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I am submitting herewith a dissertation written by Ronald H. Cox entitled "A Comparison of Cardiovascular Responses in Reactive and Non-Reactive Individuals to Psychological and Physical Challenge." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

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A COMPARISON OF CARDIOVASCULAR RESPONSES IN REACTIVE AND NON-REACTIVE INDIVIDUALS TO PSYCHOLOGICAL AND PHYSICAL CHALLENGE

A Dissertation

Presented for the

Doctor of Philosophy

Degree

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Ronald H. Cox

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DEDICATION

To my wife Janet, for the countless times she put me first.

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ABSTRACT

The difficulty encountered in attempts to induce a permanent hypertension in animals with psychologically stressful paradigms has lead many investigators to doubt the importance of the contributions of psychological stress to hypertension. However, recent evidence indicates that selective breeding can produce an animal which will develop hypertension when exposed to chronic stress. This finding has contributed to a renewed interest in individual differences which might produce a vulnerability to stress-induced hypertension. A cardiovascular system which is highly responsive to stress may be one manifestation of such a vulnerability. The pathogenic potential of a cardiovascular system that is reactive only in one situation is probably limited. For cardiovascular reactivity to have significance in the etiology of hypertension it must be demonstrable in a variety of situations. This study was undertaken in an effort to demonstrate the generality of cardiovascular reactivity and to obtain basic information about the cardiovascular and oxygen uptake capacities of individuals who differ in reactivity to stress.

Thirty-four male undergraduate volunteers were exposed to three forms of psychological challenge: 1) a reaction time-shock avoidance task (RT-AV); 2) a reaction time-money reward condition (appetitive or RT-AP); and 3) a mental arithmetic stress (MA). Heart rate, systolic and diastolic blood pressure and urinary excretion of epinephrine and norepinephrine were measured. The

primary focus of the study was on those individuals showing extremes in cardiovascular reactivity during RT-AV. Eight subjects showing a heart rate increase of over 30 bpm were compared to six subjects who responded with less than a 10 bpm increase to the RT-AV task. A comparison of these two groups in the other conditions found that the reactive group displayed a greater change in heart rate to the RT-AP task but not the MA condition. Systolic blood pressures of the reactives while not different at rest, were higher during the RT-AV, RT-AP and MA conditions. No difference in urinary excretion of catecholamines between the two groups was detected but significant positive correlations between baseline epinephrine values and resting heart rate and mean heart rate change in all psychological conditions were found. A significant relationship between cardiovascular reactivity and familial hypertension was also found.

The reactive and non-reactive groups did not differ in aerobic capacity or maximum heart rate and both met the metabolic demands of exercise with similar rises in cardiovascular parameters. There was evidence that as a group the reactive subjects showed higher heart rates and systolic blood pressures than the non-reactive group to the same relative and absolute workloads. The results are discussed in respect to the contribution of cardiovascular reactivity in producing a vulnerability to hypertension.

PREFACE

The idea that psychological factors, such as stress or lifestyle, can contribute causally to the development of hypertension is an old one that is enjoying renewed popularity (Buell and Elliot, 1979; Marx and Kolita, 1978; Marx, 1977). The support marshalled for this hypothesis comes from a variety of disciplines and empirical approaches in addition to some intuitive leaps. Despite research supporting the deleterious effect of stress on blood pressure, the hypothesis that stress is causally related to hypertension has not gone unscathed. The purpose of chapter one is to examine the evidence bearing on this issue. Both epidemiological and experimental investigations which have given rise to the popularity of the stress concept in hypertension are presented, as are the results which have encouraged a dissillusionment with it. It is an interpretive review in the sense that I have tried to identify the assumptions and beliefs about stress and high blood pressure which are often offered either without empirical support or that are implied but not explicitly formulated. Attention is also given to evidence which has promoted a cognizance of the importance of individual differences in the development of hypertension.

In chapter two the nature of the possible individual differences which might lead to a vulnerability to stress are discussed. The principle focus is on the autonomic nervous system (ANS). Measurements of catecholamines in hypertensive populations and observations of the autonomic response to physical and psychological challenge in

normal and hypertensive groups are included. Evidence which suggests that autonomic function differs among normal individuals and the implications of these findings are also examined.

The emphasis on psychological and neural elements in the pathogenic process leading to hypertension is not a reflection of a belief in the dominance of these factors in this state, but a matter of choice. Excellent accounts of the interplay of renal, neurogenic and hemodynamic factors in hypertension have been provided in the dissertations of my predecessors in the cardiovascular psychophysiology lab, David Murray (1978) and R. Allan Buchholz (1979). So as not to duplicate their efforts, I have chosen to emphasize a different body of evidence.

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CHAPTER I

PSYCHOLOGICAL STRESS

An association between stress and high blood pressure (BP) was alluded to even before standard techniques to measure BP were developed Geisboch (1905)[1] measured systolic (S) BP with a finger plethysmograph and described his hypertensive patients as those who "had a great deal of responsibility and demanding jobs, and who after a long period of psychic overwork, became nervous." This was one of the first of many anecdotal observations suggesting a connection between "psychic exertion" and a permanent cardiovascular maladaptation. However, the most pervasive argument in favor of stress as an etiological factor stems from the observations of the cardiovascular adjustments to acute stress.

Hemodynamic Changes in Acute Stress

Animals. A number of studies have documented the hemodynamic response to stressors demanding an active coping mode of behavior. These stressors are often the product of operant schedules with aversive contingencies to which chronically instrumented animals are exposed. Lawler, Obrist and Lawler (1975) measured cardiac output (CO), heart rate (HR), stroke volume (SV), BP and total peripheral resistance (TPR) in four dogs during ten days under a Sidman avoidance schedule. The dogs were subjected to the schedule for one hour per day. During active

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[1] Julius, S. and Esler, M. (Eds.), The nervous system in arterial hypertension, Springfield: Charles Thomas Publisher, 1976, p. xiii.

avoidance BP increased significantly into the hypertensive range, despite a decline in TPR. The rise in BP was the result of an increase in CO brought about by an elevation in HR and SV. An additional observation of interest was the differences in reactivity of the animals. The pattern of increased CO, decreased TPR and increased BP was observed in two of the dogs. The other two dogs were much less reactive. The authors noted that the differences in the cardiovascular (CV) responses were related to "personality" differences in the dogs (p. 11).

These observations, in general, are similar to those of Anderson and Tosheff (1973). Their dogs showed an elevation in BP that was maintained by an increased CO during the avoidance session. During the period preceding the avoidance session an increase in BP was maintained by an increase in TPR. The CO was below control values during this period. This dichotomy in response between preavoidance and avoidance was not observed in the Lawler et al. (1975) study and was probably a result of the difference in training; Anderson and Tosheff's dogs had many more conditioning sessions.

Additional studies showing an increase in CO via increases in HR and SV during avoidance sessions were conducted by Langer, Obrist, and McCubbin (1978) using dogs and Forsyth and Harris (1970) and Forsyth (1971) using monkeys. The study by Forsyth (1971) employing a 72 hour Sidman avoidance schedule deserves further mention. Early in the experimental session he observed a rise in BP that was the result of an increase in CO. Later in the session CO returned to control levels and BP was maintained by an increase in TPR. The rise in TPR was the result of a decrease in muscle blood flow. This sequence of

physiological events has been posited to mimic the hemodynamic developments in essential hypertension. This contention will be elaborated on in a later section.

Human. Brod and his colleagues have investigated the hemodynamic responses to various challenges in normotensive and hypertensive human populations (Fencl, Hejl, Jirka, Madlafousek and Brod, 1959; Brod, Hejl and Ulrych, 1963; Brod, 1960; 1971). The most popular of these challenges has been mental arithmetic. The response to four minutes of this task in normotensives was an increase in HR, CO and muscle vasodilation, while TPR decreased 13% (Brod, 1960). Termination of the stress resulted in a quick return of the hemodynamic variables to baseline. The similarity of these responses to those accompanying exercise and the fight or flight reaction was noted. Hypertensive subjects showed similar responses to the mental arithmetic, except for a small tendency to respond with an increase in TPR. However, this tendency was not significantly different than the response of normotensives. The most salient feature of the hypertensives' response was its persistence after the termination of the stressor.

The picture which emerges from these studies is one in which the stress situation produces a cardiovascular mobilization. Blood pressure rises, primarily due to an increase in CO since TPR remains the same or decreases. Elevations in HR and SV may both contribute to the augmented CO. Initially, splanchnic blood flow is decreased and muscle blood flow is increased. Zanchetti (1972) has pointed out that muscle blood flow is dependent on the physical demand and action required of the muscle and that muscular vasodilation is not an either/or process. However, in general, this does not invalidate the scenario presented above.

The Psychosomatic Hypothesis

There can be no doubt that various psychological and environmental disturbances can produce an acute tumult in the cardiovascular system. The observation of these often striking but transient disruptions in cardiovascular status has suggested a psychogenic component in essential hypertension (Folkow and Neil, 1971; Brod, 1960). The nature of the relationship between psychological events and a chronically elevated blood pressure has been the object of a great deal of thought and debate, and from that the psychosomatic hypothesis, as it has been called (Davies, 1971), has evolved. Though it is the result of contributions from many investigators, in general, it can be stated as follows: Particular situations (e.g., active coping) elicit blood pressure elevations. The size and duration of the cardiovascular responses will be determined by the responsiveness of the individual and the severity of the stress situation. If the individual is repeatedly exposed to these challenges the BP will increasingly fail to return to its original level so that eventually there will be a "fusion" of responses and essential hypertension will be produced. An important point in the psychosomatic hypothesis is the emphasis on the malignant nature of acute changes. The possibility or likelihood that acute elevations in BP and cardiac activity produced by psychological stress will lead to hypertension has been alluded to by numerous investigators (Brod, 1960, p. 778; Wolff, 1950, p. 1074; Selye, 1949; Gutmann and Benson, 1971).

Reasons offered in support of this possibility have varied. It is sometimes stated that the stress is not "dissapated" (Elliot and Forker, 1976) or that it produces "wear and tear" (Brod, 1960).

Though these notions have construct validity or, more simply stated, intuitive appeal, they do not have physiological analogs, consequently they do little to convince anyone of the validity of the psychosomatic hypothesis. In addition, as some writers have pointed out, there is no basis in physiology for believing that the body's systems are not resilient enough to withstand repeated homeostatic disruptions (Grollman, 1973). Consequently it is necessary to look elsewhere in order to understand why there is such a willingness to believe large, repetitive, acute changes in circulatory parameters are potentially pathogenic.

There are at least three reasons why acute changes to environmental stimuli are thought to be relevant to chronic blood pressure elevations: 1) subjective experience; 2) growing evidence that the central nervous system (CNS) can contribute substantially to the initiation and maintenance of the hypertensive state; and 3) nature's frugality. Each of these reasons is briefly discussed and their cogency assessed.

It is not difficult to believe that something subjectively unpleasant, such as psychological stress, can lead to unpleasant consequences for the body. After all, common experience indicates that situations or stimuli that elicit pain (negative subjective experience) also produce physical damage. The notion that negative affects produce catabolic and deleterious repercussions is suggested by a number of writers (MacLean, 1949; Frankenhauser, Froberg, and Mellis, 1965; Frankenhauser, Mellis, Rissler, Bjorkval and Patkai, 1968; Gellhorn, 1970), and its influence on Russian views of hypertension are also

apparent (Lang, 1950). The primacy of the psychological state in the initiation of various physiological processes is a conceptualization that is still seen in Western writing (Betz, 1979), but there is little to indicate that situations producing an unpleasant affect elicit physiological and biochemical processes fundamentally distinct from pleasant ones (Levi, 1964; 1965; 1966; Patkai, 1971; Folkow and Neil, 1971, p. 345; Anderson and Brady, 1972; Kelleher, Morse and Herd, 1976; Wiedeking, Lake, Ziegler, Kowarski and Money, 1977). While it is prudent to remain open to opposing evidence concerning this issue, in general it appears that physiologically the organism prepares for behavior not affect. Accordingly, it can be assumed that the subjective experience accompanying particular actions and peripheral changes (i.e., heart rate, gastrointestinal motility) is a product of the context or situation in which it occurs. The situation provides a cognitive label for physiological processes that are probably identical whether one is running away from a punishment or toward a goal (Schachter and Singer, 1962). In other words, the physiological "cost" is probably the same whether it is enjoyment or suffering that reigns subjectively. As a result, subjective experience per se does not bode convincingly for the psychosomatic hypothesis.

The importance of the CNS for the hemodynamic compensations demanded by continuous behavioral adjustments has further strengthened the conviction that BP and stress are linked (Weiner, 1976). According to this argument if neural elements are involved in the control of BP then agents which provoke these elements are suspected of responsibility for aberrations in BP. Psychological stress, by definition, exerts its influence through alterations in neural elements, and the potency

of this influence on physiological parameters has been recognized since the time of Cannon (1929). The involvement of neural factors in hypertensive states has been suggested by a number of observations but not always unequivocally. A large and sustained pressor response has been reported as a result of stimulation of the posterior hypothalamus (Folkow and Rubenstein, 1966), but some question as to the reality of the sustained elevation has recently been raised by Bunag and Riley's (1979) failure to replicate this effect. Stronger support for the role of the CNS in hypertension is found in the catastrophic BP elevations produced by destruction of the nucleus and tractus solatarius. In the rat these lesions result in a fulminating hypertension and death within hours (Reis, Doba and Nathan, 1976, p. 35). The interconnections between this area and the hypothalamus have also been documented (Ciriello and Calaresu, 1979). Because the hypothalamus is firmly established as a part of the neural substrate for emotional and appetitive behaviors it could be inferred that emotional factors could induce functional changes similar to those produced by lesions.

At present the CNS has been implicated in many forms of experimental hypertension, including those involving renal mechanisms. The relevance of these studies and the various neurogenic models of hypertension to the human case is very much debated. It is not the intention here to resolve this debate but merely to point out part of the foundation on which a belief in the psychosomatic hypothesis rests--a belief that often relies more on the plausibility of proposed mechanisms than to direct empirical support.

The last reason supporting a belief in the virulent properties of acute CV change is one of physiological economics. The CV responses produced by some psychological challenges appear to violate Nature's sense of economy. The theme that Nature never does more than is required is often found in expositions on evolution but W. B. Cannon (1929) also emphasized the penurious and purposeful character of organismal responses. The role of the CV system in the maintenance of a living organism can be stated rather simply: It serves to transport to the tissues substances necessary for survival and to remove the by-products of metabolism. Changes in oxygen supply and regulation of body temperature are also met by CV adjustments, through changes in both the vascular and cardiac components (Strandness and Sumner, 1975). The demands of matabolism are most often met with an efficiency and swiftness that is striking. Therefore, situations that allow the tight coupling between metabolic demand and CV response to become dissociated appear potentially pathogenic (Langer, Obrist and McCubbin, 1979; Seminginovsky, Novak, Sobotka and Zalud, 1979). Psychological stress is one such situation. However, the apparent extravagance of the CV response in and of itself is not sufficient grounds for substantiating the detrimental nature of psychologically induced acute CV changes. This idea would achieve more credence if a pathophysiological mechanism could be found that is activated by metabolically unwarranted CV responses. A number of physiologically viable mechanisms have been hypothesized which could produce a persistent elevation of BP as a result of acute CV mobilizations. These are discussed in the context of the major problem facing those who propose that hypertension can be induced through psychological influences and attention is now turned toward them.

There is one observation which is not consistent with the hypothesis that acute changes in BP produced by stress can eventually result in hypertension, and it represents a major problem. The difference in hemodynamics sustaining the BP elevations between established essential hypertension and acute stress has not been satisfactorily explained and a psychosomatic theory of hypertension deriving its strength from observations of the acute circulatory responses in stress must be able to account for it. The studies of acute psychological stress provide clear evidence that the elevated BP produced by these paradigms is the result of an increase in CO with little or no change in TPR. It is also well accepted that the increase in BP in established hypertension is the result of an increase in TPR with a normal or low CO. This difference in hemodynamics raises doubts about the relevance of psychological stress to the development of hypertension. Brod (1960) apparently recognized this inconsistency and interpreted his data as showing an elevation in TPR with stress, even though this was not supported statistically. This appears to be an attempt at making psychologically produced perturbations in BP more meaningful for studies of hypertension. These contortions are not necessary. Within the last ten to fifteen years the infatuation with TPR has ebbed and there has been a renewal of interest in, and cognizance of, myocardial influences on BP in hypertension (Tarazi, Ferrario and Dustan, 1977; Leading article in Lancet, 1964; Sannerstedt, 1966). The observation of high CO hypertension or borderline hypertension has contributed to this renewal (Frohlich, Dustan and Page, 1966; Frohlich, Tarrazi and Dustan, 1969; Dustan, Tarazi and Bravo, 1972). In this class of

hypertension the increased CO is generally the result of an increase in sympathetic nervous tone and a decrease in parasympathetic tone. Though the parallels with stress induced circulatory changes are striking, the question remains as to the relevance of borderline hypertension to the 90% of hypertensive cases classified as essential. Whether it is simply a small subclass of essential hypertension or is the first stage in a progression of stages that eventually will terminate in an established hypertension sustained by an increased TPR and normal CO is presently under investigation.

The observations of Eich, Cuddy, Smulyan and Lyons (1966) are relevant to this question. They observed a change in the hemodynamics of a group of hypertensives after a period of time. Initially the elevated BP was maintained by an abnormally high CO. A follow-up examination indicated that CO had returned to normal levels and hypertensive levels of BP were now sustained by an abnormally high TPR. Pfeffer and Frohlich (1973) observed this same trend in the Okamoto-Aoki strain of spontaneously hypertensive rat (SHR). This rat is considered a good model of human essential hypertension (Hällback and Weiss, 1977). The suggestion from these observations is that the hemodynamic pattern in essential hypertension is progressive and does not always consist of an elevated TPR. At one point it appears that the hemodynamic state is similar to that seen during acute psychological stress. What is not known is by what mechanism the high CO state, as seen in acute stress or some hypertensive classes, is transformed into a high TPR hypertension. A mechanism that could explain the transition from a high CO hypertension to one characterized by a high TPR might

also explain how a high CO induced by psychological stress is transformed into a permanent hypertension.

A number of physiological scenarios have been proposed to explain how repeated acute elevations in pressure could lead to a permanent hypertension. The concept of whole body autoregulation as proposed by Guyton, Coleman, Bower and Granger (1970) and Coleman, Granger and Guyton (1971) is not specifically directed at the question of psychological stress but has been borrowed with temerity nonetheless (Langer et al., 1978). Guyton and his colleagues place a great deal of emphasis on local control of circulation. In accordance with what is known of the circulation, the tissues appear to regulate their blood flow in accordance with their needs. When tissues are in need of O_2, a vasodilation occurs and blood flow increases. If O_2 is over supplied, a compensatory vasoconstriction occurs thereby realigning supply and demand. Within this context the normal result of an increased CO, which may be produced by psychological stress, is an "overperfusion" of the tissues. The body's response to this "luxury" perfusion is hypothesized to be a "whole body" vasoconstriction. The increase in resistance increases pressure, which produces a pressure diuresis. The diruesis decreases volume and therefore venous return and CO is reduced. Now, however, the elevation in BP, originally produced by an augmented CO, is sustained by an increased TPR.

The whole body autoregulation concept is attractive because: 1) it is simple; 2) it provides a mechanism that links the hemodynamics of acute psychological stress with those observed in established hypertension; and 3) it also fits our notions about the economy of nature

and the deleterious consequences which ensue when this is violated. However, the time scale of this compensatory adaptation may be incompatible with that observed in the transition of hypertensive states. The autoregulatory phenomena occur quickly, on the order of days to weeks. The transition from high to normal or low CO hypertension is on the order of years (Eich et al., 1966). Whether this will prove to be an irreconcilable difference is not clear at this time. A more formidable obstacle to its acceptance is the persistence of the increased TPR (and hence pressure) after the CO and overperfusion are reduced. Guyton proposes changes in the kidney which compromise its function so that BP must now be maintained at elevated levels to provide an adequate renal perfusion and diuresis. Without this increased BP the kidney will fail to excrete appropriate amounts of fluid and volume will expand. There is no evidence, however, at the present time, for renal changes in the early stages of essential hypertension.

A second hypothesis, not incompatible with autoregulation, concerns vessel restructuring. Changes in the structure of the blood vessels as a result of the increased pressure or catecholamine (CAT) levels have been suggested by a number of writers as a means by which acute elevations could lead to a permanent elevation of BP (Dickenson, 1965; Folkow and Neal, 1971; Folkow, Hallback, Lundgren, Sivertsson and Weiss, 1973). Folkow et al. (1973) propose that a vascular restructuring occurs in response to a pressure overload. The hypertrophy that occurs in the vessel reduces the lumen/wall ratio resulting in a decrease in flow and by definition an increase in TPR. A sustained elevation of

pressure is the consequence of the increase in TPR. Compounding the problem is the fact that since the lumen/wall ratio is smaller a given amount of vasoconstrictor agent will produce a more potent effect. Consequently "normal" levels of pressor compounds, e.g., CATS in the plasma of these individuals, will exert a more impressive increase in TPR and as a result a greater increase in BP than in those with no vascular hypertrophy. In other words, reactivity is increased despite an ANS that may be responding normally.

Reis, Doba and Nathan (1976) found decreases in the adenosine levels in the aortas of rats subjected to high levels of pressure. They associated these changes with processes involving growth and restructuring of the vessel. More recently Thadani and Schanberg (1979) reported increases in ornithine decarboxylase (ODC) in rat blood vessels as a result of sympathetic challenge. The significance of their finding is that sympathetic challenge was achieved, in some cases, without a pressor response. By administering hydralizine, a vasodilator, a reflex activation of the sympathetic nervous system (SNS) was obtained. This technique also resulted in an increase of ODC indicating that an elevated pressure was not the critical variable. They pointed out that ODC is induced in skeletal muscle during periods of growth. They speculated that perhaps ODC reflects the process of hypertrophy in vascular smooth muscle. This finding is especially provocative because it provides a mechanism for vascular change due to CATs without requiring an elevated pressure, a possibility that has not been seriously considered previously (Page and McCubbin, 1962). As will be pointed out later, CAT levels can be elevated without large

alterations in blood pressure. Extrapolating the findings of Thadani and Schanberg (1979) a bit further, it could be concluded that subtle elevations in CAT levels induced by psychosocial changes could be initiating a pathological process in the vessels, a process that would go unnoticed until its expression as a case of essential hypertension.

A review of possible assumptions underlying a belief in the pernicious nature of acute CV mobilizations induced by psychological stress has been presented as have some of the problems facing this belief. On the basis of the foregoing discussion it is not unreasonable to conclude that repeated episodes of psychological stress with concomitant CV mobilization may set into motion a series of physiological processes that eventually result in a sustained hypertension. However to document this possibility it is not sufficient that the physiological scenario be shown to be plausible, but the development of hypertension after repeated bouts of acute CV mobilization must be demonstrated. The following sections examine the efforts to do this. These studies have focused on situations in which acute CV reactions are repeatedly provoked (i.e., chronic stress). These studies are the primary reserve from which many theorists sympathetic to the psychosomatic hypothesis have drawn their evidence.

I. CHRONIC STRESS

There are basically two approaches available for evaluating the capability of chronic psychological stress to initiate and sustain hypertension. The first is through epidemiological studies. By definition this is the study of disease in identifiable groups or populations. The rationale here is that groups thought to be under

chronic stress will have their hypothalamic defense reactions repeatedly provoked, resulting in acute CV mobilization with all its attendant sequelae (Henry, 1976; Gutman and Benson, 1974; Henry and Cassels, 1969). The groups under stress are expected to demonstrate a higher incidence of hypertensive disease than a group not similarly stressed. A number of key studies in this area are reviewed, as are the conclusions of several writers.

The second approach is an experimental one. Since the goal of this research is to produce a permanent hypertension via psychological stress, for ethical reasons, it is confined to animals. The strategies involved in these studies require a group of animals to be subjected to aversive stimulation, territorial conflict, or classical or operant paradigms for extended periods of time. The experimental studies are reviewed in light of their success in producing psychological stress and whether these manipulations resulted in a permanent hypertension.

Epidemiological Studies

> " . . . hypertension may accumulate in populations living under permanent emotional stress." Brod (1971), p. 319.

One of the major problems facing epidemiologists who attempt to document a relationship between the incidence of hypertension or BP level and emotional stress has been one of definitions. A consensus on what constitutes stress on a social or cultural level has not been achieved. As a result there is little theoretical foundation for predicting which lifestyle or situation, etc., is most stressful. Culture change, rapidity of culture change, urban life, civilization

per se, and pressure to adapt new social roles have all been suggested as important in the etiology of hypertension (Weiner, 1977). With each unexpected result a new hypothesis is born. However, the proliferation of hypotheses is more an indicator of confusion than theoretical progress. Most investigators will agree that groups or populations subjected to cataclysmic events are exposed to great psychological peril with attendant somatic disturbances. Blood pressure in a number of these situations has been examined. Ruskin, Beard and Schaffer (1948) found BP elevated two weeks after an explosion that destroyed a large urban area in Texas. One hundred-three of 180 casualties (57%) were observed to have a diastolic (D) BP greater than 95 mm Hg compared to only 34% of a group of surgical patients. Whether the traumatic event was sufficient to produce a sustained elevation is unknown but appears unlikely. The contribution of the study was in the documentation of an elevation in BP due to "real life" stressors.

War. War has also served as a "naturalistic" experiment on stress induced hypertension. The psychological stress associated with war arises from a number of fears: 1) fear of death, pain, injury or mutilations; 2) fear of gross incapacitation by fear reactions, with resulting inability to guard oneself or discharge duties adequately; and 3) fear of exhibiting fear and thus losing caste with the combat group (from Hanson, 1949). The descriptions of the combat experience by Grinker and Speigle (1945) and Hansen (1946) depict an existence filled with repeated scenes of death and loss of friends which is frequently coupled with a lack of opportunity to retaliate. I would

suspect a sense of frustration and helplessness might also be prominent features of this experience.

Repeated exposure to a situation that gives rise to violent SNS reactions might be expected to produce hypertension. A number of studies have reported changes in BP as a response to war conditions. Miasnikov (1962) reported an "epidemic of hypertension" among civilians as a result of the seige of Leningrad during World War II. Pickering (1968) cites a number of studies of the same vein: Fraser and Cowell (1919) reported higher BP in soldiers engaged in combat than in the support elements of the same regiment; Ehrstrom (1945) found higher pressures in Finnish soldiers in the front lines than during peace conditions; and Kammerer and Molitor (1917) reported that soldiers in combat had higher BPs than a control group of civilians.

The most frequently reported study on this subject is by Graham (1945). This study was conducted on 695 men of a British Armoured Brigade whose ages ranged from 20 to 38 years. They had been in combat for a minimum of one year and many for 2 to 3 years. At the time BP measurements were made they had been away from combat for 4 to 8 weeks. During this period relaxation and recreation were available. Graham reported that 27% of this sample was hypertensive and that after two months a follow-up group of 33 hypertensive men were examined again and 28 were found to be normal. These figures are often cited (e.g., Henry and Cassels, 1969); however, they are a bit conservative. Graham used a criterion of 100 mm Hg or greater DBP as a sign of hypertension. As a result the 27% classified as hypertensive had a mean BP of 178/114 mm Hg. After two months the pressure of the follow-up group was 158/92,

which was close to the mean BP of the entire group (154/90 mm Hg). Since DBP was below 100, they were considered normal, a conclusion that is open to some disagreement. Whether or not the pressures continued to decrease is not known. Regardless, this is the most striking example of environmentally induced BP rises reported in humans. However, to attribute the stress of combat entirely to psychological factors is a gross overstatement. The intense emotional component involved is often superimposed on a "fatigue of extreme grade and duration" (Hanson, 1949, p. 3). The sleepless nights and poor eating habits produce a physical state that is even more vulnerable to the emotional ravages of combat. The vivid descriptions by Ernie Pyle (1943) convey best the physical plight of one caught in war:

> A narrow path comes like a ribbon over a hill miles away . . . . Along the length of this ribbon there is now a thin line of men. For four days and nights they have fought hard, eaten little, washed none, and slept hardly at all. Their nights have been violent with attack, fright, butchery, and their days sleepless and miserable with the crash of artillery. The men are walking . . . . Their walk is slow, for they are dead weary, as you can tell even when looking at them from behind. Every line and sag of their bodies speaks their inhuman exhaustion. On their shoulders and backs they carry heavy steel tripods, machine-gun barrels, leaden boxes of ammunition. Their feet seem to sink into the ground from the overload they are bearing. They don't slouch. It is the terrible deliberation of each step that spells out their appalling tiredness. Their faces are black and unshaven. They are young men, but the grime and whiskers and exhaustion make them look middle-aged. In their eyes as they pass is not hatred, not excitement, not despair, not the tonic of their victory--there is just the simple expression of being here as though they had been here doing this forever, and nothing else. [(pp. 247-248) from Hanson p. 5]

The reader can judge the cogency of Pyle's observation for himself, but there is ample documentation that the psychological stress of war is confounded with a physical stress of immense proportion. Consequently,

conclusions about the contribution of psychological stress to the elevation of BP must be made with caution.

In addition to the problem with confounding, conclusions derived from the war literature must also be tempered by two other considerations. The first concerns the relevance of the stress reactions elicited by war conditions to those experienced in "stressful modern life" during peace time. Besides the physical stress (i.e., exhaustion, fatigue) involved in war, the autonomic responses elicited by combat are of a different order of magnitude than those elicited in "western" lifestyles. The descriptions of these responses leave little doubt about the severity of the stress producing stimuli associated with combat. Graham (1945) observed that "for days on end men taking part in a big battle show evidence of hyperadrenalinaema (sic), with a fast pulse, pale face, and enlarged pupils, even when there is no immediate danger" (p. 240). Heath and Powdermaker (1944) found evidence of "overreaction" of the SNS in some individuals consisting of tachycardia and body tremor for over a year following combat. The intensity of these reactions makes them practically unique, and their resemblance to the stresses of modern life minimal. Despite this difference many insist on parallels which seem incredulous (Gutman and Benson, 1971; Henry and Cassels, 1969). Maintaining a distinction between cataclysmic events and normal everyday stresses and "hassles" has also been suggested by Lazarus and Cohen (1977).

The second problem encountered in attempts to use war time responses as evidence of a psychogenic component in hypertension is the apparent transience of the BP rise. Though the levels of BP found in

Graham's study were hypertensive by most standards, they were decreasing. In the few sources which deal with psychosomatic problems induced by combat experiences hypertension is conspicuous by its absence (Grinker and Speigle, 1945; Hanson, 1949). Grinker and Speigle reported that 2.3% of the psychosomatic cases they treated were hypertension. By far, the majority of the cases stemmed from gastrointestinal problems (p. 255). Hanson's analysis is in agreement. Perhaps this should not be a surprise. Helplessness, as pointed out previously, may be a prominent aspect of war experiences, and it has been shown to be a potent stimulus for the generation of ulcers in animals (Seligman, 1975). However, since hypertension is generally asymptomatic, it is possible that many cases of hypertension went undetected in Grinker and Speigle's study. They were primarily interested in "war neuroses" and not in physical symptoms per se. I know of no studies which have examined the prevalence of hypertension among combat veterans. This type of study would indicate whether the extreme stress endured by these men favored the development of hypertension. However, it would still have little bearing on the etiology of most cases of essential hypertension.

Civilization-Urbanization. The attention of epidemiological studies has also been focused on psychosocial factors that pale in comparison to the intensity of war but which would appear to have relevance to the pathogenesis of hypertension. The putative complexities of Western civilization became a suspect early in the search for psychosocial causes of hypertension, presumably because some less advanced societies were thought to be free of hypertensive disease. For example, the Chinese with their "easy going nature" and simple

lifestyles (Scotch and Geiger, 1963) were one such group. Schroder (1953) typified the prevailing outlook with his statement that:

> . . . hypertension is a disease of civilization as we know it with its attendent strains and stresses, competitive urges, complexities of living and repetitive impacts. Only in Eastern European races has man developed techniques for explaining and controlling the forces of an adverse nature; in so doing he has built himself an environment so complex for existence and so many faceted for living that he survives only at the expense of continuous struggle . . . the more "civilized" the individual the greater are his chances for developing hypertension, regardless of climate, diet or race. (pp. 54-57)

A similar theme was echoed by Miasnikov (1962) who claimed that hypertension was an "atonement for civilization" (p. 157). Wolff (1950) was only slightly different in his assertion that "societies undergoing rapid cultural change are especially likely to create settings which engender insecurity and hence the development of protective reaction patterns" (p. 1087). The enthusiasm of these obloquies belies their dearth of epidemiological support. Not until the 1960's were studies conducted which could seriously attempt an assessment of the effect of "Western Civilization" on BP.

Closely allied with the idea that modern society is conducive to hypertension is the notion that urban environments, being more complex, etc., will have a higher prevalence of hypertension than rural ones. There are a number of studies which sought to document this assertion and they are discussed in conjunction with cross-cultural studies.

Cruz-Coke (1960) provided evidence of the impact of environment on BP. He examined frequency distribution curves for BP in various groups. One study involved 50 Peruvian policemen, 21 of whom left their "ecologic niche" in the Andean highlands in a primitive society and moved to

Western civilization (i.e., Lima). The other 29 remained behind until they became policemen. The curve for DBP for the "western" policemen was flatter and had a higher mean (76.8 mm Hg) than the eastern curve which had a high positive kurtosis and a mean of 65.1 mm Hg. The conclusion was that the new environment brought out more phenotypic variation. Though he did not state it directly, Cruz-Coke implied that stress in the environment was responsible for the differences.

The question of whether BP rises with age drew the attention of a number of investigators in the 1960's and was considered relevant to the preceding question of social-cultural influences on BP. The basic premise was that if BP could be shown to be stable with a group across age then environmental factors were implicated in groups that demonstrated a rise (Cruz-Coke, 1960; Pickering, 1968, p. 275). There followed many attempts to identify cultures or societies that exhibited no age related rise in BP (Lowenstein, 1961).

Kaminer and Lutz (1960) measured the BP in 42 male and 36 female bushmen. The mean BPs were 108/66 for males and 112/69 for females. There was no increase with age. They suggested that these low BPs and the lack of an age related rise were due to the environment of these primitive people.

Maddocks (1961) compared the BP of two Pacific island populations. The Fijians and Gilbertese islanders showed pressures similar to Londoners up to the ages of 50 to 59. At that point the Londoners' began to increase (i.e., the curves began to flatten and become positively skewed). Since the Fijians showed a slightly greater spread

and skewness of BP than the Gilbertese the stresses of Western culture were suspected. Though Western traditions had not pervaded the Fiji Islands to any great extent, the influence was thought to be present because of a large immigrant population.

In a further attempt to implicate the "Western way of life" in BP elevation Maddocks (1961) compared the BP of a group of rural Indians on Fiji with a group in business and the professions in the city of Suza, Fiji. The regression of BP with age indicated that the slopes were not different but the levels were consistently higher in the urban group. The mean SBP for all ages was 132.7 mm Hg in 121 urban residents and 126.8 in 1208 rural residents. Diet, alcohol intake, lack of exercise and the frequency of psychologically stressful situations were all considered potentially relevant to the observed differences.

Lowenstein (1961) compared the BP rise with age in two Brazilian Indian tribes: The Mundurcus (N-77) and the Carajas (N-89). There was no increase in BP with age in the Carajas. Since they were considered a more primitive group, Lowenstein postulated that the rise with age in the Mundurcus was due to civilization (i.e., acculturation). Though the Mundurcus appeared outwardly happy the possibility that BP might be elevated because of inner conflicts between their old animistic beliefs and their newly adopted Catholicism was entertained. This explanation was a valiant attempt to salvage the importance of psychological factors, but the increased consumption of table salt reported may be a more parsimonious explanation.

Scotch (1963) compared the prevalence of hypertension in Zulu tribesmen living in an urban vs. a rural setting. The Ns equaled 505

and 548, respectively. The results could not have been expected. On the basis of the hypothesis which suggests that culture change is potentially pathogenic, individuals moving from a rural to an urban environment and changing their lifestyle should manifest a greater prevalence of hypertension. Scotch defined hypertension as a DBP greater than 90 mm Hg. He found a greater number of hypertensive cases in the urban setting; however, it was related to those who maintained their traditional cultural practices. This finding was at variance with the predictions of Cruz-Coke, Wolff and others and apparently was an impetus for an influx of hypotheses that has not ceased (Oglesby, 1977). The higher frequency of hypertension in the urban group was attributed to higher levels of stress. Some support for this was found in the relationship between length of time in the city and hypertension. Since hypertension is a long term process (Page and McCubbin, 1960) a greater prevalence should be expected in the residents living in the city the longest. This was observed in men but not in women.

A contradictory finding was reported by Gampel, Slome, Slome, Scotch and Abramson (1962). They reported on 240 females and 112 males in rural and urban environments. They classified them in terms of the proportion of their lives spent in an urban area. Females living in the city the longest showed rates of hypertension lower than either rural or intermediate length female urban residents. Males showed the same trend but it was not statistically significant. The conflicting nature of these studies should be troubling to those supporting the hypothesis that urban environments are related to hypertension.

