a number of significant cardiovascular effects are known, the details of their involvement in various effects of psychological stress management procedures largely remain to be discovered. With the advent of more powerful neurophysiological, pharmacological and biochemical techniques, the investigation of such details should be a fruitful area of research.

The Assessment of Key Variables in the Implementation of Psychological Stress Management Procedures

Psychological stress management procedures designed to reduce reactivity requires assessment on two levels. The first of these, referring to the process of treatment, will be discussed in this section. The second, involving the assessment of treatment outcome will be discussed in the following section.

Process variables refer to indices employed to monitor the course of treatment independent of treatment outcome. Typically, they involve changes that occur during the treatment phase in physiological and behavioral parameters that are related to the treatment procedure.

Physiological changes. In choosing physiological variables to monitor the treatment process, preference should be given to parameters reflecting the
skill acquisition. For example, in a study utilizing temperature feedback, temperature changes within treatment sessions should be documented. Demonstration of physiological changes should be measured, not only during resting conditions, but also during exposure to stressors within treatment sessions. Evaluation of the latter condition has often been lacking.

Behavioral changes. Behavioral changes during stress management procedures are also important to ensure appropriate skill acquisition. Examples of assessment strategies are provided by the literature on relaxation. Behavioral assessment of relaxation effects achieved within treatment sessions can be done utilizing behavioral checklists. Unobtrusive measures of compliance to home practice using relaxation tapes include electronic monitoring of relaxation tape usage or monitoring of minor preprogrammed changes in the relaxation instructions. In addition, monitoring of home practice by significant others may be valuable. Utilization of mere self-reports of compliance is likely to be biased and is cautioned against unless employed in conjunction with other measures.

Expectancy. In addition to physiological and behavioral changes, it is useful to assess an individual's expectancy of treatment benefits. It appears to be quite common for the individual's expectations to influence responses to the procedures and, thus, to treatment effects. The power of expectancy and instruction to determine treatment effects has been demonstrated in quite a few studies of the effect of stress management on cardiovascular reactivity.

Criteria for Evaluating Treatment Outcome and Effectiveness

A number of considerations are important for evaluating the effectiveness of a stress management procedure for reducing reactivity. At a basic level, stress-induced reactivity measured in the laboratory and in the natural environment prior to treatment must be demonstrated to decline at posttest to a significantly greater extent for subjects undergoing a stress management procedure than for subjects in a no treatment control condition. Coupled with this, where long-term followup is possible, one should see
lower incidence of CVD following training in the stress management procedures. Reduction in medications and the appearance of unintended health benefits; e.g., cessation of smoking and engaging in exercise, are also potentially important criteria for evaluating the efficacy of stress management procedures.

In studies of biofeedback, it is important to evaluate the extent to which changes in reactivity in the physiological mode for which biofeedback was provided generalize to reactivity in other physiological parameters; e.g., does heart rate biofeedback reduce pressor responses as well as heart rate reactivity? Moreover, in studies of general relaxation-based procedures, are general changes in psychophysiological reactivity observed? In addition, do stress management procedures lead to changes in recovery time as well as peak reactivity? Finally, changes in the tonic response levels affected by a stress management procedure should be assessed for correlations with changes in magnitude of reactivity. For example, does degree of decrease in BP following biofeedback correlate negatively with pressor responses?

Persistence of treatment effects is an important criterion that can be evaluated by one or more followup assessments. Finally, individual difference variables should be examined to determine whether a stress management procedure is more effective for certain kinds of individuals than others.

Key Research Questions

The foremost research question is whether stress management procedures reduce reactivity; that is, do they work? Subsequently, it is important to identify which component or components of the treatment package is/are the important or active ingredient(s) of the package. Moreover, the mechanisms by which the active ingredients achieve their effects, (e.g., via primarily psychological avenues, physiological avenues) need to be elucidated.
As is desirable in evaluating the efficacy of any treatment procedure, it will be important to identify which stress management procedure is most effective for what kinds of subjects, particularly with respect to the main modality in which subjects exhibit their reactivity. Furthermore, one kind of stress management procedure may be more effective for reducing pressor reactivity in one particular socioeconomic or cultural group while another kind may be more effective for individuals with other subject characteristics. Finally, the ultimate research question is whether a particular stress management procedure, which has been demonstrated to reduce reactivity will actually reduce the incidence of CVD.
PHARMACOLOGIC AGENTS AS MODULATORS FOR STRESS

Group Leaders: Alvin Shapiro, Clarence Grim

Group Members: Thomas Clarkson, Katherine Detre, Peter Kaufmann, David Krantz, Robert Miller, Kristina Orth-Gomer, Redford Williams

The theme of the task group was the role of pharmacologic agents as modulators of the peripheral manifestations of cardiovascular reactivity to stress, anxiety, and other environmental stimuli. We decided to discuss this problem from the following points of view:

1. What is the role of pharmacologic agents which inhibit peripheral reactivity in stress management?
2. Does peripheral reactivity affect behavior?
3. What are the negative considerations involved in pharmacologic modulation of stress, particularly by beta blockers?
4. Are there behavioral consequences of cardiovascular disease states and how are they affected by drugs?
5. What is the relationship of pharmacologic therapy to relieve consequences of stress vs. relaxation and other nonpharmacologic behavioral techniques?
6. What is the future role for studies in animal models to answer some of these questions?

Most pharmacologic attempts at modulating cardiovascular concomitants following environmental stimuli have in the past concentrated on affecting processes at the level of the CNS. However, the development of potent pharmacologic agents which influence reactivity by blocking receptors in the peripheral organs has led to both philosophical as well as heuristic considerations concerning their use and the need for carefully designed studies. The prime example of this approach is the increasing research and clinical use of beta blockers for both symptomatic and physiologic states in which the disturbances manifest themselves by stimulation of these various peripheral receptors. Thus, for instance, tachycardia and the changes in BP which can occur
with stress or its anticipation can often be controlled by beta blockers. This approach has been employed in situations as diverse as stage fright in musicians, tachycardia in ski jumpers, and even to "ameliorate" the Type A personality. In such situations, apparent impairment of performance has not been noted when it is looked at in terms of the specific task being done. In considering these approaches, particularly in clinical situations, a number of cautions were voiced by the group:

1. All beta blockers are not alike in their duration of action, their selectivity for beta_1 and beta_2 receptors, and their solubility—the latter a property which affects their metabolism and their CNS effects. Investigators should recognize these differences and their dose-response relationships in experimental designs.

