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BLOOD PRESSURE AND HEART RATE RESPONSES DURING CHRONIC EXPOSURE TO SIDMAN AVOIDANCE AND YOKED CONTROL PROCEDURES IN THE RAT

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

David M. Murray

December 1978

1371160

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DEDICATION

This effort is dedicated to my parents, Carl and Tina. Without their love, their prayers, their unfailing support and encouragement, I might have stopped long ago. They have given me life more than once.

ACKNOWLEDGMENTS

It is difficult to adequately express my appreciation for the efforts of James E. Lawler, my major professor. Our relationship has passed through several stages, some very difficult. I often strained his patience but possibly increased his sensitivity as well. I feel a great loss in leaving his laboratory at the very moment I sense our relationship moving into a new stage, one of deeper understanding and mutual respect.

I wish to thank John Malone, Eric Sundstrom and Schuyler Huck who have served as members of my committee. Their careful reading and frequent suggestions have added greatly to the final form of this Dissertation.

I want to thank Greg Barker and Larry Crawford who diligently assisted in the collection of the data. A special thanks goes to Greg without whose efforts I would never have completed analysis of the data on time.

I wish to thank Rene Culver who initiated me into the world of electronics and solid state circuits. Her teachings and guidance made possible the construction of much of the equipment described here.

I want to thank Kathy McNally who sat up with me late into the night working on my discussion chapter. Her suggestions were most helpful.

I want to thank Ethel Eissenberg who really got me into this field in the first place. Her support and friendship over the past 5 years are greatly appreciated.

Several persons need consideration for their enduring moral and spiritual support. Debra Kirby, often my only apparent friend in my work, deserves special mention; I have greatly valued our relationship. Rene Culver has offered long distance moral support in times of great need. John Malone lent an objective ear when it was most needed.

Jim Striegel and Jamey Judge have propped me up when I was sinking on several occasions. My family has gone through this experience with me, offering support and encouragement, and offering assistance whenever possible.

Perhaps no one has helped more than Paula Jane Denman. She came into my life just before the most difficult period in my graduate program and at a major turning point in my life. She stood by me and comforted me, encouraged me, massaged my aching heart and soul. Without her, I surely would not have completed this work and might have failed altogether. I only hope that I can continue to earn her love and respect, for she surely has mine.

ABSTRACT

Twenty-four normal Long-Evans hooded rats were exposed for 3 months to either Sidman avoidance, yoked control or non-shock control procedures. While previous work indicated that psychological stressors might play a causal role in the etiology of essential hypertension, the long term effects of these oversize procedures were unclear. Blood pressure and heart rate data were collected weekly using a tail plethysmographic technique. Direct cardiovascular measurements were made at the end of the exposure period via an aortic cannula. The results indicated that prolonged exposure to such procedures did not adversely affect the cardiovascular responses monitored. It is suggested that the long term effects of such procedures differ from the short term effects of such procedures and that the absence of long term adverse effects may be due to adaptation to the procedures. A distinction is made between stressors and aversive events and questions concerning the adequacy of the stress induced hypertension model are discussed.

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CHAPTER I

INTRODUCTION

There should be little doubt that elevated blood pressure, from whatever cause, seriously increases the risk of coronary heart disease (CHD) and death. As early as 1944, reports of the significance of even transient elevations of pressure for later development of cardiovascular and renal disease were appearing in the literature (e.g., Levy, Hillman and Stroud, 1944). Smirk (1967) said that episodes of elevated pressures which occur repeatedly over a period of 10 to 30 years generally cause disease of the vascular bed and lead to organ dysfunction. Kannel, Schwartz, and McNamara (1969) reported that high levels of either systolic or diastolic blood pressure were closely related to the major manifestations of CHD including angina, coronary insufficiency, infarction and sudden death. More recently, Kannel, McGee, and Gordon (1976) have described a general cardiovascular risk profile based on their work in the longitudinal research program at Framingham, Massachusetts. They cited inactivity, obesity, cigarette smoking, diabetes, elevated serum cholesterol, evidence of left ventricular hypertrophy, and elevated blood pressure as the individual risk factors with the greatest combined predictability for future heart disease. Of those factors, the level of systolic blood pressure was considered to be the single most useful factor for detection of a person at high risk of cardiovascular disease.