In general, the preceding epidemiological studies have implicated environmental factors as bearing an influence on the variability of BP

seen between various cultures and groups. Whether or not these factors are of a psychological nature is unclear. An evaluation of these studies should consider that by epidemiological standards the Ns are often small (Gampel et al. 1962); therefore, generalizations must be guarded. Also, the inconsistent and even contradictory observations in regards to the effects of psychosocial influences on BP do little to support the contention that they are important variables. Dietary factors may be the source of most of the variance.

A speculative comment may not be too inappropriate at this time. The indictment of civilization and/or urban life for the ravages of hypertension probably has its intellectual roots in the diatribes against civilization put forth by Rosseau, if not before.[2] The idea of the Noble Savage is an old one and within that idea is contained the doubts about the value of civilization, and by extrapolation, its potential for harm.[3] The point of this digression is that often it seems as if there were only literary and intuitive support for the notion that civilization and/or urban life is injurious and little or no empirical support. If it is true that suspicion of civilization as an etiologic factor in hypertension owes more to the political writings of 18th and 19th century philosophers than to systematic observation, it is not too surprising that the results are equivocal.

An argument of equal appeal can be made suggesting that primitive

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[2]Rosseau, J. J. The social contract and discourses. Translated by G. D. H. Cole, 1950, p. xii.

[3]Fairchild, H. N. The noble savage. 1928, New York.

lifestyles are debilitating. It is difficult to see how civilization per se could be suspected of promoting ill health through an increase in the level of stress when it is compared to rural and primitive peoples of the world who are often genuinely involved in a "continuous struggle." Being subject to extreme physical conditions and under threat of losing elements necessary for their physiological well being, the outcome of their struggle is truly a matter of life or death. Intuitively, it seems more stressful to be in an environment in which you and your family could literally starve to death if the weather (forever capricious) became unfavorable, than one in which you are subject to the verbal abuse of an aggressive employer. A case might be made that life in a primitive setting, with its potential for severe physical privation, resembles more closely the situations observed in war than does "Western Civilization" with its long life expectancy and freedom from want. Since the physiological and psychological responses observed in war are clearly the most intense found to date and probably the most conducive to pathology it follows that the primitive life should be more stressful. Because these arguments accomplish little it may be more fruitful to look elsewhere for psychosocial influences on BP.

The question of what is stressful and therefore capable of promoting hypertension has spawned a variety of studies. Certain occupations, races, life experiences and family situations have all been suspected of being sources of stress. If different levels of stress are experienced, then variations in BP are expected. Difficulties involved in predicting the outcome of a study on the basis of differences in apparent levels of psychosocial stress are many. One problem

is defining "stress" on such a high level of analysis (i.e., societal) and another is confounding psychologically stressful provocations with factors that may be independent but potent influences on BP nonetheless (e.g., differences in diet associated with various life-styles). The remaining studies reviewed here are examined with regard to the problems of definition, confounding and inconsistency.

Race. Differences in BP between blacks and whites are well established (Gillum, 1979). A point of controversy arises over the relative contribution of genetic and environmental factors to the higher blood pressure found in blacks. Many of those favoring the environmental hypothesis believe that psychological factors are the origin of the environmental differences as opposed to dietary or other physical factors (Schulze and Schwab, 1936; Bhagat, 1974). According to this argument, attempts by blacks to contend with social conditions (e.g., discrimination) can give rise to psychological states that are conducive to hypertension. For example, Bhagat (1974) maintains, "It [hypertension] is because the Negro is trained by experience from earliest childhood in the suppression of aggression" (p. 128). However, the difficulty in operationalizing "suppression of aggression" and other loosely formulated terms has precluded any meaningful testing of this hypothesis.

Most investigators are not as dogmatic as Bhagat and in addition provide a formulation of stress more conducive to vigorous analysis. Harburg, Schull, Erfert and Schork (1970) found higher rates of hypertension among residents of areas characterized by economic deprivation, residential and family instability, crime and crowded living conditions.

Since a greater proportion of blacks in our society live under these conditions, it follows that they should show a disproportionate prevalence of hypertension. The Harburg et al. (1970) study was an admirable attempt to measure the stressful characteristics of urban living. Fifty-six family sets were analyzed and it was found that 32% of those in high stress tracts in Detroit had hypertension (SBP > 160 or DBP > 95) as opposed to 19% of those in low stress areas. Harburg, Erfurt, Hauenstein, Chape, Schuell and Schark (1973) reported similar findings in an expanded follow-up study. They found that high stress areas were associated with higher rates of hypertension regardless of race, but black high stress males showed the highest BP levels. However, the finding that BP was significantly and linearly related to skin color[4] in blacks, a result which has been confirmed by a number of investigators (Gillum, 1979), indicates that genetic differences cannot be excluded in any explanation of the results.

The observation of black-white BP differentials in other surveys, e.g., Africa and the West Indies (Hoobler, 1962) and high levels of BP in non Western blacks such as the Bantu of Africa (Ordman, 1948) suggest influences other than environmental ones are operative. The sodium excretion rate of blacks in response to a salt load often distinguishes them from whites and supports the contention that factors other than psychological ones contribute to the BP differential between them (Gillum, 1979). However, stress may exacerbate a physiological

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[4]Skin color was noted on a four point scale by nurse interviewers.

proclivity for hypertension and cannot be excluded on the basis of current evidence.

Occupation. The responsibility and stress associated with certain occupations are sometimes thought to contribute to the development of hypertension. Lee and Schneider (1958) observed 1,083 executive and 293 non-executive men over a five year period. Five to 7% of these men showed evidence of hypertension; however executive and nonexecutive groups did not differ in incidence of hypertension. Furthermore, CV disease in general was disproportionately low in the executive group. In explanation of their results, Lee and Schneider emphasized the importance of individual capacities to withstand stress as a factor affording protection from hypertension, a theme which will become increasingly familiar in later sections of this paper.

Miall (1962) reported a study in which professional occupations had lower pressures than heavy laborers, a result which appears at variance with expectations if professionals are thought to have more responsibility and consequently more stress. Kannel and Dawber (1973) found no consistent pattern between BP and job stress in the Framingham Study, a result similar to that reported a few years previously by Dawber, Kannel, Kaga, Donabedian, McNamara and Pearson (1967).

The study by Cobb and Rose (1973) stands out as the most notable example of an effect of occupation on BP. They examined the health records of 4,325 Air Traffic Controllers (ATC) and 8,435 Second Class Airmen (A). The prevalence of hypertension (BP > 140/90) was four times higher in ATC; the incidence or rate of new cases per year was six times higher in ATC. The possibility that this difference was due to

the stressful nature of the ATC's work was strengthened by the finding that a 1.6 times greater incidence of hypertension was found in ATC at high stress centers (i.e., greater traffic). This is the most exciting of the epidemiological studies in terms of the psychosomatic hypothesis, but standing, for the most part, alone, it will need confirmation before it is fully assimilated and accepted (Syme, 1978).

The effect of the loss of one's occupation was studied prospectively by Kasl and Cobb (1970; 1977). They observed a group of 56 men (Plant A), aged 35 to 60 from the time of their anticipated or real unemployment through a two-year follow-up. The plant at which these men were employed was shut down permanently. Of the 56, one quarter were never unemployed (presumably they found jobs immediately), one-quarter suffered unemployment longer than two months, and the remainder found work in less than two months. Forty-six men continuously employed at another plant served as controls. The controls showed no appreciable change in BP over the time the study was conducted. The plant A personnel on the other hand showed elevated levels of SBP and DBP in anticipation of unemployment or the early phases of unemployment compared to the later stabilization periods. Only change scores were reported and they are modest: a mean change of 5.3 mm Hg SBP and a mean change of 3.0 DBP. The mean BP of all men, controls included, was 131/82.

The authors admitted that from a clinical viewpoint the changes were not significant. Further doubt about the clinical significance of these results was provoked by a follow-up study by Kasl, Cobb and Thompson (1977). They reported that BP levels had decreased in the

unemployed so that their BPs were the same as the employed men. It could be concluded that prolonged unemployment is not stressful (not an unlikely possibility today) or that prolonged stress not only fails to produce hypertension but even to sustain a modest BP elevation.

Other. The confusion over what is stressful and the lengths to which explanations must go to resolve unexpected results are seen in the treatment of studies dealing with BP in prisons. It can be argued that prisoners are subjected to overcrowding (D'Atri and Ostfelf, 1975), dietary hardships and the threat of violence from other prisoners (Duffy, 1950), any of which can be considered stressful and, therefore, hypertensinogenic. On the other hand, it can be argued that prisoners are not subjected to the stresses of normal life. Alvarez and Stanley (1930) proposed that studying BP in prisoners is advantageous because " . . . they have been freed from the hurry and strain and fatigue incident to earning a living" (p. 18). Which is it?

The contention of Alvarez and Stanley was supported in their study of 5,364 white prisoners though probably not for the stated reasons. The mean SBP of prisoners was 118 mm Hg, and the mean SBP of 442 guards was 133.5. Twenty-nine percent of the guards aged between 16 to 24 had a SBP > 140 mm Hg compared to 5% of the inmates in that age group. Hypertension was defined as a SBP > 140 mm Hg. Henry and Cassels (1969) found these results "puzzling" and attempted to resolve the "paradox" of a higher BP in guards than in prisoners with the following explanation:

> . . . this study was carried out when the prison administration was moving from a somewhat repressive and authoritarian to a strongly liberal humanitarian bias. Earlier, no doubt, the

> pressures of the guards and the prisoners might have been reversed. At the point in time of the survey, however, the prisoners had relative security and more hope for the future. The older guards, on the other hand, may have experienced frustration at the change in traditions as well as anxieties generated by the fear that the prisoners' new mood demanded enhanced vigilance. (p. 192)

This rather strained explanation of the results characterizes the predicament of many attempts to document the psychosomatic hypothesis with epidemiological data. The fact that the guards tended to be heavier may account for their BPs and the validity of the explanation itself is doubtful. This study was apparently done at the San Quentin maximum security prison in California in the late 1920's.[5] Clinton Duffy, who became the warden of that institution in 1940, described the deplorable conditions he corrected when he came to his position of authority (Duffy, 1962) but it was ten years after Alvarez and Stanley did the study. It can be argued that conditions at the time of the study did not offer as much "hope and security" as Henry and Cassels contend.

Conclusions

The wealth of conflicting studies has spawned heroic but vain attempts to provide coherence. It may be hopeless. Syme and Torfs (1978) reported that: "Every one of the hypotheses presented by psychosocial epidemiologists regarding the etiology of essential hypertension is balanced by as much negative evidence as positive" (p. 43). It may

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[5]The article does not state this, but L. L. Stanley is listed as being from San Quentin, Ca. Henry and Cassel (1969) state that the study was done there also.

be a failure to examine the negative evidence which has resulted in a number of reviews of the epidemiological literature which optimistically concluded that psychosocial factors were implicated in the etiology of hypertension (Syme, 1977; Cochrane, 1971; Gutman and Benson, 1971; Henry and Cassels, 1969). This contention is supported by the Syme and Torfs (1978) review in which they retract the conclusions of Syme (1977). In the former paper they pointed out that the "selective" review of Syme (1977) was an attempt to provide a coherent and simplified picture of the epidemiology of hypertension at the expense of accuracy. Similar conclusions, regarding the fruitless attempts to impugn stress in the epidemiological literature have been voiced by Glock and Lennard (1957), Davies (1971), Grollman (1973), and Oglesby (1977). The comments of Grollman (1973) summarize the status of these data:

> Epidemiologic studies give no support for the theory that essential hypertension is a consequence of acculturation or of such environmental influences as economic status, climate or psychogenic stress. (p. 80)

Syme and Torfs concluded that "research in this field has reached a dead end" (p. 43). There appear to be three reasons for this view: 1) the inconsistency of the findings; 2) lack of rigorous definitions of societal stress; and 3) confounding of various pressor influences, primarily as a result of the lack of precision or resolution inherent in epidemiological investigations. The inconsistency of the findings is the major sign that research efforts have reached a cul de sac, and since it is closely linked with the other two reasons it is discussed in conjunction with them. Recently, rigorous operational definitions of stress have been applied to laboratory investigations of

psychosomatic hypotheses. No such rigor characterizes the epidemiological attempts to define high stress populations. This is beginning to change (see Syme, 1977) though it had a forerunner 13 years ago (Ostfield, 1967). The emphasis on control and predictability seen in the experimental realm is now being reflected in a new epidemiological approach. The significant findings, such as Cobb and Rose (1973), fit with this paradigm nicely and lend further support to the utility of predictability and controlability as working hypotheses. Whether adaptation of this paradigm will yield more consistent results remains to be seen.

The lack of resolution in epidemiological studies is not easily remedied. The psychological factors involved in hypertension may be so subtle that their effect is obscured by the gross level of analysis afforded by epidemiological investigations. Recognition of this has initiated examination of nuances in individual reactions and behavior which may indicate a vulnerability to stress (Syme and Torfs, 1978). When the individual characteristics and the features of stress which are associated with hypertension are more clearly defined, then populations which differ on them can be compared and epidemiological investigations may succeed in documenting a stress-hypertension relationship. High resolution analysis, however, is a necessary first step and it is best carried out in the laboratory. In the next section a review of experimental results pertaining to stress-induced hypertension is presented with an emphasis on their contributions and shortcomings in establishing stress as an etiologic factor in essential hypertension.

Experimental Studies

> The conclusion is inescapable that hypertension can be produced in animals as a direct result of psychological stress. Cochrane (1966), p. 65.

> Prolonged BP elevation due to stress increases the chances of hypertension (a time-honored hypothesis for which no solid empirical evidence exists). Kasl and Cobbs (1970), p. 35.

The vindication of the psychosomatic hypothesis requires more than the few positive studies reported in the epidemiological literature, or the enthusiastic endorsement of reviewers (e.g., Cochrane, 1966). To give credence and provide evidence of cause and effect, as well as delineate key variables, experimental studies are required. This section examines a number of studies purporting to show the effect of environmental stress on BP. The objective of this section is to marshall the evidence which bears on the issue of whether or not psychological stress is capable of producing hypertension. In this review, attention was focused on two features of the studies: 1) Did it employ a psychological stressor?; and 2) Did the experimental manipulations result in a sustained hypertension? A third and minor aspect of evaluation considered the physiological mechanism which elevated the BP. In keeping with the original aims of this chapter, the focus is primarily on the evidence both empirical and intuitive, on which a belief in the deleterious effects of stress on BP rests. A detailed examination of putative mechanisms at this point was not considered critical to these aims.

Excellent reviews of experimental models of stress induced hypertension are contained in the dissertations of D. Murray (1978) and R. A. Buchholz (1979). Much of the information in the following section was borrowed from their work and much is owed their industry.

Sensory stimulation. A number of studies utilizing auditory, visual and motion stimuli, or a combination of the three have been cited in the psychosomatic literature as support for the hypertension producing capabilities of environmental stress. Medhoff and Bongiovanni (1945) exposed rats to an audiogenic stimulus for up to two years. Seventeen of 31 rats exposed for more than one year had at least one incident of SBP above 180 mm Hg. Whether this was maintained is not known.

Hudak and Buckley (1961) employed all three stressors together and found pressures exceeding 150 mm Hg in rats exposed to these stimuli for 28 weeks. The high mortality reduced the Ns enough to raise some concern about interpretation.

Buckley, Kato, Kinnard, Aceto and Estevez (1964) also reported success utilizing all three stimuli. They also noted pathological manifestations, such as left ventricular hypertrophy, as a result of the elevated pressures. However, pressures showed some decline after the eleventh week even though stress was continued. No follow-up was done to ascertain the permanence of the elevations, though the pathology data suggest it would have been permanent.

Similar findings were reported by Rosencrans, Watzman and Buckley (1966); Smookler and Buckley (1969; 1970); Smookler, Goebel and Siegel (1973); and Perhach, Ferguson and McKenney (1975). The hypertensive responses in all these studies are moderately impressive and when a follow-up was done, in many cases the elevation was sustained. An intact peripheral sympathetic nervous system was found to be necessary for these results (Smookler, et al., 1973). However, to equate these

stressors to "psychological" ones is untenable (Shapiro and Melhado, 1958). One hundred decibel auditory blasts and 60 to 140 per minute cage oscillations can and do induce physiological responses in and of themselves. The repetition of these stressors does appear to produce pathology. Therefore, we might conclude that environmental events are capable of producing a sustained hypertension, but this model is inadequate for purposes of elucidating the role of psychological stress in producing human essential hypertension and useless as support for the psychosomatic hypothesis.

Classical conditioning. The studies which employed a classical conditioning paradigm fall under the rubric "psychological." Classically conditioned stimuli (CS) have no intrinsic capability to provoke a significant physiological response prior to their association with an unconditioned stimulus (UCS). Consequently after conditioning, all responses can be attributed to psychological processes (i.e., learning). The ability of a CS to elicit transient BP and HR changes after learning is well known. However, the success in producing a sustained elevation is disappointing.

Shapiro and Melhado (1957; 1958) employed a tone CS with shock as a UCS in dogs and rats. They found no significant changes in BP or heart weight as a result of the stress; however, animals with renal insult appeared to develop hypertension at a faster rate as a result of the stress. Nonetheless they concluded that stress is not a causative agent in human essential hypertension, a premature conclusion since only a classical conditioning paradigm was utilized, and there is some question as to the degree of stress their protocol produced.

Dykman and Gantt (1960) also failed to produce a permanent elevation in BP as a result of classical aversive conditioning but did note that the CS could still elicit pressor response thirteen months after conditioning sessions were terminated. Dahl, Knudsen, Heine and Leitl (1968) cautioned against the notion that stress is a causal factor in hypertension. This was after many aborted attempts to induce a hypertension with classical aversive conditioning even when rats with a genetic predisposition to hypertension were used. However, the rats were bred for sensitivity to salt loading, not psychological stress. Nevertheless their failure is a sobering reminder that the psychosomatic hypothesis lacks experimental verification.

Simonson and Brozek (1959) reviewed the Russian research on hypertension. Classical conditioning (Pavlovian), as expected, is the most popular experimental paradigm employed in their psychological investigations. A number of failures are recounted but success in establishing a persistent hypertension is also reported.[6] The successful attempts generally involve induction of an experimental neurosis in animals selected for their emotionality. The neuroses were produced by exposing the animal to conflicting conditioning signals.

The Russian work stands conspicuously alone in its reported success in establishing a persistent hypertension with these paradigms. The reason for this is not readily apparent. The actual procedures used in the Russian experiments are slightly different than those employed

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[6]This interpretation conflicts with the review of Friedman (1980), who maintains that no permanent hypertension was shown.

in Western work. They have used both inhibitory and excitatory CSs simultaneously, in order to induce a neurosis and a concomitant hypertension. They have also selected animals characterized as having a "weak" nervous system (Pavlov's Typology). These are the only two differences from the Western work that are discernable and whether they could account for the discrepancy is a moot question. Their work is often difficult to evaluate because translations are few and when they are available, often little data are presented.

Clearly, it would be premature to attribute much credence to their work until it can be better evaluated and replicated by Western investigators. However, the cognizance of individual differences expressed in their studies is an interesting aspect and its potential for experimental exploitation has not gone unrecognized.

Psychosocial stress: Territorial conflict and overcrowding. The series of studies producing stress by engaging an animal's sense of territoriality or subjecting it to overcrowding have achieved the greatest notoriety because of an apparent success in establishing persistent changes in CV status with psychological manipulations. The protocol generally employed involves either forced overcrowding among sibling mice or raising mice in isolation and then placing them in a situation where confrontation is prolonged and constant (Henry, Meehan and Stephens, 1967; Ely and Henry, 1974; Henry, Stephens and Santisteban, 1975).

Alexander (1974) used this design with rats and achieved results which were not as spectacular as those reported in mice. Rats reared alone were placed in a population cage of interconnecting boxes, which

promoted competition for food and space. The highest systolic pressures were found in the dominant males, who are often the most challenged.

Henry, Stephens and Santisteban (1975) used the interconnecting population cage to induce a permanent hypertension in male and female mice. The mice were raised in isolation and placed in the interconnecting box system with a central food source. Territorial conflict and muricine combat were the result. Exposure to this system for less than six months elevated pressure but a permanent hypertension was not established. However, pressure failed to return to normal if the animals were maintained in this stress situation beyond six months. Cardiac hypertrophy and myocardial fibrosis were also observed in mice subjected to this regime for over six months, though replication of this effect is difficult. Repeated provocation of the hypothalamic defense reaction in these mice resulting in SNS activation was thought to underlie the hemodynamic changes. Attempts to elicit these same responses with an experimental methodology less unwieldy has been the goal of operant paradigms. In the next section attention is directed to them.

Operant. The primary focus in operant conditioning is on the consequences of behavior. The emphasis on coping with an environment, which is an inherent component in operant analysis, is particularly attractive for investigators attempting to substantiate the psychosomatic component in hypertension. First, coping is an important aspect of human existence, and second, as discussed in an

earlier section, actively coping with adverse elements is known to vigorously engage the CV system. Operant paradigms afford a well controlled and defined setting for testing whether or not persistent engagement of the CV system will lead to a sustained BP elevation. Most of the studies described here used variations of avoidance conditioning. In these situations the avoidance of a shock or an intrinsically aversive event was contingent upon the animal responding in some fashion. The response required was usually some type of lever manipulation and one or more responses were required to satisfy the contingency. In some cases a stimulus signalled the need to respond (signalled avoidance) while in others there was no signal (non-signalled or Sidman avoidance). In a few studies a physical response was not required; instead, avoidance of shock or access to food was contingent on a change in BP.

Herd, Morse, Kelleher and Jones (1969) subjected six monkeys to 4 to 11 months of signalled shock avoidance. Some monkeys were required to respond 30 times in 30 seconds (fixed ratio or FR schedule) in order to extinguish the light signal (S_D) and avoid shock while others were required to respond once within 15 seconds after the S_D had been on 2 to 4 minutes (fixed interval or FI schedule). A single shock was repeated every 15 seconds for a total of 10 shocks or until a response occurred. After a period of time four of six monkeys maintained elevated pressures outside the experimental apparatus, despite the fact that they now received fewer shocks during the sessions than initially because of increased efficiency of responding.

Forsyth (1969) employed a Sidman 20 second schedule to produce a stressful environment. Under this schedule a response was required every 20 seconds or a shock occurred. Six monkeys were subjected to this schedule 12 hours per day or 16 hours per day for 7 to 14 months. During the 4 to 5 months after training, the monkeys showed normal to low BP while on this schedule. After this point there was a steady monthly increase in BP in 3 of 4 monkeys. The average increase in BP was 28 mm Hg systolic and 19 mm Hg diastolic. The reactive monkeys also displayed emotional agitation outside the stress environment at the point when BP began to rise. The fact that the animals show changes in BP despite the fact that the physical stressor is decreasing in frequency speaks for the saliency of psychological influences. This is a strong point in favor of the utility of the operant paradigm. The observation of individual differences is also interesting. Though Forsyth does not speculate on the possible sources of vulnerability in the reactive monkeys, Herd et al. (1969) suggest SNS activity is particularly strong in this species, so differences in it may contribute to the variation observed.

While these considerations are encouraging for the psychosomatic hypothesis three points should be mentioned. First, the history of the BP elevation indicates that a "fusion" of acute CV and BP responses into a permanent elevation did not occur. In fact the CV system appears strikingly quiescent after training and during the first few months of the stress. Only after several months on the schedule does the elevation of BP present itself. This scenario does not fit easily with hypotheses and conceptualizations based on the importance of acute

CV mobilization (Brod, 1960; 1963). Second, the emotional characteristics of the animals changed and became quite noticeable. Emotional disturbances are not a conspicuous feature of human essential hypertension. Finally, the permanence of the elevations is in doubt. It is not clear from the experimental report whether the animals were followed up to determine if BP would return to normal levels. Since there was an absence of pathological findings it is not likely that BP elevations would have been maintained. These are troublesome observations which are not readily accommodated by the psychosomatic hypothesis as it is currently formulated.

Benson, Herd, Morse and Kelleher (1970) reported BP elevations in monkeys on completion of their behavioral experiments. These monkeys were exposed to an FR 30 signalled shock avoidance schedule for one hour daily. Because BPs were higher in the home cage during measurement than during the experimental session with exposure to the S_D, I suspect some methodological problems, for example, handling procedures. Again, prolonged follow-up was not done, but it is unlikely that such an undemanding schedule could produce chronic hypertension.

Benson, Herd, Morse and Kelleher (1969) reported changes in BP of 30 to 40 mm Hg mean pressure in monkeys required to elevate BP above a criterion in order to avoid shock. In view of the experimental apparatus employed, it is not unreasonable to believe that the animals learned to perform isometrics and hence increase their BP. Regardless of the mechanism producing the BP elevations, when the contingencies were reversed, BP returned close to normal levels indicating that the elevations were not permanent.

Buchholz, Lawler and Barker (1979) reported modest success in establishing elevated BP in rats with a highly stressful conflict paradigm. With this protocol the animal must respond in order to avoid a series of 5 shocks. However, if a response is made one shock is delivered. Aptly termed avoidance-avoidance conflict, the procedure resulted in SBPs consistently above 140 mm Hg several hours after the stress. This effect was not seen in all the experimental animals. The BPs of some were quite refractory to the stress.

A number of conclusions present themselves in regard to the operant studies: 1) they are clearly the most relevant to considerations of psychological influences in BP elevation; 2) physical stress can sometimes be confounded with the psychological manipulations (e.g., 16 hour sessions appear to produce fatigue [Forsyth, 1969], since some animals fell asleep in the sessions); 3) the elevations in BP are significant but generally modest; 4) most studies reporting any success utilized monkeys, an animal suspected of having a great degree of SNS tone; 5) conflict paradigms are the most successful in yielding sustained elevations; 6) the long term effect of such elevations is still not amply documented but it is encouraging; and 7) not all animals are equally vulnerable to the hypertension producing effects of the stress.

Genetic manipulations. Studies combining a genetic predisposition with an environmental stress have reported more success in establishing a sustained hypertension than those utilizing stress alone. Farris, Yeakel and Medhoff (1945) used an audiogenic stress, consisting of air

blasting, on rats selected for their emotionality.[7] The stress elicited pressures greater than 160 mm Hg in ten of the twelve experimental animals. A replication was provided by Rothlin, Cerletti and Emmenger (1956). They had little success producing hypertensive levels of BP in rats with audiogenic stimulation until they used the offspring of wild and tame rats. These studies provide a more striking example of the effects of stress than the results of Medhoff and Bongiovani (1945) reported previously. However, they are still subject to the criticism that air blasting bears little resemblance to psychological stress.

Friedman and Dahl (1975) and Friedman and Iwai (1976) employed the Dahl salt sensitive (DS) and Dahl resistant (DR) rats in an effort to provoke hypertension with psychological stress (an operant conflict paradigm). The DS rat will manifest a fulminating and lethal hypertension when salt loaded. The DR rat is refractory to this treatment. The rationale in these studies was that the DS rat is vulnerable to the hypertensinogenic effects of salt and, therefore, may show an increased sensitivity to another hypertensinogenic stimulus--stress. The results indicated that the stress was "selectively efficacious" in promoting hypertensive levels of BP in the DS rat. However, the studies are subject to several criticisms, the most damaging of which is the failure of the BP elevations to remain after the stress was

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[7] Emotionality in rats was determined with the use of an open field test. This is a well known procedure. Rats exhibiting the least exploration and the most defecation on an open surface are classified the most emotional. The test can be quantified because the surface is marked into grids.

discontinued. Friedman and Dahl (1975) noted that the elevations remained in some of the rats and concluded that "there is probably a genetic component involved in the CV reaction to stress that promotes the development of hypertension, just as there is to other hypertensinogenic stimuli" (p. 415).

The study providing the most convincing evidence for the veracity of the psychosomatic hypothesis is Lawler, Barker, Hubbard and Allan (1980). The F1 generation (BHR) of the SHR and the Kyoto-Wistar were subjected to an avoidance-avoidance conflict similar to Buchholz et al. (1979). The SBP of the BHR rose from 150 mm Hg before stress began to 186 mm Hg at the termination 15 weeks later. Controls did not show a similar elevation. A 10 week follow-up indicated that the resulting hypertension was permanent. Pathological examination revealed an increased heart weight to body weight ratio and evidence of extensive myofibrillar degeneration in the experimental animals (Lawler, 1980). The importance of Lawler's study has been acknowledged (Friedman, 1980) but the mechanisms that initiate and sustain the elevated BP remain to be defined. In view of the parental history (SHR), involvement of the SNS is suspected.

It is surprising that studies combining genetic and environmental manipulations have not been pursued more extensively. In almost every exposition on the hypertensinogenic effects of stress, allusion to or overt statements regarding the importance of individual differences are made. Some investigators have referred to a "vulnerability" to stress (Elliot and Forker, 1976) others a "susceptibility" (Oglesby, 1977) but always a "predisposing" factor is acknowledged (Brod, 1960; Bridges,

1974; Schroeder, 1953; Davies, 1971; Buell and Elliot, 1979; Harris and Forsyth, 1973; Elliot and Forker, 1976). The nature of the physiological system or characteristic which distinguishes the "vulnerable" from those who are not has eluded definition but a number of suggestions have been proposed (Obrist, Langer, Grignolo, Sutterer, Light and McCubbin (1979); Oglesby, 1977; Charcot, Dell and Folkow, 1967; Glock and Lennard, 1957). In general these involve allusion to the notion of reactivity of the ANS. This might manifest itself as a tendency to show exaggerated basal activity or unusual responsiveness to common challenges, such that in a reactive individual a given stress will have a greater impact on CV homeostasis. In the next chapter the evidence and rationale underlying this choice is explored in more depth.

CHAPTER II

THE AUTONOMIC NERVOUS SYSTEM IN HYPERTENSION

Consideration of the evidence accumulated to date warrants the conclusion that psychological stress alone is an insufficient stimulus for the production of hypertension. However, it can be argued that some individuals are vulnerable to psychological stress because chronic exposure often results in a sustained elevation of BP. Since the CV reactions to stress are mediated directly or indirectly through alterations in the activity of the ANS it is only logical that it be suspected of involvement in vulnerability to hypertension. Because a neurogenic mechanism would undoubtedly be involved in any case of stress induced hypertension, the efforts to document the contribution of the ANS, specifically the SNS, to the genesis of hypertension have been evaluated here. It should be kept in mind that involvement of the ANS in essential hypertension is an issue in its own right. It is discussed here because the demonstration that the SNS is involved in the hypertensive process would establish a mechanism capable of mediating the putative effects of stress. Establishing this fact would have to weaken the reticence of many investigators to accept the notion of stress induced hypertension. Stated another way, it is difficult to establish the case for the hypertensinogenic effects of stress if the only avenue through which stress could exert its effects is thought not to be involved in essential hypertension--A position with some advocates (Korner, 1976; Wilson, 1961; see also Julius and Esler, 1976; DeQuattro and Miura, 1973; and DeChamplain, 1972; 1976 for a discussion of this issue).

The lack of a consensus on the contribution of autonomic influences to the hypertensive state is due to a lack of unequivocal evidence. However, there is considerable circumstantial evidence implicating ANS involvement in some forms of hypertension and it is reviewed below.

Resting HR

Observations of a higher resting HR in hypertensive subjects are commonly reported (Hamet, Kuchel and Genest, 1973; Korner, Shaw, Uther, West, McRitchie and Richards, 1973; Julius, Pascual and London, 1971; and Julius, 1976) though there are exceptions (Eckberg, 1979). Labile or borderline hypertension is often suspected of having a greater neurogenic component than other classifications (Julius and Esler, 1976) and therefore might be expected to be the group responsible for the HR differences. However, a failure to observe higher supine HRs in this group compared to normals has been reported (Hamet et al., 1973; Eckberg, 1979). It is also clear that elevated HRs are found in many types of hypertension (Dustan, Tarazi and Bravo, 1972). The conclusion must be that no single classification or subtype of hypertension accounts for the HR differences between normals and hypertensives when they are observed.

Table 2.1 contains a partial list of studies reporting higher HRs in hypertensive individuals. The numbers in parentheses were observed in standing subjects, all other values were obtained in supine Ss. There is no clear demarcation between the controls and the hypertensive Ss but generally the controls showed values in the 60's and low 70's while the hypertensives exhibited no values below 70 and generally they were closer to 80.

TABLE 2.1

HEART RATE IN HYPERTENSIVES AND NORMALS

Controls			Hypertensives		
STUDY	HR ($\bar{X}$±SE)	N	HR	N	TYPE
Hamet et al. 1973	(79±4)	12	(91±3)	14	Labile
Korner et al. 1973	68±5	15	83±6	32	Established?
Julius et al. 1971	63±2	16	80±4	11	Borderline
Julius 1976	64±1	90	71±1	148	Borderline
DeQuattro et al. 1975	73±2	12	83±3	24	BP 140/95
Lake and Zieler 1978	62±2 (73±3)	29	73±1 (83±2)	56	Sustained essential
DeQuattro and Chan 1972	72±1 (82±2)	15	78±2 (92±3)	37	Labile and Sustained
Franco-Morselli et al. 1977	71±2.9	11	80±3	14	Sustained
Julius and Esler 1975	63±2	28	75±2	25	Borderline
Cuche et al. 1974 (a)	70±2	14	79±1	56	Sustained Essential
Julius et al. 1971	67±1	82	76±4	77	Borderline

The elevated HR of hypertensive individuals is not solely a result of increased SNS tone. Julius, Pascual and London (1971) studied the effects of selective autonomic blockade in eleven patients with borderline hypertension characterized by high HR and CO. Propranolol infusion had a greater effect on HR and CO in the borderline Ss than it did in controls but differences remained. Only with simultaneous blockade of SNS and parasympathetic (PNS) components (atropine and propranolol) did differences between the groups disappear. Korner et al. (1973) observed similar results. He compared 32 subjects with established hypertension with 15 normotensives. On the basis of ANS blockade studies he concluded that "the higher HR in established hypertension was predominately due to change in vagal rather than cardiac sympathetic effects" (p. 107). However, hypertensive Ss showing the highest HR are often found to have the highest levels of norepinephrine (NE) or cyclic adenosine monophosphate (cAMP) which is an index of beta adrenergic stimulation (DeChamplain, Farley, Cousineau and Ameringen, 1976; Hamet et al., 1973).

The observation of differences in HR and other CV parameters in hypertensives fails to implicate SNS hyperactivity alone. However, it is clear that ANS function has been altered.

Urinary Catecholamines in Hypertension

The sine qua non of sympathetic nerve activity is evidence of the transmitter itself. Recognition of the potent pressor effects of the CATS and their role in the SNS has led to many attempts to document high levels in the urine of hypertensive individuals.

The results of these studies have been reviewed by DeChamplain (1972; 1976), Nestel and Esler (1970) and Brunjes (1964). Their conclusions are, in general, similar. Urinary CAT measures have failed to provide evidence of increased sympathetic activity in hypertensive individuals. The most that can be said is that in a variable proportion of the hypertensive population, there exists a group which shows abnormally high levels of excreted CATS.

The values found in most of the studies which have reported differences between normotensive and hypertensive individuals are presented in Table 2.2. Studies published after the reviews are also included even if results are negative. The number of subjects and CAT values (all have been converted to excretion per 24 hours) are listed. Accepted reference values for normals are found in Becker and Kreuzer (1970). Book and Riek (1965) have been included because they reported a significant difference between 13 hypertensives and 22 controls in E, NE and NE per E ratio, but they reported no values.

The explanations advanced for the failure of the urinary studies to reliably document differences include desperate as well as cogent ones. DeChamplain (1976) warns that renal function must not be compromised, which is sound enough, but many would take issue with his assertion that CATS vary with urine volume. Becker and Kreuzer (1970) and Karki (1956) found that CAT excretion was independent of urine volume in all of the 300 plus subjects they studied. VonEuler (1956) reported similar findings in over 500 subjects (see also DeQuattro and

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[1]There are a number of errors in his reviews. Generally, they consist of attributing to particular authors results which they did not find.

TABLE 2.2

URINARY CAT EXCRETION IN HYPERTENSIVES AND CONTROLS
(mg PER 24 HOURS)

	Controls				Hypertensives			
STUDY	NE	E	TOTAL	N	NE	E	TOTAL	N
Nestel and Doyle[+] 1968	22.56	11.28	33.84	58	39.6	17.52	57.12	33
Cuche et al.[+] 1974	55.68	12.96	68.64	12	134.4	30.24	164.64	--
DeQuattro[+] 1971	--	--	53	6	--	--	135	4
DeQuattro and Sjoerdsma 1968	32.	8.0	40.0	5	42.0	8.0	50.0	8
vonEuler 1956	--	--	--	--	--	--	57.6 - 86.4	500
Nestel, 1969	22.8	10.8	33.6	17	26.16	13.44	39.6	20
Ikoma, 1965[+]	--	--	--	--	--	--	--	87
Serrano et al.[+] (1964)	--	--	40.6	96	--	--	47.5	99
Boak and Riek[+] 1965	No values reported			22	No values reported			13
[o]Kuchel et al.[+] 1970	36.1	7.0	43.1	6	56.1	--	--	7

TABLE 2.2 (continued)

STUDY	Controls NE	E	TOTAL	N	Hypertensives NE	E	TOTAL	N
Goodall and Bogdonoff 1961	32.3	15.7	48.0	--	73.9% show normal values			500
Becker and Kreuzer 1970	24.3	7.1	31.4	16	--	--	--	--
Weil-Malherbe and Bone 1957+	35.47	15.7	51.17	32	46.4	33.9	80.3	11
Lorimer et al. 1971	30.9	14.1	45.0	15	25.4	13.7	39.1	15

+Significant difference.