2. Although some purported CNS effects may in fact represent the consequence of dampened peripheral responses (e.g., fatigue may equal slowed pulse rate and impaired cardiac response), nevertheless other side effects, and particularly long-term consequences, have not been explored fully.

3. The consequences of physiologic mechanisms of increased catecholamines with end organ B-receptor blockade or the utilization by stress mechanisms of alternate pathways of response is not well understood.

4. The implications of treating outcomes by drugs rather than input by social and behavioral changes is a philosophical issue worth consideration, although there are ample examples of treatment situations in which we do this regularly (e.g., using nitrates and other drugs for angina, propylthioracil for hyperthyroidism, and even antibiotics for infectious diseases due to poor hygiene).
5. An interesting question that has not been studied in humans is to what extent beta-adrenergic arousal may "feed back" to the CNS so as to affect behavior in certain positive or negative fashions which would be prevented or aborted by beta blockade. There are studies in animals concerning autonomic nervous system feedback that provide the basis for such investigations.

The task group felt that although beta blockers should be used in disease states (e.g., hypertension and coronary artery disease) to minimize reactivity, their role as primary preventive agents for cardiovascular risk remains uncertain, particularly in view of the above questions. A major concern is that by definition, the subjects for such a trial would be asymptomatic and therefore likely to be intolerant of side effects that are known to occur with all pharmacologic agents, especially those directed at modifying either the perception of stress or the physiologic response to perceived stress. While it seems clear from large scale trials of known disease (e.g., BHAT study) that the side effect profile of beta blockers was similar to that of placebo, the profile in asymptomatic patients may be different. All of the beta blockers have been associated with central effects (drowsiness, dreams, fatigue, depression, changes in cognitive functioning) and/or peripheral disturbances (bronchospasm, vasospasm, bradycardia and heart failure). In addition, the drugs may adversely effect the response to hypoglycemia, the hepatic metabolism of other drugs, and perhaps plasma lipoprophiles. While the brain has an abundant supply of beta receptors, the relationship of these to central side effects is not known.

Concern was expressed that there are indications that certain uses of these agents, such as for the prevention of stage fright, are becoming widespread without the long-term effects as described above being known in nondisease subjects. Similarly, there has also been some clinical use of beta blockers in the treatment of patients who develop high levels of BP with exercise, even though their BP is normal at rest. The rationale has been that such a response is a predictor of
future hypertension, which is by no means clear; and particularly to
the cardiologist doing exercise tests, a rise in pressure often
results in the opinion that one is dealing with a "healthy" heart.

The task group therefore recommended that although the use of beta
blockers in established known disease states can be encouraged, their
application to prevent reactivity and possibly preventing eventual
disease in healthy individuals should be undertaken only in
small-scale studies aimed at understanding mechanisms; and that at the
same time, as will be mentioned below, a major effort be undertaken in
animal studies to elaborate primary prevention.

The task group spent relatively little time in discussion of alpha
blockers in this context or in the use of CNS modulators, which can
inhibit reactivity but usually at the price of CNS depression. Unless
such latter agents can be developed to the point where CNS output is
inhibited while input and cognitive processing are unaffected, they
will have little role as pharmacologic modulators in humans.

Interest was expressed in further studies on behavioral consequences
of cardiovascular disease states as a background to determining how
drugs may affect these consequences. These considerations apply to a
variety of pharmacologic agents used for hypertensive and coronary
artery disease including beta blockers, calcium channel blockers, and
nitrates. In such studies confounding variables such as age, sex,
demographic and psychosocial status, and other vascular disease (e.g.,
carotid artery circulation) need consideration in evaluating outcomes.
In brief, the task group would urge looking at what types of
behavioral change occur with cardiovascular illnesses and how the
different drugs which treat the basic disease affect these behavioral
consequences.

The contrasting and/or complementing effects of various pharmacologic
agents on the outcome of treatments with relaxation and other
behavioral techniques aimed at cardiovascular diseases such as
hypertension, angina, Raynaud's, migraine, etc. need continuing
examination, both in terms of comparison of magnitude and duration of effects, as well as side effects and cost/benefit outcomes. For instance, in hypertension, a number of studies now suggest more effective results with beta blockers than with relaxation, and no additive effects by combining the two. However, in other instances, such as Raynaud's disease, additive effects of vasodilator drugs and relaxation have been noted. Further resolution here remains clearly necessary.

Several members of the group spoke of the need for long-term studies of risk factors and their manipulation by drugs and other means in closed populations. The advantage of using the monzygotic twin model was briefly discussed.

In regard to animal studies, the continued use of small animal models such as the SHRs for pharmacologic studies should be encouraged. However, the consensus of the group was that studies which are concerned with primary prevention consequent to pharmacologic agents should be limited to primates since large differences in drug metabolism, cholesterol metabolism, etc. make the transfer of observations from nonprimates more problematic than from primate models. Ongoing studies in monkeys of the long-term interaction of beta blockade in atherogenesis are under way and should be supported and the results carefully assessed before entering into similar, infinitely more expensive studies in humans.