The increasing awareness of the importance of blood pressure for future cardiovascular distress has led to a tremendous research effort aimed at understanding blood pressure and its control system. It has

also led to considerable research aimed at discovering the mechanisms underlying the various forms of hypertension. This paper describes the results of a study aimed at evaluating the role of Sidman avoidance and yoked control procedures (serving as psychological stressors) as possible initiating events in the development of hypertension in rats.

Psychological stress has been considered as a possible initiating mechanism in essential hypertension, the most prevalent of the arterial hypertensive diseases, for some time (cf. below). The investigation of this possible role requires expertise in several disparate fields. The study of the disease itself and the physiology involved cannot be placed in a secondary position to the consideration of psychological variables. One must have some familiarity with cardiovascular physiology and anatomy to determine whether it is even conceivable that psychological factors play a role in producing hypertension. This necessitates both the study of normal cardiovascular regulation and function as well as the study of animal models of hypertension. Finally, if animal models are to play any explanatory role in human hypertension, one must also learn about the known and suggested mechanisms of human hypertension.

The purpose of this introduction is to be representative of the knowledge related to normal arterial blood pressure regulation, known mechanisms for arterial hypertension, the physiology of human essential hypertension, animal models of hypertension, and animal studies of psychological stress and physiological responses. Each of these will be considered in turn.

A. THE REGULATION OF ARTERIAL BLOOD PRESSURE

Recent reviews on the regulation of arterial blood pressure are numerous (Braunwald, 1974; Guyton, Coleman, and Granger, 1972; Herd, 1970; Korner, 1971; Linden, 1972; Ross, 1971; Sagawa, Kumada and Schramm, 1974; Scher, 1977; Smith, 1974; Vatner and Braunwald, 1975). Only a brief overview will be given here. The regulation of arterial pressure will be considered as coming from one of three sources: (1) cardiovascular hemodynamics, (2) neural actions, or (3) the renin-angiotensin-aldosterone system. These three components are by no means the only ones involved in arterial pressure regulation nor are they independent. Indeed, these components are intimately interrelated.

Cardiovascular hemodynamics

Blood pressure, the force of the blood against the blood vessel wall, is the product of total peripheral resistance (TPR) and cardiac output (CO); the cardiac output is the product of heart rate (HR) and stroke volume (SV) (Feigl, 1974). TPR is a measure of the resistance offered to the flow of blood and therefore is a measure of the degree of vasodilation or vasoconstriction of the vasculature. The greater the vasodilation, the lower the TPR; conversely, the higher the vasoconstriction, the greater the TPR. The degree of vasoconstriction of the vessels is determined by several factors, most important of which are the degree of alpha adrenergic stimulation and local metabolite concentration. Activation of alpha adrenergic receptors located in the smooth muscle surrounding the blood vessels, particularly the arterioles, causes contraction of the smooth muscle and subsequent vasoconstriction. High

concentrations of local metabolities, e.g. those produced during exercise, cause vasodilation.

CO refers to the volume of blood ejected from the heart in one minute. SV refers to the volume of blood ejected from the heart in one myocardial contraction and HR of course refers to the number of such contractions in one minute. HR is primarily under neural control while SV is under both neural and non-neural control. Non-neural factors involved in SV include the contractility of the heart (the forcefulness with which the heart contracts), venous return (the amount of blood emptied into the heart between contractions), and the aortic pressure (the pressure against which the heart must work to eject blood).

Neural activity

Neural involvement in arterial pressure regulation may be seen as deriving from four sources: (1) arterial baroreceptor reflex, (2) direct neural action on the heart, (3) innervation of the adrenal gland, and (4) innervation of the smooth musculature of the blood vessels.

The principal receptors involved in the arterial baroreceptor reflex are located at two sites: the carotid receptors located at the bifurcation of the common carotid arteries and the aortic receptors found along the common carotid artery and at the points of origin of the subclavian arteries. Afferent neural fibers from the carotid receptors feed into the glossopharyngeal nerve while those from the aortic receptors travel in the vagus nerve. All afferents enter the brain stem with their respective cranial nerves and travel to the area of the obex in the medulla. They synapse in close proximity to the nucleus and tractus solatarius and

the dorsal motor nucleus of the vagus, areas which serve as major components of the sympathetic and parasympathetic branches of the autonomic nervous system.