*Hypertensive subjects.

oOriginal values were presented as a function of creatinine excretion and have been converted to ug/24 assuming an excretion of 1 mg/min. of creatinine.

Miura, 1973, p. 364). Differences in the medication history and practice of the hypertensive subjects studied has probably also contributed to the failure to find systematic differences.

The effect of age on urinary CATS is not clear though Ziegler, Lake and Kopin (1976) reported an increase in plasma CATS with age. Generally, this variable has not been controlled in urine studies. DeQuattro (1971) and most of the others do not report ages for their Ss, but the hypertensives in Nestel and Doyle (1968), Kuchel et al. (1970) and Cuche et al. (1974) are older than the normotensive controls employed. Whether this contributed to the significant differences reported is unknown, but it might be expected to.

The failure to reliably detect differences between normotensive and hypertensive populations probably owes more to the heterogeneity of the hypertensive population than to any other single factor. The heterogeneity is manifested as variation both in the severity and duration of the hypertension. Many of the studies have used hypertensive patients with sustained or long established disease. This practice might result in negative findings for two reasons: 1) hypertension can result from dysfunction of any of a number of physiological systems, not only the SNS; and 2) the contribution of the SNS to the hypertensive state may change with the course of the disease. If the influence of the SNS to the hypertensive condition is no longer of significance in later stages of the disease, it should be no surprise that urinary excretion values fail to discriminate between normal and hypertensive subjects.

There is also some doubt as to whether urine values can adequately reflect actual differences in SNS activity of the magnitude thought to

exist between essential hypertension and the normal state (Nestel and Esler, 1970; Nestel and Doyle, 1968). Since only a small fraction of the NE released at the synapse will appear in the urine, nuances in neural activity may well be obscured by uptake, catabolism, renal clearance, etc. Plasma values of CATS are thought to be a more accurate reflection of SNS neural activity (Lake, Ziegler and Kopin, 1976) and consequently, it has been predicted that they will demonstrate differences between hypertensive and normotensive individuals (Julius and Esler, 1976).

Plasma Catecholamines in Hypertension

Prior to the early 1970's little success was found in detecting differences in plasma CATS between hypertensives and normals. Peart (1966) reviewing the evidence to that point concluded that "there is hardly any evidence of note which relates to increased circulating catecholamines in the ordinary case of hypertension"(p. 668). The poor sensitivity of the methods was a major problem. With the advent of radioisotope technology in the early 1970's chemical techniques achieved the resolution required to reliably measure plasma levels of CATS (Engelman and Portnoy, 1970; Passon and Peuler, 1972).
Table 2.3 contains the results of all the studies measuring plasma CATS in hypertension within the last 10 years. Most were done with radio-isotope techniques. A few studies using other methods have been included because they are frequently cited as support for a particular position. Overall 13 studies have reported a difference in plasma CATS between hypertensives and normotensive controls and 9 have not. All values in the table have been presented as pg per ml of plasma. In

TABLE 2.3

SUMMARY OF PLASMA CATECHOLAMINE STUDIES IN HYPERTENSIVES AND CONTROLS

	Controls (C)					Hypertensives (H) (Values are expressed in pg/ml and were taken in the recumbent position)					
STUDY	N	AGE	E	NE	TOTAL	N	AGE	E	NE	TOTAL	COMMENTS
Vlachakis (1979)	14	49	38	145	283	14[1] 24	41 52	Not different than controls			
Floras et al. (1979)	--	--	--	--	--	12	--	--	541	--	No controls
Watson et al. (1979)	--	--	--	--	--	8	43	--	480	--	No controls
Lake and Ziegler (1978)	29	40	--	253	--	56	46	--	249	--	No difference
Philipp et al. (1978)	29	33	--	173	--	29	--	--	215	--	Significant Difference
Esler et al. (1977)	20	?	--	136	--	16[2] 15[3]	-- --	-- --	250 178	-- --	Significant difference
Franco-Morelli et al. (1977)	11	45	41	247	288	14	48	84	290	374	E values are significantly different

TABLE 2.3 (continued)

	Controls (C)					Hypertensives (H) (Values are expressed in pg/ml and were taken in the recumbent position)					
STUDY	N	AGE	E	NE	TOTAL	N	AGE	E	NE	TOTAL	COMMENTS
Grobecker et al. (1977)	6	30-40	--	300	--	12	?	--	300	--	No different, does not report values
Lake et al. (1977)	84	?	--	304	--	67	?	--	339	--	No difference
Sever et al. (1977)	44	46	--	403	--	56	46	--	411	--	Greater Δ in H on standing
Brecht et al. (1976)[5]	15	28-36	--	135	--	59	18-55	--	257	--	Significant difference and less Δ in H on standing
DeChamplain et al. (1976)	15	?	--	218	--	22	?	--	370	--	Significant difference and greater Δ in H on standing
Esler et al. (1976)	12	?	--	136	--	17[4] 15[4]	20-50	-- --	173 98	-- --	Significantly lower in low renin
Lake et al. (1976)	30	--	--	334	--	--	--	--	--	--	No difference
Lake et al. (1976)	74	33	--	292	--	24	43	--	306	--	No difference

TABLE 2.3 (continued)

	Controls (C)					Hypertensives (H) (Values are expressed in pg/ml and were taken in the recumbent position)					
STUDY	N	AGE	E	NE	TOTAL	N	AGE	E	NE	TOTAL	COMMENTS
Planz et al. (1976)	8	30	--	300	--	8	31	--	690	--	Significant difference
Chodakowska et al. (1975)[5]	8	30	330	108	438	14	34	318	590	908	Significant difference but E values not realistic
DeQuattro et al. (1975)	29	31	--	--	166	12 8	31 --	-- --	-- --	276 264	Significant difference
Pedersen and Christensen (1975)	32	40	47	254	301	19	41	34	241	275	No difference
Cuche et al. (1974)	6	--	--	250	--	7	--	--	680	--	Significant difference
Louis et al. (1974)	14	26-60	--	200	--	28	26-60	--	400	--	Significant difference
Christensen and Christensen (1973)	9	49	--	250	--	8	54	--	260	--	No difference

TABLE 2.3 (continued)

	Controls (C)					Hypertensives (H) (Values are expressed in pg/ml and were taken in the recumbent position)					
STUDY	N	AGE	E	NE	TOTAL	N	AGE	E	NE	TOTAL	COMMENTS
Geffen et al. (1973)	8	26-60	--	160	--	20	20-60	--	400	--	Significant difference
Imai et al. (1973)	6	38	--	1033	--	3	46	--	6916	--	Significant difference, values are improbable
Jiang et al. (1973)[5]	?	?	--	--	320	--	--	--	320	--	No difference
Louis et al. (1973)	--	--	--	--	--	19	26-60	--	338	--	No controls r = .729 between NE and DBP
DeQuattro and Chan (1972)	25	16-63	--	--	273	27	24-54	--	--	354	Significant difference
Engelman and Portnoy (1970)	32	?	--	--	240	18	?	--	--	450	Significant difference
Holmberg et al. (1965)[5]	7	?	--	300	--	8	?	--	600	--	Significant difference
Goldfien et al. (1961)[5]	12	?	480	1550	--	125	--	530	3420	--	No difference, values are improbable

[1]Labile [2]High Renin [3]Normal Renin [4]Low Renin [5]Flurometric

some cases (e.g., Louis et al., 1973) values were calculated from available information such as regression lines. If male and female data were reported separately in the paper a single weighted mean was calculated and presented in the table, since significant differences between male and females in plasma values have not been reported.

Despite these adjustments the studies are not always directly comparable. A number of studies (Christensen and Christensen, 1973; DeQuattro, Miura, Lurvey, Cosgrove and Mendez, 1975; Jiang, Stoffer and Pikler, 1973) report only total CATS (i.e., combined epinephrine or E and norepinephrine or NE), others only NE. Nevertheless, a number of comments can be made. Engelman and Portnoy (1970) and Cryer, Santiago and Shah (1974) have established reference values for the supine position of approximately 200 pg per ml NE and 50 pg per ml E for plasma CATS. The actual values found in the hypertension studies are in agreement with these standards with a few exceptions.

Imai, Wang, Yoshihue and Tamura (1973) and Goldfien, Zileli, Goodman and Thorn (1961) reported highly inflated values. They were approximately ten fold above the normally accepted values but they were not exaggerated by the same degree under all conditions. For example, the values observed after exercise in the Goldfien et al. (1961) study (three mile run) were approximately 8000 pg per ml which may only be about 2 to 4 fold above normal after a stress of this type (assuming an effort of 60 percent max $\dot{V}O_2$ for a duration of 30 minutes).

It appears that the error is not systematic, since high values (exercise) are inflated less than low values (rest). Since the hypertensive values are higher than the controls they may be overestimated to a smaller degree than the control values. This effect would serve to

bring the values closer together, and thus obscure a difference that may, in fact, exist. Regardless, interpreting data which bear little resemblance to accepted values is dangerous. Goldfien et al. (1961) has been cited as support for the position that hypertensives do not have elevated CAT levels (Lake and Ziegler, 1978), but it may be more prudent to delete it from the debate.

Imai et al. (1973) found higher levels in hypertensives using a gas chromatography method, but it is difficult to understand how they did. The values are not realistic and are based on 6 controls and 3 hypertensives. Repeated measures were made on the hypertensives (6 samples); one subject had 3 samples taken, the second had 2 and only one was taken from the third. This was apparently done in an effort to achieve equal Ns. One subject's values varied five fold. The difference in BP between the two groups was not very great. Two of the controls had SBP of 140 and another 138 mm Hg. Observing differences under these circumstances and protocols does little to support the concept of heightened SNS activity in hypertension.

Lake, Ziegler, Coleman and Kopin (1976; 1977) and Lake, Ziegler and Kopin (1976) failed to find elevated CATS in hypertensives and while their values are certainly appropriate the controls showed levels of 334, 292 and 304 pg per ml respectively. These are a little high and may account for the failure to distinguish between the groups. Circulating levels of ca 300 pg per ml are what is often reported for hypertensive groups when differences are detected, with controls showing ca 200 pg per ml (Louis, Doyle and Anavekar, 1973; Louis, Doyle, Anavekar and Johnston,1974; DeChamplain, Farley, Cousineau and

vanAmeringen, 1976; DeQuattro and Chan, 1972; Engelman and Portnoy, 1970; DeQuattro, Miura, Lurvey, Cosgrove and Mendez, 1975). However, the procedures and reliability of the Lake group appear beyond reproach so that their failure to detect differences is not easily discharged.

Watson, Hamilton, Reid and Littler (1979) and Floras, Hassan, Jones, Sever, Sleight and Turner (1979) did not use normotensive controls but the values reported for the hypertensives were 480 and 541 pg per ml respectively. These values are clearly elevated in comparison to the control values reported in the other studies and tc the reference values. The subjects in the Watson et al. study were classified as mild to moderate hypertensives and no description of subjects is provided by Floras et al.

Ziegler, Lake and Kopin (1976) reported a correlation between plasma CATS and age and suggest that this may account for the differences often reported between hypertensives and normals since the hypertensives are often older than the controls. However, Lake and Ziegler (1978) failed to observe an age effect and Sever, Birch, Osikowska and Turnbridge (1977) saw it only in normals and not hypertensives. This is still an open question, but before the differences are dismissed as an artifact of age two points should be considered: 1) it is generally easier to find elevated CATS in younger, moderately hypertensive subjects than in older, well established cases; and 2) there is growing evidence that SNS activity as measured by plasma levels of CATS is compromised with age, not enhanced (Lakatta, 1979).

The plasma studies are bringing into focus the contribution of the SNS in various stages and classifications of hypertension. As with the

urinary investigations they point out the heterogeneity of the phenomenon termed hypertension. It is now clear that there is little value in comparing "hypertensives" to normotensives without some effort to characterize the hypertensives in regard to age, renin level, duration of the disease, etc. Sever et al. (1977) failed to find a difference in plasma NE between normals and hypertensives as a whole but when they compared the hypertensives under age 50 with the controls they found that the hypertensive values were elevated. Ten of 34 hypertensives in this age group had values outside the 95% confidence interval for their age matched controls. They also showed a greater increase in NE levels in response to standing. The idea that SNS activity may be greater in young hypertensives (i.e., early phases of the disease) had been proposed by a number of investigators (Nestel and Doyle, 1968; Brod, 1971).

Esler, Julius, Zweifler, Randall, Harburg, Gardiner and DeQuattro (1977), and Esler, Randall, Bennett, Zweifler, Julius, Rydelek, Cohen and DeQuattro (1976) reported investigations of NE levels in hypertensives characterized by low, normal or high renin levels. Low renin hypertensives had significantly lower NE values than did controls or normal renin hypertensives. The high renin hypertensive Ss free from secondary complications had increased NE levels compared to normal renin hypertensives or controls (Esler et al., 1977). The high renin Ss tended to be younger than the low renin ones (ranges 18 to 35 versus 21 to 50 respectively). It may be that age, renin status, and SNS involvement are all related to the duration or phase of the hypertension. This point is further explored in a later section.

Plasma CATS in Perspective

The results of the plasma investigations have rekindled the hope of documenting the contribution of the SNS to the development of hypertension. The results of the plasma studies are not conclusive, but it would not be imprudent to suggest that elevated levels are found in some groups of hypertensives. The less these groups of hypertensives are diluted by inclusion of subgroups with normal or even low adrenergic activity, which is characteristic of later stages of the disease, the greater the frequency of positive findings. However, a discussion of the role or function of the plasma CATS involves more speculative comment.

Not everyone agrees that the increased circulating levels of NE reflect SNS neural hyperactivity. Watson et al. (1979) caution against inferring differences in SNS activity because differences in resting CATS are observed. They suggest that differences in distribution volume and clearance rate may contribute to the variation observed in addition to differences in neural activity. However, it is generally accepted that deficiencies in enzymes which catabolize CATS or reuptake processes are not responsible for differences in normals and hypertensives (Mendlewitz, 1979). Fluid volume differences between normals and hypertensives are not established with any certainty (Birkenhager and Schalkamp, 1976). The significant correlations reported between CV parameters and resting plasma CATS (Louis et al., 1973; DeQuattro et al., 1975) also point to a more direct relationship between SNS activity and circulating levels of the CATS than Watson et al. (1979) suggest.

Even if plasma CATS are a direct reflection of SNS activity, an observation of higher levels in hypertensives is not easily interpreted as cause-effect. Since the work of Goldenberg, Pines, Baldwin, Greene and Roh (1948), the potent effect of infused NE and E on CV parameters, most particularly BP, has been recognized. This raises the possibility that the increase in circulating CATS observed in some hypertensives may be directly responsible for the elevated BP. This notion has been entertained, with reservations, by Engelman et al. (1970) and DeQuattro and Miura (1973). However, since that time new data have become available which strongly militate against that likelihood.

The data arguing against a cause-effect relationship originate from three observations. The first involves the difference between "physiological" levels of plasma CATS and those resulting from pharmacological doses capable of eliciting meaningful CV reactions. Unfortunately to date there is little systematic investigation of the relationship between plasma levels of both NE and E, pharmacological doses of both amines and CV responses in any single study. However, by combining studies that have manipulated and measured different variables a reasonably complete picture emerges.

Rizzer, Haymond, Cryer and Gerich (1979) infused E into humans at a dose of 50 ng per Kg per minute. This dosage resulted in a plasma concentration of between 500 to 1000 pg per ml. This is a level 10 to 20 times higher than rest values. To place them in perspective it might be pointed out that the lower value might be reached during extreme, exhaustive exercise. Cardiovascular measurements were not taken, but the information is available from Goldenberg et al. (1948). They reported an increase in systolic BP from 121 to 147 mm Hg with an

infusion rate three times that used by Rizzer et al. (i.e., 150 ng per Kg per minute or 10.5 ug per minute for a 70 Kg man). These comparisons certainly cast doubt on the contribution of E to circulatory homeostasis and the importance of E to hypertension.

Two recent studies have helped to define the physiological significance of circulating NE. Silverberg, Shah, Haymond and Cryer (1978) investigated the hemodynamic effects of NE infusion in five healthy males. An infusion rate of 5 ug per minute was necessary to elicit meaningful cardiovascular responses. At that infusion rate SBP rose from 107 to 131 mm Hg and DBP rose from 64 to 80 mm Hg. These responses are similar to those observed by Goldenberg et al. for a dose of 7.0 ug per minute (assuming they used the proverbial average 70 Kg man). The steady state plasma level of NE was 2,150 pg per ml, a value on the average ten fold greater than supine rest.

Luft, Rankin, Webs, Henry and Weinberger (1979) measured plasma NE levels and CV responses to infusion rates of 1, 2, 4 and 8 ug per minute of NE. The 8 ug per minute infusion rate resulted in a Mean BP increase of 25 mm Hg. This corresponds well with the BP change observed by Goldenberg et al. for a similar infusion rate. At that infusion rate Luft et al. found plasma levels between 6000 to 8000 pg per ml, values which are clearly outside the scope of hypertensive levels except in severe cases of pheochromocytoma. A question arises as to whether the 8 ug per minute infusion rate which resulted in plasma levels of 6000 to 8000 pg per ml is consistent with the 2100 pg per ml concentration found at a 5 ug per minute infusion rate by Silverberg et al. (1978). Further work in this area seems warranted.

The accurate measurement of plasma levels in pheochromocytoma is the second observation arguing against cause-effect. The elevation in BP in this disorder is a consequence of the high circulating levels of the amines. The average values reported for pheochromocytoma range between 2300 pg per ml (Christensen and Christensen, 1973) and 5000 pg per ml (Engelman, Portnoy and Sjordsma, 1970). These levels are of a different order of magnitude than that found in the subgroup of essential hypertensives with elevated CATS. However, some pheochromocytoma patients have been found to have circulating levels as low as 540 pg per ml which overlaps many essential hypertensives. Lastly, the fact that some psychiatric disorders (e.g., depression) manifest plasma levels of the same magnitude as in essential hypertension without high HR and BP suggests that the circulating levels may be a secondary phenomenon (Engelman et al., 1970).

There may be some cases of hypertension which result from highly elevated CAT levels, with all its circulatory sequalae, without a chromafin tumor. This could result from a combination of increased sensitivity to CATS plus a moderately high level of circulating amines (ca 500 pg per ml or more). However, the slightly exaggerated plasma CATS observed in the subgroup under question is probably the result of selective vasomotor hyperactivity. The "spillover" from this excessive activity from some part of the sympathetic tree is detected in the plasma as a small increase in NE.

Adrenergic Blocking Drugs

The hypotensive effects of adrenergic antagonists have served as the most persistent reminder that a sympathetic component is involved

in hypertension. Though there is no consensus on what this means in terms of the SNS's contribution to hypertension, it is not easily dismissed or explained. The effect of Beta adrenergic bloackade on BP is paradoxical. Theoretically, inhibition of beta receptors should result in an increase of vascular resistance, since they mediate vasodilation. Despite this they are effective in the treatment of hypertension.

There are at least four putative mechanisms through which beta adrenergic blockade could lower BP (Amer, 1977). First is their long recognized capacity to reduce CO. This should result in a reduced BP. Beta blockers reduce CO almost immediately but arterial pressure does not fall with it. In addition, individuals characterized by high CO hypertension are no more responsive to beta blockers than are other hypertensives. A second mechanism is the suppression of renin secretion (DeQuattro and Miura,1973; Zanchetti, Leonetti, Morganti, Terzoli, Chidsey, Bianchetti and Morselli, 1975). While there is no question about the efficacy of beta blockade for reducing renin, other investigators have questioned the significance of this mechanism on the basis of four inconsistencies: 1) the dose required to lower renin levels is less than that required to decrease BP; 2) the time course of the BP change and renin change do not coincide; 3) there is no correlation between the change in renin and the change in BP; and 4) the BP changes are not tied to changes in TPR and it is not probable that a reduction in renin could produce a change in BP other than through alterations of TPR (Niarchos and Tarazi, 1975; Julius and Esler, 1975; Birkenhager, de Leeuw, Webster, Kho, Vandougen and Falke, 1979).

The effect of beta-blockers on the CNS has been suggested as a third potential hypotensive mechanism. As a consequence of central blockade, SNS outflow could be reduced. However, the capability of beta blockers to reduce BP is not directly related to their capacity to reach the brain. Some beta-blockers (e.g., propranolol) do cross the blood brain barrier, but others (e.g., practolol) do not, yet both are effective agents. It is also not uncommon for circulating NE to increase after the initiation of therapy with beta blockers (Birkenhager et al., 1978). This also argues against a mechanism purportedly exerting its effects through a decrease in SNS discharge.

Lastly, beta antagonists could conceivably reduce BP by reversing cardiac hypertrophy. This possibility has some attractive features but it fails to explain the rapid return of hypertension when drug therapy is discontinued.

The widespread and successful use of sympatholytic agents in the treatment of hypertension is perhaps the most impressive evidence suggesting a role for the SNS. However, the basis of their therapeutic effect remains an enigma. No single mechanism of action is without flaws and it would be imprudent to insist that they implicate CATS as Raab (1961) suggested. It is possible that adrenergic blockade works for the "wrong" reasons. In the conclusion a synthesis is attempted.

The Spontaneously Hypertensive Rat (SHR)

Various animal models of human essential hypertension have been developed. None are thought to be exact simulations of the human condition but the Okamoto-Aoki strain of SHR has been recognized as a realistic choice (Hallback and Weiss, 1977). The relevance of this

model for the present discussion is the finding that the SHR has an increase in SNS activity early in its life span which is thought to be of etiological importance. The nature and significance of this aberrant SNS functioning is controversial but if the SHR can be taken as a model of human hypertension it provides indirect support for a contribution of the SNS in the human situation.

Judy, Watanabe, Murphy, Aprison and Yu (1979) and Judy, Watanabe, Henry, Besh, Murphy and Hackel (1976) reported an increase in SNS activity in the SHR with a technique which allows direct recording of neural activity. They found that SNS activity increased with age and was associated with an increase in mean arterial pressure. The offspring of SHRs that were genetically backcrossed with normals were found to have lower SNS activity and lower BP. They contend that the SNS makes a significant contribution to the hypertension exhibited by the SHR.

Somewhat different results have been reported by investigators using CAT levels as an index of SNS activity. McCarty and Kopin (1978) and Chiueh and Kopin (1978) failed to observe a difference in the resting levels of circulating CATS between SHR and control rats (i.e., WKYs). However, in response to stress the SHR showed a greater increase than the WKY. They speculated that the hyperreactivity of the SNS may be an important factor in the development of an elevated BP in SHRs.

Whether the conflict between these investigators is the result of the different techniques employed is not known but appears likely. Catecholamine measurements do not have the resolution of direct neural recording, so there may in fact be a difference at rest. Regardless of the outcome it appears certain that aberrant functioning of the SNS in some form is characteristic of the SHR.

A heightened activity in the SNS is not a stable or permanent characteristic of the SHR. Hallback (1976) and Hallback and Weiss (1977) marshalled evidence indicating a SNS hyperreactivity in the SHR. However, they found that this reactivity characterizes the initial stages of the hypertensive process, early in the life of the SHR, while in later stages it is no longer obvious. This observation has some parallels in human hypertensive populations as evidenced by the plasma CAT levels at rest.

The influence of the SNS to the hypertension of the SHR is generally thought to be exerted at an early phase of the disease. At this point the SNS triggers other physiological mechanisms which maintain the elevated BP (e.g., vascular hypertrophy and restructuring). According to this scenario the impact of the SNS decreases over time but the pathological process continues.

The relevance of the observations done on SHRs to human hypertension remains subject to question but the notion of a hyperreactive SNS is attractive for the psychosomatic hypothesis. Environmental conditions could theoretically play a role in hypertension by provoking the SNS, which in turn initiates a sequence of reactions that ultimately results in a sustained hypertension. In the next section the evidence bearing on the CV and SNS reactivity in human hypertension is examined.

SNS Response to Physical and Psychological Challenge in Human Hypertensives

A number of maneuvers have been utilized to provoke the SNS in an attempt to assess its function and possible participation in hypertension. Four of the most popular are isometric exercise, aerobic exercise, tilt and psychological stress.

Tilt. Birkenhager and Schalekamp (1976) have summarized the investigations which have used passive head up tilt as a SNS stimulus. They report that E excretion and secretion appear to be attenuated in established hypertensives as compared to normotensives and mild hypertensives. The response to tilt in normotensives is usually a slight increase in Mean BP. The response in hypertensives can be an exaggerated increase in Mean BP or a decrease (orthostatic hypotension). The hypotensive response is seen most often in well established hypertension and is a result of defective SNS response. The compromised response of individuals with severe hypertension is in agreement with the indices of SNS function utilizing plasma levels of CATS at rest. It provides further evidence that the contribution of the SNS to hypertension changes with progression of the disease.

Isometric exercise. Isometric exercise has become increasingly popular as a potential diagnostic tool for screening hypertensive and coronary heart disease (CHD) populations. The isometric load which is usually a sustained handgrip, produces a marked rise in HR, BP and CATS (Lake et al., 1976). The mechanism producing this CV response is not altogether clear (Donald, Lind, McNicol, Humphreys, Taylor and Staunton, 1967) but it appears that the HR increase is due to vagal withdrawal and the BP elevation is due to an alpha-adrenergic influence (Freyschuss, 1970).

The studies available which measured plasma CAT levels in normal and hypertensive individuals offer conflicting results. Nazar, Chavolbinska-Moneta and Zukowska-Grojec (1979) found no differences between hypertensives and normals during the first two minutes of the handgrip test

but by the end of the period (fourth minute) the hypertensives had significantly lower levels of NE. However, the values reported are extremely high for a challenge of this intensity which raises some concern about their methodology. Vlachakis, Mendlowitz and Krakoff (1977) and Vlachakis (1979) on the other hand, reported an exaggerated NE and E response in the hypertensives during a slightly more severe test (i.e., 2/3 maximum voluntary contraction or MVC for 3 minutes). Since details about the Ss were not included it is not known whether resolution of the conflict would occur if the duration of the disease was known but the Vlachakis (1979) study offers some insight. He employed labile, sustained and normotensive groups in an investigation of the NE and E response to 2/3 MVC sustained for 3 minutes. The resting CAT levels were similar in all three groups, with a non-significant trend toward higher levels in the labile group. However, the exercise demand resulted in a significantly greater change in NE and E in the labile group compared to the normals. The sustained hypertensives showed a NE response that was not significantly different than the normal controls, though their E response was greater. Once again it appears that the characteristics or responses observed depend to a great extent on the category of the hypertension or its duration.

Aerobic exercise. The tremendous CV and sympathetic responses resulting from aerobic exercise (Astrand and Rodahl, 1977) make it particularly well suited for investigations of the autonomic and hemodynamic characteristics of hypertensives. Any abnormalities or idiosyncracies of the hypertensive state should be amplified as the body reacts to the disruption of resting homeostasis brought by vigorous exercise.

Hamer, Fleming and Shinebourne (1967) investigated the effect of graded treadmill walking on CO, BP, HR and TPR in three groups of hypertensive patients. Though the patients were classified as severe, fixed or labile all showed fundal changes and left ventricular hypertrophy which indicates all had relatively severe hypertensive disease. Therefore, it may be that the divisions were more arbitrary than real. The highest workload reached was moderately heavy for the subjects under study (mean age equals 50 years). It elicited a mean HR of 150 bpm and an oxygen uptake ($\dot{V}O_2$) of approximately 26 ml O_2 per Kg (of body weight) per minute. The highest values of TPR observed during exercise were in the severe hypertensives. The labile group showed BPs during exercise of the same magnitude as the fixed group. Exercise abolished the differences in BP seen at rest between the labile and fixed groups, indicating they had a larger response to the exercise stress. Whether or not this was the result of a hyperresponsive SNS is not known since no CAT measures were taken.

The differences in hemodynamics between hypertensives and normals have been investigated by a number of workers. Sannerstedt (1966) compared normals with three age groups of hypertensives at a workload that could be maintained a minimum of 5 minutes or up to 10 to 12 minutes. The workloads varied from 200 to 1200 Kgm per minute (9 to 35 ml O_2 per Kg·minutes). No subject ever worked at more than two loads and most at only one. The workloads varied for each subject, depending upon individual tolerance. However, a test of maximum aerobic power apparently was not given so it is not clear how tolerance was determined.

The group I hypertensives, mean age 34.9, was composed of 14 males with essential hypertension. They evidenced a higher CO and HR at rest than did the controls. This was coupled with a higher $\dot{V}O_2$ consumption. During exercise they maintained the HR difference observed at rest but the increase was of the same order as in the controls.

Heart rate was increased significantly more as a result of the exercise in groups II and III as compared to controls. The mean ages of these two groups were 47.5 and 49.0 respectively. Group II consisted of 30 essential hypertensives and three with renovascular hypertension. Eleven individuals with essential hypertension and two with chronic glomerulonephritis made up Group III. Systolic BP showed a pattern similar to HR in Groups II and III in its disproportionate increase to exercise compared to controls.

All three hypertensive groups evidenced a smaller fall in TPR upon exercise than did the controls. This is particularly significant as regards group I. Their TPR at rest was within normal limits, but the response during exercise indicated that the peripheral vascular bed was already beginning to manifest characteristics of more advanced stages of hypertensive disease.

Though the TPR response occupied the greater part of Sannerstedt's interest, the HR response is of interest also. Whether or not this response was the result of hyperreactive SNS is not known. Since the response occurs in the oldest not in the youngest groups (of males), it does not fit easily with the picture emerging from the resting CAT data, in which older sustained hypertensives show the least SNS activity.

We might expect a high SNS reactivity to be expressed in younger not older Ss.

One aspect of Sannerstedt's work limits its utility for investigations of individual differences between normotensive and hypertensive Ss. This is the cross sectional nature of the investigation. Because each S was exercised at only one or at most two levels of work, individual patterns of response were obscured. Preferably, the protocol should include a variety of workloads for each subject.

Julius, Pascual, Sannerstedt and Mitchell (1971) observed TPR anomalies in 77 borderline hypertensives similar to Sannerstedt's. At the single workload employed (300 Kgm per minute) the 82 normals were characterized by lower BP and TPR than the borderlines. No other significant differences were observed. The authors emphasized the contribution of resistance changes to the BP response even in this form of hypertension. The use of only one light exercise load places some limitations on this study also.

Occasional but persistent observations of other hemodynamic differences suggests that more than TPR may distinguish hypertensives from normals during exercise. The work of Lund-Johansen (1967; 1973) supports this assertion. He compared 94 hypertensives with 77 normotensive controls on bicycle ergometer work of 300, 600 and 900 Kgm per minute. The principle characteristic distinguishing the hypertensives from the controls was again a higher TPR. However, the youngest patients had higher HRs during exercise than did the controls. The oldest hypertensive group had lower HRs than their age matched controls. If this represented a difference in SNS tone it would be the same type of pattern

observed in various other stress situations and the investigations of resting plasma levels of CATS in hypertensives and controls. While some investigators have observed a HR difference in exercise between hypertensives and controls (Taylor, Donald and Bishop, 1957; Planz, Gierlichs, Hawlina, Planz, Stephany and Rahn, 1976; Julius and Conway, 1968) others have not (Levy, Taboken and Hanson, 1967; Amery, Julius, Whitlock and Conway, 1967). At this point it remains an interesting, although inconsistent observation.

The study by Julius, Amery, Whitlock and Conway (1967) provides the control data for two studies which investigated the aerobic capacity and hemodynamic responses of borderline hypertensives (Amery et al., 1967; Julius and Conway, 1968). The sixty-one hypertensive subjects studied by Amery et al. (1967) responded with higher absolute SBP and TPR than normotensives to a progressive workload. The change in SBP was larger only in the two oldest groups, the youngest group showed a BP response similar in magnitude to the controls, only starting at a higher baseline.

There were no differences in maximum (max) $\dot{V}O_2$ or HR responses at the various exercise intensities. At the highest workloads CO failed to increase in the youngest hypertensives despite an increasing $\dot{V}O_2$. By definition this means their arterial-venous (A-V) O_2 difference was enlarging and provided the increase in $\dot{V}O_2$. However, it was not significantly larger than the control group's.

Julius and Conway (1968) observed somewhat different results in regard to HR in 83 subjects with borderline hypertension. The HR of the youngest group of hypertensives (18 to 34) was higher at rest and all levels of exercise, including maximal effort, than the controls.

Their aerobic capacity was no different. The older hypertensive groups showed a HR response similar to the age matched normals. Unlike previous studies the mean BP change to exercise was the same as in normals. Because exaggerated BP responses to exercise so often observed in hypertensive populations are probably the result of sclerosis of the large vessels, with resulting rigidity, it was concluded that these borderline hypertensives did not have extensive vessel disease.

Levy, Tabakin and Hanson (1967) studied 20 young, untreated, labile hypertensives and their age matched normal controls. The SBP, DBP and mean BP levels during exercise were significantly higher than the controls but the relative change was no different. Heart rate, CO and VO_2 did not differ significantly in the two groups. However, there appear to be some methodological problems with this study. The reported VO_2 values do not correspond with the expected oxygen requirements for the workloads presented. At the lowest workload the discrepancy is only 6.3% but it becomes progressively larger so that the heaviest load resulted in an O_2 consumption 26% less than expected. I assume that the Ss increasingly held onto the treadmill as the test progressed. At the steepest grade (25%) they were probably holding on constantly, thus reducing the O_2 requirement by approximately 25% (Howley, personal communication). The low respiratory (R) ratios $\left[\frac{VCO_2}{VO_2}\right]$ also supports this contention. At the high workloads involved they should be on the order of .9 to 1.0 and above, not .7 and .8, because the subject would be hyperventilating and thus eliminating large amounts of CO_2. The high SVs necessary at the COs and HRs reported are improbable for subjects of this degree of fitness. Levy et al. reported values of approximately

140 ml per beat which is usually seen only in fit youth. It is also 26% above supine values, which are normally very near maximum values (Astrand and Rodahl, 1977; Rushmer, 1976). The value of the study is diminished by these faults, but probably not impugned totally. However, familiarity with all aspects of exercise testing certainly is lacking.

The problems detailed here, or similar ones, are often found in many studies employing exercise protocols. The maximum HRs and $\dot{V}O_2$s reported in Amery et al. (1967), Julius et al. (1967), and Julius and Conway (1968) are all uncharacteristically low but evidence of a breach in protocol or faulty workmanship is not readily apparent. It might be that attention to the finer points of exercise testing is sometimes missed when sophisticated measurements (e.g., CO determinations) are taken. The values which then result are often compromised and it then becomes difficult if not impossible to relate them to the values carefully accumulated in the exercise literature. Knowledge of the absolute physiological capacities and characteristics of hypertensive populations is certainly to be preferred to data of a more relative nature.

Most of the studies using exercise as an experimental variable described above sought to clarify only hemodynamic adjustments to exercise. Since measurements of autonomic activity were not available, my suggestions concerning the influence of the SNS in these hemodynamic adjustments are admittedly bold. However, the results of investigations of the SNS response to exercise provide a more direct test of the SNS differences between normal and hypertensive Ss.

Chodakowska, Nazar, Wocial, Jarecki and Sarka (1975) measured NE and E in 14 hypertensives (mean age was 34.5 years) and 8 normals (mean age was 30.0) during exercise requiring HRs of 120, 140 and 160 bpm. There were no differences in plasma CAT values at rest between the two groups. A different picture emerged during exercise. Epinephrine increased significantly after exercise at all workloads in the hypertensive Ss, but only after the heaviest in the controls. All exercise intensities elicited NE increases but these were significantly greater in the hypertensives at the 140 and 160 bpm loads. The hypertensives also displayed significantly greater BP changes. The authors suggested that the SNS of these hypertensives "may exhibit abnormal response to upright exercise" (p. 514).

Similar conclusions were reached by Planz, Gierlichs, Hawlina, Planz, Stephany and Rahn (1976). They subjected 8 normotensives and 8 hypertensives to bicycle ergometer work of 300, 600 and 900 Kgm per minute. Their ages were 30 ± 1.8 and 31 ± 2.8 respectively. Resting levels of CATS were higher in the hypertensives and increased significantly more at the highest workload than they did in the controls. Interestingly, in view of Chodakowska et al. (1975), this workload required a HR of 150 to 160 bpm.

The NE response to a short duration high intensity work bout was investigated by Philipp, Distler and Cordes (1978) in 29 normotensives and 29 patients with established hypertension. The mean ages of the two groups were 33.2 and 37.9 years respectively, with a range of 20 to 49 years. Hypertensives exhibited elevated resting levels of NE relative to the normotensives (173 versus 215 pg per ml) and the difference was

enhanced by the exercise. Though the patients involved in this study were considered to be examples of established hypertension the majority were less than 40 years of age which is a relatively young group by most standards (Sever et al., 1977).

Because of the small number of Ss employed in these studies caution is demanded in assuming differences in SNS responsivity. But the fact that the Ss were relatively young fits nicely with the recurring pattern found in other investigations of SNS activity in hypertension.