In summary, the task group recognizes that the use of pharmacologic agents to prevent peripheral stress reactions which can be harmful to the organism are not without precedent in terms of the history of treatment of medical disease. Insofar as one wishes to apply such agents to "healthy" individuals undergoing stress, considerable further work needs to be done to establish their long-term safety, both physiologically and psychologically. Nevertheless, in disease states these agents have been shown to be probably protective against further damage to the organism from stress and have opened up new horizons for further study and evaluation.
ALCOHOL AND REACTIVITY

Group Leaders: Robert Levenson, Benjamin Natelson

Group Members: James Ruell, Elaine Eaker, George Kaplan, Hector Myers, Barbara McCann, Edward B. Parks, Orville Smith

The effects of chronic, excessive ethanol consumption are documented to be definitely unhealthy: chronic alcoholism is associated with a variety of life-shortening disease entities including congestive cardiomyopathy, cirrhosis of the liver, chronic pancreatitis, a variety of chronic brain syndromes (including Korsakoff psychosis), muscle myocytolysis, hypertension, sudden cardiac death, suicide and depression.

Good data now exist that prolonged use of large amounts of alcohol is directly organotoxic. Specifically, the drug causes fatty infiltration of the liver (which can progress to cirrhosis), cardiomyopathy with an increased susceptibility for arrhythmias, and cerebrotoxicity with secondary hydrocephalus.

The CNS effects of alcohol can produce confounds in assessing reactivity. Intoxication is an acute brain syndrome—a lethargic state due to toxic bilateral brain dysfunction. The clinical hallmark of this state is a confusional state. Thus, the subject in a reactivity study may be unable to comprehend fully the instructions. Furthermore, if the reactivity study is done on long-time alcoholics whose cognitive abilities have deteriorated due to alcohol-induced dementia, they, too, may be unable to comprehend what demands are being made of them.

Ethanol has powerful, acute physiologic effects on cardiovascular functioning: studies by Regan, among others, have demonstrated that ethanol is a myocardial depressant when administered acutely and appears to have some effects on total peripheral resistance associated with transient vasodilation. In selected cases, alcohol can induce various degrees of AV block. Another effect is the inhibition of ADH hormone release, which causes contracted plasma volume. As removal from the cardiodepressant
effects of alcohol appears, the literature suggests a rebound hypersympathetic and adrenergic state associated with a pressor response and a lower threshold for ventricular rhythm disturbances. It is perhaps for this reason that sudden cardiac death appears more prevalent in the young alcoholic. The association between systolic hypertension and alcohol consumption might also be related to this response; however, the mechanisms that link hypertension and alcohol ingestion remain controversial. Suffice it to say, in doses used to produce a state of drunkenness, alcohol is a powerful cardiovascular drug causing significant myocardial depression and arteriolar dilation with most likely compensatory reflex tachycardia. These profound alterations in cardiovascular physiology, together with alcohol's known effect on cognitive emotional functioning seriously color the psychophysiological responses in the individual.

The relationship between amount of alcohol consumption and coronary heart disease has been examined in a number of studies. Some investigators have concluded that there is a J-shaped association between amount of alcohol consumed and risk of mortality from coronary heart disease. Although there are some conflicting results, these studies indicate that moderate drinkers are at lower risk than abstainers or heavy drinkers. This comparative advantage associated with moderate alcohol consumption is thought by some researchers to be associated with higher levels of HDL cholesterol in moderate drinkers; however, recent analyses of the LRC San Diego population do not support HDL as the explanatory pathway.

In addition to amount of alcohol typically consumed, there is also evidence that the timing of drinking is important. For example, there are reports of increased risk of coronary events associated with weekend and binge-drinking.

Studies of hypertensive patients also reveal relatively higher levels of alcohol consumption than found in normotensives. Similarly, alcoholics appear to have higher rates of hypertension than nonalcoholics. Some controversy exists over the relationship. Studies of alcoholics reveal increased risk of many types of cardiovascular disease.
Alcohol and Other Risk Factors for Coronary Heart Disease

We believe that drinking may well interact with other risk factors to increase the risk for coronary heart disease. For example, high rates of smoking are common among heavy drinkers. Heavy drinkers may experience dietary problems that may be associated with mild malnutrition on the one hand, and obesity on the other. When drinkers consume alcohol in bars, salty foods are often provided to enhance their thirst and increase their drinking, thus increasing the total salt intake by heavy drinkers. Descriptive studies are needed to corroborate these impressions, but we believe that these social factors involved with drinking will combine with other risk factors to increase the likelihood of coronary heart disease.

Alcohol and the Basal Psychophysiological State

Alcohol markedly alters the psychophysiological state of the nonalcoholic human subject. This state is complex insofar as it encompasses a set of both stimulant and relaxant effects. In terms of mood, subjects consuming a moderate to high dose of alcohol (i.e., 0.5 g ethanol/1 kg body weight to 1 g/kg) report feeling more "pleasant," more "energized," and less "anxious." In terms of basal cortical effects, intoxicated subjects show a slowing of the dominant alpha frequency in the resting brain. In terms of autonomic nervous system effects, intoxicated subjects show faster basal heart rate, higher skin conductance levels, longer pulse transmission times, and greater peripheral vasodilation compared to sober subjects. These shifts in psychophysiological basal levels are important to consider in any study of cardiovascular reactivity in which subjects consume alcohol prior to experiencing a stressor, since their prestressor state will be quite different from that of sober control subjects. Fortunately, in the range of doses typically used in human studies, none of these effects on basal levels is so pronounced as to run the risk of running up against biological ceiling or floor limits. Still, a change score or covariance strategy to quantify reactivity is clearly necessary.

Alcohol and Cardiovascular Reactivity

At the 1g/kg dose, alcohol dampens the cardiovascular response to stress.
Increases in heart rate and decreases in pulse transmission times, which are produced by two different kinds of stressors (i.e., anticipated electric shock and giving a self-disclosing speech), are both dampened by alcohol. Since pulse transmission times reflect the influence of both cardiac contractility and vascular distensibility, combining the HR and pulse transmission time results produces a picture of an underreactive cardiovascular system produced by alcohol. But the situation is not that simple. Alcohol is a powerful and pervasive drug. It exerts its effects at all levels of the organism, thereby making the determination of its effects on stress and reactivity extremely difficult to ascertain.