The mechanism of the arterial baroreceptor reflex has been well studied and described (e.g., Kirchheim, 1976; Scherr, 1977). When arterial blood pressure falls, activity of the pressure receptors decreases resulting in a reflex increase in sympathetic activity combined with a decrease in parasympathetic activity. The results include an increase in heart rate via decreased vagal tone and increased activity from the right branch of the ansa subclavia, and an increase in contractility via increased activity from the left branch. In addition, alpha adrenergic stimulation of the smooth muscles of the peripheral vasculature results in vasoconstriction. The effect of these actions upon blood pressure is to increase it via increased CO and TPR. When arterial blood pressure rises, these actions are reversed and pressure falls. That the reflex can be modulated by the activity of higher centers has been demonstrated (Gebber and Klevans, 1972). The reflex is active over a moderate range of pressures and seems to act to maintain arterial pressure within narrow limits of what has been referred to as the set point or normal pressure (cf. Korner, 1971). Several authors have argued that the significance of this reflex is minimal for long term regulation of pressure although it is important in short term regulation (e.g., Guyton et al., 1972). The action of this reflex is very rapid.

Direct neural action on the heart independent of the baroreceptor reflex also affects pressure. The sinoatrial node, located on the surface of the right atrium, receives input from both the sympathetic and

parasympathetic branches. Vagal stimulation reduces heart rate while a reduction in basal vagal tone increases heart rate. Sympathetic stimulation increases heart rate and, via receptors in the ventricles, increases contractility through beta adrenergic action.[1]

Sympathetic stimulation of the adrenal medulla results in increased release of epinephrine and nonrepinephrine, sympathetic agonists, into the bloodstream. These circulating catecholamines have direct effects on the vasculature as well as the heart.

Direct sympathetic stimulation or circulating catecholamines act via alpha adrenergic innervation of the peripheral vessels, primarily the arterioles, to increase vasoconstriction, resulting in increased TPR and pressure as described above. This action is also a component of the baroreceptor reflex as described above.

There are also more centrally mediated neural actions. Osmoreceptors located in the supraoptic and paraventricular nuclei of the hypothalamus are sensitive to the osmolarity of the blood and cause the posterior pituitary gland to release anti-diuretic hormone (ADH) when the blood is hypertonic. ADH acts to promote water retention. The hypothalamus also determines the rate of release of corticotropin releasing factor which acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal cortex causing the release of cortisol

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[1]Beta adrenergic action refers to sympathetic action mediated by beta receptors. The sympathetic system includes at least two receptor types. The alpha receptors are found primarily in the peripheral vessels and mediate vasoconstriction. The beta receptors are found primarily in the heart and mediate changes in heart rate and contractility. There are in addition actions of both receptor types in noncardiovascular systems.

and enhancing the release of aldosterone (cf. below). Cortisol increases the rates of protein, fat, and carbohydrate metabolism and has mild effects on water balance, resulting in sodium retention and increases in total blood volume.

The Renin-Angiotensin-Aldosterone System

The hemodynamic and neural components of the arterial pressure regulatory system act primarily by changing the resistance of the vasculature or the force of the blood flow. The renin-angiotensin-aldosterone system acts not only via these routes but also via its effect on the volume of blood (plasma volume).

Renin release is controlled by three mechanisms: (1) intrarenal receptors found in the macula densa and the renal afferent arteriole, (2) renal sympathetic nerves, and (3) circulating agents such as the catecholamines, sodium and potasium ions, and several hormones (Davis and Freeman, 1976). A drop in renal perfusion pressure results in an increase in renin release. Renin acts on a-2-globulin in the plasma to produce angiotensin I which is converted in the lungs into angiotensin II. This substance acts on the adrenal cortex to cause the release of aldosterone. Aldosterone then acts on the renal tubules to enhance sodium reabsorption (Woodbury, 1974). Aldosterone also enhances the release of ADH in the pituitary. Both actions serve to increase the plasma volume. An increase in plasma volume serves to increase blood pressure, all things being constant, thereby improving renal perfusion pressure and providing closure for a negative feedback loop.

In addition to these actions on volume, this system, through angiotensin II, has other effects. Angiotensin II has direct pressor

effects on the alpha adrenergic receptors in the peripheral vasculature, thereby raising TPR.

The renin-angiotensin-aldosterone system is really only one component of renal involvement in blood pressure regulation. Guyton, Coleman and Granger (1972) have argued that the kidney is the single most important component in the arterial pressure regulation system. They suggest that through the renal function of sodium balance (matching urinary output to sodium intake), long term blood pressure regulation is achieved.