The exercise studies provide some evidence that challenge may elicit an autonomic response which distinguishes young hypertensives from normals. The difference in HR reactivity reported in a few studies provides some support, albeit weak for this notion, while stronger evidence is found in the results of investigations of the CAT response to exercise. An exaggerated BP response to the exercise stimulus is not consistently reported in younger hypertensives. Older patients almost always respond with extreme pressure changes. As mentioned previously, this is probably the result of vessel rigidity. Consequently the same pressor stimuli produce greater pressure changes in the older subjects.

Selection of young hypertensive subjects may play an important role in whether a hyperresponse is observed. The classification of borderline or labile hypertension is still found to be a heterogeneous group. It is probable that different etiological mechanisms and predispositions are operating in this group. In some subset of young patients it may be that a hyperresponsive SNS is operative, in others it may have no significance whatsoever. Further investigations will be necessary to

establish the reality of an increased SNS responsivity in hypertension.

Psychological stress. Emotional challenges are particularly attractive as SNS stimuli because of their ubiquity in modern life. Since a disturbed CV adaptation to the environment would most likely be the result of psychological stresses, as opposed to physical ones, a number of attempts have been made to document a pathogenic response to it. Laboratory efforts in this regard have attempted to mimic the emotional challenges of everyday life in an admittedly artificial environment. As with the use of physical stressors, the objective is to determine if hypertensives demonstrate an exaggerated HR, BP, or SNS response to the provocation.

Jost, Riulmann, Hill and Gulo (1952) compared 47 normal individuals selected from medical students, nurses and other medical school personnel with 12 unspecified hypertensives. Both groups were subjected to a series of experimental tasks consisting of digit recall, interview and sensory stimulation. The hypertensives exhibited a greater change in BP than did normotensives. The greatest increase was 7 mm Hg which occurred during the interview period. Heart rate changes showed the opposite trend with normotensives demonstrating greater responses than the hypertensives, though the hypertensives had higher resting rates (89 versus 82 bpm). The digit recall was the most potent elicitor of HR changes, though none of the tasks appeared to be powerful CV stimulants.

Schwartz (1957) reported similar findings in 15 normals and 18 hypertensives. He employed a cold pressor test and situations designed to elicit either anger or fear. The hypertensives responded with a change in SBP of 26 and 17 mm Hg during anger and fear respectively.

The normotensive response was only 15 and 8 mm Hg for the two situations. Heart rate failed to differentiate the two groups. Though little information is given on the status of the hypertensives, 14 of the 18 had a diagnosis of sustained hypertension. If in fact they were established hypertensives the attenuated HR response might be predicted.

Engel and Bickford (1961) found that 15 of 20 hypertensives showed a tendency to respond to a variety of stresses with BP elevations compared to only 5 of 20 normotensives. They implied that this response stereotypy is in part responsible for the hypertension. They reasoned that the somatic expression of stress in these individuals will be a rise in BP, as opposed to disturbances in other organ systems. Chronic stress would then produce continual elevation of BP in these individuals. An alternative interpretation was discussed in the previous section on aerobic exercise. It was based on the fact that due to the continually high BP in hypertensives, sclerosis and rigidity of the vessels results; consequently, a given pressor response could be greater in them than in normotensives without invoking differences in reactivity.

Hardyck and Singer (1962) reported large increases in SBP (40 mm Hg) to an interview situation in hypertensives, but no control group was used. However, the study by Stevenson, Duncan, Flynn and Wolf (1952) did use one. The hypertensive subjects showed a greater BP response to the interview than the controls. The only other CV measure which discriminated between the groups was TPR. The hypertensives exhibited less of a decrease in relation to the increase in CO which was elicited by the interview.

Moos and Engel (1962) reported a greater HR reactivity in 12 arthritic patients compared to 12 hypertensive ones in a verbal conditioning situation, but this assertion was not borne out statistically. The BP response was no greater in the hypertensives though absolute levels were higher. The resting BP levels of the hypertensives was 209/115 indicating a severe and probably well established hypertension.

Shapiro (1961) provided an interesting and enlightening aspect to an investigation of differences in 36 normal and 50 hypertensive individuals. He analyzed separately a group of 14 normals with a family history of hypertension. This group showed the greatest change in HR to venipuncture and also a higher resting SBP than the normals without family history. The greatest change in BP was observed in those with hypertension followed by normals with a family history of hypertension and normotensives without one. This might be interpreted to mean that an increased responsivity is present before the expression of hypertension, and if confirmed would be a significant contribution to our understanding.

Sapira, Scheib, Moriarty and Shapiro (1971) observed a greater HR and BP response in 19 hypertensives with mild to moderate disease after viewing a movie depicting sensitive interactions between a patient and doctor. However, they failed to find a difference in the urinary excretion of NE and E between the normal and hypertensive groups. The magnitude of the CV changes may explain this discrepancy: The HR change in the hypertensives was only 8 bpm and the change in the normotensives was only 2 bpm. The maximum change in Mean BP was less than 10 mm Hg in

the hypertensives. It is doubtful if urinary measures of CATS have the sensitivity to reflect such subtle changes.

Nestel (1969) compared the response of 20 labile hypertensives with 17 controls to a 40 minute stress test (i.e., visual puzzles). The labiles showed larger changes in DBP, SBP, E and NE in response to the test. Heart rate was not measured. They concluded that the hypertensive patients had a notably greater sympathetic response to mild mental stress than did the controls.

Baumann, Ziprian, Godicke, Hartrodt, Naumann and Lauter (1973) used mental arithmetic under time pressure as a stress. They compared 30 males with mild hypertension between the ages of 15 and 25 with 20 age matched controls. The HR and BP responses were increased in the hypertensives relative to the controls. The immediate response of plasma CATS was similar in both groups but the normals quickly showed a fall while the hypertensives remained elevated. The method used was the trihydroxyindole method but the values appear to be realistic if the graph of the results is consulted and not the text (i.e., a typographical error is suspected, since values are presented as mg per ml not ng per ml which is a difference of 10^6).

Negative results were reported by Esler and Nestel (1973) and Lorimer, MacFarlane, Provan, Duffy and Lavine (1971). Esler and Nestel (1973) failed to observe a difference in CAT excretion between 10 hypertensives and 6 normals after a 45 minute period of visual puzzles. This appears to conflict with Nestel (1969) but 8 of the 10 hypertensive subjects in Esler and Nestel's study were established hypertensives (as opposed to labile) which may account for the discrepancy. The stress of

solving visual puzzles failed to elicit significant changes in NE excretion from baseline in either group of subjects, so its potency as an SNS stimulus in this case is doubtful.

The task of sorting 250 steel ball bearings of various sizes into appropriate groups was employed by Lorimer et al. (1971). It failed to differentiate normal and hypertensive subjects in terms of NE and E excretion. Again, the stress failed to reliably produce changes from rest levels in NE. Norepinephrine must be considered the amine of greatest interest in studies of SNS function and reactivity and, therefore, a failure to elicit changes in it must be considered a major limitation. The use of older established hypertensive patients also reduces the chances of finding a significant difference.

The studies grouped under the rubric "psychological stress" have employed a diversity of stressors. Nevertheless, the results concur with the findings of previous analysis. Sympathetic response is most reactive in young, mildly hypertensive subjects. With progression of the disease SNS function becomes blunted.

A greater BP response in the hypertensives compared to normotensives is universally reported. However, the greater increase in BP is probably not due to an increase in SNS activity but a reflection of the greater sensitivity in hypertensives which results from a narrowed, hypertrophied vascular system (Mendlowitz, 1979). Because of this phenomenon, exaggerated BP changes in hypertensives must be interpreted with caution. The hyperreactivity is most likely the result of the hypertension per se, and whether it was characteristic of these individuals prior to the hypertension is still unclear. This property

of hypertensives makes it treacherous to conclude that response stereotypy or specificity (Engel and Bickford, 1961) preceded the hypertension.

Conclusion

No single index of SNS function provides conclusive proof that the SNS is involved in the genesis or maintenance of hypertension. Together, however, they furnish a more persuasive case. A few generalities can be offered with limited reservations.

Hypertension is a disorder with a myriad of causes and precipitating stimuli. In a subset of these cases the SNS appears to be implicated. Generally, these are younger patients, with normal to high renin and often some signs of a hyperkinetic circulation. The number of studies reporting differences in SNS response to challenge, resting plasma CATS and urinary CATS in younger, less severely hypertensive patients supports this contention (DeChamplain, 1972; DeQuattro and Miura, 1973).

The results of sympathectomy in hypertensive patients make it clear that the SNS is not responsible for the abnormal TPR and BP so characteristic of established hypertension (Blakemore, Jeffers, Sellers, Itskovitz, Cooper, Wolferth and Zintel, 1961; Cort et al., 1962, p. 265; Korner, 1976; Wilson, 1961). Evidence is also accumulating that the capability of the SNS to respond to challenge is diminished in long established hypertension. These cases manifest many characteristics of subnormal SNS activity (decreased CO, decreased renin, decreased CATS; and attenuated HR response to stress).

What then is the status of the SNS in hypertension? Two scenarios which speculate on the possible influence of the SNS in the hypertensive process are described below.

Amer (1977) presented an hypothesis to explain the mechanism of beta-blockade therapy in hypertension, but it is relevant to the issue at hand. He proposed a decrease in beta-adrenergic receptor sensitivity as a principle problem in hypertension. Since beta-stimulation mediates vasodilation, a decrease in sensitivity would promote an increase in TPR.

Since prolonged and excessive exposure to a stimulant will bring about a decrease in the sensitivity of a receptor, excessive sympathetic stimulation brought about by "stress or emotionality" could provide a milieu conducive to a decrease in sensitivity. The function of the beta-blockers is to protect the receptor and allow it to regain its sensitivity. The details of this proposal are not of concern but the putative mechanism is. In some individuals with a predisposition to respond with excessive SNS activity, stress would elicit abnormal levels of CATS, which in turn would change the functioning of vascular receptors. These receptors could show a permanent loss of sensitivity which would account for the sustained hypertension when the SNS is no longer hyperreactive.

Amer's notion of a decreased sensitivity in the beta-receptor contrasts with others who suggest an increase in sensitivity (Lake and Ziegler, 1978; Frohlich, Tarazi and Dustan, 1969). This conflict may be resolved by invoking the idea of changes with different stages of hypertension. For example, low renin hypertension shows many signs of decreased SNS responsiveness, while high renin shows the opposite (Esler et al., 1976; 1977).

Amer's emphasis is on the vascular system. Brown, Lever and Robertson (1969) emphasize the renal component. They propose a functional change in the kidney, as a result of increases in BP. Overactivity in the SNS could provoke these BP changes. This hypothesis resembles Guyton et al. (1970). Since it is accepted that excessive pressure will bring about changes in the kidney which will then maintain the pressure, only two postulates are necessary. The first concerns the transformation time of the kidney which is the length of time required to effect structural and/or functional changes in the kidney as a result of increased pressure. The second involves the capacity of the individual to respond with a great rise in pressure (i.e., SNS reactivity).

A scenario based on the proposal of Brown et al. might proceed as follows: An individual with a reactive SNS will respond to environmental and psychological demands with large elevations in BP. Repeatedly presenting the kidney with these BP elevations will result in a change in renal function if a short transformation time is also operating. As the kidney changes, BP is maintained at successively higher levels. The process will continue to build on itself until an established case of hypertension is produced.

The theories of Amer and Brown et al. have a nexus at the SNS. They both posit a sympathetic neural involvement which is greatest in the initial stages and becomes less significant after time as other pathophysiological processes exert increasing influence. This is in accord with the observations of the SNS in hypertension, and is not difficult to explain. It has long been recognized that the SNS is under reflex

control. As BP becomes greater with time, it is quite possible that the SNS responds to this stimulus by diminishing its output. Older, well-established hypertensives show the highest pressures and also the least tendency to manifest SNS over activity.

To implicate SNS hyperreactivity as a causal factor in hypertension, at the least, it must be observed prior to the diagnosis of hypertension. If the activity of the SNS is important to the development of pathological levels of BP, measures of it should be of some aid in the prediction of hypertension. In the next section, the literature concerned with individual differences in ANS function and attempts to characterize and predict individuals prone to hypertension is reviewed.

I. INDIVIDUAL DIFFERENCES

> What is, I suppose the most serious, as it is certainly the most conspicuous shortcoming of all [Psychology] is the absence of any mention of the body as a conditioning factor in the formation of a personality, or as a determinant of thoughts, feelings and behavior. Aldous Huxley (1960)

In general, there has been a reluctance in American psychology to systematically pursue the subject of individual differences. Variation between subjects has been considered more a source of error than one of information (Lykken, 1975). Nevertheless, there has been a persistent, though small, interest in physiological and constitutional factors which might distinguish one individual from another. Some of these factors have relevance to the issue of vulnerability to hypertension, the most important being the functioning of the ANS in normal, healthy individuals.

The point merits repetition that identification of ANS and reactivity differences between normals and hypertensives could be the

result of the hypertension, not the cause of it. This was discussed in relation to the BP reactivity of hypertensives and normals to various stressors but additional observations also support this possibility. Epstein, Fitzimmons and Rolls (1970) and Dworkin, Filawich, Miller, Craigmyle and Pickering (1979) provided evidence that behavioral and affective changes may occur as a result of changes in BP and the resulting biochemical sequalae. Because of these observations, documenting differences in the functioning of autonomic and neural systems mediating stress reactions in non-hypertensive individuals is a necessary first step in establishing their etiological significance.

One of the first suggestions that differences among normal individuals in the activity of the ANS were related to potential illness was the statement by Eppinger and Hess (1915) that " . . . many diseased states are associated with autonomic stimulation, and that the possiblity exist(s) that a constitutional tendency of the organism, to react in a definite way to such stimulation might be at the root of the matter" (p. 86). They believed that "an increased or decreased tonas in one of the two systems" [PNS or SNS] was the basis for a multitude of illnesses. The "imbalance" in the ANS was diagnosed with various agents that either stimulated or blocked one or the other branch of the ANS, such as atropin, ergotoxin, muscarin, philocarpin, and physostigmin.

As is usually the case with initial theories and proposals, the situation revealed itself to be more complicated than originally suspected. The recognition of the role of reciprocal feedback and the

complexity of autonomic regulatory mechanisms (Darrow, 1942) produced a climate inhospitable to the poorly operationalized and global terms of Eppinger and Hess. In reacting to the research spawned by their theory, Darrow (1942) said that " . . . reference to such terms as 'autonomic balance,' 'sympathicotonia,' and 'parasympathicotonia' without physiologic qualification partakes almost of mysticism" (p. 18). Despite this Darrow conceded that these terms might be "useful for purposes of classification." And so it has been, that the desire to systematically "categorize" or evaluate individuals in terms of ANS response has shown remarkable tenacity and resilience enabling it to conform to the prevailing intellectual and scientific conditions.

Later efforts in this direction have not attempted such a universal or ambitious description as that proposed by Eppinger and Hess, but they clearly have their antecedents with them. The efforts to document response differences currently involves more modest but rigorous use of operational categories. Identifying response differences is not as difficult as implying that they are a reflection of real constitutional differences or reliable response tendencies. There are a number of reports throughout the animal and human experimental literature of observations of significant differences in physiological response to stress with the implication that they may be related to a vulnerability to disease. A few of these are discussed below.

The work of Hines and Brown (1933; 1936) and Hines (1940) involved the classification of BP responses to a cold pressor test. A normal response consisted of an increase in SBP of 10 to 20 mm Hg. A response greater than 20/15 mm Hg pressure increase was considered a

hyperreaction and thought to be indicative of a prehypertensive state. Indirect support was found in a study of 400 school children. The hyperreactors were found to have at least one family member with hypertension (Hines, 1937).

However, the variable results and failures of other investigators to relate these responses to subsequent hypertension has called into question the significance of the cold pressor test (Lovallo, 1976) and its use as a reliable predictor of hypertension (Page and Corcoran, 1945). Harlan, Oberman, Mitchell and Graybill (1973) compared the rise in SBP to a one minute cold immersion in 385 men at age 24 to the level of SBP at age 54. Despite using criteria similar to Hines they failed to observe any relationship. They concluded that the cold pressor test did not predict future hypertension.

The poor prognostic power of the cold pressor test diminished its attractiveness as a SNS stimulus and a means by which to differentiate individuals in terms of reactivity. Other efforts to document the notion of a "reactive" individual have employed a variety of stimuli and conditions. Some were attempts to show that hyperreactivity was a characteristic of a pre-morbid state, while others sought only to deal with some esoteric aspect of a theory, since forgotten, but they all imply that individuals and even animals differ in their response to stress.

Smith (1972) operationally defined "personality" in monkeys in terms of CV reactivity to various standardized behavioral tasks such as lever pressing for food reward. He observed reactive and non-reactive animals and proposed that the development of CV disease might

be related to this response dimension. Froberg, Karlson, Levi and Lidberg (1971) observed great differences in the urinary excretion of E to psychological stress and suggested that hyperreactors might be more prone to illness. This has not been pursued.

Mefferd and Wieland (1966) compared the response of anticipated hypoxia to the response of actual hypoxia. They observed large differences in the reaction of the Ss to the anticipated stress--"some reacted hardly at all, while others had an alarm reaction." The Ss maintained their relative rank order when exposed to the hypoxia itself. The study demonstrates differences in SNS reactivity (i.e., NE values were differentially elevated) which reflect more than perceptual differences since the differences were maintained during the physical stressor also. Whether the differences in reactivity would have been similarly expressed in other situations is not known.

Patton (1969) attempted to assess the generality of SNS response in 24 Army enlisted men to a variety of situations. The HR, SBP and skin conductance (SC) responses to heat (110° F), cold (50° F), timed anagram solution and viewing movies of surgical procedures were related to their initial autonomic balance scores (see Wenger, 1968). Patton reported that Ss classified as sympathetic had consistently higher HRs and palmar SC levels during all four stressors than those Ss categorized as parasympathetic.

Conclusions must be tempered because this study is subject to a number of criticisms on the basis of its methodology. Because it utilized indirect measures of SNS activity it is open to the same criticisms that Darrow leveled at Eppinger and Hess. Heart rate is

under both SNS and PNS control and BP can be affected by changes in cardiac status; therefore, the system producing the changes is unclear. This criticism can be surmounted but it has a particularly strong sting in this case. If the situation under investigation is known to elicit SNS activation, HR and SBP can be used to follow it but viewing graphic, bloody movies is more likely to elicit a parasympathetic response than a sympathetic one (Carruthers and Taggart, 1973). Therefore, it is possible that fluctuations in PNS tone were responsible for the observed changes.

The control measurements (non-stress) took place during viewing of a comedy film. In light of Levi's (1964) work, it could be argued that this evoked a larger SNS reaction than the "stress" films. Since Ss were classified as either SNS or PNS dominant at this time, this represents a poor methodolgical procedure. The design is attractive for investigations of the issue at hand, but different stressors are necessary.

Paul Obrist and his colleagues at the University of North Carolina, Chapel Hill, are interested in the notion of reactivity of the SNS and its contribution to hypertension. They have provided data that show that the type of stressor involved will have a effect on whether the SNS is the primary neural system activated. If an individual is overreactive in this system (i.e., SNS) because of heredity, developmental factors, etc., then stressors which affect it will result in a hyperactivation of the physiological systems subserved by it (e.g., HR, BP).

They propose that situations demanding behavior characterized by active coping will elicit CV responses indicative of beta-sympathetic stimulation. The notion of beta-sympathetic activation arises from the predominance of cardiac influences in the circulatory response, such as increases in BP via an augmented CO and cardiac contractility. It does not refer to a change in cAMP levels, or any other biochemical index of beta receptor activation, though these may in fact change accordingly.

Obrist has placed the most emphasis on research dealing with situations which elicit a beta-sympathetic activation and on those individuals most responsive to those situations. He has contributed a sophistication to the conceptualization of stress and individual differences which must be recognized by future studies which seek to demonstrate differences in the reactivity to psychological stress. Since the present research is patterned on his scheme, it is described more closely below.

The stressors which Obrist et al. (1977) utilized differed in the degree of control the individual had over them. Therefore, active or passive coping behavior was differentially elicited. The effect of the stressors was ascertained through psychophysiological measurements such as HR, BP, pulse propagation time (PPT) and the first derivative of the carotid pulse wave (carotid dp/dt).

The passive stressors were those to which the individual was simply exposed, such as a pornographic film and a cold pressor test. The active stressor employed was a shock avoidance task, wherein the subject could avoid (i.e., control) shock by responding within a

certain time. Carotid dp/dt, an index of sympathetic nervous system activation, was significantly elevated above baseline values only in the active stress situation. Heart rate and SBP were significantly elevated in all three stress situations, but the effect was significantly more pronounced in the active coping situation. On the basis of these data, Obrist concludes that the active coping situation invokes a large sympathetic input into the heart, just as in exercise. The passive coping situation (no control) has a small sympathetic component, but it is essentially masked by large vagal activation.

The observation of interest here is the differences in reactivity. Some Ss showed an HR acceleration to the shock avoidance of over 40 bpm, while others showed less than 9 bpm. There was little relationship between HR reactivity in shock avoidance to the other situations. This should be no surprise, since the other conditions cannot be considered true active coping situations. However, it is puzzling that other situations thought to elicit a beta-sympathetic response were not also tested in order to ascertain the generality of this reactivity.

Efforts to obtain more information about individuals showing a CV reactivity to stimuli evoking active coping have been carried out in this laboratory (Lawler, Lawler and Cox, 1978; Lawler, 1980). The individuals involved all had BP in the normal range at rest, but when exposed to a mental arithmetic task differences in HR reactivity were observed. The reactive individuals also showed higher HR at rest and to tasks demanding attention. They also showed a tendency toward larger BP changes and a significantly higher overall BP. These responses appear to be manifestations of enhanced SNS activity and if so they

resemble characteristics of individuals with early or borderline hypertension.

II. STATEMENT OF RATIONALE AND PURPOSE

Differences between individuals in the response of the SNS to physical and psychological challenge may be found before overt signs of hypertension develop and may reflect a predisposition to succumb to this disorder. The differences are most marked during tasks which demand an active coping mode of behavior. These situations are said to elicit a beta-sympathetic response. However, efforts to establish SNS reactivity as a reliable characteristic of an individual and one which is expressed in a variety of these situations are only in their early stages.

The principle aims of the present research were to: 1) gather some fundamental information on those individuals differing greatly in CV reactivity; 2) test the generality of this reactivity by utilizing a variety of active coping situations which differ in apparent motivation and affective quality; and 3) provide further evidence that the reactivity differences are related to variation in SNS arousal.

In order to meet these aims a variety of measurements and protocols were utilized. The measurements of HR, SBP, DBP and urinary excretion of NE and E were taken during a series of challenges which are purported to resemble active coping, or beta-sympathetic activating situations. These included reaction time shock avoidance (RT-AV), reaction time for monetary reward (appetitive or RT-AP), mental arithmetic (MA), and aerobic exercise.

The use of aerobic exercise is attractive for a number of reasons: 1) constitutional or genetic factors account for a large percentage of the variance between people in exercise responses. Therefore, these responses provide more information about the individual than simply their state of training (Klissouras, 1971; Astrand and Rodahl, 1977); 2) maximum exercise allows the determination of particular physiological characteristics such as maximum HR and max $\dot{V}O_2$; 3) the quantification and description of the physiological responses observed in psychological stress can be accomplished by comparing them to those responses seen at workloads requiring various percentages of the individual's maximum exercise response; and 4) it also results in a large beta-sympathetic response, and therefore lends itself to the testing of certain predictions. Since Obrist hypothesizes individual differences in reactivity to beta-sympathetic stimuli, differences during exercise could be predicted.

The assessment of individual reactivity and of beta-sympathetic influences during exercise was indirect. The relationship between HR during exercise and $\dot{V}O_2$, expressed as a percentage of an individual's maximum aerobic power, was used to assess reactivity. It is hypothesized that some individuals are "uneconomical" in their cardiovascular reactions to exercise in the same way they are "uneconomical" during psychological stress.

Individual differences in the HR-$\dot{V}O_2$ relationship have been reported (Astrand and Rodahl, 1977, p. 349). There are a number of possible factors which can influence this relationship (e.g., mechanical efficiency) but constitutional differences of the type suggested by

Obrist must also be viewed as potential influences. It has been shown that beta-sympathetic blockade lowers the HR for the same relative $\dot{V}O_2$ (Ekblom, Goldberg, Kilbom and Astrand, 1972). This suggests that a lower level of sympathetic input will result in a lower HR for the same relative workload.

A comparison of "normal" college students during exercise, who differ ostensibly only in reactivity to a psychological stimulus, has additional value in that it may serve to broach two separate research literatures. Exercise challenge has been employed in research investigations of hypertension. The hemodynamic responses of hypertensives have been compared to normal control groups. However, it is often impossible to tell whether the differential response sometimes reported is due to the disease condition or is a manifestation of some aberrant physiological process operating before the diagnosis of the disease and which might be instrumental in the genesis of the disease. If the reactive group displays a response during work resembling a hypertensive population a possible link between reactivity and future pathology is closer to being established.

The use of urinary measures of CATS as an index of SNS response to the psychological challenges represents an attempt at cross validation. The arousal of the SNS in active coping situations is often inferred from indirect psychophysiological measurements. Though these are valid, confidence in the contribution of the SNS to the observed changes would be strengthened by assessment of CAT excretion.

The following were specific questions of interest in this study:

1) Do groups showing a difference in HR reactivity to an RT-AV task maintain HR differences during RT-AP and MA tasks?

2) Do SBP and DBP in the variety of situations employed distinguish groups separated on the basis of HR to the RT-AV task?

3) Do values for NE and E excretion distinguish reactives and nonreactives?

4) Do reactives and nonreactives show differences in maximum HR?

5) Do reactives and nonreactives differ in their max $\dot{V}O_2$?

6) Does graded exercise elicit similar HR and SBP responses in the two groups (i.e., is CV "economy" the same)?

7) When the CV response to psychological challenge is expressed as a percentage of the max $\dot{V}O_2$, which elicited the same CV change in exercise, does it still separate the two groups?

CHAPTER III

METHODS

I. EXPERIMENT I: PSYCHOLOGICAL CHALLENGE

Subjects

Thirty-four male undergraduates served as subjects in this phase of the investigation. All subjects were volunteers who had agreed to participate in the experiment after reading a posted description of it (Appendix I). Subjects received the maximum allowable extra credit towards introductory psychology for their participation, plus any money accumulated during the RT-AP task. (One subject was not enrolled in any psychology class). The subjects ranged in age from 18 to 25, with a mean ($\pm$ standard deviation) of 19.4 $\pm$ 1.4 years.

Apparatus and Materials

Experimental chamber. The experimental sessions were conducted in a small subject room adjacent to the room housing the recording equipment. The room contained a cushion, reclinable lounge chair, a small shelf and a table. A square one-way window was mounted in the common wall. A polished, wooden board was placed across the arms of the chair during the RT-AV and RT-AP sessions to hold the reaction time and signal apparatus.

The recording room housed a Grass model 7D polygraph, an Arteriosonde BP monitoring device, a shock generator and electronic equipment for the presentation of signals for the reaction time tasks.

Physiological monitoring equipment. Heart rate in both raw and integrated form was recorded continuously by a Grass model 7P4F pre-amplifier and model 7D AF driver amplifiers as part of the Grass model 7D polygraph. Three Beckman biopotential regular electrodes transduced the EKG. The electrodes were filled with Beckman electrode paste and one was placed on the right side below the clavicle, another on the left bottom of the rib cage and the ground electrode was placed on the right bottom rib cage.

The Arteriosonde measured blood pressure. A small detector in the cuff was placed over the brachial artery pulse. The principle of operation was based on the Doppler effect. Systolic and diastolic pressure were registered on two separate mercury columns which held the last detected value.

Treatment of urine. A Fisher model 230 pH meter was used to determine urine pH. Concentrated HCl was added to the urine to bring it to a pH of between 1.5 to 2.0 units and served as a preservative. A pyrex #7060 10 ml pipette marked in .10 ml divisions was used to obtain a 10 ml aliquot of urine. This was stored in screw type plastic, nonreacting bottle with 200 ul of a glutathione, EGTA solution. The 200 ul delivered 18 mg EGTA and 12 mg of glutathione. This solution had a pH of between 6.0 to 7.4. The pH meter was calibrated with Fisher product standard buffer solutions.

Shocker. The shocker used in the RT-AV task was a Lafayette model #82426. It had a maximum output of 5 mA, with a voltage source of 2500 VAC. In order to meet safety requirements for human subjects an

additional isolation transformer (Triad model N48X) was placed in the subject output to conform to the diagram in Appendix II. The output meter was calibrated with known resistances and an ammeter. A single electrode was connected to the subject via an output in the rear panel. The concentric circle electrode allowed a maximum current density of 4 mA per cm^2.

Reaction time. The measurement of reaction times, delivery of signals and control of shock and reward signals were done with transistor, transistor logic (TTL). The components were housed in a small pyrex box situated in the recording room.

Procedure

In almost all cases the subject was given a reminder call the evening before their scheduled session. This call was meant to reassure the subject and to remind him that drinking adequate amounts of water was important to insure adequate hydration.

Upon arriving at the laboratory the subject was given a consent form (Appendix III) and briefly reminded about the nature of the experiment, if this was necessary. After signing the form, he was given a cup of water. Skin fold measurements and family history were taken along with information about exercise habits (Appendix IV). The subject was asked to sit quietly in the lounge chair. If he wished to read he was allowed to do so. He was encouraged to drink water.

After 25 to 30 minutes of rest the subject was asked to void completely and this urine was discarded. The time at this point was recorded and another 30 minute rest period was begun. At the end of this period the subject was asked to void and the volume of urine was

carefully measured. A 10 ml aliquot of acidified urine was labeled and stored as the baseline measurement. At this point the subject's skin was prepared for the EKG electrodes and BP cuff and the equipment put in place.

The subject was informed that a rest period would follow and that the experimenter would return to provide the necessary instructions before any task began. This and all remaining rest periods were 3 minutes long. A BP measurement was taken 30 seconds before the end of each rest period.

The subject was exposed to three different tasks, each separated by a 3 minute rest period. The order of the task presentation was determined by a Latin square so that there were three possible combinations: 1) MA, RT-AV, RT-AP; 2) RT-AP, MA, RT-AV; 3) RT-AV, RT-AP, MA. This insured that each task occurred first, second or third at least one time. The subjects were randomly assigned to the task orders such that equal filling occurred.

RT-AV. The subject was told that a rapid button push in response to a light signal was required to avoid a one second, 3.5 mA shock to the leg. He was told that a small red light would turn on at random intervals during this period. His task was to react as quickly as possible. If he improved upon his preceding time or approached his best he would avoid all shocks. If he was slower than his preceding time he might receive a shock, but it would come 10 seconds after the light reaction signal, not immediately. After all questions were answered, the electrode was placed on his leg. If this was the first reaction time task of the session, the subject was told that he would

receive three practice trials to acquaint him with the procedure. After the practice trials the subject was given a sample shock. The subject was warned when this would occur. Approximately one minute after this sample shock the experimenter signalled the start of the session. The subject received 13 trials. The inter-signal interval averaged 25 seconds, with a range of 20 to 30 seconds. The order of intervals was selected from a random mix of 20, 25 and 30 second intervals. The frequency of shocks was held to 2 per subject excluding the sample shock. No shocks were given during the first three trials, one occurred during the next four trials and one in the succeeding four. In all cases, shocks were given after those trials in which the subject failed to show improvement, from the previous trial.

RT-AP. The instructions and protocol were essentially the same as for the RT-AV. The major difference was that instead of a shock the display screen flashed ".25" 10 seconds after all criterion responses. The subject was told that this signal represented twenty-five cents and that the accumulated total would be paid to him after the experiment was over. If the RT-AP task was given before RT-AV, practice trials as described under RT-AV were given before the actual sessions began.

MA. This task consisted of five minutes of mental calculations. Continuous subtractions by 7 were followed by single problems of multiplication and subtraction. The subject was encouraged to perform as quickly as possible at two different points during the session with the words "quickly please."

After all sessions were completed, the last three minute rest period took place and the time was recorded. The electrodes were removed from the subject quietly and he was asked to remain seated. A questionnaire was given to the subject and one half hour after the end of the last task the final urine sample was obtained. This constituted the stress sample. The subject was paid the money he had earned and thanked for his participation.

Variables

Heart rate. The HRs for each minute of each rest, MA, RT-AV, and RT-AP conditions were quantified. This was done by counting the number of R waves occurring on 30 cm of physiograph paper. The speed of the polygraph was 5 mm per second, therefore, 30 cm equals one minute (distance ÷ rate = time).

Blood pressure. A systolic and diastolic reading was obtained at the beginning of the experiment and during the third minute of each rest period. A BP value was obtained after the second, fifth, eighth, eleventh and thirteenth trials of the reaction time tasks. This corresponded to the first, third, fifth, seventh and eighth minutes of the task. During the MA the reading was obtained during the first, third and fifth minute.

Heart rate reactivity. Those who showed a peak one minute heart rate change from baseline to the RT-AV condition of 30 or more were termed Reactors (R). Those who showed a peak one minute HR change to the RT-AV task of 10 bpm or less were termed Non-Reactors (NR). The baseline measurement for these calculations was the third minute of the first rest

period. Subjects falling between these extremes were not computed in the analysis of the data.

II. EXPERIMENT II: EXERCISE CHALLENGE

Subjects

Five R and five NR subjects volunteered for the follow-up exercise studies, after receiving a letter explaining the procedure (Appendix V). The subjects were free of any overt symptoms of CV disease. They had a mean age of 19 years, and received a payment of $4.00 per hour for their participation.

Apparatus

The procedures were carried out in the exercise laboratory located in the Health, Physical Education and Recreation Building. This laboratory contained a Quinton model 24-72 treadmill, capable of speeds from 0 to 25 mph and 0 to 40% changes in elevation.

Physiological Recording

Ventilation and gas exchange. Oxygen uptake and CO_2 output were measured by the open circuit method utilizing meteorological balloons and a Daniel's valve. A Beckman E-2 O_2 analyzer and Beckman LB1 CO_2 analyzer provided electronic analysis of expired gases. Composition of calibration gases for these analyzers were determined by the Scholander microchemical technique.

Inspired minute ventilation was measured by a Parkinson-Cowan CD-4 dry gas meter and recorded with a Narco Biosystems PMP-4A recorder. A 120 liter Tissot gasometer provided the standard against which the gas

meter was calibrated. Relative humidity, temperature and barometric pressure were recorded before each test. Inspired ventilation was expressed in terms of standard temperature, pressure, dry (STPD). Oxygen uptake was calculated using the Haldane transformation.

Heart rate. This was recorded with a Grass model 7B polygraph. A raw EKG was obtained by a Grass model 7P3B preamplifier and model 7DAD driver amplifier. Electrodes and placement configuration similar to that used in the psychological experiments were used to transduce the HR during exercise sessions.

Blood pressure. A sphygmomanometer and stethoscope were used to detect blood pressure. The detection of the first Korotkoff sound was used as systolic pressure, and was read from a dial which was calibrated with a mercury column (the accurate detection of diastolic pressure is not possible with non invasive techniques during treadmill exercise).

Perceived exertion. A subjective estimate of the severity of the workload was obtained with a rating scale (Borg, 1970). This scale is found in Appendix VI.

Procedure

Maximal oxygen uptake test. Either the standard or Super Standard Balke work capacity treadmill test was used to determine the max $\dot{V}O_2$ of each subject. The test protocols are found in Appendices VII and VIII. The subjects were shown the equipment and given a consent form Following this, the subject's skin was prepared for the EKG electrodes by vigorous rubbing with acetone. After the application of the

electrodes a 10 minute rest period began while the individual was sitting in a chair on the treadmill. An adaptation period followed the rest period. During this period the subject walked on the treadmill until he was comfortable with it. A two minute recovery period preceded the actual test.

The test consisted of walking on the treadmill at 80 m per minute (Standard) or 100 m per minute (Super). The first stage was on a level plane. Every two minutes, or one minute for Super, the grade was increased 2.5% which increased the oxygen demand by 3.5 ml per Kg bwt per minute. At the beginning of the second minute of each level the degree of perceived exertion was elicited from the subject. The treadmill was raised until the point of voluntary failure. If the subject elected to proceed to the next higher level he was encouraged to finish out at least one minute. Gas collection began when the subject reported the work as being "Hard" (number 15 or 16 on the RPE). Gas samples over one minute intervals were collected continuously from that point, and the max $\dot{V}O_2$ was taken as the highest value reached. Heart rate was recorded continuously during the test.

Progressive, submaximal exercise test. On the basis of the individual's max $\dot{V}O_2$ capacity, workloads approximating 30%, 50%, 70% and 90% of this oxygen requirement were determined. These formulas assume an oxygen requirement of .1 ml O_2 per Kg bwt minute per meter minutes during horizontal walking at speeds between 50 and 100 m per minute. The vertical work component is calculated by assuming a requirement of 1.8 ml O_2 per Kg bwt minute of work. The oxygen requirement

for basal processes is included by adding 3.5 ml O_2 per Kg per minute to the total calculated from the above.