We have already discussed the direct effects that alcohol has on cardiovascular end organs as well as its depressant effects on the brain. There are other effects as well. Alcohol is known to produce peripheral neuropathy; therefore reactivity could be influenced by a conductor deficit. Alcohol also has a depressant effect on synaptic transmission. The cortical evoked potential provides further indication of the strong CNS depressant effects of alcohol. Compared to sober subjects, the amplitude of the cortical evoked potential to loud tones is reduced by approximately 40 percent in subjects who have consumed a 1g/kg dose. With such pervasive CNS depressant effects being produced, it is likely that some of the dampened cardiovascular response produced by alcohol is secondary to dampened CNS response. The intoxicated subject may well appraise the stressor as being less stressful, and a diminished cardiovascular response appropriate to that appraisal could ensue.

Teasing apart the direct dampening effect of alcohol on cardiovascular response from an indirect dampening effect secondary to altered cognitive appraisal is a very difficult problem. Some new findings (Levenson, personal communication), however, may help to begin to untangle this issue. Using fine grained coding of facial expressions that occurred in anticipation of electric shock, in response to the shock, and after the shock was over, the effects of alcohol were found to be most pronounced on the anticipatory facial expressions that occurred before the shock. Intoxicated subjects showed sharply reduced occurrence of facial behaviors
thought to evidence attempts at emotional control (e.g., lip biting, lip pressing, false smiles). The facial behavior of sober subjects suggested that they appraised the impending shock as threatening, that of the intoxicated subjects suggested that they appraised it as much less bothersome. These results suggest that some of the reduced cardiovascular response produced by alcohol is due to altered appraisal--how much is not certain. It should be noted that these results were obtained with nonalcoholic college students with no familial history of alcoholism who were drinking in a laboratory setting. In the alcohol literature, some investigators have argued that both the social context of drinking and familial history of alcoholism can interact with the effects of alcohol in yet unspecified ways.

Measurement Issues

Because alcohol has an effect on physiological reactivity, it is important to assess alcohol consumption in study participants. The actual assessment techniques used and the detail of information collected depend on the purpose of the research study. For example, one may want to assess alcohol consumption as a covariate in order to stratify subjects by history of alcohol use, overall alcohol intake, and pattern of intake. It should also be determined when the subject last had a drink. In studies concerned with the actual effect of alcohol on reactivity, a much more detailed ascertainment would be necessary.

The aforementioned self-report measures are useful in determining patterns of long-term alcohol use. Other assessment techniques that do not rely on self-report are available; however, many of them have the disadvantage of being relatively invasive. For example, the presence of excessive ketones could suggest recent (within the past 24 hours) heavy alcohol consumption. However, this particular measure could reflect the presence of other conditions, such as poorly managed diabetes. Actual liver dysfunction can be measured via liver enzyme studies, however, these tests will not necessarily yield positive results in chronic alcohol abusers. Blood alcohol levels may be assessed by either direct assessment (which requires venipuncture) or through blood gas chromatography. The latter assessment
technique is a simple, noninvasive procedure which has been employed frequently in laboratory studies of the effects of alcohol consumption.

Reactivity studies that assess alcohol intake either as a covariate (i.e., possible confounding variable) or as substantive study variable should consider using carefully structured self-report measures of alcohol use. These can range from a few select questions designed to measure such variables as: usual amount consumed per week (e.g., number of shots, glasses, or cans per week), age the person started drinking, how long the person has been drinking at the present level, and under what circumstances they usually drink (e.g., to celebrate, to relax/relieve stress, to be sociable, because they like it, etc.). Great care should be exercised to be specific in the questions asked.

More detailed, longer and standardized protocols such as the MAST (Michigan Alcoholism Screening Test) should be considered when history of alcohol use and pattern of regular alcohol consumption are considered important research variables—as, for example, when the question of interest is the possible effect of regular alcohol use on patterns of reactivity to laboratory stressors.

Conclusions

1. The health-promoting effects of chronic moderate ethanol ingestion are controversial, but moderation in the behavior appears to be associated with longevity compared to total abstinence or excessive consumption behaviors.

2. The effects of chronic, excessive ethanol consumption are documented to be definitely unhealthy.

3. Ethanol has powerful acute physiologic effects on cardiovascular and cognitive functioning which severely color psychophysiologic responses.

4. Chronic and acute consummatory behaviors must be accurately assessed in subjects in any study of reactivity and adjusted for in any examination of the relation between reactivity and cardiovascular disease.
ABSTRACTS
ANALYSIS OF HEART RATE VARIABILITY IN DIABETICS

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Heart rate varies considerably in normal people but becomes much more regular in diabetics with severe disease. This is usually attributed to loss of respiratory sinus arrhythmia due to peripheral autonomic neuropathy in diabetics. Typically, heart rate variability has been assessed by gross measures of variability, such as the standard error. In this study, we used spectrum analysis to evaluate the sources of variability in heart rate data in greater detail. The spectrum decomposes variability into its constituent frequencies, and recent evidence suggests that particular frequencies reflect the activity of different cardiovascular control systems.

We recorded heart rate from 14 diabetics and 12 normals. Subjects were asked to lie quietly for 15 minutes, then their ECG was recorded for 10 minutes and the digitized record of heart rate was stored on a computer. Spectrum estimates were computed by fast fourier transform. As predicted by the clinical literature, diabetics exhibited significantly less heart rate variability at the respiratory frequency (0.3 Hz) than normals (p < 0.01). This is consistent with other evidence of parasympathetic dysfunction in the control of diabetic heart rate. Surprisingly however, diabetics exhibited significantly more heart rate variability in the low frequency band (< 0.06 Hz) than normals (p < 0.01). This means that diabetics actually exhibited larger slow changes in heart rate than normals.