Summary

The regulation of arterial blood pressure is complex and involves several interrelated systems. Hemodynamic forces define blood pressure instantaneously . Neural actions serve to maintain pressure within tight limits on a short term basis. The sodium balance actions of the kidney and renin-angiotensin-aldosterone system serve to regulate pressure on a more long term basis. It is generally accepted that hypertension is a disease of regulation and that it results from a dysfunction in one or more of the regulating systems described above. Some of these specific and identified dysfunctions are described in the next section.

B. KNOWN MECHANISMS FOR ARTERIAL HYPERTENSION

Hypertension is commonly referred to as a disease of regulation (Page and McCubbin, 1965). This view holds that hypertension is the result of a dysfunction in the pressure regulatory system and is an a attempt by the body to compensate for the dysfunction. Thus, hypertension is a symptom of some underlying disturbance; to make the situation more

difficult, often the high pressure masks the original disturbance producing a situation in which certain measures, which early in the development of the disease may have given some indication of the dysfunction, later appear normal since the elevated pressure has compensated for the disturbance. Presented below is a brief review of the known mechanisms for arterial hypertension with an emphasis placed on relating the disease states to the regulatory system described above.

Sir George Pickering, long an opponent of the notion of "hypertension" and a proponent of the view that hypertensives simply represent the upper end of a normal distribution of blood pressures, has recently described the types of hypertension, their natural histories and their consequences (Pickering, 1972). The material presented below is in part adapted from his presentation.

Renal Disease

A large number of disease states of the kidney produce hypertension. Nephritis, a localized or generalized inflammation of portions of the kidney, may be seen in at least 51 varieties.[2] Many lead to elevated pressure and many are fatal. Pyelonephritis is an extended form and includes inflammation of the pelvic region. Renal artery stenosis, the narrowing of the renal artery, reduces renal perfusion pressure and can induce hypertension through the renin-angiotensin-aldosterone system described above. The reduced perfusion pressure would cause increased output of renin, eventually leading to enhanced sodium retention and

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[2]This figure was taken from Dorland's Illustrated Medical Dictionary, twenty-fifth edition. Philadelphia: Saunders, 1974.

expanded plasma volume and vasoconstriction. Both factors would elevate pressure even though pressure was not low to begin with. Any one of a number of primary disturbances can cause secondary renal artery stenosis. Renal stones or other materials or lesions obstructing the urinary tract can predispose the individual to pyelonephritis. Atherosclerosis involving vessels of the kidney can be a primary cause leading to restricted renal blood flow. Certain tumors can cause renal dysfunction leading to hypertension.

Coarctation of the Aorta

This condition is characterized by a severe narrowing of the lumen of the initial segment of the aorta. This section of aorta is normally very important in absorbing much of the energy generated by the ejection of blood from the heart into the aorta and usually maintains systolic pressure at a normal level. When the vessel is restricted, the blood is forced through collateral channels which do not have the elasticity which the aorta has and therefore cannot absorb the energy in the same way. The result is an abnormally high systolic pressure and pulse pressure (Dustan, Tarazi and Bravo, 1972).

Pheochromocytoma

This condition involves a tumor of the chromaffin tissue of the adrenal medulla or of the sympathetic ganglia in the neck. The effect is a sustained, abnormally high release of catecholamines resulting in very high pressure. Removal of the tumor is effective treatment.

Cushing's syndrome

Cushing's syndrome involves hypersecretion of cortisol from the adrenal cortex; the hypersecretion may be due to some disorder of the adrenal gland or to hyperactivity of the anterior pituitary gland resulting in elevated ACTH levels (cf. above). The increase in retention of sodium may lead to edema in the walls of the arterioles (Tobian, 1972), thus increasing TPR. Cushing's syndrome requires elevated cortisol secretion over an extended period of time.

Primary aldosteronism

Also called Conn's syndrome, primary aldosteronism involves hypersecretion of another adrenocortical steriod, aldosterone. This form of hypertension is fairly easy to detect since the abnormally low blood potassium levels found are not associated with other forms of hypertension. Aldosterone is a very potent agent for renal sodium retention and the resultant increase in total plasma volume, the major cause of the elevated pressure.

Toxaemia Hypertension in Pregnancy

There are several forms of this metabolic disorder, all of which involve the absorption of bacterial toxins from the stomach or other portion of the gastrointestinal tract. This often occurs in late pregnancy and involves hypertension, edema, and albuminuria (the presence in the urine of albumin, a protein normally found in the blood).