The progressive test was given one week after the max test in most cases and within two weeks in all cases. The subject was prepared for this test in the same manner as was done for the maximal work test. In addition an inflatable BP cuff was secured to the left arm with surgical tape. After a 10 minute rest period the subject began walking at the grade calculated to require 30% of his aerobic capacity. Each exercise load was maintained for 5 minutes and then without a break the treadmill was raised to produce the next level of intensity until all four loads were completed. The total work time was twenty minutes.

The RPE was taken between minutes 2.5 and 3. Blood pressure was taken after the third minute and a one minute gas collection took place during the last minute (fifth minute).

After the test the subject was paid for his time and thanked for his participation.

Variables

Heart rate. The HRs for each minute of the test were quantified and the average value for the last three minutes of the load was considered the HR for that particular percentage of maximum capacity.

Blood pressure. During the fourth minute of the test a systolic blood pressure value was obtained. The detection of the first Kortokoff sound was the criterion used.

Oxygen uptake. A one minute gas collection was obtained during the last minute of the load (i.e., fifth minute).

RPE. After two and one half minutes of the test an RPE was taken.

III. CALCULATIONS AND STATISTICS

Oxygen uptake for the maximum performance test and progressive work tests was calculated using the Haldane equation:

$$\dot{V}O_2 = \dot{V}_I \times F_IO_2 - \frac{F_EO_2 - F_IN_2}{F_EN_2} ;$$

where $\dot{V}O_2$ = rate of oxygen uptake per minute

$\dot{V}_I$ = rate of inspired ventilation per minute

F_IO_2 = fraction of oxygen in the inspired air

F_EO_2 = fraction of oxygen in the expired air

F_IN_2 = fraction of nitrogen in the inspired air

F_EN_2 = fraction of nitrogen in the expired air.

A comparison of R and NR groups on behavioral tasks, in terms of percent max $\dot{V}O_2$ was done with individual regression lines.

A regression line of percent max $\dot{V}O_2$ and double product was obtained on each subject in the exercise experiments. The double product which occurred during the psychological tasks could then be converted to a percent of max $\dot{V}O_2$ score. This score would represent the percent of max $\dot{V}O_2$ which was associated with the CV response (i.e., double product) that occured during exercise.

The model regression equation is: $y = mx + b$

where, y = double product

m = slope

x = percent max $\dot{V}O_2$

b = the intercept.

In the analysis involved for this comparison, the double products in the psychological experiments are known, therefore x (percent of max $\dot{V}O_2$) must be solved. This was done as follows:

$$x = \frac{y - b}{m}$$

The analysis of variance used for evaluation of psychological challenge was a two factor mixed design with repeated measures on one factor. A posteriori analysis involved the use of multiple comparison t tests. Student's t test and comparison of regression lines were used to evaluate the difference in exercise response between R and NR groups. The F* statistic was used to test the difference between the R and NR regression lines (Neter and Wasserman, 1974). Statistical analysis was confined to the research questions outlined in the Statement of Rationale and Purpose in Chapter II.

IV. CATECHOLAMINES ASSAY PROCEDURE

The radioenzymatic procedure described here is the result of adaptations of the procedures used by UpJohn Diagnostics and Painter (1976), and is presented here in a "cookbook" form.

Principle of operation. The E and NE of the plasma are converted to ^{3}H metanephrine and ^{3}H normetanephrine respectively during incubation with catechol-o-methyl-transferase (COMT) and ^{3}H s-adensyl methionine (^{3}H-SAM). The corresponding methanephrines are extracted from other organic products with a series of toluene-isoamyl alcohol washes. Metanephrine and normetanephrine are separated with thin layer chromatography (TLC). They are eluted from the TLC silica gel and

oxidized to vanillin with sodium periodate. This is done because vanillin is more soluble in toluene, the organic solvent in which the radioactivity is counted, than are the methylated CATS. The output of a liquid scintillation counter is proportional to the ^{3}H CATS.

Reagents. 1. Buffer. To 10 ml of water (distilled) add: 6.05 gm of THAM; 1.9 gm EGTA·Na_2; 3.05 gm $MgCl_2 \cdot 6H_2O$. Adjust pH to 8.3 with concentrated HCl or NaOH. The initial pH will be close to this. Bring volume to 25.0 ml with water.

2. .1 molar Glutathione. Add 30.7 mg to a small test tube and add 1 ml of water. Vortex lightly, if necessary. Make prior to using and keep in ice bath.

3. Stopping solution. A 1.0 M boric acid and .2 M EDTA·Na_2 buffer is prepared by adding 1.55 gm boric acid and .93 gm EDTA·$2H_2O$·Na_2 to 20 ml of water. Adjust pH to 11.1 and bring to 25 ml volume with water. To 5 ml of this borate EDTA stopping solution add 4.67 mg of metanephrine and 4.39 mg of normetanephrine prior to use. A 50 ul aliquot will then provide .2 umoles of each carrier.

4. Toluene-isoamyl alcohol (3:2). Combine 300 ml of toluene (Fisher #T-324) and 200 ml of isoamyl alcohol (Fisher #A-393).

5. .1 N Acetic acid. 2.95 ml of glacial acetic acid to 500 ml.

6. 4% w/v $NaIO_4$. 1 gm up to 25 ml of water--prepare fresh daily.

7. 10% Glycerol V/V. 1 ml up to 10 ml of water.

8. .05 M NH_4OH. .33 ml up to 100 ml of water.

9. 1.0 N HCl 8.3 ml of concentrated HCl up to 100 ml;

   .01 N HCl 1.0 ml of 1.0 N HCl to 100 ml;

   .001 N HCl 1.0 ml of 1 N HCl to 1000 ml.

10. 100 pg Standards. Unstable, prepare only before use.

    a. 100 ul of 50 ug/ml E stock and 100 ul of 50 ug/ml are brought to a volume of 50 ml with .01 HCl.

    b. Bring 10 ml of this solution to 100 ml with .001 HCl

    c. 10 ul of this solution equals 100 pg of E and 100 pg of NE

11. Enzyme. From Axelrod and Tomcheck (1958) and Painter (1976).

Procedure

1. Turn on water bath and set to 37° C.

2. Prepare two sets of test tubes (13 x 100 mm) in triplicate. The first set is for reaction and incubation and should be kept in ice bath, the second is for extraction.

3. Remove enzyme, samples, buffer, ^{3}H SAM and stopping solution from freezer. Thaw and store in ice bath prepared from ice, water and NaCl.

4. Use a conical centrifuge tube that has been in ice bath and add in the following order in amounts sufficient for assay plus 2 (see below): Buffer solution, Glutathione and ^{3}H SAM; vortex lightly; COMT enzyme solution; vortex lightly; keep in ice.

Assay	x 1	x 20	x 50	x 100
Buffer	5 ul	100 ul	250 ul	500 ul
Glutathione	1 ul	20 ul	50 ul	100 ul
^{3}H SAM	10 ul	200 ul	500 ul	1,000 ul
Enzyme	24 ul	480 ul	1.2 ml	2.4 ml
Total Value	40 ul	800 ul	1.95 ml	4.0 ml

5. Incubation mixture. Use a glass micropipette for accuracy in pipetting. The first set of test tubes will receive the following:

a. Blanks

1) 50 ul of sample vehicle (i.e., H_2O that is mixed with sample tubes)

2) 40 ul of enzyme cocktail (#4)

3) 10 ul of .001 N HCl

b. Standards (Internal)

1) 50 ul of plasma

2) 40 ul of enzyme cocktail

3) 10 ul of 100 pg standard

c. Plasma Samples

1) 50 ul of plasma

2) 40 ul of enzyme cocktail

3) 10 ul of .001 HCl

d. Vortex tubes lightly and centrifuge briefly (30 seconds).

6. Incubation. One hour at 37° C in an oscillating water bath.

7. In second set of test tubes, add 100 ul of .1 N acetic acid. An automatic pipette is adequate.

8. Stop incubation by placing reaction tubes in an ice bath and adding 50 ul of Borate-EDTA-Metanephrine buffer solution (vortex well).

9. Extraction.

a. Add 2 ml of (3:2) toluene-isoamyl alcohol to incubation tubes. Vortex vigorously. Centrifuge 2 minutes at 800 x g.

b. *Quick freeze: by submerging tube to level of aqueous phase for 15 seconds. Use a timer.

c. Blot outside of tube. Decant the organic phase into its corresponding tube with .1 N acetic acid (discard aqueous phase).

d. Vortex and centrifuge (solution should be clear).

e. *Quick freeze. Aspirate off organic phase without touching suction tube to the frozen pellet (tilt tube).

f. Thaw the aqueous phase. Add 1 ml of 3:2 toluene-isoamyl alcohol. Vortex vigorously and centrifuge. Quick freeze, aspirate and discard as in step 5.

10. TLC.

a. Add 100 to 150 ul of absolute (or 95%) ethanol to the thawed acetic acid from step 9f. Vortex briefly and centrifuge at #4 for 1 minute (add ethanol only for the number you are about to spot to avoid evaporation.

b. Pull some ethanol into spotting syringes and gently expell so that needle still contains ethanol. This will eliminate air bubbles.

c. Slowly pull acetic acid-ethanol solution into syringe. Do not pull air into syringe.

d. Turn on dryer and spotter (Caution: to insure small spots allow silica gel plate to warm-up thoroughly).

e. Place dryer approximately 3 cm from plates and set temperature control between 200 to 300.

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*Ice bath: Place dry ice in a beaker with Methyl alcohol, that is surrounded by dry ice.

f. Position syringes so that tips touch TLC plates. Set plunger speed to slowest possible speed.

g. Prepare 44 ml of developing solution (6:2:3) in a 50 ml graduate.

1) 24 ml tertiary amyl alcohol

2) 8 ml benzene

3) 12 ml methylamine

4) Mix gently (solution should be clear).

h. Put developing solution in developing tank immediately before use. Carefully place plates in tank. Develop for 50 minutes or until solvent front has moved completely up the plate.

i. Dry plates and visualize spots under UV light. Utilizing a scalpel, carefully outline the spots.

j. Scrape spots into acid washed scintillation vials (use a scalpel). The metanephrines are the top zone and normetanephrines are the bottom zone.

11. Oxidation.

a. Add 1 ml of .05 M NH_4OH to vials. Vortex vigorously.

b. Line up vials and add 50 ul of 4% periodate solution at time intervals. Vortex vigorously.

c. Stop reaction by adding 50 ul of 10% glycerol solution, five minutes after step b. Maintain order and timing of step b

d. Add 1 ml of .1 M acetic acid to each vial and vortex.

e. Add 10 ml of toluene-Liquifluour (1000:50 v/v) to each scintillation vial. Shake by hand vigorously (for about 10 seconds).

f. Count each vial for a minimum of 10 minutes.

CHAPTER IV

RESULTS

A total of thirty-four male undergraduates were exposed to the psychological tasks. The results in this chapter are focused only on those fourteen subjects that met the criteria for either the reactive group (N=8) or the non-reactive group (N=6). The results from the remaining subjects were ignored unless it served to illustrate a point more strongly than the R and NR groups alone. The results are discussed within two major divisions: psychological challenge and exercise challenge. Within each of these divisions the R and NR groups are compared on each of the physiological and behavioral variables that were measured. Under psychological challenge this includes RT, HR, SBP, DBP and urinary excretion of NE and E, and in exercise, HR, SBP, $\dot{V}O_2$ and RPE response.

I. PSYCHOLOGICAL CHALLENGE

Reaction time. Each subject received thirteen trials under each of the RT tasks. A mean RT for each subject, for each condition, was computed and used in the comparison of the R and NR groups. The mean RTs in milliseconds for each group under each condition are shown in Table 4.1. There was no statistically significant difference in RT between groups, $F(1,12) = 1.38$, $p > .05$, or conditions, $F(1,12) = 1$, $p > .05$. There was no significant interaction, $F(1,12) = 1.84$, $p > .05$.

TABLE 4.1

MEAN REACTION TIMES (± S.D.) FOR THE R AND NR GROUPS DURING RT-AV AND RT-AP

	RT-AV	RT-AP
R	253.3 ± 31	261.8 ± 29
NR	284.6 ± 41	269.0 ± 39

Heart rate. Since HR in response to the RT-AV condition was used to assign the subjects into R and NR groups, these data were not subjected to statistical analysis. The HRs achieved and the change in HR from rest during each minute of the RT-AV task are shown in Tables 4.2 and 4.3, respectively. A clear difference in response between the two groups during this task can be seen. A difference is also evident during the rest period, $t = 3.37$, 12 df, $p < .05$.

TABLE 4.2

MEAN HEART RATE AT REST AND DURING EACH MINUTE OF RT-AV IN THE R AND NR SUBJECTS

	Rest	1	2	3	4	5	6	7
R	66	102	102	100	105	106	102	101
NR	56	61	61	61	60	61	61	61

TABLE 4.3

MEAN HR CHANGE FROM REST IN R
AND NR GROUPS DURING RT-AV IN BPM

Min.	1	2	3	4	5	6	7
R	36	35	34	38	39	36	35
NR	5	4	5	4	5	5	4

The HR change provoked by the RT-AP task was less dramatic than that for RT-AV, but a difference in response between the two groups was still apparent and is shown in Figure 4.1. The greater change in HR shown by the R group illustrated in Figure 4.1 was significant, $F(1,12) = 5.76$, $p < .05$. A significant effect of trials (or minutes) is also evident, $F(6,72) = 2.36$, $p < .05$.

A similar pattern was seen for the MA condition which is shown in Figure 4.2, but the difference is more apparent than real since simple analysis of variance failed to indicate significance, $F(1,12) = 3.01$, $p > .05$. However, significant correlations between the peak HR change (Δ HR) in the RT-AV task with the peak Δ HR in RT-AP and peak HR in MA indicated there was some relationship between reactivity in RT-AV and reactivity in the others. The correlations (Pearson r) are shown in Table 4.4 for R and NR individuals. (Correlations between these measures for all 32 subjects, though lower, were also significant).

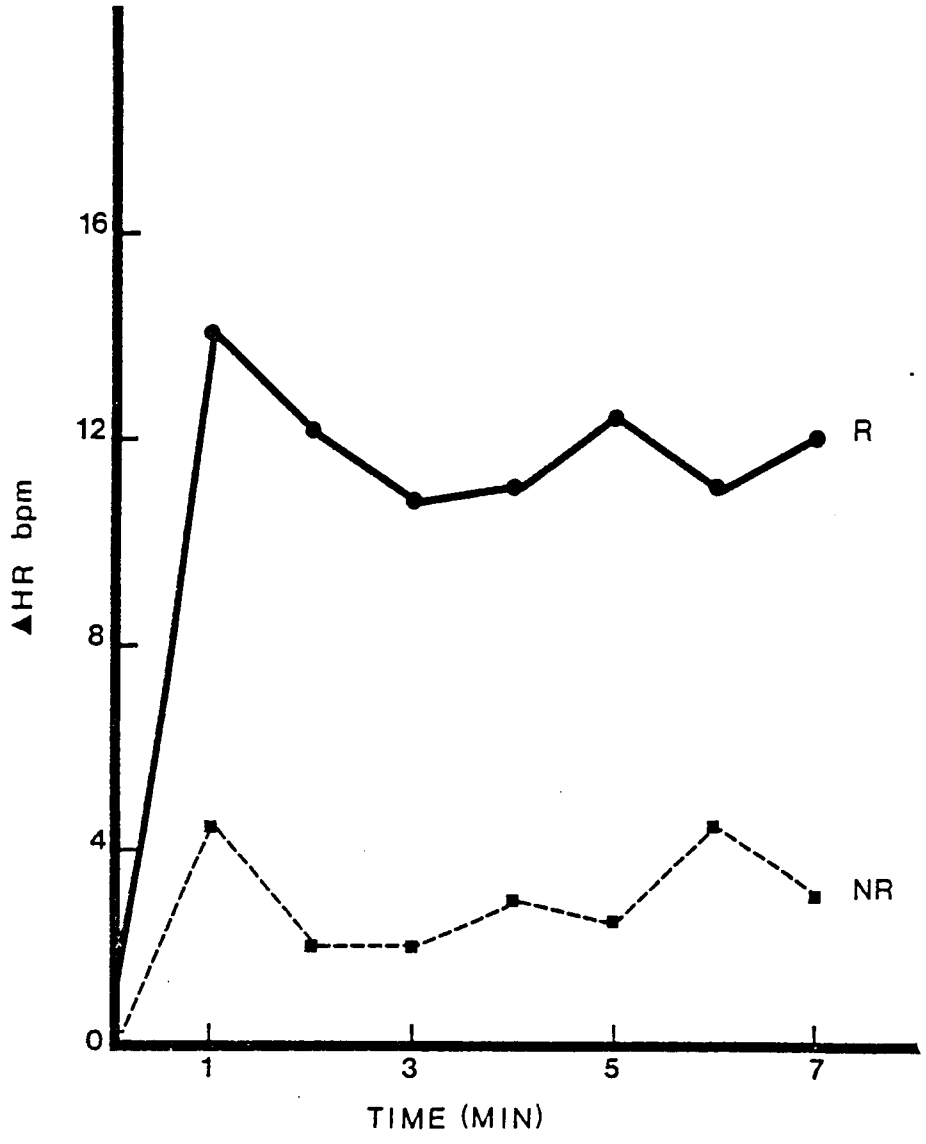


Figure 4.1. Change in heart rate at each minute of the R T-AP condition in the R and NR groups.

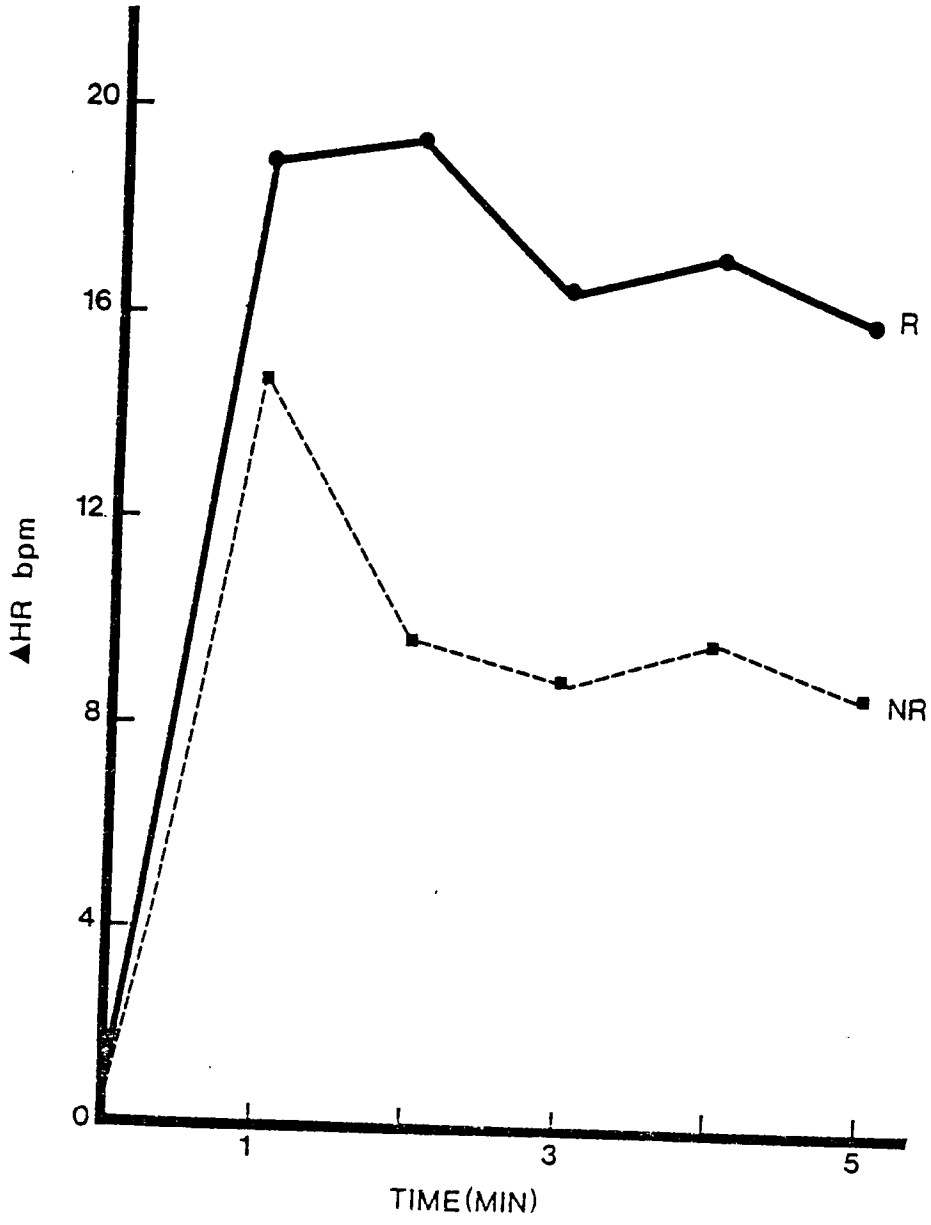


Figure 4.2. Change in heart rate at each minute of the MA condition in the R and NR groups.

TABLE 4.4

CORRELATIONS BETWEEN PEAK Δ HR IN RT-AV AND PEAK Δ HR IN MA AND PEAK Δ HR IN RT-AP FOR R AND NR INDIVIDUALS

	MA	RT-AP
RT-AV	$r = .533$	$r = .733$
	$p < .05$	$p < .05$

Systolic blood pressure. The average SBPs during rest one, RT-AV, RT-AP and MA for the R and NR groups are shown in Figure 4.3. These averages were derived by collapsing the minute values within each condition, consequently each subject had one value for each condition. The analysis of variance indicated a significant effect of groups, $F(1,12) = 7.94$, $p < .05$; conditions, $F(3,36) = 79.94$, $p < .05$; and groups by conditions interaction, $F(3,36) = 12.29$, $p < .05$. Tests of simple main effects for each group showed that the R group only demonstrated an effect of the conditions. Post hoc analysis of the simple main effects indicated that SBP in RT-AV, RT-AP and MA was significantly higher than rest for the R group.

Further tests of simple main effects were done by comparing R and NR groups at each condition with t-tests. These revealed that no difference existed at rest one, but a difference appeared at the RT-AV condition. Only one tailed t-tests showed significant differences between R and NR subjects at the RT-AP and MA conditions.

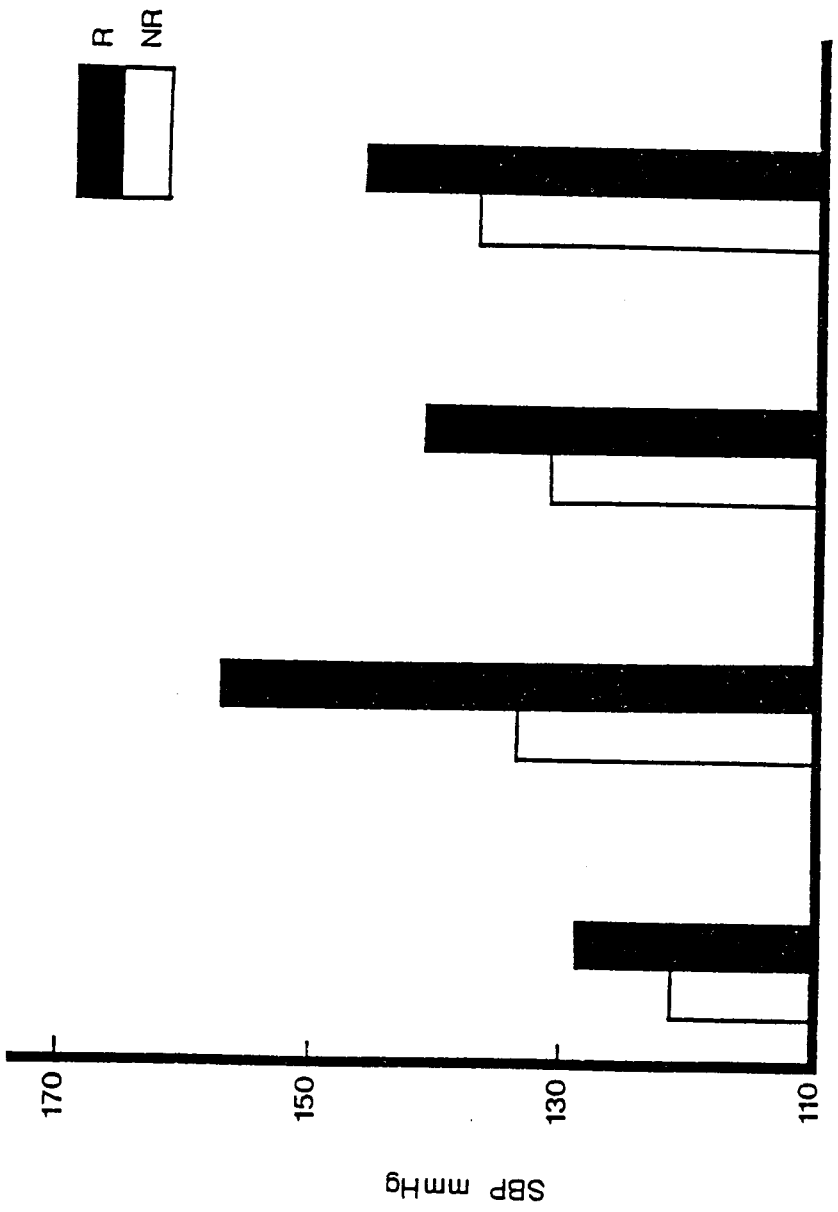


Figure 4.3. Mean systolic blood pressure for each experimental condition and the first rest period in the R and NR groups.

The change in SBP from rest one in RT-AV, RT-AP and MA in each of the groups was analyzed. The change scores for each minute were collapsed within each condition and subjected to analysis of variance. Significant effects for groups, $F(1,12) = 5.10$, $p < .05$; conditions, $F(2,24) = 33.4$, $p < .05$; and groups by conditions interaction, $F(2,24) = 19.84$, $p < .05$ were found. Analysis of simple main effects revealed that the change in SBP across conditions was different only in the R group. The Post Hoc analysis found that the change in SBP was significantly higher in the RT-AV condition than in either RT-AP or MA. The changes in SBP in MA and RT-AP were not significantly different from each other. Comparisons of the R and NR groups at each condition with t-tests indicated that the difference was confined to the RT-AV task. The contrast in the response of these two groups across minutes of this task is shown in Figure 4.4.

Diastolic blood pressure. The average DBP for each group at each condition is shown in Figure 4.5. The data reduction and analysis were similar to that performed on SBP with the exception that the rest period occurring at the termination of the experimental session was included in the analysis of variance. This was done in an effort to obtain a reliable rest measurement. A pattern similar to the other CV variables is obvious in Figure 4.5, but the statistical analysis showed that no significant difference between R and NR groups on DBP existed, $F(1,12) = 4.28$, $p > .05$. A significant effect of conditions was found, $F(4,48) = 3.26$, $p < .05$. Post hoc analysis indicated that DBP in the last rest period was significantly lower than in the MA condition.

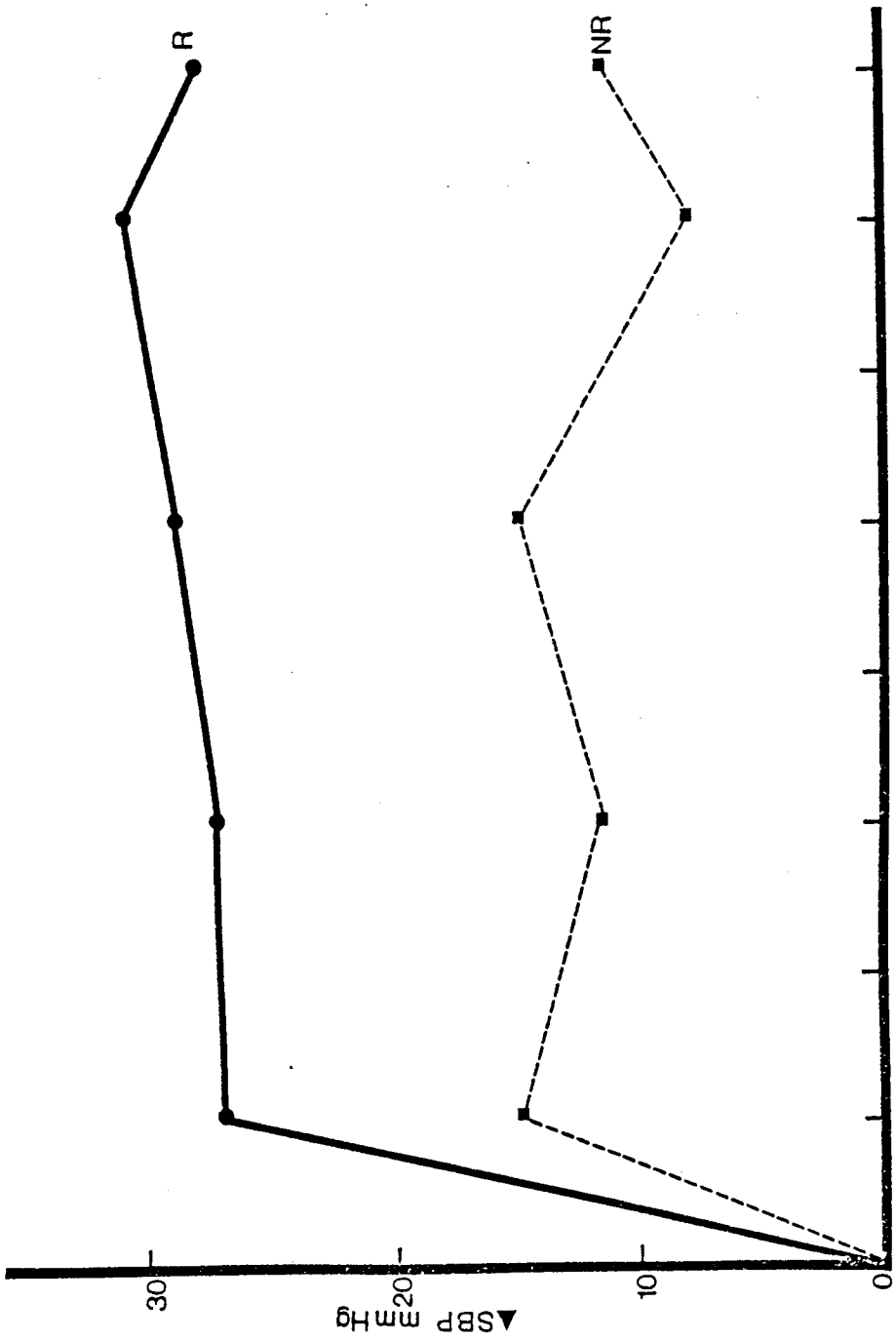


Figure 4.4. Change in systolic blood pressure at each minute of the RT-AV condition in the R and NR groups.

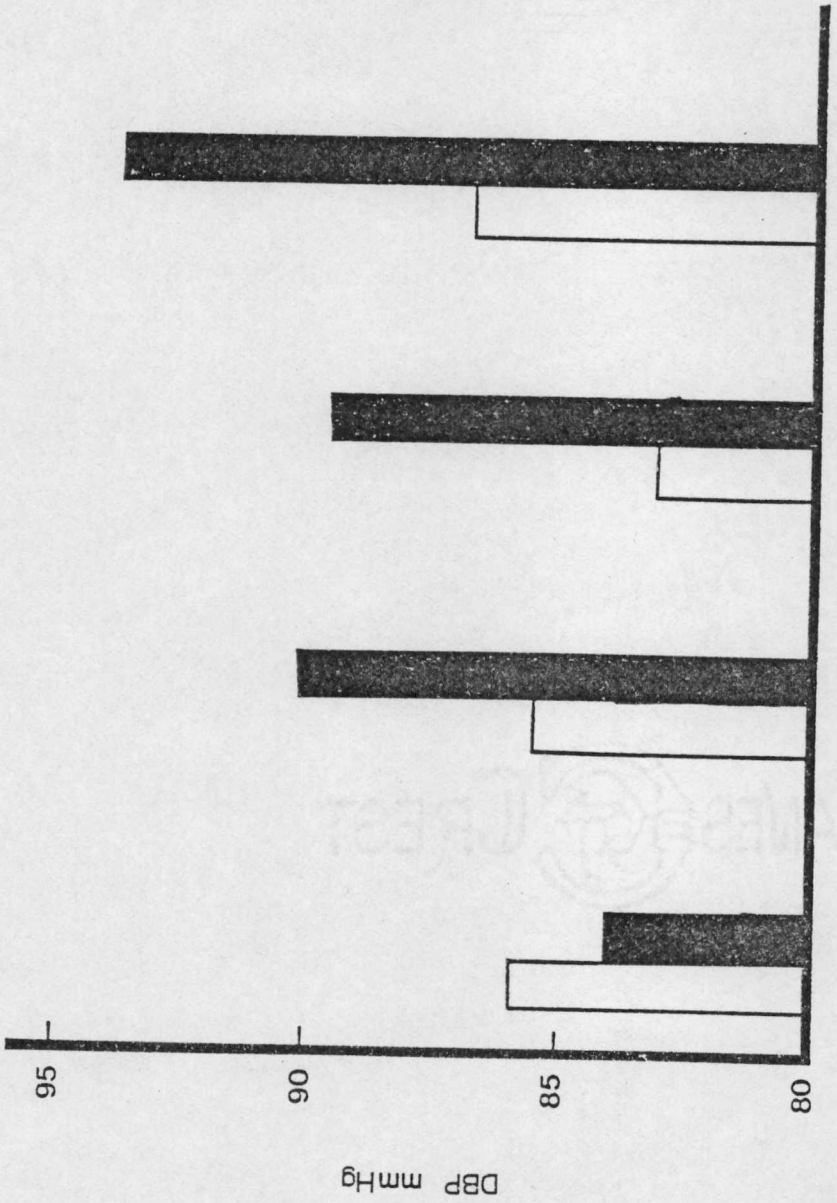


Figure 4.5. Mean diastolic blood pressure for each experimental condition and the first rest period in the R and NR groups.

Catecholamine excretion. The excretion of E and NE in ng per minute for each group during baseline and stress conditions is shown in Figure 4.6. The analysis of variance revealed that only E reflected the change from baseline conditions to stress, $F(1,12) = 10.37$, $p < .05$. The tendency of the R group to show higher rates of E and NE excretion than the NR group during baseline and stress was not supported statistically, $F(1,12) = 2.46$, $p > .05$ for E, and, $F(1,12) = 1.0$, $p > .05$, for NE.

Baseline measurements of E were related to a number of HR measurements. The correlations (Pearson r) for these calculations are shown in Table 4.5. Baseline values for NE were significantly related to resting SBP, $r = .552$, $p < .05$, but not with resting HR, $r = .481$, $p > .05$. Because NE failed to show a significant change with the stress, further analysis of this variable was not carried out.

TABLE 4.5

CORRELATIONS BETWEEN BASELINE EXCRETION OF E AND HR MEASUREMENTS, WITH 12 df

Rest HR	$r = .627$	$p < .05$
$\bar{X}$ ΔHR in MA	$r = .603$	$p < .05$
$\bar{X}$ ΔHR in RT-AV	$r = .608$	$p < .05$
$\bar{X}$ ΔHR in RT-AP	$r = .565$	$p < .05$

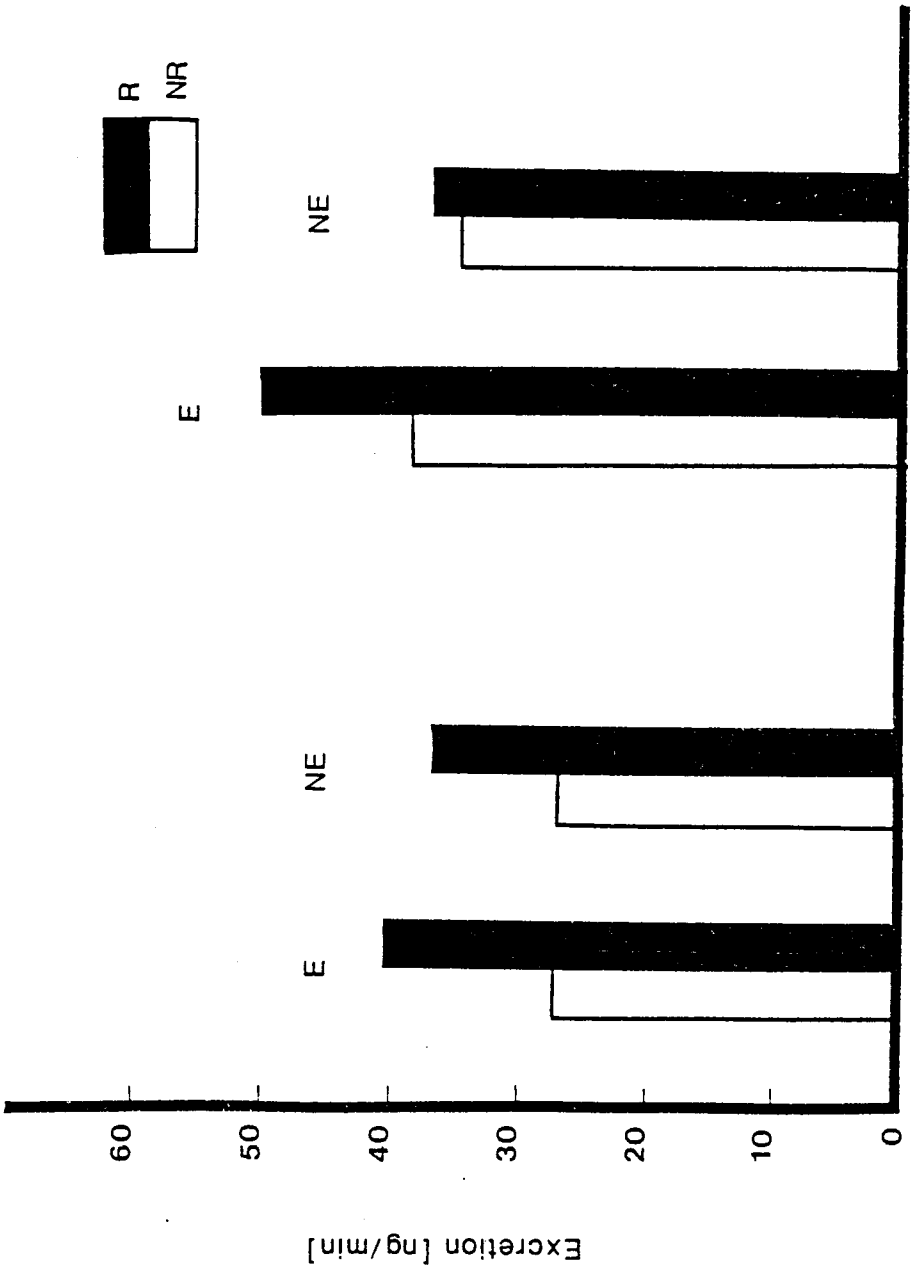


Figure 4.6. Epinephrine and norepinephrine excretion expressed as ng per minute during baseline and after stress in the R and NR groups.