Heart rate variability along this slow time course can reflect parasympathetic and sympathetic influences. However, because of their frequent parasympathetic deficits, it may be reasonable to regard the low frequency band of most diabetics as predominantly sympathetic. This interpretation is supported by the finding that diabetics with signs of frank sympathetic dysfunction such as orthostatic hypotension had markedly reduced low frequency power. These patients exhibit flat spectra
with low power (i.e., variability) across all frequencies that would be consistent with loss of both parasympathetic and sympathetic inputs to the heart. In contrast, patients with increased low frequency variability may have early renal disease which is manifested by subtle changes in the renin-angiotensin system. In pharmacological experiments, inhibition of angiotensin converting enzyme increased amplitude in the low frequency band. If this hypothesis can be supported, it will mean that spectrum analysis of heart rate may be a useful noninvasive tool in the detection of early renal dysfunction in the diabetic patient. Regardless of this, however, these data indicate that changes in heart rate variability in diabetics are far more complex than was previously appreciated.
SOME WORKING HYPOTHESES ON THE SIGNIFICANCE OF BEHAVIORAL-EVOKED CARDIOVASCULAR REACTIVITY TO PATHOPHYSIOLOGY

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Hyperresponsivity of cardiovascular function to behavioral events has long been believed to be a necessary condition in the etiology of cardiovascular disease, yet there is evidence that hyperresponsivity per se has minimal predictive powers. There are circumstances where it is a necessary adaptive event such as when one exercises, and still other circumstances where it reflects nothing but noise in the system, with little or no consequence. There are different ways one could place responsivity in a perspective which might act to delineate when it eventuates in pathophysiological consequences. One we propose is to evaluate the metabolic necessity and efficiency of cardiovascular adjustments and whether metabolic excessive adjustments can be a precursor to more long-term vascular consequences. The research cited focuses on both myocardial and renal reactions associated with behavioral events in young healthy adult humans and healthy conscious dogs. The goal is to determine whether hyperresponsivity in these two vital organs can acutely disrupt the control of blood pressure, which over time leads to a more permanent disregulation of blood pressure. To date we have succeeded in demonstrating that behavioral challenges can evoke: (1) increases in both heart rate and cardiac output which are inappropriately high relevant to metabolic requirements as assessed by O2 consumption and (2) increased retention of sodium exceeding that normally retained by the kidney. Either event, taken singly or together, could have direct influences on vascular resistance and hence result in blood pressure disregulation. Such consequences could also be relevant to any influence blood pressure has on atherosclerosis.
SALT LOADING DECREASES INTRADAY CARDIAC VARIABILITY IN DOGS

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Several recent studies have shown that the acute cardiovascular response to behavioral stress or to adrenergic stimulation is increased in salt-loaded humans and laboratory animals. The present study examined the 24-hour variability of heart rate of laboratory dogs under conditions of significant increased in intraarterial intake of isotonic saline. Heart rate of each of eight dogs residing 24 hours per day in an experimental environment was monitored continuously via a tether system which also enabled infusion of isotonic saline. During a baseline period of seven days, saline was infused at a low rate of 150-300 ml/day, resulting in a daily intake of 26-52 mEq sodium. During a salt loading period, also of seven days duration, the speed of the infusion pump was increased so that each dog received 200-225 mEq sodium/day. For four dogs, there was no experimental stimulation during these two, 7-day periods. For the other four dogs, avoidance schedules were in effect during both low and high salt-loading periods.

Salt loading did not significantly affect mean heart rate levels in this group of eight dogs. During the baseline period, group mean heart rate was 76.2 BPM. During the salt loading period, group mean heart rate was 77.7 BPM. Variability of heart rate was analyzed in terms of the standard deviations of the hourly mean heart rates within each 24-hour day. For each dog, the mean of the seven standard deviations for baseline days was compared to the mean of the seven standard deviations for salt loading days. Mean variability during the salt-loading period was 22, 18, 11, 9, 8 and 6 percent smaller than that observed during the baseline period for six dogs, and larger by only 3 percent and 2 percent in the other two. The mean change of -8.6 percent was statistically significant (t=3.09; p<0.05).
These data are consistent with the hypothesis that increased sodium intake is associated with decreased chronotropic responsivity to intermittent changes in autonomic nervous system activity, conceivably due to a sodium-induced "down regulation" of beta-adrenergic receptors. Variability of blood pressure of these subjects under the same conditions is currently being evaluated, but clearly does not show the same patterns as observed for heart rate.
REPEATED ASSESSMENTS OF LEFT VENTRICULAR EJECTION FRACTION IN AMBULATORY SUBJECTS

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Left ventricular ejection fraction (EF) has been difficult to measure directly although it has clear hemodynamic relevance in many cardiac patient populations.

Recent developments in biomedical engineering have made possible a portable, miniature, gated scanner from which repeated measures of ejection fraction can be obtained. The detector, computer and battery pack weigh less than 12 pounds. The detector is held over the left ventricle by a rigid plastic vest. After labeling red blood cells with technetium, the scanning can proceed for as long as 6 hours. EF measures are gated and stored in memory every 2 minutes. We have been using this system, simultaneously examining EF, blood pressure, pulse, and plasma catecholamines in healthy, normal volunteers.

We examine the responses during a psychological stress interview, mental arithmetic calculations, a base line period, and cold immersion.

EF increases significantly in response to psychological stressors.
HOW MUCH OF THE BLOOD PRESSURE VARIABILITY DURING 24 HOUR AMBULATORY RECORDINGS CAN BE EXPLAINED BY CHANGES OF PHYSICAL ACTIVITY?