Summary

The six categories listed above virtually exhaust all known mechanisms for arterial hypertension. Each of these, except perhaps

toxaemia, is a disease of the regulatory process. While these mechanisms are fairly well defined, they do not explain the vast majority of cases of hypertension, as described in the next section.

C. THE PHYSIOLOGY OF ESSENTIAL HYPERTENSION

While the list of known causes for arterial hypertension is rather long, perhaps 80 to 90 percent of all cases of arterial hypertension fall into a different category, essential hypertension (Page and McCubbin, 1965). Essential hypertension is defined as an elevation in blood pressure with no identifiable cause. A tremendous quantity of work has been done over the past 15 years concerning the hemodynamics and physiology of essential hypertension, particularly in the last 5 years. A review of that literature will be presented below. The outline of this section is adapted from that used in a recent and excellent review of the mechanisms of essential hypertension by Birkenhager and Schalekamp (1976). The topics to be discussed are system hemodynamics, renal hemodynamics and renal function, body fluids in essential hypertension, the adrenergic system in essential hypertension, and renin, angiotensin and aldosterone. It is to be stressed that these physiological systems are not independent. They do interact and to focus attention entirely upon one area is to make a serious error.

System hemodynamics

A distinction must be drawn between two subclasses of essential hypertension, particularly in regard to system hemodynamics. The two subclasses are labile hypertension and chronic hypertension.

Labile hypertensives, it is generally agreed, display abnormally high variability in pressure and occasionally have pressures in the hypertensive range. Chronic hypertensives on the other hand show normal variability in pressure and have pressures which remain at hypertensive levels (approximately 150/95 mm Hg although some would suggest that the line be set higher). As there are two subclasses of essential hypertension as regards variability and normal readings, so there are two classes of system hemodynamics.

Eich, Cuddy, and Smulyan (1966) observed that labile hypertensives generally displayed abnormally high CO and normal or slightly low TPR while chronic hypertensives displayed the opposite pattern. They suggested that the elevation in pressure in labile hypertensives was due to the increased CO while that of the chronic hypertensives was due to the increased TPR. They offered no explanation for the elevated CO or the mechanism for the transition from the first pattern to the second (since they argued that the early pattern was simply a precursor to the second). Their observation has since been confirmed repeatedly and the two patterns are generally accepted (Birkenhager and Schalekamp, 1976; Dustan, Tarazi, and Brava, 1972).

Considerable effort has been expended in attempts to discover the cause of the increased CO in labile hypertensives, for the increased TPR in chronic hypertensives, and for a mechanism by which the transition from the first to the second occurs. Frohlich, Tarazi, and Dustan (1969) have suggested that the elevated CO in labile hypertension is due to abnormally increased sympathetic outflow combined with abnormally decreased parasympathetic outflow. Other possible causes include increased venous return and increased contractility.

While the question of why CO is increased remains unanswered, the reason for increased TPR seems to be emerging. There is limited data suggesting that even in labile hypertensives there is a decrease in the compliance of the peripheral vessels. This comes from observations that such hypertensives do not vasodilate under extreme excercise to the same extent that normotensives do (Tobian, 1972). It is possible that a process of arterial vascular change is begun at that stage. It is clear that such changes occur in chronic hypertensives and that they lead to a reduction in the lumen of the vessels thereby increasing TPR (Folkow, Hallback, Lundgren and Weiss, 1970).

The mechanism for the transition from high CO, low TPR hypertension to low or normal CO, high TPR also remains a point of controversy and considerable research. Birkenhager and Schalekamp (1976) have suggested that the elevated CO in labile hypertensives may be due to a sustained contractile force acting on the heart and blood vessels thereby increasing pressure and that this prolonged elevated pressure results in structural changes in the vessels, providing a mechanism for permanent and chronic hypertension. The permanent pressure elevation would then mask the contractile force were it still operative. They do not name the contractile force but hint that it might be sympathetic activity.

Renal Hemodynamics and Renal Function

The kidney is a likely suspect when considering the etiology of essential hypertension since so many forms of renal disease include hypertension as a symptom, and since so many forms of experimental hypertension involve procedures affecting the kidney (cf. the section below concerning

animal models for essential hypertension). It is also quite clear that the kidney is a central target in many hypertensive diseases. The question to be dealt with is whether the kidney's role is primary or secondary.