II. EXERCISE CHALLENGE

The data reported in this section are from the five R and five NR subjects who took part in the exercise studies. The data, for the max $\dot{V}O_2$ test and progressive test, are presented separately.

Maximum Oxygen Uptake Test

A number of physiological characteristics of the subjects were obtained during this test. The individual values for max $\dot{V}O_2$, max HR and bodyweight are found in Table 4.6. A summary of the findings for the R and NR groups and their statistical evaluation are shown in Table 4.7. The max $\dot{V}O_2$ is expressed in terms of both liters per minute and milliliters per Kg per minute. No statistically significant difference between the groups on these measurements was seen. A tendency for the R group to be heavier accounts for the slightly higher $\dot{V}O_2$ in liters per minute and lower $\dot{V}O_2$ in ml per Kg per minute. The difference in maximum HR was not significant.

Progressive Exercise Test

The mean HR, SBP, Ventilation (V_I), $\dot{V}O_2$ and RPE for the R and NR groups seen at workloads that approximated 30, 50, 70 and 90 percent of the individual's max $\dot{V}O_2$ are shown in Table 4.8. The similarity of the oxygen requirement, RPE and oxygen pulse elicited for both groups are striking. However, the NR group shows a consistent trend toward lower HR and SBP for work requiring approximately the same relative $\dot{V}O_2$. There is a tendency for V_I to be higher in the NR group also. Since the work requirement that was calculated for each subject

TABLE 4.6

INDIVIDUAL DESCRIPTIVE DATA ON R AND NR SUBJECTS

Reactives

S	bwt (Kg)	max $\dot{V}O_2$ (l/min)	max $\dot{V}O_2$ (ml/Kg)/min	max HR
1	82.9	3.41	41.1	204
2	77.0	3.51	45.6	188
3	72.3	3.97	54.9	202
4	91.8	4.38	47.7	190
5	76.9	3.44	44.8	188

Non Reactives

S	bwt (Kg)	max $\dot{V}O_2$ (l/min)	max $\dot{V}O_2$ (ml/Kg)/min	max HR
1	72.5	3.46	47.7	184
2	76.9	3.81	49.5	184
3	88.3	4.30	48.7	180
4	64.0	3.29	51.5	204
5	67.9	3.13	46.1	188

TABLE 4.7

t-TESTS FOR VARIOUS PHYSICAL CHARACTERISTICS OF THE R AND NR SUBJECTS

	R		NR				
	$\bar{X}$	s.d.	$\bar{X}$	s.d.	t	df	p
max $\dot{V}O_2$ (l/min)	3.74	.422	3.59	.466	.511	8	ns
max $\dot{V}O_2$ (ml/Kg)	46.8	5.1	48.7	2.0	.765	8	ns
max HR (bpm)	194.0	7.5	189.0	9.38	1.16	8	ns
max V_I (l/min)	101.0	9.0	112.3	18.1	1.24	8	ns
bwt (Kg)	80.1	7.5	73.9	9.38	1.16	8	ns

may have demanded more or less than the target levels (i.e., 30, 50, 70 or 90% of max $\dot{V}O_2$) statistical evaluation of the data involved the comparison of the regression lines for each group. Table 4.9 contains the regression equation and Pearson r for each pair of variables that was analyzed.

Heart Rate. Figure 4.7 shows the regression of HR against the percent of max $\dot{V}O_2$ for each group. The line of best fit for each group was calculated from twenty data points (i.e., five subjects x four loads). A close relationship existed between HR and percent max $\dot{V}O_2$. The correlation (r) between these two measurements was .967 and .969 in the R and NR groups respectively. The analysis indicated that the two regression lines were significantly different

TABLE 4.8

A SUMMARY OF SELECTED PHYSIOLOGICAL RESPONSES DURING EXERCISE AT VARIOUS PERCENTAGES OF MAX $\dot{V}O_2$ FOR R AND NR GROUPS

% max $\dot{V}O_2$		30%	50%	70%	90%	max
HR	NR	96±6	119±11	150±11	174±7	189±9
	R	105±12	130±18	158±15	182±9	194±8
$\dot{V}O_2$	NR	1.10±.12	1.79±.20	2.53±.33	3.14±.45	3.59±.46
	R	1.22±.15	1.87±.25	2.62±.32	3.27±.39	3.74±.42
V_I	NR	23.2±2.2	38.7±5.6	61.7±12.1	90.0±15.1	112.3±18.1
	R	23.2±4.4	37.9±7.5	60.0±12.3	83.2±15.3	101.0±9.0
SBP	NR	127.0±10.3	138.0±6.0	159.0±12.9	169.4±11.6	---
	R	135.8±11.1	155.2±10.0	166.6±10.2	183.8±10.5	---
RPE	NR	6.4±.5	9.8±.8	13.4±1.6	15.8±1.3	---
	R	7.2±.8	10.0±1.2	13.6±.9	17.0±1.5	---
O_2 Pulse	NR	11.6±1.7	15.3±2.6	17.0±2.9	18.2±3.1	19.2±3.2
	R	11.6±1.3	14.5±2.0	16.6±1.7	18.1±2.1	19.3±2.4

(Table 4.9). A higher HR for the same relative workload was found in the R group, $F(2,36) = 5.7$, $p < .05$. Analysis of the slopes failed to detect a significant difference. Consequently the rise in HR in both groups is similar. In other words, the R group does

TABLE 4.9

THE REGRESSION EQUATIONS AND CORRELATIONS FOR THE R AND NR GROUPS ON EACH PAIR OF MEASUREMENTS

Variables X	Y	R	NR	p <
% max $\dot{V}O_2$	HR	y=1.438x + 57.16 r = .967	y=1.392x + 51.23 r = .969	.05
% max $\dot{V}O_2$	SBP	y=.807x + 111.68 r = .859	y=.755x + 103.14 r = .844	.05
% max $\dot{V}O_2$	HR x SBP	y=346.04x + 2739.73 r = .961	y=306.92x + 2042.67 r = .980	.05
% max $\dot{V}O_2$	RPE	y=.171x + 1.62 r = .941	y=.167x + 1.32 r = .967	ns
% max $\dot{V}O_2$	O_2 Pulse	y=.108x + 8.67 r = .784	y=111x + 8.88 r = .695	ns
% max $\dot{V}O_2$	V_I	y=1.13x - 17.10 r = .967	y=1.20x - 18.24 r = .952	.05
Load	HR	y=3.88x + 101.50 r = .847	y=4.20x + 85.11 r = .950	.05
HR	RPE	y=.109x - 3.76 r = .892	y=.116x - 4.34 r = .968	ns

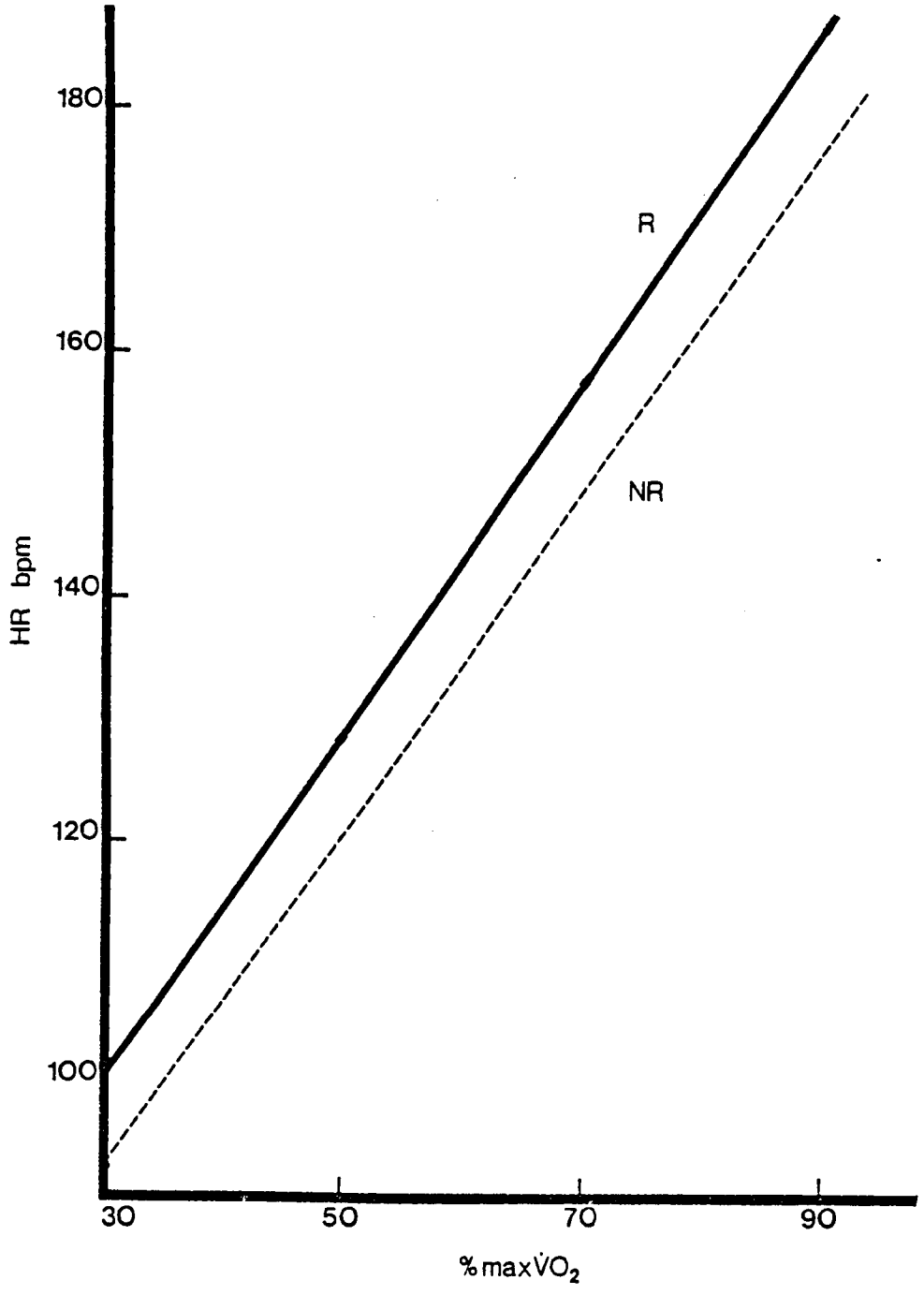


Figure 4.7. The regression lines of HR against percent of maximum oxygen uptake capacity for the R and NR groups.

not show an increased reactivity, but only maintains a consistently higher HR.

The HR response to the absolute workload in the R group was compared to the response in the NR group through analysis of the regression lines for these two variables (Table 4.9). The R group was found to have a regression line significantly higher than the NR group, $F(2,36) = 4.06$, $p < .05$.

Systolic Blood Pressure. A rise in SBP occurs with each increase in workload in both groups (Table 4.8). A comparison of the regression lines for SBP with percent max $\dot{V}O_2$ shows a significant difference (Table 4.9). The difference in slopes between the lines is within the 95% confidence limits; consequently, the difference is in the elevation. The R group shows a higher SBP with the same relative percent of max $\dot{V}O_2$.

An index of myocardial oxygen consumption is the product of SBP and HR. Regressions of this variable with percent max $\dot{V}O_2$ in the two groups are also included in Table 4.9. Figure 4.8 shows the difference between the two groups on double product. The statistical analysis indicates the difference depicted is real, $F(2,36) = 14.7$, $p < .05$.

Stroke Volume. The oxygen pulse can be used as an estimate of the SV. This variable is simply the absolute $\dot{V}O_2$ divided by the HR at each load and is expressed in ml of oxygen per beat. There was no difference between the R and NR regression lines when this

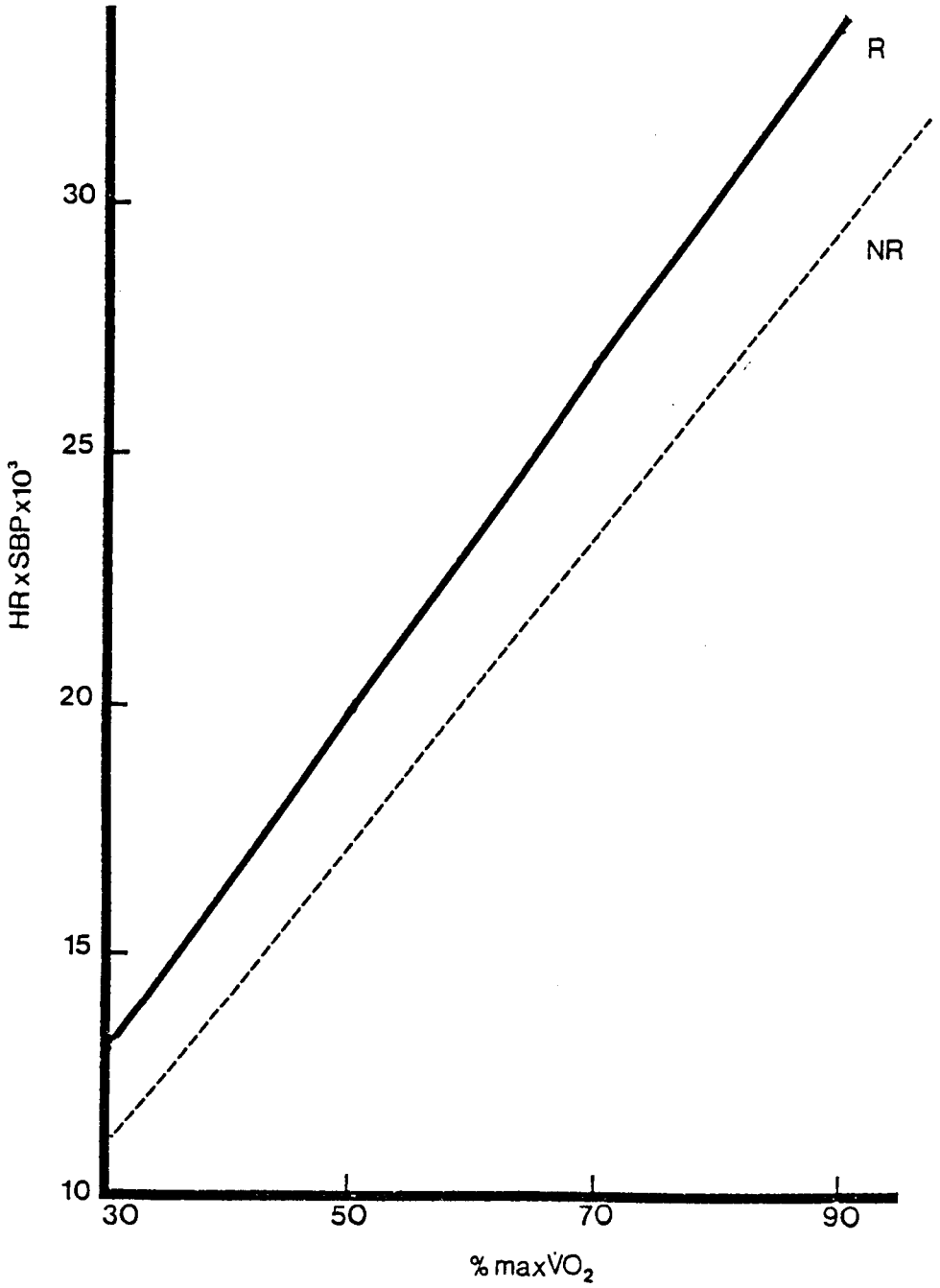


Figure 4.8. Regression lines of double product against percent of maximum oxygen uptake capacity for the R and NR groups.

variable was expressed as a function of percent max $\dot{V}O_2$, $F(2,36) = .3$, $p > .05$.

Inspired Ventilation (V_I). The regression of V_I on percent max $\dot{V}O_2$ shows a trend for the NR group to ventilate slightly more than the NR group. The regression line for the NR group is significantly higher than the R group $F(2,36) = 11.75$, $p < .05$ (Table 4.9).

Rating of Perceived Exertion. The RPE response shows a reliable increase across workloads (Table 4.8). The R and NR groups did not differ in their rating of the workload. The regression of RPE on percent of max $\dot{V}O_2$ was essentially the same for both groups, $F(2,36) = 1.01$, $p > .05$.

The RPE value was also related to the exercise HR. The regression line of RPE on HR was higher in the NR group but not significantly so, $F(2,36) = .788$, $p > .05$.

III. PSYCHOLOGICAL CHALLENGE IN TERMS OF THE EXERCISE RESPONSE

The double product at each minute of each of the psychological challenges is shown in Figure 4.9. The analysis of variance for each condition shows that the R group is at a higher level than the NR group on RT-AV, $F(1,12) = 47.3$, $p < .05$ and the RT-AP condition, $F(1,12) = 11.9$, $p < .05$, but not the MA condition. However, when the double product is expressed as a percent of max $\dot{V}O_2$ which elicited a similar double product the situation changes

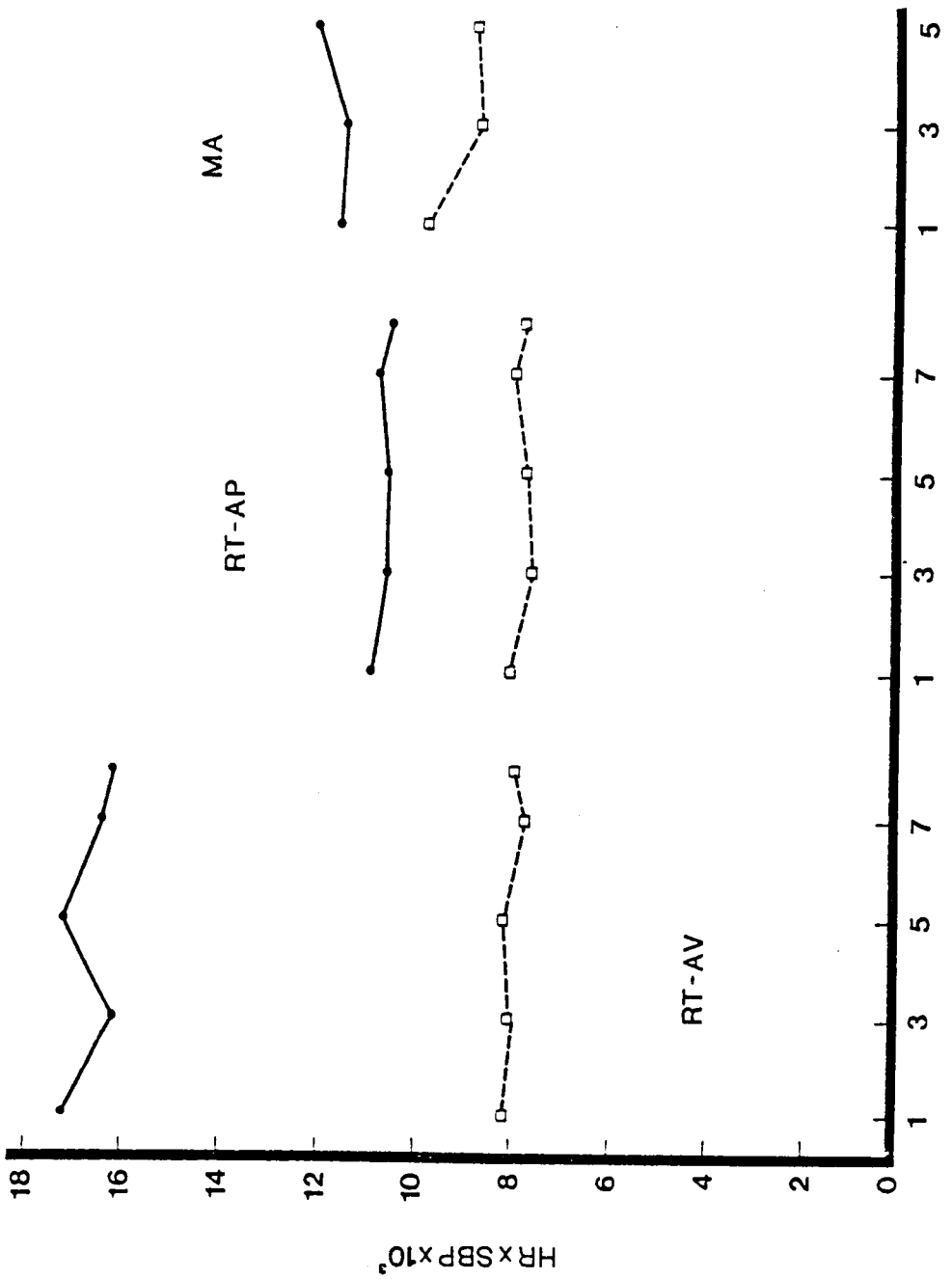


Figure 4.9. Mean double product at each minute of each experimental condition in the R and NR groups.

(Figure 4.10). The R group is still significantly higher than the NR group during RT-AV $F(1,12) = 47.6$, $p < .05$, but not during RT-AP or MA.

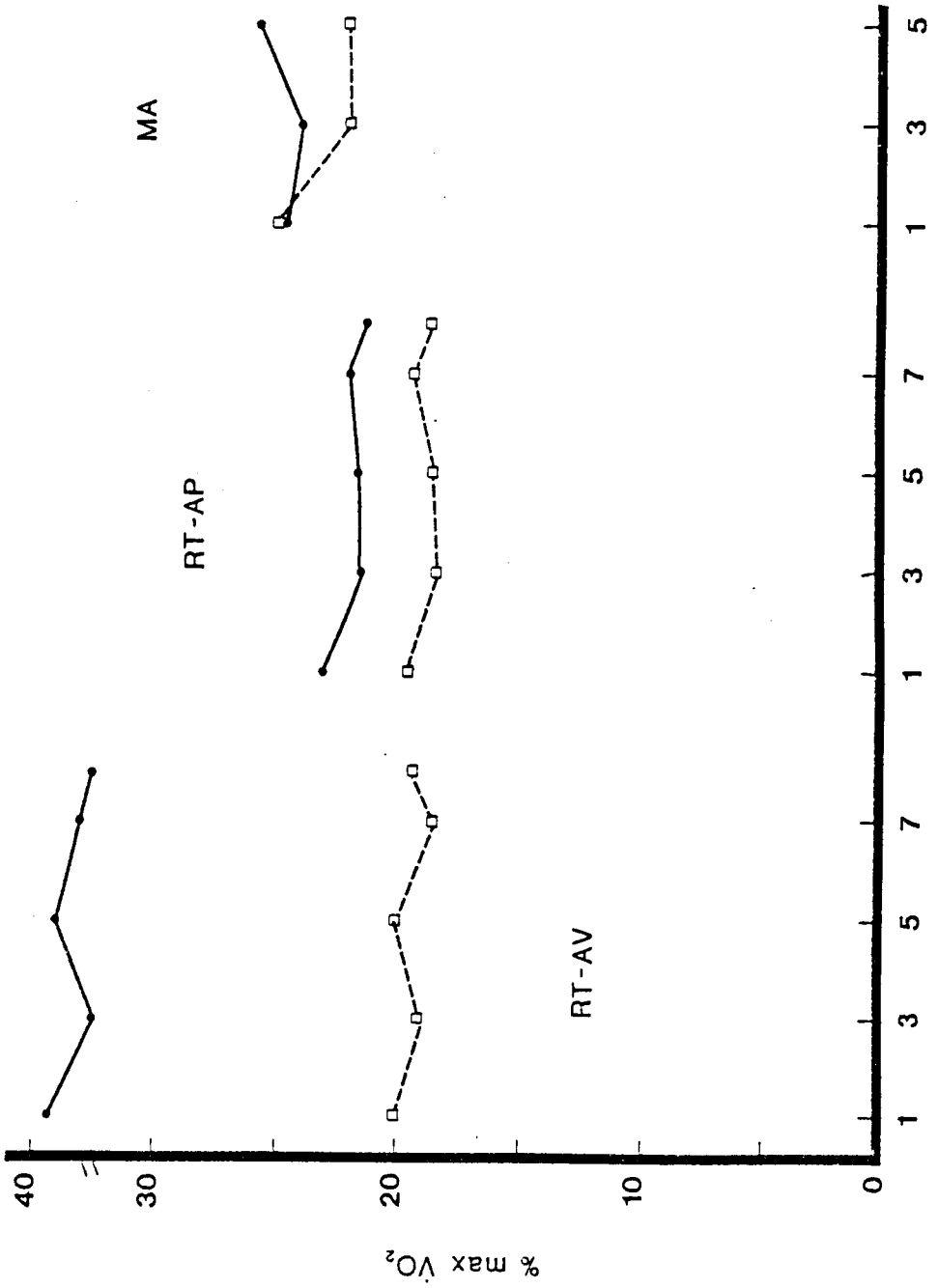


Figure 4.10. Double product at each minute of each experimental condition expressed as a percent of maximum oxygen uptake capacity which elicited the same double product in the R and NR groups.

CHAPTER V

DISCUSSION

The results of this study provide partial support for the hypotheses that CV reactivity is a characteristic of an individual which manifests itself in a variety of situations and that CV function differs between R and NR groups. There are, however, a number of qualifications and limitations related to this contention which must be addressed. The purpose of this chapter is to: 1) point out the evidence which supports this contention; 2) address the failures to consistently demonstrate a difference between the R and NR groups; 3) describe some observations which were not always anticipated but are of interest because they appear to be characteristics of highly reactive subjects and lend support to the idea that reactivity is related to hypertension; and 4) acknowledge the principal weaknesses of this study. Discussion of these points must invariably overlap, but the attempt is to address each separately. The relationship of this work to other reports in the literature which addressed similar issues or employed similar measurements, will be assessed where appropriate.

Observations in support of CV differences. There are a number of observations in the present study which suggest a difference in CV functioning between the R and NR groups. The most salient observation involves the exaggerated HR response of the R group in the RT-AP task. However, the R group also achieves higher levels,

relative to the NR groups, on a number of CV parameters, in a variety of conditions. These include: SBP in RT-AV; SBP during RT-AP and MA; double product in RT-AV and RT-AP; and HR, SBP and double product during exercise at absolute and relative workloads. The significant correlations between the peak HR change in RT-AV and peak HR changes in RT-AP and MA also support the contention that reactivity is a reliable characteristic of an individual. These correlations were statistically significant when based on both the entire subject pool and the fourteen subjects comprising the R and NR groups. The highest correlations were between RT-AV and RT-AP despite the difference in subjective or affective quality which must characterize each experience. The behavioral similarity of these two probably accounts for this.

The significance of these findings, which admittedly were sometimes equivocal, can only be appreciated within the context of the failures by Obrist et al. (1979) to demonstrate the generality of CV reactivity. Obrist et al. (1979) concluded that CV over reactivity was situation or task specific and, therefore, an individual showing large responses in one situation was not necessarily responsive in others. They based this conclusion on the findings that HR and SBP changes in RT-AV did not reliably predict changes during a cold pressor test or viewing of a pornographic film. They attributed the insignificant correlations between responses in the various conditions to the differences in coping patterns and the degree of beta sympathetic arousal that was elicited by their tasks. The success reported here was probably

the result of the use of tasks that evoked only an active coping mode of behavior with concommitant beta-sympathetic arousal. This point is discussed in more detail in later sections.

The CV changes elicited by the psychological challenges observed here resemble the responses reported by others for active coping (Obrist et al., 1978; Lawler, 1980; and Manuck, Harvey, Lechleiter and Neal, 1978; Manuck and Schaefer, 1978; and Brod, 1960). The SBP values reported here are higher than those reported in Lawler et al. (1978) and Lawler (1980) for MA and can be attributed to the method of data collection. The SBP was recorded during the session in this study, whereas, Lawler's results were based on readings taken after the MA stress.

It appears that the NR group was, in fact, refractory to the demands imposed by RT-AV and RT-AP, except for the physical cost required to perform the task. The difference between these two challenges in the NR group was not significant. On the other hand, the RT-AP task elicited significantly less change in HR and SBP in the R group than did the RT-AV task. There was still a significant difference between the two groups during RT-AP, but only when absolute levels of HR change, SBP and double product were compared. I will return to this point in a later section.

No measure of cognitive or affective state (e.g., mood adjective check list, Nowlis, 1965) was involved other than a verbal debriefing of the subjects. Therefore, it is not possible to determine if the difference in CV response could be attributed to differences in pain threshold or affective state between the two groups. If

differences in pain threshold or the amount of "stress" experienced by the subjects existed, it could be argued that this was the origin of the CV variation and not the reactivity or lability of the CV system. There are a number of arguments and observations which can be mounted against this position.

Casual debriefing seemed to indicate that R and NR subjects did not differ in their feelings about the shock. For example, one NR subject said the shock felt, "as if a nail was being driven into his leg," while an R subject shrugged his shoulders and said, "it wasn't so bad." Despite this the R subject maintained an HR increase of 60 bpm for the duration of the RT-AV task (mean HR of 131 bpm). More information on the relationship between verbal reports of aversive experiences and physiological response is necessary before any definitive statements can be advanced, but it sometimes seems as if personal reports of the aversiveness of a situation bear little resemblance to the CV reaction. Similar observations have been made on individuals differing on test anxiety (personal communication, K. Lawler, 1980).

A more empirical check on the equality of the experience involved the administration of shock. The shock generator was calibrated against a range of resistances and monitored during the tests, so it can be confidently stated that each subject received similar amounts of shock. This might not produce the same subjective experience in all individuals, but it did insure equality of the physical stimulus.

The differences in CV response between the two groups can be argued to be the result of differential SNS activation. This

assertion is based on the findings of Obrist et al. (1978). They reported that the HR and SBP responses to RT-AV tasks were greatly attenuated by beta-adrenergic blockade. This was not found for other passive elicitors of CV response such as the cold pressor test. In general the observations made here agree but those which failed to confirm Obrist are discussed in a later section.

The observations indicating a difference in the exercise response are, to my knowledge, new and deserve further mention. The exercise responses reported here show good agreement with those observed by Astrand, Ekblom, Messin, Saltin and Stenberg (1965) in untrained subjects for work at similar relative workloads. As expected, HR, SBP and $\dot{V}O_2$ were all highly and linearly related to workload, and thus support the assumption that the data reported are valid and a realistic reflection of actual values.

The differences in CV response during exercise that exist between the two groups cannot be attributed to variations in aerobic capacity. This assertion is supported by: 1) the lack of a statistically significant difference in max $\dot{V}O_2$ (t-test); 2) by the failure to find a significant difference between the regression lines for load and percent max $\dot{V}O_2$, $F(2,36) = 1.1$, $p > .05$, in the R and NR groups; and 3) the workload comparisons between the R and NR groups on HR, SBP and double product were corrected for the relative degree of exertion by using percent of max $\dot{V}O_2$ as the independent variable.

A factor that could account for the higher HRs in the R group is the rather mundane possibility that their hearts are smaller and,

therefore, SV is less. A smaller SV would demand a higher HR to achieve a CO comparable to the NR group. There are two observations which argue against this possibility. First, on the average the R group was heavier and a larger, not a smaller heart might be expected. Secondly, SV as measured by oxygen pulse showed no difference between the groups. The latter point raises some interesting issues. If SV is the same for both groups but HR is higher for the R subjects at the same relative or absolute load, it indicates a greater CO in these individuals. This is admittedly bold speculation, but the relationship to Guyton's overperfusion hypothesis is too tempting to resist. In actuality it may not be overperfusion, but over consumption in the R group. To check this possibility the difference in regression of $\dot{V}O_2$ (ml/Kg) against load for the two groups was tested. It approached significance, $F(2,36) = 2.30$, $p > .05$. The regression lines were extremely close and the correlations between $\dot{V}O_2$ and load were over .98 in both cases, but the lines crossed. At low workloads $\dot{V}O_2$ was higher in the R group but became lower at the high loads. Again, the lack of significance reduces discussion of this variable to idle speculation.

The higher regression line for V_I against percent max $\dot{V}O_2$ in the NR groups is puzzling and no explanation is offered. Generally, higher ventilation rates are seen in larger individuals. The R group tended to be heavier but V_I tended to be lower. The finding on this variable does argue against the possibility that the differences between R and NR groups on CV parameters are simply an artifact of the tendency for R subjects to be heavier. If all variables were

following size, V_I would also be expected to be higher in R, not lower.

The exercise data can be summarized as follows: No difference in aerobic capacity could be found between the groups and, as a group the R subjects appear to show a greater HR, SBP and double product for the same relative and absolute levels of work. It should be emphasized that the difference in CV response during exercise is much closer than in the psychological challenges. The differences during exercise are also one of absolute values and not change. The adjustment to exercise is the same in both groups, only the baselines are different. This fact, however, raises some interesting points which are discussed later within the context of R - NR comparisons in psychological stress utilizing percent max $\dot{V}O_2$.

Evidence against. There were a number of failures to demonstrate a CV difference between R and NR subjects in this investigation. Also, a number of differences were detected that must be evaluated carefully before a final conclusion is rendered. Heart rate change failed to differentiate the groups in the MA condition. There was certainly more variation in response to this challenge and with the small number of subjects involved a significant difference was impossible to find. There did appear to be a trend for the NR group to be less responsive, however. Table 5.1 shows the number of subjects who showed an HR increase of over 20 bpm in two or more minutes of the MA condition, and those who did not. If HR response in MA is expressed as the number of minutes in which an HR increase exceeded 20 bpm, the number

TABLE 5.1

NUMBER OF SUBJECTS IN EACH GROUP SHOWING AN HR CHANGE OVER 20 BPM IN TWO OR MORE MINUTES OF THE MA CONDITION AND NUMBER WHO DID NOT REACH THIS CRITERION

Group	2 min≥20 bpm	2 min≤20 bpm
NR	0	6
R	5	3

of criterion responses out of the total possibilities can be shown (Table 5.2). In the R group there were eight subjects and each had five minutes of MA. Therefore, forty criterion responses would have resulted if each subject showed a criterion response in every minute. The total possible for the NR group is thirty (six subjects x five minutes).

TABLE 5.2

NUMBER OF MINUTES IN WHICH HR CHANGE EXCEEDED 20 BPM OUT OF THE TOTAL POSSIBLE IN EACH GROUP

	R	NR
Criterion	17	1
Possible	40	30

The data presented above imply that the groups differed on this task but it must be admitted that planned comparisons failed to document a difference between the groups.

There is one aspect of MA that limits its utility for discriminating between CV reactive and nonreactive individuals. It is often difficult to evaluate the performance component in MA. Some subjects are quite proficient at this exercise and consequently respond verbally at a high rate. It may well be that these individuals show the greatest CV change as a result of the activation (verbal) that they are undergoing. Further investigations employing this instrument should assess the performance of each subject, and thus control for physical activation. The simplest way to do this would be to record the number of responses attempted within each time frame of the test.

A difference between R and NR groups on SBP level at RT-AP and MA conditions was significant if a one-tailed test was used. It is difficult to get enthusiastic about one-tailed tests of significance. It can, however, be argued that there is sufficient justification for expecting (i.e., predicting) a higher level in the R group during these tasks. It is not the purpose here to argue the case for one-tailed t-tests, but only to acknowledge the less than convincing nature of this piece of statistical evidence.

The failure to detect differences in DBP between R and NR groups might be expected. Obrist et al. (1978) found that DBP was elevated less on active coping tasks than on passive ones. In addition, they found that beta-adrenergic blockade enhanced DBP changes. This may explain the observations of Manuck and Schaefer (1978). They found only low and inconsistent correlations between HR change and DBP changes in active coping stress. If HR change is indicative of SNS activity in active coping then little relationship to DBP should result. It could be argued that DBP is not a suitable variable for detecting differences in SNS reactivity. Consequently, the failure

to show consistent differences between the groups on this variable is not particularly damaging to the notion of increased CV reactivity in the R group.