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Ambulatory 24 hour blood pressure recordings were made in 85 untreated ambulant subjects, whose average 24 hour BP (Av 24 BP) ranged from 93/72 mm Hg to 193/125 mm Hg. Readings were taken at 15 minute intervals, and activity recorded each time in a diary. No subjects went to work during the recordings. Two-way analysis of variance was used to estimate the contributions of interpersonal differences and activity on BP variability. Interpersonal differences in Av 24 BP accounted for 60 percent of overall BP variability. Differences in activity accounted for 25 percent of the remaining BP variability: of 16 activities surveyed, those producing significant increases of both systolic and diastolic BP from Av 24 BP included eating (+5/4), shopping (+6/4), and telephoning (+5/3); significant decreases occurred during sleep (-17/11 mm Hg), reading (-5/3), relaxing (-11/7), watching TV (-6/5), and music (-2/3). BP variability was related to AV 24 BP for systolic but not diastolic BP. The data did not support an additional effect due to diurnal variation.

We conclude that change in activity is an important determinant of BP variability during ambulatory recording, but time of day is not.
DO CHRONICALLY REPEATED PRESSOR EPISODES CAUSE SUSTAINED ELEVATIONS IN BLOOD PRESSURE?

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Etiologic hypotheses in clinical hypertension often have assumed that chronically repeated pressor episodes eventually lead to sustained hypertension. Nine male baboons with indwelling arterial catheters underwent operant diastolic blood pressure conditioning. All the animals had large-magnitude (mean 22 mm Hg) elevations in diastolic pressure during 12-hour training sessions which were repeated daily, usually for several months. Six of the baboons had progressive increases in resting, intersession averaged pressure (mean increase 8.4 mm Hg diastolic during conditioning among the nine subjects). Baseline, pretraining heart rate and diastolic pressure predicted the magnitude of this intersession increase in pressure ($r=0.70$ and $r=0.67$, $p<0.05$ in each case). Primates experiencing repeated, conditioned pressor episodes can eventually have increases in resting blood pressure.
CLONIDINE SUPPRESSION TESTING IN ESSENTIAL HYPERTENSION

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To assess the contribution of sympathetic outflow to blood pressure in patients with essential hypertension, we measured blood pressure and plasma norepinephrine (NE) responses to clonidine, an antihypertensive agent which decreases central sympathetic outflow, in 44 patients and in 41 normotensive control subjects of similar age. Among the hypertensives, resting plasma NE was significantly related to the decrease in mean arterial pressure three hours after a single oral dose of 300 mcg clonidine ($r=0.62, p<0.001$). The magnitude of the depressor response in the patients also was correlated significantly with the decrease in plasma NE after clonidine ($r=0.60, p<0.001$). These results suggest that increased sympathetic outflow plays a pathophysiologic role in some patients with essential hypertension, i.e., that their hypertension has a neurogenic component.
DISREGULATION THEORY, REACTIVITY AND CARDIOVASCULAR DISEASE

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Schwartz (1983, 1984) has proposed a general framework for understanding the relationship between reactivity and disease. Drawing on general systems theory with particular emphasis on cybernetic mechanisms, it has been proposed that diseases share in common an underlying process termed disregulation. Disregulation refers to the process whereby the negative feedback essential to healthy self-regulation (i.e., homeostasis) is impaired. The degree of disregulation can vary depending upon the extent to which the negative feedback is delayed, diminished, distorted, or in extreme cases disconnected. The causes of the disregulation may be initiated at biological, psychological and/or social levels. Moreover, the various levels may interact so as to increase (or decrease) the degree of disregulation. The consequence of increased disregulation is increased disorder in the functioning of a system. The increased disorder will be expressed as a dynamic process, including not only increased reactivity to relevant stimuli, but equally important, decreased recovery to the stimuli (since recovery in physiological systems is typically an active process requiring the connection and appropriate processing of negative feedback information from the periphery to the central nervous system). The increased disorder observed in systems contributes to the diagnosis of disease.

It has been hypothesized that one psychological mechanism that can increase disregulation is disattention. Defense mechanisms such as repression (as well as aspects of the Type A behavior pattern) include disattention to emotional and bodily cues. It follows from disregulation theory that psychological disattention should be accompanied by a relative functional disconnection within the central nervous system (e.g., increased disconnection between the two hemispheres). A series of studies reviewed in Schwartz (1983, 1984) illustrates 1) how it is possible to assess
disattention objectively using psychometric techniques, 2) how a repressive defensive coping style is associated with increased reactivity to stressful stimuli, 3) how repressive defensiveness is associated with evidence of increased functional disconnection between the two hemispheres as a function of positive versus negative emotions, 4) how increased repressiveness and cerebral laterality for positive versus negative emotions are correlated with increased reactivity in hypertensive patients, and 5) how these processes are related to general health.

It is proposed that more systems oriented, dynamic measures of disregulation (recovery, time series) could be fruitfully employed in future studies to assess the extent to which impaired negative feedback plays a role in the development of cardiovascular disease, as well as determine how various psychological techniques such as biofeedback and awareness training techniques may decrease disregulation and encourage normal biobehavioral self-regulation.
ECTOPIC BEATS AND ST SEGMENT DEPRESSION ARE RELATED TO PSYCHOPHYSIOLOGICAL RESPONSE AND CORONARY PRONE BEHAVIOR

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Stress has been related to acute increases in a number of ectopic beats and degree of ST segment depression. In these reports, stress has been globally defined and, at least in the human studies, degree of concommitant sympathetic and parasympathetic influences on the heart has not been specified. The aim of the current work was to relate autonomic responses to specific task challenges to ectopy, ST segment change and to behavioral variables.

Patients with verified diagnoses of ischemic heart disease (n=11) were compared to similarly aged controls (n=11). All had received a prior exercise stress test but none were taking adrenergic blocking drugs or major tranquilizers. Incidence of ectopy and ST segment depression was assessed during pre- and posttask resting conditions relative to five tasks: Type A Structured Interview, an interview assessing disease severity, fixed interval reaction time, mental arithmetic, and combined reaction time-mental arithmetic. Cardiac and vascular indexes from the latter tasks were combined to estimate the relative degree of task-induced sympathetic and vagal influence. V1, V5 and Lead III electrocardiograms, blood pressure and pulse transit times were measured.