The strongest proponent for the primary role of the kidney is Guyton (Guyton, Coleman, Cowley, Manning, Norman, and Ferguson, 1974; Guyton, Coleman, Cowley, Scheel, Manning, and Norman, 1972; Guyton, Coleman, and Granger, 1972). His argument is persuasive, at least in part. Normally an increase in blood pressure would produce enhanced natriuresis (excretion of sodium and concomitant excretion of water in the urine) leading to a return of pressure to normal values. Guyton and his colleagues have argued that the only way to effect long term alterations in blood pressure is to alter the blood pressure/urinary sodium output relation such that a higher pressure is required to excrete the same amount of sodium. Sodium balance would be achieved at the expense of elevated arterial pressure. Guyton et al. (1974) listed about 15 factors which can act directly on pre-tubular pressure or tubular pressure to change the shape of the renal function curve (a plot of urinary sodium output against blood pressure), but stressed the pre-tubular factors. Those factors included plasma osmotic pressure, glomerular filtration coefficient, intrisic afferent arteriolar resistance, sympathetic stimulation, renin secretion, renal interstitial pressure and postglomerular resistance.

The available data on renal function in essential hypertension offer some support for this position. Glomerular filtration remains fairly

normal until late in the disease state when the kidney begins to fail. On the other hand, renal blood flow, and therefore renal pressure, drops off considerably due to increased renal vascular resistance. As the disease progresses, it has been proposed that renin levels rise as renal stenosis develops, providing elevated renin levels in the face of diminished renal function. This could provide a mechanism for sustaining the hypertension even if the cause for the initial elevation were no longer present (Birkenhager and Schalekamp, 1976).

This description does not answer the question of how the pressure becomes elevated in the first place, however. Guyton et al. (1972a, 1972b, 1974) began with the assumption that pressure was already high due to elevated cardiac output caused by increased total blood volume. His premise that total blood volume is increased is open to question, at least in borderline or labile hypertension (Birkenhager and Schalekamp, 1976). There is even evidence that increased CO is not a universal finding (Fletcher, Korner, Angus and Oliver, 1976), although it is generally accepted as the first stage of essential hypertension. There is no clear understanding as to how or why this initial increase in CO occurs. While Guyton's proposal has considerable merit as a mechanism for sustaining hypertension, one must question whether his system really stands alone as evidence for a primary renal role in the etiology of essential hypertension. It appears more likely that the role of the kidney is secondary.

Body Fluids in Essential Hypertension

Early investigators reported an elevation in plasma and extracellular fluid volumes in a certain percentage of essential hypertensives

(Jose, Crout, and Kaplan, 1970). Laragh (1973) recently cited this paper, circumstantial evidence based on findings in primary aldosteronism and the effects of diuretics to further expound that position.

Birkenhager and Schalekamp (1976) reviewed the work concerning elevated plasma and extracellular fluid volumes in essential hypertension and found it lacking. They cited many papers demonstrating no increase in fluid volumes. Indeed, there was some question as to whether the levels were normal or somewhat below normal. These authors concluded that body fluid volumes played no central role in essential hypertension.

The Adrenergic System in Essential Hypertension

Autonomic nervous system involvement in the etiology of essential hypertension via sympathetic activity has long been proposed. Since Cannon (1923) demonstrated that psychological stimuli could elicit changes in the activity of the autonomic nervous system, many have argued for adrenergic involvement including Selye (1946), Alexander (1950), and Mahl (1953). Yet the precise role of the adrenergic system in essential hypertension remains to be elucidated. Below is a brief review of recent work in this area.

Sympathetic activity can be crudely evaluated using a measure of HR or blood pressure (BP) in response to postural adjustments. Borderline hypertensives showed no more than a normal response to such adjustments while chronic hypertensives displayed an exaggerated increase in HR and BP (Birkenhager and Schalekamp, 1976). This finding is suggestive of increased adrenergic activity, but could be due to a normal adrenergic response in chronic hypertensives who had structural thickening of the vasculature.

Another line of evidence suggestive of enhanced adrenergic activity is increased plasma norepinephrine often found in hypertensive patients. (Birkenhager and Schalekamp, 1976). To the extent that plasma nonrepinephrine is a true measure of sympathetic activity, this would suggest that increased sympathetic activity may contribute to hypertension.