The inability to document differences in CAT excretion is a more serious disappointment. This finding must be evaluated in the context of several possibilities before its significance is established. It is possible that the response of the groups did not differ sufficiently to be reflected in urinary CAT excretion. However, I am reluctant to attribute the failure to this. The difference in the RT-AV task is tremendous and I believe that alone should be enough to distinguish the groups.

It is also possible that the differences in CV reactivity are a reflection of differences in receptor sensitivity, so that a given level of CATS at the receptor has a greater effect in some individuals than in others. Investigations of plasma levels of CATS will be required to determine the likelihood of this event.

Originally, the change in CAT excretion, particularly NE, was the parameter of interest. As it turns out the baseline values for both amines tend to be higher in the R group, which shows less change with the stress than does the NR group. It may be that significant differences between the groups exist at baseline, but due to the between day variability of the assay, this was obscured. If the baseline values are higher in the R group, an asymptote may have been reached. This would diminish the change from baseline to stress and lead to the conclusion that no difference exists between the two groups.

The observation that NE did not reflect a change from baseline to stress is a surprise in view of the large CV responses observed.

There are reports in the literature which indicate E may be the most responsive amine in laboratory stress situations. Nestel (1969) reported an increase in E in all subjects but the NE response was variable and Lorimer et al. (1971) found a greater rise in E than NE after a demanding task. Nonetheless, NE is the sine quo non of beta sympathetic activity and it is puzzling that it did not show a reliable increase. It is possible that capacities for reuptake or deactivation were not exceeded to an extent necessary to result in a demonstrable increase in urinary values. A more serious question concerns the actual values for E that are reported. This concern is discussed in the last section of this chapter.

Observations of interest. Establishing a relationship between CV reactivity and hypertension can only be done through longitudinal investigations. Nonetheless, some observations of a more immediate nature are suggestive of a relationship between the two. A number of those observations are reported here, in addition to speculation on the significance of some of them.

Table 5.3 shows the number of subjects in the R and NR groups who reported a mother or father with hypertension. A point biserial correlation between peak HR change in RT-AV and a father or mother with hypertension done with all the subjects (N=32) was $r_{pb} = .522$, $df = 30$, $p < .05$. This relationship has also been reported by Hastrup, Light and Obrist (1979). The genetic component implied in this observation further supports the contention that reactivity is a characteristic of an individual which shows some relationship to hypertension. Mechanisms involved in this putative relationship, of course, are still undefined.

TABLE 5.3

THE NUMBER OF SUBJECTS IN THE R AND NR GROUPS REPORTING A MOTHER OR FATHER WITH HYPERTENSION

	YES	NO	TOTAL
R	5	3	8
NR	0	6	6

There are numerous reports in the literature which indicate that a high resting HR is predictive of hypertension (Levy, White, Stroud and Hillman, 1945; Paffenbarger, Thorne and Wing, 1968; Thomas and Greenstreet, 1973). The resting HR of the R group is significantly higher than the resting HR of the NR group. This does not appear to be a fortuitious occurrence. The resting HR is highly related to a number of parameters measured in this study. The correlations between resting HR and the peak HR changes during psychological challenge for the fourteen subjects in the R and NR groups are shown in Table 5.4 and are all highly significant.

TABLE 5.4

CORRELATIONS BETWEEN RESTING HR AND PEAK HR CHANGES IN PSYCHOLOGICAL CHALLENGE

	P Δ HR RT-AV	P Δ HR RT-AP	P Δ HR MA
Rest HR	.707	.714	.641

The correlations are higher than those found between the peak HR change in RT-AV with the peak changes in RT-AP and MA. It appears that resting HR is as good a predictor of reactivity as any of the other variables measured. In an effort to examine that possibility, the thirty-two subjects on which complete data were available were divided on the basis of HR. There were sixteen subjects with resting HRs of 61 bpm or more and sixteen with rates of 60 bpm or less. The HR change for these two groups across conditions are presented in Figure 5.1. A clear differentiation in response can be seen on the RT-AV condition and a less obvious dichotomy during RT-AP. There is no difference on MA.

The RT-AV response represents an interesting effect. The observation of a large change in a parameter that is already high is an unusual biological event (Law of Initial Values). It may be that a high resting HR and reactivity are all a reflection of a single process, namely a CV system that is "set" high, by enhanced SNS activity.

The proper elaboration of this notion requires keeping in mind Figure 4.10 (p. 144). That figure shows the double product response during psychological challenge in the R and NR groups expressed as a percent of max $\dot{V}O_2$ which gave a similar double product during the progressive exercise test. The similarity of the response for RT-AV and RT-AP in the NR group is striking. It appears that the CV cost of performing the task is similar to that seen at 20% of max $\dot{V}O_2$. There is no statistically significant difference between the R and NR groups on RT-AP when the response is expressed in these terms

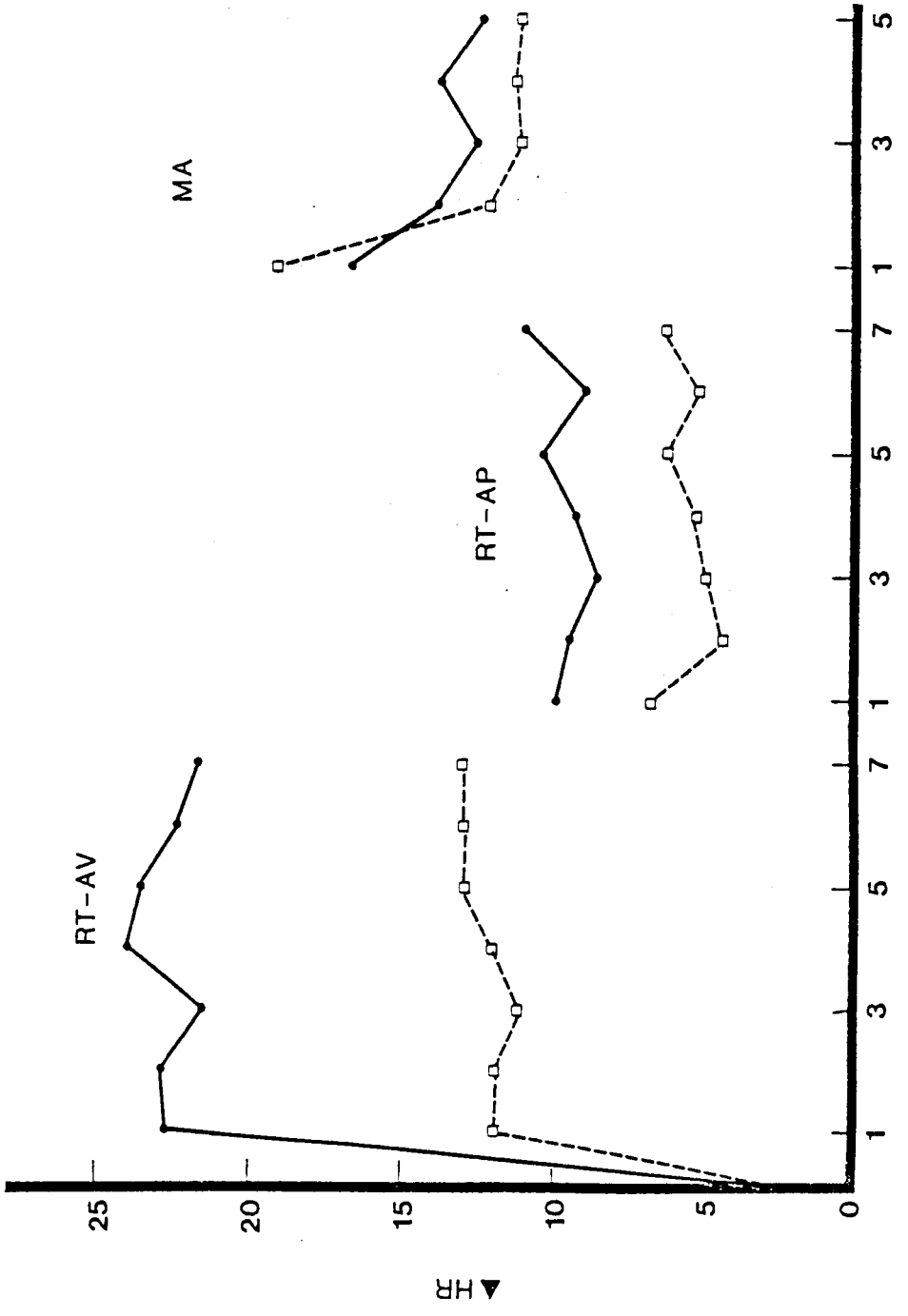


Figure 5.1. Change in heart rate at each minute of each experimental condition in subjects differing on the basis of resting heart rate.

(i.e., percent max $\dot{V}O_2$). However, in absolute terms (Figure 4.9) the double product is significantly higher in the R group. Since the double product is an index of myocardial oxygen consumption, it appears that the physiological "cost" is higher for the R group to do the same relative work (i.e., respond with a button push), just as it is in treadmill walking.

To imply that the extra "cost" is potentially pathogenic is reminiscent of the old argument that there are "only so many beats in the heart and when they are gone. . .," but it is not meant to be. Differences in CAT levels may be the critical factor which shift the relationship between CV response and demand to one that is somewhat uneconomical, or excessive, and in the process set into motion a process conducive to pathology. Some additional support for this speculative scenario is available from the CAT values in this study. The only relationships of significance between CAT values and response characteristics reported in this study were the correlations between baseline E excretion, mean HR changes in the psychological challenges and resting HR. It suggests that SNS activity underlies the higher resting HRs and variations in reactivity observed here. One way this might be viewed is that the baseline period was associated with greater SNS activity in some subjects. This was expressed as a higher resting HR and greater excretion of E. It should be kept in mind that E is probably only a marker for SNS activity in that preganglionic sympathetic fibers innervate the adrenal medulla. A diffuse SNS discharge would activate CV receptors as well as the medulla. The result is a higher resting HR and elevated E levels, the E itself is not causing the CV response.

The subjects showing the greatest SNS activity at rest also respond the greatest when challenged because the SNS response is less tightly coupled to the CV response that is required. Whether the task is mildly physical (i.e., RT-AP) or vigorous (treadmill walking) CV activity is in excess of the actual demand. Besides a CV activity that is slightly high, a genuine over reaction can occur. This is evident in the excessively high response of the R group in the RT-AV task even when double product is converted to percent max $\dot{V}O_2$ (Figure 4.10). As unusual and interesting as that over reaction may be, the mundane, small, but constant excess in SNS activity exhibited day in and day out may be the true bearer of disease.

Limitations and qualifications. The most glaring limitation of this investigation is the small number of subjects involved. This places severe restraints on the generality of the results and provides a formidable obstacle to achieving statistical significance. It also places speculations and generalizations of the magnitude presented here in a particularly vulnerable position. This fact is offered without apology. While it is true that more subjects would certainly have been desirable it should be kept in mind that those involved were a highly select group, which ordinarily tends to bias in favor of finding significant differences. The process of selecting reactive subjects differs in some important respects from other investigations of this topic. The criterion for reactivity used in Obrist et al. (1978) involved the HR increase in the first minute of an anticipated shock situation. The protocol here included a sample

shock. This was meant to equate the experience of all the subjects with the shock but it also has been shown to decrease reactivity to the actual RT-AV task (Obrist et al., 1978), though there is conflicting evidence on this point.

Despite highly selected subjects, a high degree of variability is still obvious in the reactive group. A number of these subjects sustained HR increases of over 30 bpm for the entire RT-AV task, and all reached the criterion level within the first two minutes. Two of these maintained 50 to 60 bpm increases for the duration of the task. On the other hand one R group subject showed the criterion response but it occurred in the middle of the RT-AV task and it quickly disappeared. At all other times he appeared quite non-reactive. His response was quite distinct from the others in the group, but technically he qualified as a reactive subject. He contributed a great deal of variation to the R group in the other situations.

The E values reported here are of some concern, particularly in regard to the baseline values. The normally accepted values for E expressed as excretion per minute are 5 to 10 ng per minute (Becker and Kreuzer, 1970). The values for baseline reported here were 27.1 and 40.2 for the NR and R groups respectively. A series of control measurements and checks of the CAT standards were made to validate these measurements. The E standard was providing the correct reference value as indicated by the assays of plasma which were done for another study at the same time. Consequently, the E values could

not be inflated because they were related to a falsely labeled standard.

Because the determination of CAT values are based on the proportion of an unknown to a known it was thought that low activity in the standard might result in a false high in the unknown. This does not appear to be the case. Epinephrine internal standards gave maximum readings. Consequently, unknowns could not be high because a standard was registering less activity than it should.

In defense of the values it might be said that a number of NR subjects gave values of E in the low teens, and NE values are quite acceptable. Also, the subjects with the extreme values were assayed a second time with excellent duplication, and lastly the E values are related to certain CV parameters in the expected way.

While these values are bothersome because they appear inflated by many standards, they are by no means unprecedented. Lorimer et al. (1971) reports E values after a much less demanding task of approximately 25 ng per minute and vonEuler (1974) reports much higher values in a subject working at submaximal work. The purpose in the digression has simply been to acknowledge the unusual character of the reported values.

BIBLIOGRAPHY

BIBLIOGRAPHY

Alexander, N. Psychosocial hypertension in members of a Wistar rat colony. Proc. Soc. Exp. Biol. Med., 1974, 146, 163.

Alvarez, W. and Stanley, L. Blood pressure in six thousand prisoners and four hundred prison guards. Arch. Int. Med., 1930, 46, 17.

Amer, S. Commentary: Mechanism of action of beta-blockers in hypertension. Biochemical Pharmacology, 1977, 26, 171.

Amery, A., Julius, S., Whitlock, L. and Conway, J. Influence of hypertension on the hemodynamic response to exercise. Circulation, 1967, 36, 231.

Anderson, D. and Brady, J. Differential preparatory cardiovascular responses to aversive and appetitive behavioral conditioning. Conditional Reflex, 1972, 7, 82.

Anderson, D. and Tosheff, J. Cardiac output and total peripheral resistance changes during pre-avoidance periods in the dog. J. of Applied Physiology, 1973, 34, 650.

Astrand, P., Ekblom, B., Messin, R., Saltin, B. and Stenberg, J. Intra-arterial blood pressure during exercise with different muscle groups. J. Applied Physiology, 1965, 20, 253.

Astrand, P. and Rodahl, K. Textbook of Work Physiology. N.Y.: McGraw-Hill, 1970, 1977.

Axelrod, J. and Tomcheck, R. Enzymatic o-methylation of epinephrine and other catechols. J. Biol. Chem., 1958, 232, 702.

Baumann, R., Ziprian, H., Godicke, W., Hartrodt, W., Naumann, E. and Lauter, J. The influence of Acute psychic stress situations on biochemical and vegetative parameters of essential hypertensives at the early stage of the disease. Psychother. Psychosom., 1973, 22, 131.

Becker, E. and Kreuzer, F. Catecholamine excretion by the healthy adult human. Pflugers Arch., 1970, 316, 95.

Benson, H., Herd, J., Morse, W. and Kelleher, R. Behaviorally induced hypertension in the squirrel monkey. Circ. Res., 1970, 26 and 27 (Suppl. 1), 21.

Benson, H., Herd, J., Morse, W. and Kelleher, R. Behaviorial induction of arterial hypertension and its reversal. Am. J. of Physiol., 1969, 217, 30.

Betz, B. Some neurophysiologic aspects of individual behavior. Am. J. of Psychiatry, 1979, 136, 1251.

Bhagat, B. The role of catecholamines in cardiovascular disease. Springfield, Ill: Charles C. Thomas, 1974.

Birkenhager, W. and Schalekamp, M. Control mechanisms in essential hypertension. Amsterdam: Elsevier Scientific Publishing Co., 1976.

Birkenhager, W., de Leeuw, P., Webster, A., Kho, T., Vandongen, R. and Falke, H. Therapeutic effects of beta-adreno-receptor blocking agents in hypertension. In Onesti, G. and Klimt, C. (Eds.), Hypertension: Determinants, complications and intervention. New York: Grume and Stratton, 1979.

Blakemore, W., Jeffers, W., Sellers, A., Itskovitz, H., Cooper, D., Wolferth, C. and Zintel, H. Sympathectomy and adrenalectomy in the treatment of hypertension. In Brest, A. and Moyer, J. (Eds.), Hypertension: Recent advances. Philadelphia: Lea and Febiger, 1961, 64.

Boak, W. and Riek, L. Urinary excretion of catecholamines and metabolites in hypertensives and normotensives subjects. Clin. Res., 1965, 13, 202.

Borg, G. Perceived exertion as an indicator of somatic stress. Scand. J. Rehab. Med., 1970, 2-3, 92.

Brecht, H., Banthien, F., Ernest, W. and Schoeppe, W. Increased plasma noradrenaline concentrations in essential hypertension and their decrease after long term treatment with a beta receptor blocking agent (prindolol). Clin. Sci. Mol. Med., 1976, 51, 485 S.

Brecker, E. and Kreuzer, F. Catecholamine excretion by the healthy adult human. Pflugers Arch., 1970, 316, 95.

Bridges, P. Recent physiological studies of stress and anxiety in man. Biol. Psychiatry, 1974, 8, 95.

Brod, J. The influence of higher nervous processes induced by psychosocial environment on the development of essential hypertension, In Levi, L. (Ed.), Society stress and disease vol. I. London: Oxford U. Press, 1971, 312.

Brod, J. Essential hypertension: Hemodynamic observations with a bearing on its pathogenesis. Lancet, 1960, 2, 773.

Brod, J., Nejl, Z. and Ulrych, M. Metabolic changes in the forearm muscle and skin during emotional muscular vasodilation. Clin. Sci., 1963, 25, 1.

Brown, J., Lever, A. and Robertson, J. Pathogenesis of essential hypertension. Lancet, 1976, 1, 1217.

Brunjes, S. Catecholamine metabolism in essential hypertension. New Engl. J. Med., 1964, 271, 120.

Buchholz, R. The effect of acute avoidance and chronic conflict schedules on the blood pressure and heart rate of rats. Dissertation, 1979, University of Tennessee, Knoxville, Tn.

Buchholz, R., Lawler, J. and Barker, G. The effects of short vs. long term psychological stress on the blood pressure of rats. The Physiologist, 1979, 22, 16.

Buckley, J., Kato, H., Kennard, W., Aceto, M. and Estevez, J. Effects of reserpine and chlorpromazine on rats subjected to experimental stress. Psychopharmacologia, 1964, 6, 87.

Buell, J. and Eliot, R. Stress and cardiovascular disease. Modern concepts of CV disease, 1979, XLVIII, No. 4, 19.

Bunag, R. and Riley, E. Chronic hypothalamic stimulation in awake rats fails to induce hypertension. Hypertension, 1979, 1, 498.

Cannon, W. Bodily changes in pain, hunger, fear and rage. Boston: Charles T. Brandford Co., 1929.

Carruthers, M. and Taggart, P. Vagotonicity of violence: Biochemical and cardiac responses to violent films and television programs. Br. Med. J., 1973, 3, 384.

Charvat, J., Dell, P. and Folkow, B. Mental factors and cardiovascular diseases. Cardiologia, 1964, 44, 124.

Chiueh, C. and Kopen, I. Hyperresponsivity of spontaneously hypertensive rat to indirect measurements of blood pressure. Am. J. of Physiology, 1978, 234, H 690.

Chodakowska, J., Nazar, K., Wocial, B., Jarecki, M. and Sarka, B. Plasma catecholamines and renin activity in response to exercise in patients with essential hypertension. Clin. Sci. Mol. Med., 1975, 49, 511.

Christensen, M. and Christensen, N. Plasma catecholamines in hypertension. Scand. J. Clin. Lab. Invest., 1973, 30, 169.

Circulation in essential hypertension. Leading article. Lancet, 1964, 2, 1323.

Ciriello, J. and Calaresee, F. Direct projections from the nucleus tractus solitarius to the hypothalamus in the cat. Abst. 9th Annual Meeting, Society for Neuroscience, Atlanta, Ga., Nov. 2-6, 1979.

Cobb, S. and Rose, R. Hypertension, peptic ulcer, and diabetes in air traffic controllers. JAMA, 1973, 224, 489.

Cochrane, R. High blood pressure as a psychosomatic disorder: A selective review. Br. J. of Social and Clinical Psych., 1971, 10, 61.

Coleman, T., Granger, H. and Guyton, A. Whole-body circulatory autoregulation and hypertension. Circ. Res., 1971, 28-29, 76.

Cort, J., Fencl, V., Neijl, Z. and Jerka, J. (Eds.) Symposium on the pathogenesis of essential hypertension. Proceedings of the Prague Symposium, 1960, New York: Pergamon Press Book MacMillian Co., 1962.

Cruz-Coke, R. Environmental influences and arterial blood pressure. Lancet, 1960, 2, 885.

Cryer, P., Santiago, J. and Shah, S. Measurement of NE and E in small volumes of human plasma by a single isotope derivative Method: Response to upright posture. J. of Clinical Endocrinology and Metabolism, 1974, 39, 1025.

Cuche, J., Kuchel, O., Barbeau, A., Langlois, Y., Boucher, R. and Genst, J. Autonomic nervous system and benign essential hypertension in man. Circ. Res., 1974, 35, 281.

Dahl, L., Knudsen, K., Heine, M. and Leitl, G. Hypertension and stress. Nature, 1968, 219, 735.

D'Atri, D. and Ostfeld, A. Crowding: Its effects on the elevation of BP in a prison setting. Prev. Med., 1975, 4, 550.

Darrow, C. Physiological and clinical tests of autonomic function and autonomic balance. Physiological Review, 1942, 23, 1.

Davies, M. Is high blood pressure a psychosomatic disorder? A critical review of the evidence. J. Chron. Dis., 1971, 24, 239.

Dawber, T., Kannel, W., Kagan, A., Donabedian, R., McNamara, P. and Pearson, G. Environmental factors in hypertension. In Stamler, J., Stamler, R. and Pullman, T. (Eds.) The epidemiology of hypertension. New York: Grune and Stralton, 1967, 255.

DeChamplain, J. Evaluation of the neurogenic component in human hypertension. In Esler, J. and Esler, M. (Eds.) The nervous system in arterial hypertension. Springfield, Ill.: Thomas, 1976.

DeChamplain, J. Hypertension and the sympathetic nervous system. In Smyder, S. (Ed.) Perspectives in neuropharmacology. New York: Oxford Univ. Press, 1972.

DeChamplain, J., Farley, L., Cousineau, D. and vanAmeringen, M. Circulating catecholamine levels in human and experimental hypertension, Cir. Res., 1976, 38, 109.

DeQuattro, V. Evaluation of increased norepinephrine excretion in hypertension using L-dopa ^{3}H. Circ. Res., 1971, 28, 84.

DeQuattro, V. and Chan, S. Raised plasma-catecholamines in some patients with hypertension. Lancet, 1972, 806.

DeQuattro, V. and Miura, Y. Neurogenic factors in Human hypertension: Mechanism or myth? The Am. J. of Med., 1973, 55, 362.

DeQuattro, V., Miura, Y., Lurvey, A., Cosgrove, M. and Mendez, R. Increased plasma catecholamine concentrations and vas deferens norepinephrine biosynthesis in men with elevated blood pressure. Circ. Res., 1975, 36, 118.

DeQuattro, V. and Sjoerdsma, A. Catecholamine turnover in normotensives and hypertensive man: Effects of anti-adrenergic drugs. J. Clin. Invest., 1968, 47, 2359.

Dickenson, C. Neurogenic hypertension. Oxford: Blackwell, 1965.

Donald, K., Lind, A., McNicol, P., Humphreys, P., Taylor, S., and Staunton, H. Cardiovascular responses to sustained (static) contractions. Circ. Res., 1967, 20 (Suppl.), 1.

Duffy, C. The San Quentin story. Garden City: Doubleday, 1950.

Duffy, C. 88 men and 2 women. Garden City: Doubleday, 1962.

Dustan, H., Tarazi, R. and Bravo, E. Physiologic characteristics of hypertension. Am. J. Med., 1972, 52, 610.

Dworkin, B., Filewich, R., Miller, N., Craigmyle, N. and Pickering, T. Baroreceptor activation reduces reactivity to noxious stimulation: Implications for Hypertension. Science, 1979, 205, 1299.

Dykman, R. and Gantt, W. Experimental psychogenic hypertension: Blood pressure changes conditioned to painful stimuli. Bull. Johns Hopkins Hosp., 1960, 107, 72.

Eckberg, D. Carotid baroreflex function in young men with borderline blood pressure elevation. Circ., 1979, 59, 632.

Ekrstom, M. Psychogene Bluldrucksteigerung. Kriesshypertonien: Acta. med. scand., 1945, 122, 546.

Eiche, P., Cuddy, R., Smulyan, H. and Lyons, R. Hemodynamics in labile hypertension: A follow-up study. Circulation, 1966, 34, 299.

Ekblom, B., Goldbarg, A., Kilbom, A. and Astrand, P. Effects of atropine and propranol on the oxygen transport system during exercise in man. Scand. J. clin Lab. Invest., 1972, 30, 35.

Elliot, R. and Forker, A. Emotional stress and cardiac disease. JAMA, 1976, 236, 2325.

Ely, D. and Henry, J. Effects of prolonged social deprivation on murine behavior patterns, blood pressure, and adrenal weight. J. of Comp. and Physio. Psych., 1974, 87, 733.

Engel, B. and Bickford, A. Response specificity. Arch. Gen. Psychiatry, 1961, 5, 478.

Engelman, K. and Portnoy, B. A sensitive double-isotope derivative assay for norepinephrine and epinephrine (normal resting human plasma levels). Circ. Res., 1970, 26, 53.

Engelman, K., Portnoy, B. and Sjoerdsma, A. Plasma catecholamine concentrations in patients with hypertension. Circ. Res., 1970, 26 and 27 (Supple. 1), I-141.

Eppinger, H. and Hess, L. Vagotonia (trans.) New York: The Nervous and Mental Disease Publishing Co., 1915.

Epstein, A., Fitzimmons, J. and Rolls, B. Drinking induced by injection of angiotensin into the brain of the rat. J. Physiol., 1970, 210, 457.

Esler, M., Julius, S., Ziveifler, A., Randall, O., Harburg, E., Gardiner, H. and DeQuattro, V. Mild high-renin essential hypertension. New Engl. J. of Med., 1977, 296, 405.

Esler, M. and Nestel, P. Renin and sympathetic nervous system responsiveness to adrenerigic stimuli in essential hypertension. Am. J. Cardiol., 1973, 32, 643.

Esler, M., Randall, O., Bennett, J., Zweifler, A., Julius, S., Rydelek, P., Cohen, E. and DeQuattro. Suppression ofSNS in low renin essential hypertension. Lancet, 1976, 2, 115.

Fairchild, H. The noble savage: A study in romantic naturalism. New York: Columbia Univ. Press, 1928.

Farris, E., Yeakel, E. and Medhoff, H. Development of hypertension in emotional gray Norway rats after air blasting. Am. J. Physiol., 1945, 144, 331.

Fencl, V., Hejl, Z., Jirka, J., Madlafousek, J. and Brod, J. Changes of blood flow in forearm muscle and skin during an acute emotional stress (mental arithmetic), Clin. Sci., 1959, 18, 491.

Floras, J., Hassan, M., Jones, J., Sever, P., Sleight, P. and Turner, K. Baroreflex sensitivity and plasma noradrenaline concentration in relation to the blood pressure during dynamic exercise in hypertension. Proceedings J. Physio. (London), 1979, 291, 44P-45P.

Folkow, B., Hallback, M., Lundgren, Y., Sivertsson, R. and Weiss, L. Importance of adaptive changes in vascular design for extablishment of primary hypertension, studied in man and in spontaneously hypertensive rats. Circ. Res., 1973, 32-33 (Suppl.), 1, 2.

Folkow, B. and Neil, E. Circulation. New York: Oxford Univ. Press, 1971.

Folkow, B. and Rubinstein, E. Cardiovascular effects of acute and chronic stimulations of the hypothalamic defence area in the rat. Acta Physiologica Scandinavica, 1966, 68, 48.

Forsyth, R. Blood pressure response to long term avoidance schedules in the restricted rhesus monkey. Psychosom. Med., 1969, 31, 300.

Forsyth, R. Regional blood flow changes during 72-hour avoidance schedules in the monkey. Science, 1971, 173, 546.

Forsyth, R. and Harris, R. Circulatory changes during stressful stimuli in rhesus monkeys. Circ. Res., 1970, 26 and 27 (Suppl. 1), 13.

Franco-Marselli, R., Elghozi, J., Joly, E., DiGuulio, S. and Meyer, P. Increased plasma adrenaline concentrations in benign essential hypertension. Br. Med. J., 1977, 2, 1251.

Frankenhaeuser, M., Froberg, J. and Mellis, I. Subjective and physiological reactions induced by electrical shocks of varying intensity. Neuroendocrinology, 1965-66, 1, 105.

Frankenhaeuser, M., Mellis, I., Rissler, A., Bjorkvall, C. and Patkai, P. Catecholamine excretion as related to cognitive and emotional reaction patterns. Psychosom. Med., 1968, 30, 109.

Fraser, J. and Cowell, E. A clinical study of the blood pressure in wound conditions. In Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions. Spec. Rep. Ser. Med. Res. Coun., 1919, 25, 49.

Friedman, R. Experimental psychogenic hypertension. In Whealley, D. (Ed.) Stress and the Heart, New York: Raven, 1980.

Friedman, R. and Dahl, L. The effect of chronic conflict on the BP of rats with a genetic susceptibility to experimental hypertension. Psychosom. Med., 1975, 37, 402.

Freidman, R. and Irvai, J. Genetic predisposition and stress induced hypertension. Science, 1976, 193, 161.

Freyschuss, U. Elicitation of heart rate and blood pressure increase on muscle contraction. J. of Appl. Physiol., 1970, 28, 758.

Froberg, J., Karlsson, C., Levi, L. and Lidberg, L. Physiological and biochemical stress reactions induced by psychosocial stimuli. In Levi, L. (Ed.) Society, stress and disease. (Vol. 1) London: Oxford Univ. Press, 1971.

Frohlich, E., Dustan, H. and Page, I. Hyperdynamic beta-adrenergic circulatory state. Arch. Intern. Med., 1966, 117, 614.

Frohlich, E., Tarrazi, R. and Dustan, H. Hyperdynamic beta-adrenergic circulatory state. Arch. Intern. Med., 1969, 123, 1.

Gampel, B., Slome, C., Scotch, N. and Abramson, J. Urbanization and hypertension among Zulu Adults. J. Chronic Dis., 1962, 15, 67.

Geffen, L., Rush, R., Louis, W. and Doyle, A. Plasma dopamine-beta-hydroxylase and noradrenaline amounts in essential hypertension. Clin. Sci., 1973, 44, 617.

Geisbock, F. Die bedeutung der blutdruckmessung fur die praxis. Dtsh. Archiv. Fur Klin. Med., 1905, 83, 363. trans. from The nervous system in arterial hypertension. Julius, S. and Esler, M. (Eds.) Springfield: Thomas, 1976, p. XIII.

Gellhorn, E. The emotions and the ergotropic and trophotropic systems. Psychol. Forsch., 1970, 34, 48.

Gillum, R. Pathophysiology of hypertension in blacks and whites. A review of the basis of racial blood pressure differences. Hypertension, 1979, 1, 468.

Glock, C. and Lennard, M. Studies in hypertension V. Psychologic factors in hypertension: An interpretative review. J. Chronic Dis., 1957, 5, 174.

Goldenberg, M., Pines, K., Baldwin, E., Greene, G. and Roh, C. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med., 1948, 5, 792.

Goldenberg, M. and Rapport, N. Norepinephrine and epinephrine in human urine (Addison's disease, essential hypertension, pheachromocytoma). J. Clin. Invest., 1951, 30, 641.

Goldfien, A., Zileli, S., Goodman, D. and Thorn, G. W. The estimation of epinephrine and norepinephrine in human plasma. J. Clin. Endocrinology and Metabolism, 1961, 21, 281.

Goodall, M. and Bogdonoff, M. Essential hypertension with an elevated noradrenaline excretion. Am. Heart J., 1961, 61, 640.

Graham, J. High blood pressure after battle. Lancet, 1945, 1, 239.

Grinker, R. and Spiegel, J. Men under stress. New York: McGraw-Hill, 1945.

Grobecker, H., McCarty, R., Saavedra, J., Chiueh, C. and Kopin, I. Dapamine beta-hydroxylase activity and catecholamine concentrations in plasma: Experimental and essential hypertension. Postgrad. Med. J., 1977, 53 (Suppl. 3), 43.

Grollman, A. Epidemiology of essential hypertension, a survey of significance. In Onesti, G., Kim, E., and Moyer, J. (Eds.), Hypertension: Mechanisms and management. New York: Grune and Stratton, 1973, 75.

Gutman, M. and Benson, H. Interaction of environmental factors and systemic arterial blood pressure: A review. Medicine, 1971, 50, 543.

Guyton, A., Coleman, T., Bower, J. and Granger, H. Circulatory control in hypertension. Circ. Res., 1970, 26-27 (Suppl. 2), 135.

Hallback, M. Interaction of central autonomic hyper-reactivity and environmental stimuli: Importance for the development of spontaneously hypertensive rats. In Onesti, G. Fernandes, M. and Kim, E. (Eds.), Regulation of blood pressure by the central nervous system. New York: Grune and Stratton, 1976.

Hallback, M. and Weiss, L. Mechanisms of spontaneous hypertension in rats. Symposium on hypertension medical clinics in North America, 1977, 61, 593.

Hamer, J., Fleming, J. and Shinebourne, E. Effect of walking on blood pressure in systemic hypertension. Lancet, 1967, ii, 114.

Hamet, P., Kuchel, O. and Genest, J. Effect of upwright posture and isoproterenol infusion on cAMP excretion in controls patients with labile hypertension. J. Clinical Endocrinology and metab., 1973, 36, 218.

Hanson, F. Combat psychiatry. From the Historical Division, Office of the Surgeon General. The Bulletin of the U.S. Army Medical Department, 1949.

Harburg, E., Schull, W., Erfurt, J. and Schork, M. A family set method for estimating heredity and stress: I. A pilot survey of blood pressure among Negroes in high and low stress areas, Detroit, 1966-1967. J. Chronic. Dis., 1970, 23, 69.

Harburg, E., Erfurt, J., Hauenstein, L., Chape, C., Schull, W. and Schork, M. Socio-ecological stress, suppressed hostility, skin color, and black-white male AP. Detroit. Psychosom. Med., 1973, 35, 276.

Hardyck, C. and Singer, M. Transient changes in affect and blood pressure. Arch. Gen. Psychiatry, 1962, 7, 15.

Harlan, W., Oberman, A., Mitchell, R. and Graybiel, A. A thirty year study of blood pressure in a white male cohort. In Onesti, G., Kim, K. and Moyer, J. (Eds.), Hypertension: Mechanisms and management. New York: Grune and Stratton, 1973.

Hastrup, J., Light, K. and Obrist, P. Relationship of cardiovascular stress response to parental history of hypertension and to sex differences. Presented at the meeting of the Society for Psychophysiological Research, Cincinnati, Ohio, 1979.

Heath, R. and Powdermaker, F. The use of ergotamine tartrate as a remedy for "battle reaction." JAMA, 1944, 125, 111.

Henry, J. Understanding the early pathophysiology of essential hypertension. Geriatrics, 1976, 31, 59.

Henry, J. and Cassel, J. Psychosocial factors in essential hypertension: Recent epidemiological and experimental evidence. Am. J. Epidem., 1969, 90, 171.

Henry, J., Meehan, J. and Stephans, P. The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. Psychosom. Med., 1967, 29, 408.

Henry, J., Stephens, P. and Santisteban, G. A model of psychosocial hypertension showing reversibility and progression of cardiovascular complications. Circ. Res., 1975, 36, 156.

Herd, J., Morse, W., Kelleher, R. and Jones, L. Arterial hypertension in the squirrel monkey during behavioral experiments. Am. J. of Physiol., 1969, 217, 24.

Hines, E. The significance of vascular hyperreaction as measured by the cold-pressor test. Am. Heart J., 1940, 19, 408.

Hines, E. Reaction of the blood pressure of 400 school children to a standard stimulus. JAMA, 1937, 108, 1249.

Hines, E. and Brown, G. The cold pressor test for measureing the reactibility of the blood pressure: Data concerning 571 normal and hypertensives subjects. Am. Heart. J., 1936, 11, 1.

Hines, E. and Brown, G. Standard test for measuring variability of blood pressure: Its significance as index of prehypertensive state. Ann. of Intern. Med., 1933, 7, 209.

Holmberg, G., Levi, L., Mathe, A., Rosen, A. and Scot, H. Comparison of the plasma catecholamine levels and the influence of propranolol on peripheral hemodynamic manifestations of emotional stress in labile hypertensives and normal subjects. Circulation, 1965, 32, suppl. 2, 11.