Task induced physiological changes consisted of a generalized activation with added sympathetic change during mental arithmetic and brief vagal effects during reaction time. Slightly under half of the total sample showed ectopy during both exercise and performance testing. A similar percentage of patients with heart disease showed ST segment depression ($\geq 0.1\, \text{mv}$) during task performance relative to the 80 percent who showed ST segment depression during exercise testing.

Ectopy was related to structured interview classification of Type A vs B, but unrelated to task performance. Ectopic beats did not occur more
frequently during any one task relative to the others. Type B patients and controls, however, showed essentially no ectopic beats. The majority of Type As, on the other hand showed ectopic beats, primarily premature ventricular contractions.

ST segment depression occurred only in the cases and predominantly in the mental arithmetic task. Incidence of ST segment depression was markedly less in reaction time and combined tasks despite the difficulty of these tasks and despite the same degree of arithmetic computation in the combined task. Analysis of cases who showed ST segment change suggested that those individuals showed greater β-adrenergic effects on heart rate and systolic timing than controls. Furthermore, such changes occurred only during mental arithmetic and were not present in three additional patients who were on blocking doses of propranolol.

The results suggest that ST segment depression can be associated with psychologically induced β-adrenergic activation and countered by phasic vagal activation. Further, they suggest--in conjunction with other studies--that at least some Type A individuals may be prone to ectopy.
CHILDREN'S CARDIOVASCULAR REACTIVITY--RACIAL DIFFERENCES IN CARDIAC INDEX AND SYSTEMIC RESISTANCE RESPONSES TO EXERCISE

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Pilot studies in our laboratory demonstrated that healthy black (B) children had higher blood pressure responses to exercise than their white (W) counterparts. To investigate the mechanism of this difference, we exercised 39 W and 62 B subjects between the ages of 6 and 18. We used a continuous protocol on a cycle ergometer with three minute stages to exhaustion. Cardiac index (CI) was measured noninvasively at 2/3 of the previously determined maximal workload; systemic resistance (SR) was calculated from mean BP and CI. The CI (L/min/m²) was higher in B males (M) (7.0) compared to WM (6.3) and B females (F) (6.1) vs. WF (5.1), p<0.04. Within each race, M values exceeded F, p<0.001. The SR (Wood units) at 2/3 maximal workload showed an inverse relationship, WM (17.1) vs. BM (14.7), WF (20.5) vs. BF (16.6); p<0.006 between races, p<0.04 between sexes. At 2/3 maximal workload, mean BP values (mm Hg) were as follows: WM 100.4, RM 98.5, WF 96.8, BF 98.0. Despite larger size of the W subjects, there were no significant racial or sex differences.

These data support the concept that B subjects have higher CI than W early in life and that this evokes an increase in SR. The SR change may cause the overwhelming difference between B and W adults in the incidence of essential hypertension. In the B adolescent, the systemic vascular bed is still reactive to maintain normal BP in the presence of excessive exercise-induced CI increases.
REACTIVITY TESTING IN PRIVATE PRACTICE

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This paper reports on a developing research data base in a private practice clinical setting. All cardiac patients have undergone reactivity testing which includes heart rate, blood pressure, mean arterial pressure, stroke volume, calculated cardiac output and total systemic resistance, and an index of cardiac contractility measured during a standardized series of physical maneuvers and mental tasks. These include breathing maneuvers, positional changes, isometrics (handgrip), sensory intake task (videogame), sensory rejection task (mental arithmetic), and the cold pressor test.

A recent research project addressed the issue of the test-retest reliability of this reactivity battery. Twenty-eight noncardiac subjects underwent repeated baseline reactivity testing over a 1 week interval. All measures showed significant test-retest correlations. This included measures of systolic blood pressure (0.91), diastolic blood pressure (0.91), stroke volume (0.92) and cardiac index (0.96). These results suggest that the methods being utilized provide consistent measures of physiological responses by which to study reactivity in the patient population. Reliability studies with cardiac patient groups are now in progress.

A second study addressed the question of whether the noninvasive cardiac output by impedance methodology being utilized in this reactivity battery was a valid measure. Ten cardiac patients simultaneously underwent noninvasive impedance assessment and invasive thermodilution assessment to independently measure cardiac output. The correlation between the impedance and thermodilution measures of cardiac output yielded a significant correlation of 0.87. This provided evidence supporting the use of this noninvasive methodology to assess cardiac output in a private practice setting.
Finally, a series of cardiac patient cases are presented to provide beginning evidence for the stability of an individual, reactivity profile over time, the effects of various medications on a patient's physiological profile and the reactivity profile's usefulness in assessing and treating the individual patient. Multivariate studies of the database which will attempt to provide empirical support for the usefulness of this battery in a private practice setting are in progress.
GENETIC, FAMILIAL AND RACIAL INFLUENCES ON BLOOD PRESSURE CONTROL SYSTEMS IN MAN

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Preventive strategies in hypertension should rely on the ability to select those individuals most likely to develop hypertension. Since racial and familial factors influence the prevalence of high blood pressure, studies of racial and familial differences in components of blood pressure regulation may allow identification of those at high risk. In addition, such studies may provide insights into the events that precede the development of hypertension.

This paper briefly reviews investigations by the Indiana University Medical Center Hypertension Research Center into genetic influences on blood pressure control systems in man. The findings are discussed in the light of recent reports by other workers on blood control systems in the offspring of a hypertensive parent(s). Our studies have utilized the families of adult identical twins to partition the relationship of age, sex and body size to the genetic contribution of blood pressure variability. These studies provide little evidence for environmental influence on the familial aggregation of blood pressure and suggest that approximately 63 percent of the variability is due to genetic factors. Studies of the renin-angiotensin-aldosterone system and of the kidney's ability to excrete sodium were also performed in identical and fraternal twins and provided further unequivocal evidence of genetic control.

Investigations of the response to psychophysiological stress are also reported. Our data suggest that the level of blood pressure is under genetic influence and that the pattern of blood pressure response to standardized laboratory stress is likewise strongly determined by genetic factors.