Other authors have gone even further. Julius and Esler (1975) have proposed that elevated renin borderline hypertension is neurogenic. They reported that propranolol reduces CO in borderline hypertensives and that alpha adrenergic blockade reduces TPR in those cases. They have stressed the importance of beta adrenergic receptors in the kidney for production of renin (cf. Zanchetti, 1977). Esler, Julius, Zweifler, Randall, Harburg, Gardiner, and DeQuattro (1977) have extended these arguments and drawn the same conclusion.

A very different approach to studying the involvement of the sympathetic nervous system in the etiology of hypertension has been employed by psychologists and psychophysiologists. These researchers have, in general, attempted to induce hypertension in animals through prolonged exposure to psychological stressors. Implicit in this work has been the assumption that such exposure leads to sympathetic activation. While it seems clear that this is the case in terms of short term actions, the long term effects have not always been clear. This literature will receive close attention in a later section.

To suggest that sympathetic overactivity or oversensitivity is the root cause of essential hypertension, and that such overactivity is masked by later developments and unncessary for later sustained

hypertension, is appealing because clinical reports that essential hypertensives are more tense, appear to be under more stress, etc., are frequent enough to suggest such a cause. It appears that many researchers are beginning to desire that sympathetic activity by shown to be the culprit (e.g. Birkenhager and Schalekamp, 1976). Yet the available data on that possibility are not convincing.

One must consider possible reasons for the lack of evidence. It is possible that the sympathetic system does not serve an initiating function no matter how appealing that possibility is. Another possibility is that our measures of sympathetic activity are poor. Only indirect methods are available and all are fraught with problems. There are no direct measures available and it may be impossible to make much progress in this area until such measures are available. A final possible explanation for the paucity in evidence is that the procedures utilized in these experiments simply were not stressful in spite of the intentions of the investigators. Morse and Kelleher (1977) have recently reminded psychologists that an event, no matter how aversive it may seem, cannot be considered to be aversive until it is considered in its context. It must have the proper impact and effect before it can be considered to be aversive. This point will be considered later after a review of this literature.

Renin, Angiotensin, and Aldosterone

The wide range of values of plasma renin and aldosterone has spurred many investigators to consider the possibility that all essential hypertensives do not share a common disease. Laragh (1973) has gone so

far as to propose that at least three subtypes of essential hypertension exist based on renin and aldosterone levels. According to his scheme, 30 percent of all essential hypertensives have low renin (LRH), approximately 57 percent have normal renin (NRH), while the remaining cases have high plasma renin (HRH)

According to Laragh, LRH is characterized by a chronic expansion of plasma and extracellular fluid volumes (a point disputed above), respond well to diuretics, and have low blood urea levels. He proposed increased salt intake, decreased renal ability to excrete sodium or potassium and adrenal disturbances as possible mechanisms.

HRH appeared to involve considerable sympathetic activity since propranolol led to a decrease in both blood pressure and renin. Renal damage was also observed.

NRH displayed normal renin, aldosterone, and sodium blanace. However, the elevated pressure should have reduced renin output and it was still normal. Laragh suggested that renal damage may have caused this dysfunction.

Birkenhager and Schalekamp (1976) have sharply disagreed with Laragh and said that the division of hypertensives into subpopulations on the basis of renin or aldosterone levels is purely arbitrary. Mitchell (1977) recently expressed a similar view. Birkenhager and Schalekamp suggested that rather than interpret the variance of renin and aldosterone measures as depicting distinct subpopulations, it was more appropriate and made more sense from the other data to consider the different levels as representing different stages in a progressive disease. They suggested that the earliest stages of hypertension are characterized by normal

renin levels, fluctuating blood pressure elevates by increased cardiac output, normal peripheral resistance, and an absence of renal damage. As the disease progresses, the elevation in pressure becomes more fixed, renin secretion is suppressed by the elevated pressure, and the cause of the elevation begins to shift from cardiac output to an elevated total peripheral resistance. As the high pressure becomes more persistent, structural changes in the vascular beds begin, including stenosis of the renal arteries. As renal perfusion pressure drops, renin secretion increases towards normal in spite of the elevated system pressure. A second type of normal renin hypertension is then present, one with renal damage. As the kidney continues to fail and the hypertension becomes malignant, the renin secretion increases further until the classic symptoms of malignant high renin hypertension are present.