Hoobler, S. Discussion. In Cort, J., Fencl, V., Hejl, Z. and Jirka, J. (Eds.), Symposium on the pathogensis of essential hypertension. Proceedings of the Prague Symposium, New York: Pergamon Press Book, MacMillian Co., 1962.

Hudak, W. and Buckley, J. Production of hypertensive rats by experimental stress. J. of Pharmacological Science, 1961, 50, 263.

Huxley, A. The oddest science. In Collected essays, New York: Bantam Books Inc., 1960.

Ikoma, T. Studies on catechols with reference to hypertension. Jap. Circ. J., 1965, 29, 1269.

Imai, K., Wang, M., Yoshihue, S. and Tamura, Z. Determination of catecholamines in the plasma of patients with essential hypertension and of normal persons. Clin. Chim. Acta., 1973, 43, 145.

Jiang, N., Stoffer, S. and Pikler, G. Laboratory and clinical observations with a two column plasma catecholamine assay. Mayo Clin. Proc., 1973, 48, 47.

Jost, H., Riulmann, C., Hill, T. and Gulo, M. Studies in hypertension. II Central and autonomic nervous system reactions of hypertensive individuals to simple physical and psychological stress situations. J. Nerv. Ment. Dis., 1952, 115, 152.

Judy, W., Watanabe, A., Henry, D., Besh, H., Murphy, W. and Hackel, G. Sympathetic nerve activity: Role in regulation of blood pressure in the spontaneously hypertensive rat. Circ. Res., 1976, Supp. II, 38, 11.

Judy, W., Watanabe, A., Murphy, W., Aprison, B. and Yu, Pao-Lo. Sympathetic nerve activity and blood pressure in normotensive backcross rats genetically related to the spontaneously hypertensive rat. Hypertension, 1979, 1, 598.

Julius, S. Neurogenic component in borderline hypertension. In Julius, S. and Esler, M. (Eds.), The nervous system in arterial hypertension. Springfield: Thomas, 1976.

Julius, S., Amery, A., Whitlock, L. and Conway, J. Influences of age on the hemodynamic response to exercise. Circulation, 1967, 36, 222.

Julius, S. and Conway, J. Hemodynamic studies in patients with borderline blood pressure elevation. Circulation, 1968, 38, 282.

Julius, S. and Esler, M. (Eds.). The nervous system in arterial hypertension. Springfield: Thomas, 1976.

Julius, S. and Esler, M. Autonomic nervous cardiovascular regulation in borderline hypertension. Am. J. of Card., 1975, 36, 685.

Julius, S., Pascual, A. and London, R. Role of para-sympathetic inhibition of the hyperkinetic type of borderline hypertension. Circulation, 1971, 44, 413.

Julius, S., Pascual, A., Sannerstedt, R. and Mitchell, C. Relationship between cardiac output and peripheral resistance in borderline hypertension. Circulation, 1971, 43, 382.

Kaminer, B. and Lutz, W. Blood pressure in bushman of the Kalahari desert. Circulation, 1960, 22, 289.

Kammerer, H. and Molitar, E. Blutdruckstudien an feldsoldaten. munch. med. wschr., 1917, 64, 849.

Kannel, W. and Dawber, T. Hypertensive cardiovascular disease: The Franungham Study. In Onesti, G., Kim, K. and Moyer, J. (Eds.), Hypertension: Mechanisms and management. New York: Grune and Stratton, 1973.

Kannel, W., McGee, D. and Gordon, T. A general cardiovascular risk profile: The Framingham Study. The Am. J. of Cardiology, 1976, 38, 46.

Karki, N. The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it. Acta. Physiol. Scand., 1956, 39 (Suppl. 132), 1.

Kasl, S. and Cobb, S. Blood pressure changes in men undergoing job loss: A preliminary report. Psychosom. Med., 1970, 32, 19.

Kasl, S., Cobb, S. and Thompson, W. Duration of a stressful life situation and reactivity of psychological and physiological variables: Can one extrapolate chronic changes from reactivity to acute stress? Paper read at meeting of American Psychosomatic Society, Atlanta, Ga., 1977.

Kelleher, R., Morse, W. and Herd, J. A pharmacological analysis of behaviorally induced changes in cardiovascular function in the squirrel monkey. In Mostofsky, D. (Ed.), Behavioral control and modification of physiological activity. Englewood Cliffs: Prentice-Hall, Inc., 1976.

Klissouras, V. Heritability of adaptive variation. J. Appl. Physiol., 1971, 31, 338.

Kolata, G. Research news. Treatment reduces death from hypertension. Science, 1979, 206 (4425), 1386.

Korner, P. Central control of blood pressure: Implications in the pathophysiology of hypertension. In Onesti, G., Fernandes, M. and Kim, K. Regulation of blood pressure by the central nervous system. New York: Grune and Stratton, 1976.

Korner, P., Shaw, J., Uther, J., West, M., McRitchie, R. and Richards, J. Autonomic and non-autonomic circulatory components in essential hypertension in man. Circulation, 1973, 48, 107.

Kozlowski, S., Brzeinska, K., Kowalewski, W. and Franczyk, M. Plasma catecholamines during sustained isometric exercise. Clin. Sci. Mol. Med., 1973, 45, 723.

Kuchel, O., Cuche, J., Barbeau, A., Brecht, M., Boucher, R. Genest, J. The role of dopamine, norepinephrine and epinephrine in the orthostatic regulation of renin in normotensive and hypertensive subjects. In Barbeau, A. and McDowell, F. (Eds.), L-dopa and parkinsonism. Philadelphia: F. A. Davis Co., 1970.

Lakatta, E. The responsiveness of the senescent cardiovascular system to adrenergic mediated stress. Presented at the 30th Annual meeting of the American Physiological Society, New Orleans, La., Oct. 15-19, 1979.

Lake, C. and Ziegler, M. Effect of acute volume alterations on norepinephrine and dopamine-beta-hydrorylase in normotensives and hypertensive subjects. Circulation, 1978, 57, 774.

Lake, C., Ziegler, M., Coleman, M. and Kopin, I. Age-adjusted plasma norepinephrine levels are similar in normotensives and hypertensive subjects. New Engl. J. of Med., 1977, 296, 208.

Lake, C., Ziegler, M., Coleman, W. and Kopin, I. Plasma norepinephrine and dopamine beta-hydroxylase in hypertension. Fed. Proc., 1976 35, 398.

Lake, C., Ziegler, M. and Kopin, I. Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. Life Sciences, 1976, 18, 1315.

Lang, G. Gipertonicheskaia Bolezn' (hypertensive disease). Moscow (Medgiz). 1950, 496.

Langer, A., Obrist, P. and McCubbin, J. Hemodynamic and metabolic adjustments during exercise and shock avoidance in dogs. Am. J. of Physiology, 1979, in press.

Lawler, J., Barker, G., Hubbard, J. and Allan, M. The borderline hypertensive rat (BHR): A genetic model for the study of stress-induced hypertension. Psychophysiology, in press.

Lawler, J., Obrist, P. and Lawler, K. Cardiovascular function during pre-avoidance, avoidance and post-avoidance in dogs. Psychophysiology, 1975, 12, 4.

Lawler, K. Cardiovascular and electrodermal response patterns in heart rate reactive individuals during psychological stress. Psychophysiology, in press.

Lawler, K., Lawler, J. and Cox, R. The relationship between attention and cardiovascular responses in potentially hypertensive individuals. Paper presented at the annual meeting of the American Psychological Association, Toronto, Canada, August, 1978.

Lazarus, R. and Cohen, J. Envornmental stress. Altman, I. and Wohlwell, J. (Eds.). Human behavior and environment. New York: Plenum Press, 1977.

Lee, R. and Schneider, R. Hypertension and arteriosclerosis in executive and nonexecutive personnel. JAMA, 1958, 167, 1447.

Levi, L. Life stress and urinary excretion of adrenaline and noradrenaline. In Raab, W. (Ed.), Prevention of ischemic heart disease: Principles and practice. Springfield, Ill.: Charles C. Thomas, 1966.

Levi, L. The urinary output of adrenaline and noradrenaline during pleasant and unpleasant emotional states. Psychosom. Med., 1965, 27, 80.

Levi, L. The urinary output of adrenaline and noradrenaline during different experimentally induced pleasant and unpleasant emotional states: A summary. J. of Psychosom. Res., 1964, 8, 197.

Levy, A., Tabakin, B. and Hanson, J. Hemodynamic responses to graded treadmill exercise in young untreated labile hypertensive patients. Circulation, 1967, 35, 1063.

Levy, R., White, P., Stroud, W. and Hillman, C. Transient tachycardia: Prognostic significance alone and in association with transient hypertension. JAMA, 1945, 129, 585.

Lorimer, A., MacFarlane, P., Provan, G., Duffy, T. and Lavine, T. Blood pressure and catecholamine responses to stress in normotensive and hypertensive subjects. Cardiovasc. Res., 1971, 5, 169.

Louis, W., Doyle, A. and Anavekar, S. Plasma norepinephrine levels in essential hypertension. New Engl. J. Med., 1973, 288, 599.

Louis, W., Doyl, A., Anavekar, S., Johnston, C., Getten, L. and Rush, R. Plasma catecholamine, dopamine-beta-hydroxylase, and renin levels in essential hypertension. Circ. Res., 1974, 34-35 (Suppl. I), 57.

Lovallo, W. The cold pressor test and autonomic function: A review and integration. Psychophysiology, 1975, 12, 268.

Lowenstein, F. Blood pressure in relation to age and sex in the tropics and subtropics, Lancet, 1961, i, 389.

Luft, F., Rankin, L., Willis, L., Henry, D. and Weinberger, M. Norepinephrine and renal function at extremes of sodium intake. Presented at Fall Meeting of American Physiological Society, New Orleans, La., Oct. 15-19, 1979.

Lund-Johansen, P. Hemodynamic alterations in essential hypertension. In Onesti, G. and Kim, K. and Moyer, J. (Eds.), Hypertension: Mechanisms and management. New York: Grune and Stratton, 1973.

Lund-Johansen, P. Hemodynamics in early essential hypertension, Acta Med. Scand., 1967, 183, Suppl., 482.

Lykken, D. The role of individual differences in psychophysiological research. In Venables, P. and Christie, M. (Eds.), Research in psychophysiology. London: John Wiley and Sons, 1975.

MacLean, P. Psychosomatic disease and the "visual brain": Recent developments bearing on the Papez theory of emotion. Psychosom. Med., 1949, 11, 338.

Maddocks, I. Possible absence of essential hypertension in two complete Pacific island populations. Lancet, 1961, ii. 396.

Maddocks, I. The influence of standard of living on blood pressure on Fiji, Circulation, 1961, 24, 1220.

Manuck, S., Harvey, A., Lechleiter, S. and Neal, K. Effects of coping on blood pressure responses to threat of aversive stimulation. Psychophysiology, 1978, 15, 544.

Manuck, S. and Schaefer, D. Stability of individual differences in cardiovascular reactivity. Physiol. and Beh., 1978, 21, 675.

Marx, J. and Kolata, G. Combating the No. 1 Killer. The science Report on Heart Research. Washington, D.C.: American Association for the Advancement of Science, 1978.

Marx, K. Stress: Role in hypertension. Science, 1977, 198, 905.

McCarty, R. and Kopin, I. Alterations in plasma catecholamines and behavior during acute stress in spontaneously hypertensives and Wistar-Kyoto normotensive rats. Life Sciences, 1978, 22, 997.

Medhoff, H. and Bongiovanni, A. Blood pressure in rats subjected to audiogenic stimulation. Am. J. of Physiol., 1945, 143, 300.

Mefferd, R. and Wieland, B. Comparison of responses to anticipated stress and stress. Psychosom. Med., 1966, 28, 795.

Mendlowitz, M. Editorial. Some theories of hypertension: Fact and fancy. Hypertension, 1979, 1, 435.

Mendlowitz, M. and Vlachakis, N. The catecholamines in essential hypertension. Am. Heart J., 1976, 91, 378.

Miall, W. The epidemiology of essential hypertension. In Cort, J., Fencl, V., Hejl, Z. and Jirka, J. (Eds.), Symposium on the pathogenesis of essential hypertension. Proceedings of the Prague symposium, 1960. New York: Pergamon Press Book, Mac-Millian Co., 1962, p. 90.

Miasnikov, A. The signifiance of higher nervous activity in the pathogenesis of hypertensive disease. In Cort, J., Fencl, V., Hejl, Z. and Jirka, J. (Eds.), Symposium on the pathogenesis of essential hypertension. Proceedings of the Prague symposium, 1960. Pergamon Press Book MacMillian Co., 1962, 153.

Moos, R. and Engel, B. Psychophysiological reactionsin hypertensives and arthritic patients. J. of Psychosom. Res., 1962, 6, 227.

Murray, D. Blood pressure and heart rate responses during chronic exposure to Sidman avoidance and yoked control procedures in the rat. Dissertation, 1978, University of Tennessee, Knoxville, Tn.

Nazar, K., Chavalbinska-Moneta, J. and Zukowska-Grojec, Z. Plasma noradrenoline response to sustained handgrip in patients with essential hypertension. Eur. J. of Appl. Physiol., 1979, 41, 181.

Nestel, P. Blood pressure and catecholamine excretion after mental stress in labile hypertension. Lancet, 1969, i, 692.

Nestel, P. and Doyle, A. The excretion of free noradrenaline and adrenaline by healthy young subjects and by patients with essential hypertension. Australas Ann. Med., 1968, 17, 295.

Nestel, P. and Esler, M. Patterns of catecholamine excretion in urine in hypertension. Circ. Res., 1970, 26-27 (Supp. II), 75.

Nester, J. and Wasserman, W. Applied Linear Statistical Models. Georgetown, Ontario: Richard D. Irwin, 1974.

Niarchos, A. and Tarazi, R. Hemodynamic effects of beta-adrenergic receptor blocking drugs. In Onesti, G., Fernandes, M. and Kim, K. (Eds.), Regulation of the blood pressure by the central nervous system. New York: Grune and Stratton, 1975, 411.

Nowles, V. Research with the mood ajective check list. In Thompkins, S. and Izard, C. (Eds.), Affect, cognition, and personality. New York: Springer, 1965.

Obrist, P., Gaebelein, C., Teller, E., Langer, A., Grignolo, A., Light, K. and McCubbin, J. The relationship among heart rate, carotid dP/dt, and blood pressure on humans as a function of the type of stress. Psychophysiology, 1978, 15, 102.

Obrist, P., Langer, A., Grignolo, A., Sutterer, J., Light, K and McCubbin, J. Blood pressure control mechanisms and stress: Implications for the etiology of hypertension. In Onesti, G. and Klimt, C. (Eds.), Hypertension: Determinants, complications and intervention. New York: Grune and Stratton, 1979.

Oglesby, P. Epidemiology of hypertension. In Genst, J., Koiro, E., and Kuchel, O. (Eds.), Hypertension--physiopathogy and treatment. New York: McGraw-Hill, Inc., 1977, 613.

Ordman, B. Review of incidence of hypertension in non-European races: Survey of blood pressures in South African Bantu. Clin. Proc., 1948, 7, 183.

Ostfield, A. and Shekelle, R. Psychological variables and blood pressure. In Stamler, J., Stamler, R. and Pullman, T. (Eds.), The epidemiology of hypertension. New York: Grune and Stratton, 1967, 321.

Paffenbarger, R., Thorne, M. and Wing, A. Chronic disease in former college students VIII. Characteristics in youth predisposing to hypertension in later years. Am. J. Epidemiology, 1968, 88, 25.

Page, I. and Corcoran, A. Arterial hypertension: Its diagnosis and treatment. Chicago: Year Book Publishers, 1945.

Page, I. and McCubbin, J. The physiology of arterial hypertension. In Hamilton, W. (Ed.), Handbook of Physiology (Circulation, Sec. 2, Vol. 3). Washington, D.C.: American Physiological Society, 1962.

Painter, P. Changes in plasma epinephrine, norepinephrine, cyclic AMP and cyclic GMP in men subjected to the same degree of progressive and continuous work. Dissertation, 1976 (June), University of Tennessee, Knoxville, Tn.

Passon, P. and Peuler, J. A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal. Biochem., 1973, 51, 618.

Patkai, P. CAT excretion in pleasant and unpleasant situations. Acta Psychol., 1971, 35, 352.

Patton, G. Interstressor consistency of subject differences in autonomic activity. J. of Psychology, 1969, 72, 199.

Peart, W. Catecholamines and hypertension. Pharm. Rev., 1966, 18, 667.

Pederson, E. and Christensen, N. Catecholamines in plasma and urine in patients with essential hypertension determined by double isotope derivative technique. Acta Med. Scand., 1975, 198, 373.

Perhach, J., Ferguson, H. and McKenney, G. Evaluation of anti hypertensive agents in the stress-induced hypertensive rat. Life Sciences, 1975, 16, 1731.

Pfeffer, M. and Frohlich, E. Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats, Circ. Res., 1973, 34 and 35 (Suppl. 1), 29.

Philipp, T., Distler, A. and Cordes, U. Sympathetic nervous system and blood pressure control in essential hypertension. Lancet, 1978, 2, 959.

Pickering, G. High blood pressure. London: J. and A. Churchill, LTD., 1968.

Planz, G., Gierlichs, H., Hawlina, A., Planz, R., Stephany, W. and Rahn, K. A comparison of catecholamine concentration and dopamine beta hydrorylase activities in plasma from normotensive subjects and from patients with essential hypertension at rest and during exercise. Klinische Wachenschrift, 1976, 54, 561.

Portnoy, B., Engelman, K. and Wyatt, R. Plasma catecholamines in hypertensives and psychiatric disorders. Clin. Res., 1969, 17, 258.

Pyle, E. Here is your war. New York: Henry Holt and Co., 1943.

Raab, W. Etiologic role of catecholamines in essential hypertension. In Brest, A. and Moyer, J. (Eds.), Hypertension: Recent advances. Philadelphia: Lea and Febiger, 1961, 369.

Reis, D., Doba, N. and Nathan, M. Neurogenic arterial hypertension produced by brainstem lesions. In Onesti, G., Fernandes, M. and Kim, K (Eds.), Regulation of the blood pressure by the central nervous system. New York: Grune and Stratton, 1976, 35.

Rizza, R., Haymond, M., Cryer, P. and Gerich, J. Differential effects of epinephrine on glucose production and disposal in man. Am. J. Physiol., 1979, 237, E 357.

Rosencrans, J., Watzman, N. and Buckley, J. The production of hypertension in male albino rats subjected to experimental stress. Biochem. Pharm., 1966, 15, 1707.

Rothlin, E., Cerletti, A. and Emmenger, H. Experimental psychoneurogenic hypertension and its treatment with hydrogenated ergotalkaloids (hydrergine). Acta Med. Scand. Suppl., 1956 (Suppl.), 312, 27.

Rousseau, J. The social contract and discourses. Translated with an introduction by Cole, G. New York: E. P. Dutton and Co., 1950.

Rushmer, R. Cardiovascular dynamics. Philadelphia: W. B. Saunders Co., 1976.

Ruskin, A., Beard, O. and Schaffer, R. Blast hypertension: Elevated arterial pressure in victims of the Texas City disaster. Am. J. Med., 1948, 4, 228.

Sannerstedt, R. Hemodynamic response to exercise in patients with arterial hypertension. Acta Med. Scand., 1966, 180 (Suppl. 458), 1.

Sapira, J., Scheib, E., Moriarty, R. and Shapiro, A. Differences in perception between hypertensive and normotensive populations. Psychosom. Med., 1971, 33, 239.

Schachter, J. Pain, fear, and anger in hypertensives and normotensives. A psychophysiological study. Psychosom. Med., 1957, 19, 17.

Schachter, S. and Singer, J. Cognitive, social and physiological determinants of emotional state. Psychological Review, 1962, 69, 379.

Schroder, H. Hypertensive diseases: Causes and control. Philadelphia: Lea and Febiger, 1953.

Schulge, V. and Schwab, E. Arteriolar hypertension in the American Negro. Am. Heart J., 1936, 11, 66.

Scotch, N. Sociocultural factors in the epidemiology of Zulu hypertension. Am. J. Publ. Hlth., 1963, 53, 1205.

Scotch, N. and Geiger, H. The epidemiology of hypertension: A review with special attention to psychologic and socioculture factors--II. Psychologic and sociocultural factors in etiology. J. Chronic Dis., 1963, 16, 1183.

Seligman, M. Helplessness. San Francisco: W. H. Freeman and Co., 1975.

Selye, H. Textbook of endocrinology. Montreal: Acta endocrinologica, 1949.

Semiginorsky, B., Novak, J., Sobotka, P. and Zalud, V. Cardiovascular, resperatory and metabolic response of healthy volunteers to emotional stress. Activitas Nervosa Superior, 1979, 21, 36.

Serrano, P. Figueroa, G., Tores, M. and del Angel, R. Adrenaline, noradrenaline and dopamine excretion in patients with essential hypertension. Am. J. Cardiol., 1964, 13, 484.

Sever, P., Birch, M., Osikowska, B. and Turnbridge, R. Plasma noradrenaline in essential hypertension. Lancet, 1977, 1, 1078.

Shapiro, A. An experimental study of comparative responses of blood pressure to different noxious stimuli. J. Chronic Dis., 1961, 13, 293.

Shapiro, A. and Melhado, J. Factors affecting development of hypertensive vascular disease after renal injury in rats. Proceedings of the Society for Experimental Biology and Medicine, 1957, 96, 619.

Shapiro, A. and Melhado, J. Observations on blood pressure and other physiological and biochemical mechanisms in rats with behavioral disturbances. Psychosom. Med., 1958, 20, 303.

Silverberg, A., Shah, S., Haymond, M. and Cryer, P. Norepinephrine: Hormone and neurotransmitter in man. Am. J. Physiol., 1978, 234, E 252.

Simonson, E. and Brozek, J. Review--Russian research on arterial hypertension. Ann. Intern. Med., 1959, 50, 129.

Smith, O. Personality and cardiovascular disease: Contributions from nonhuman primates. In Zanchetti, A. (Ed.), Neural and psychological mechanisms in cardiovascular disease. Italy: CASA Editrice, 1972, 297.

Smookler, H. and Buckley, J. Relationships between brain catecholamine synthesis, pituitary adrenal function and the production of hypertension during prolonged exposure to environmental stress. Int. J. of Neuropharmacology, 1969, 8, 33.

Smookler, H. and Buckley, J. Effect of drugs on animals exposed to chronic environmental stress. Fed. Proc., 1970, 29, 1980.

Smookler, H., Goebel, K., Siegel, M. and Clarke, D. Hypertensive effects of prolonged auditory, visual, and motion stimulation. Fed. Proc., 1973, 32, 2105.

Stevenson, I., Duncan, C., Flynn, J. and Wolf, S. Hypertension as a reaction pattern to stress. Correlation of circulatory hemodynamics with changes in the attitude and emotional state. Am. J. Med. Sci., 1952, 224, 286.

Standness, D. and Sumner, D. Hemodynamics for surgeons. New York: Grune and Stratton, 1975, 3.

Syme, L. Psychosocial determinants of hypertension. Paper presented at the Hahnemann Medical College's Fifth International Symposium on Hypertension. Puerto Rico, 1977.

Syme, S. and Torfs, C. Epidemiologic research in hypertension: A critical appraisal. J. of Human Stress, 1978, March, 43.

Tarazi, R., Ferrario, C. and Dustan, H. The heart in hypertension. In Genest, J., Koiw, E. and Kuchel, O. (Eds.), Hypertension--Physiopathology and Treatment. New York: McGraw-Hill, 1977.

Taylor, S., Donald, K. and Bishop, J. Circulatory studies in hypertensive patients at rest and during exercise. With a note on the Starling relationship in the left ventricle in essential hypertension. Clin. Sci., 1957, 16, 351.

Thadani, P. and Schanberg, S. Effect of stress and sympathetic activity on rat cardiac and aortic ornithine decarboxylase activity. Life Sciences, 1979, 25, 1009.

Thomas, C. and Greenstreet, R. Psychobiological characteristics in youth as predictors of five disease states: Suicide, mental illness, hypertension, coronary heart disease, and tumor. John Hopkins Med. J., 1973, 132, 16.

Vlachakis, N. Blood pressure and catecholamine responses to sympathetic stimulation in normotensive and hypertensive subjects. J. Clin. Pharmacol., 1979, 19, 458.

Vlachakis, N., Mendlowitz, M. and Krakoff, L. Abnormal responses to isometric stress and norepinephrine infusion in hypertensive patients. Circulation, 1977, 56 (Suppl. III), 161.

vonEuler, U. Noradrenaline. Springfield: Thomas, 1956.

Watson, R., Hamilton, C., Reed, J. and Littler, W. Changes in plasma norepinephrine, blood pressure and heart rate during physical activity in hypertensive man. Hypertension, 1979, 1, 341.

Weil-Malherbe, H. and Bone, A. The estimation of catecholamines in urine by a chemical method. J. Clin. Path., 1957, 10, 138.

Weiner, H. Lessons taught by experimental high blood pressure research. [Editorial]. Psychosom. Med., 1976, 38, 297.

Weiner, H. Personality factors and the importance of emotional stresses in hypertension. In Genst, J., Koiw, E. and Kuchell, O. (Eds.), Hypertension--physiopathology and treatment. New York: McGraw-Hill, Inc., 1977.

Wenger, M. and Cullen, T. Autonomic balance. In Greenfield, N. and Sternbach, R. (Eds.), Handbook of Psychophysiology. New York: Holt, Rhinehart and Winston, Inc., 1972, 535.

Wiedeking, C., Lake, R., Ziegler, M., Kowarski, A. and Money, J. Plasma noradrenaline and dopamine-beta-hydroxylase during sexual activity. Psychosom. Med., 1977, 39, 143.

Wilson, C. Etiological considerations in essential hypertension. In Brest, A. and Moyer, J. (Eds.), Hypertension: Recent advances. Philadelphia: Lea and Febiger, 1961, 64.

Wolff, H. Life stress and bodily disease--a formulation. In Wolff, S. and Nare, C. (Eds.), Life stress and bodily disease. Baltimore: Williams and Wilkins Co., 1950, 1074.

Zanchetti, A. (Ed.) Neural and psychological mechanisms in cardiovascular disease. Italy: Casa Editrice, 1972.

Zanchetti, A., Leonetti, G., Morganti, A., Terzoli, L., Chidsey, C., Bianchetti, G. and Morselli, P. Correlation between renin-suppressive and hemodynamic effects of beta-adrenergic receptor blocking agents. In Onesti, G., Fernandes, M. and Kim, K. (Eds.), Regulation of blood pressure by the central nervous system. New York: Grune and Stratton, 1976, 451.

Ziegler, M., Lake, C. and Kopin, I. Plasma noradrenaline increases with age. Nature, 1976, 261, 333.

APPENDICES

APPENDIX I

WIN MONEY AS WELL AS PSYCH. CREDIT

Research is being conducted which examines cardiovascular and metabolic responses to various tasks. The ultimate goal of this research is to contribute some understanding of the role of psychological factors in hypertension.

The experiment lasts approximately 2 hours. Most of this time (i.e. 90 minutes) is spent sitting quietly. You may bring something to read if you wish.

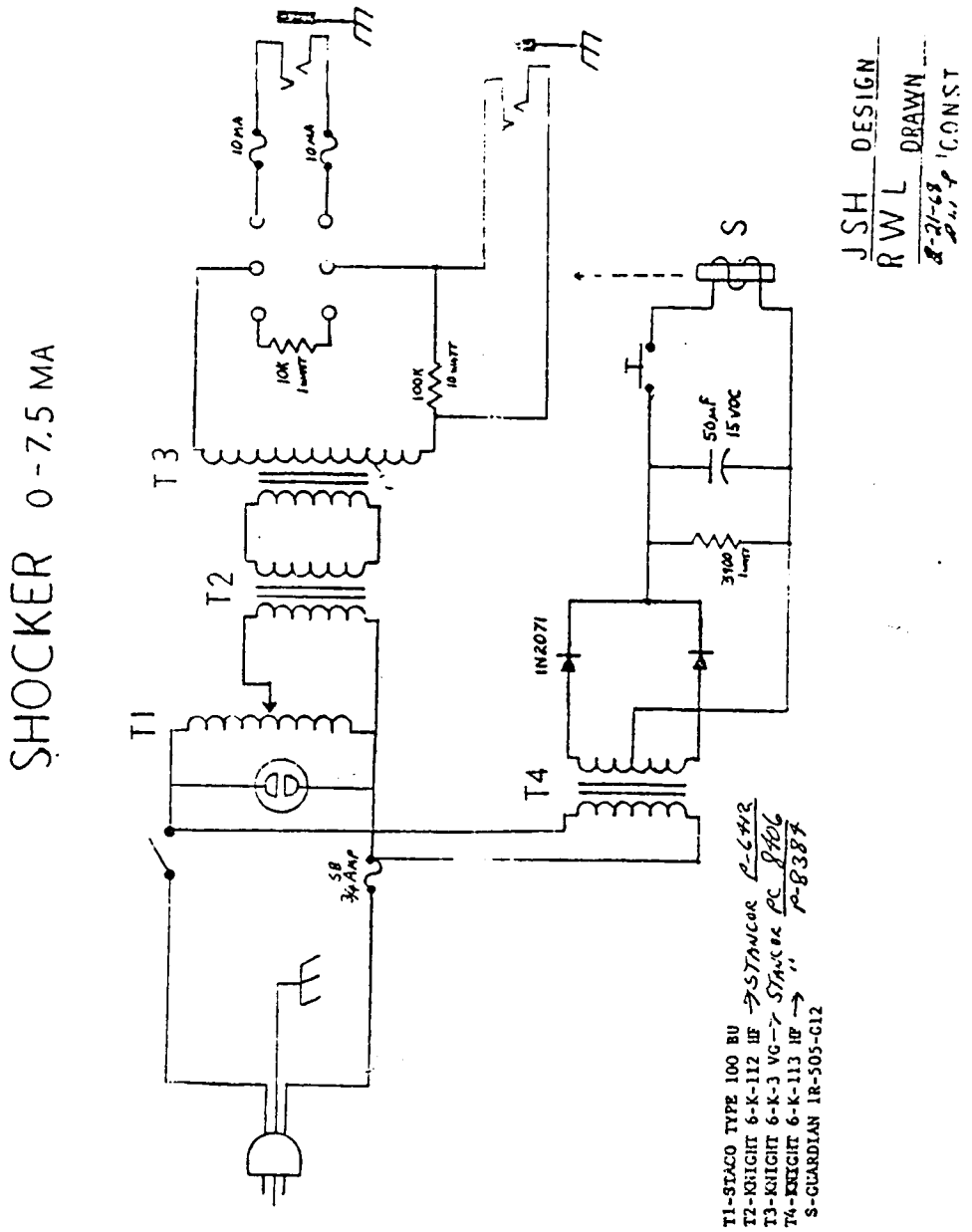
One five minute period involves a reaction time task. Most individuals win up to $2.00 during this period. However, there is also a possible penalty for very slow reaction times. The penalty is a shock. The shock will not harm you, but it is unpleasant.

The study also involves a urinalysis. Therefore it is very important that you be adequately hydrated prior to the experiment. This can be easily done by drinking a couple of glasses of water the night before or the morning of the experiment.

If you have any questions please feel free to call: Ron Cox at home 573-5708 or school 974-8142.

APPENDIX II

SHOCK GENERATOR DIAGRAM



APPENDIX III

INFORMED CONSENT FORM

Informed consent for participation in the study to measure cardiovascular responses to various physical and psychological challenges.

I, _____,- hereby volunteer to participate in a research study designed to measure the changes in heart rate, blood pressure and urinary catecholamines to various psychological tests. I am aware that electrical shock is involved in one of the tests. On the other tests I will solve problems, and react to a light. In addition I may be contacted at a later time for further tests. I realize I am under no obligation whatsoever to take part in these future studies.

I am aware that I am earning extra credit toward Psychology 2500. Nevertheless I will be allowed to withdraw from this research study at any time without penalty. I understand that in the event of physical injury resulting from the research procedure, financial compensation is not available and medical treatment is not provided free of charge. All my questions regarding these experiments have been answered to my satisfaction.

Signature: _____

Date: _____

Witness: _____

APPENDIX IV

BACKGROUND INFORMATION SHEET

1. Subject # _____ 2. Date: _____

3. Name: _____ 4. Time of Day: _____

6. Age: _____ 7. Phone #: _____ 5. Temp: _____

8. Smoker: YES NO Amount: _____

9. Height: _____ Weight: _____

10. Physical Activity: NONE LIGHT MODERATE HEAVY
Explain:

11. Health Problems - Subject: YES NO Specify:

Family:

Medication:

12. Future Participation: YES NO

13. Birth Order: _____ of _____ children.

14. Arm Circumference: _____

15. Skin Fold:

a. Tricep: _____ _____ _____ $\bar{X}$ _____

b. Umbilical: _____ _____ _____ $\bar{X}$ _____

c. TOTAL: _____

16. Time since last food was taken: _____ Amount: _____

17. Coffee/Cola: YES NO Daily Am't _____ Today _____

18. Sleep: _____

19. Other: _____

20. Order of Experimental Treatments: _____ MA _____ RT-AV _____ RT-AP

21. I - E Score= _____ N= _____ L= _____

22. Urinary Catecholamines: YES NO

NE _____ - _____ E _____ - _____ Total: _____ - _____

23. $\bar{X}$ RT-AV: _____ $\bar{X}$ RT-AP: _____ Money Won: _____

APPENDIX V

LETTER TO POTENTIAL SUBJECTS

THE UNIVERSITY OF TENNESSEE

COLLEGE OF LIBERAL ARTS
DEPARTMENT OF PSYCHOLOGY

Knoxville TN 37916
615-974-2531

May 3, 1979

This letter is part of a follow-up and a thank-you for an experiment you participated in for Psychology credit that was conducted during the Spring and Winter Quarters. That research was funded by the Department of Psychology and made possible by funds from the American Heart Association.

The results of those tests are now being analyzed and on the basis of those tests a select group of individuals are being asked to participate in a short series of experiments. These new experiments are quite different from the reaction time and mental arithmetic tasks you performed earlier. Basically these experiments are comprised of walking on a treadmill while your heart rate, blood pressure and oxygen consumption are monitored. The present plans include having the volunteers return to the laboratory in the HPER Building three times. This would be done with one visit a week, for three weeks. Each visit would be for about one hour. The present plans include paying you at a rate of four dollars ($4.00) per hour. Even if a visit was less than an hour a full hourly payment would be made.

I want to emphasize the voluntary nature of this participation but also the fact that you are a unique individual (not in an unhealthy or derogatory way) and the success of this research does depend on your participation.

I will call you in a few days to get your response.

Thank You,

Ronald H. Cox
Doctoral Candidate
Dept. of Psychology

APPENDIX VI

BORG SCALE OF RPE

6

7 Very, Very Light

8

9 Very Light

10

11 Fairly Light

12

13 Somewhat Hard

14

15 Hard

16

17 Very Hard

18

19 Very, Very Hard

20

APPENDIX VII

STANDARD TREADMILL TEST

Test Phase	Duration min.	Energy Mets	Requirements VO_2 ml/kg/min.	% grade at 80 m/min.
Rest	10-20	1	3.5	---
Accommodation Period	3	4	14.0	2.5
Recovery	2	1	3.5	---
Actual Test	2	4	14.0	2.5
	2	5	17.5	5.0
	2	6	21.0	7.5
	2	7	24.5	10.0
	2	8	28.0	12.5
	2	9	31.5	15.0
	2	10	35.0	17.5
	2	11	38.5	20.0
	2	12	42.0	22.5
	2	13	45.5	25.0
	2	14	49.0	27.5
	2	15	52.5	30.0

From B. Balke.

APPENDIX VIII

SUPER-STANDARD TREADMILL TEST

Test Phase	Duration min.	Energy Mets	Requirements $\dot{V}O_2$ ml/kg/min.	% grade v = 100m/min.
Rest	10	1	3.5	---
Accommodation Period	3	6	21.0	4
Recovery	2	1	3.5	---
Actual Test	1	6	21.0	4
	1	7	24.5	6
	1	8	28	8
	1	9	31.5	10
	1	10	35	12
	1	11	38.5	14
	1	12	42	16
	1	13	45.5	18
	2	14	49	20
	2	15	52.5	22
	2	16	56	24
	2	17	59.5	26
	2	18	63	28
	2	19	66.5	30

From B. Balke.

VITA

Ronald H. Cox was born in Washington, D.C. on January 11, 1950. He attended elementary school in Kensington, Maryland. In 1968 he graduated from Good Counsel High School in Wheaton, Maryland and entered Frostburg State College in September of that year. He received a Bachelor of Science degree in psychology from that institution in 1972.

After spending one year at Appalachian State University completing course requirements for the Master of Arts degree in psychology, he entered The University of Tennessee, Knoxville in September of 1974. There he completed the requirements for the Master of Arts degree from ASU, and the Doctor of Philosophy with a major in Experimental Psychology.

The author received a National Service Research Award from the National Institute of Health to continue study in the Department of Zoology and Physical Education. This work will involve comparisons of the physiological and hormonal responses that occur in psychological and exercise stress. He is a member of the American College of Sports Medicine and the American Association for the Advancement of Science. He is married to the former Janet Lynn Arseneault of Cheverly, Maryland.