Studies in first degree relatives of patients with essential hypertension have demonstrated higher plasma renin levels and a
decreased ability to excrete a sodium load when compared to first degree relatives of normotensive parents.

Further, we have compared blood pressure, plasma renin levels and the ability to excrete sodium in black and white subjects. Blacks have a decreased ability to excrete a sodium load and a greater rise in blood pressure with sodium loading than do whites.

We suggest that the heritability of blood pressure is directly related to a genetic influence on the level of renin and that this increase in renin level results in subtle increases in angiotensin II. These chronic elevations of angiotensin II directly increase blood pressure and decrease the kidney's ability to excrete sodium by either a direct renal effect or indirectly by stimulating aldosterone dependent sodium retention.
CAFFEINE POTENTIATES CARDIOVASCULAR RESPONSES TO STRESS

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Caffeine and psychological stress are known to have similar physiological effects on the cardiovascular system. This suggests that these two stimuli may interact in the elicitation of cardiovascular reactivity. The effects of consumption of 250 mg of caffeine on heart rate, blood pressure (SBP, DBP), and forearm blood flow and vascular resistance responses to psychological stress were examined in this study. Thirty-three male undergraduates participated in a two-session, counterbalanced, double-blind study of caffeine and placebo. Cardiovascular measures were assessed at rest and during performance of a challenging mental arithmetic task. Caffeine had no noticeable effect on HR or FVR. Compared to placebo, it elevated resting SBP and DBP (6/5 mm Hg), an elevation which added to that produced by stress (11 mm Hg). Caffeine did not affect resting FBF, but potentiated the FBF response to stress. This stress response was almost 50 percent higher after caffeine than after placebo. These effects were not related to the presence (n=16 or absence (n=17) of a family history of hypertension. These results confirm earlier reports that caffeine consumption can add to the effects of stress and provide new evidence that caffeine may in some cases actually magnify the effects of stress on the cardiovascular system.
PHENYLPROPANOLAMINE/CAFFEINE: AN ENVIRONMENTAL STRESS?

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Over-the-counter diet preparations contain the sympathomimetic phenylpropanolamine (PPA) and until recently the methylxanthene, caffeine. Ten to twenty million Americans ingest over-the-counter diet preparations every year. Both PPA and caffeine are pharmacologic stimulants and can elevate blood pressure. As such they are environmental stressors.

Phenylpropanolamine is structurally and functionally similar to amphetamine. It is sold on the street as an "upper" in addition to its presence in over-the-counter diet preparations plus both prescription and nonprescription nasal decongestants. Clinical complications reported in association with ingestion of drugs containing PPA often in combination with caffeine include psychic disturbances, headaches, seizures, cerebral hemorrhage (stroke) and death in previously healthy people. The more severe complications reported related to PPA ingestion--headache, seizures stroke and death -- can be attributed to the vasoconstrictor properties of the drug leading to an elevation in blood pressure. Caffeine may accentuate this effect since it, too, can elevate blood pressure. An acute increase in mean arterial pressure can lead to loss of cerebral blood flow autoregulation and "breakthrough" of the blood-brain barrier. The clinical manifestations of such a disruption are severe headache, seizures and/or cerebral hemorrhage (stroke).

Often, clinical data are suggestive, but not definitive, because conditions cannot be controlled as they can be in animal experiments. In order to determine if PPA/caffeine could lead to cerebral hemorrhage (stroke) during controlled conditions, animals were examined after PPA/caffeine administration for histologic evidence of stroke. Normotensive and hypertensive rats were administered PPA/caffeine in six times the allowed human dose calculated on a per weight basis for the rats two times per day for 5 days. Saline treated controls were also studied. Subarachnoid and cerebral hemorrhage was noted in 18 percent of the drug treated
hypertensive rats but in none of the saline treated or normotensive rats. A single PPA/caffeine administration (same dose) lead to acute hypertension in both the normotensive and hypertensive animals but not the saline treated matched controls. These results suggest that PPA/caffeine can lead to cerebral hemorrhage in previously hypertensive animals when administered in greater than the allowed dosage. An acute elevation in blood pressure may be a contributing factor.

These studies suggest that PPA/caffeine may act as an environmental stress leading to cardiovascular and cerebrovascular complications. One can conjecture that hypertensive humans may be at the greatest risk.
EFFECTS OF BETA-BLOCKADE ON CARDIOVASCULAR REACTIVITY TO MENTAL AND PHYSICAL STRAIN

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In order to study whether β-blockade (Metoprolol) attenuates cardiac reactivity to laboratory and daily life stress, we examined two groups of patients with myocardial infarction (MI) below the age of 45 (12 patients with and 8 patients without β-blockade) and a healthy control group (19 subjects). Variations in heart rate and systolic blood pressure were compared in four psychomotor performance tests, three emotional challenge tests, a cold pressor test, a standardized physical exercise test and in intermediate progressive relaxation periods. HR variations were also recorded by 24 hour Holter monitoring in an ordinary work and home setting.

As MI patients on β-blockade had a significantly lower minimum HR (p < 0.03) but a significantly higher SB (p < 0.008) during relaxation, no difference in rate-pressure product (RPP) was observed in comparison to MI patients without β-blockade and healthy controls. Nor were differences in HR and SBP reactions observed in the two patient groups to any of the tests performed, the only exception occurring at the peak of physical effort, during which MI patients with β-blockade attained a significantly lower HR (135.7 vs. 156.0, p < 0.04) at the same maximum physical load. Since the SBP response was higher in patients with β-blockade, RPP did not differ between patient groups.

If the rationale for the use of β-blockade in post-MI patients is protection of the damaged myocardium against the strain of everyday life, it seems that the treatment is only effective at maximum physical effort, whereas no protection is indicated neither during performance and emotional laboratory testing nor during 24 hour Holter monitoring. Definite answers to these questions, however, can only be based on studies with random allocation to treatment with β-blocking agents.