Their proposal does explain the heterogeneity of renal condition observed in normal renin hypertensives, as well as the conflicting reports on response to hypertensive drugs in this group. As Birkenhager and Schalekamp point out, further information concerning the natural course of the hypertensive disease state is needed before accepting their proposal. It is important to recognize however that their suggestion does provide a potential mechanism for the transition from labile to stable hypertension.

Summary

The general hemodynamic pattern of the disease is clear, if one is willing to assume that what has been termed the labile stage is just that and is a precursor to the stable stage. The disease state is initially

characterized by elevated pressure due to increased cardiac output and normal total peripheral resistance. The data provide a possible initiating mechanism, acting through the adrenergic system, which could produce the initial elevation in cardiac output. The mechanism whereby this occurs is far from understood. The data suggest a potential explanation of how the transition from the labile to the stable phase occurs, assuming one views the renin activity data in the way that Birkenhager and Schalekamp do. But even if the transition involves a shift from low renin to high renin, their explanatory mechanism remains to be confirmed. Guyton provides a possible sustaining mechanism through his proposal that over the long term, changes in the relationship between urinary output and sodium balance result in normal balance at the cost of elevated pressure.

Several items remain to be settled. Obviously, each of the points outlined above is very tentative and requires considerable research in the future. The verification of Guyton's work and Birkenhager and Schalekamp's proposal would provide considerable help to the researchers in this field. The question which remains wide open is that of the initiating mechanism, however. The next section will deal with several proposed initiating mechanisms.

D. PROPOSED INITIATING MECHANISMS FOR ESSENTIAL HYPERTENSION: ANIMAL MODELS

Renovascular Mechanisms

Goldblatt (1934) first demonstrated that hypertension could be experimentally induced with restriction of renal artery blood flow. This was an important step in understanding the importance of renal artery

stenosis and its effects. Hypertension can also be induced by continuous infusion of renin or angiotensin, although the elevations are not as great. A normal kidney, when faced with continued elevations in pressure, will alter its function so as to sustain the elevations in pressure, as shown by the finding that hypertension may be induced by restricting the flow of blood in one kidney while leaving the other kidney alone.

Salt and Mineralocorticoid Excess

Hypertension may be induced in rats by adding salt to their drinking water. Desoxycorticosterone can also cause hypertension unless the diet is salt free.

Neurogenic

Bilateral transection of the carotid sinus and aortic nerves produces hypertension except in sleep. The baroreceptor reflex is disconnected and unable to cope with changes in pressure demands or physical or emotional stressors. Bilateral lesions of the nucleus and tractus solatarius abolish baroreceptor reflexes and result in a fulminating hypertension due to intense sympathetic discharge and peripheral vasoconstriction by alpha receptors. The stroke volume and cardiac output are reduced while heart rate is increased.

Genetic

Several strains of spontaneously hypertensive rats have been bred. The mechanisms which produce the hypertension in these strains are not understood. Other strains have been bred which are especially sensitive to hypertension due to other interventions such as salt loading; again,

the mechanisms which operate to produce the hypertension are not clearly understood.

Environmental and Psychological

Environmental stressors produce clear cardiovascular changes which last but a short time. The relationship between these short term responses and permanent hypertension is still not established. A much more extensive review of the literature concerning environmental and psychological initiating mechanisms for essential hypertension is given in the next section.

Summary

Several animal models have been developed for essential hypertension. Each of the animal models discribed here is under continuing investigation. The model of interest in this paper is that involving environmental and psychological stressors; for that reason, the next section will devote considerable space to careful review of the research related to that model.

E. PSYCHOPHYSIOLOGICAL RESEARCH IN SUPPORT OF STRESS INDUCED HYPERTENSION

Chronic Exposure to Sensory Stimulation

Auditory stimulation. Medoff and Bongiovanni (1945) reported that rats receiving audiogenic stimulation for a period of one to two years had a significantly greater incidence of pressures above 180 mm Hg than their controls. No such difference obtained for animals having less than one year of such stimulation. Farris, Yeakel, and Medhoff (1945) reported

that more than 80 percent of the experimental animals receiving such stimulation who scored high in emotionality in an open field test developed pressures greater than 160 mm Hg after about 8 months; however, control subjects and experimental subjects who scored low on the emotionality test had normal pressures.

It is of interest to note that of the 10 hypertensive animals in the older group used by Medoff and Bongiovanni (1945), 6 were littermates and half were controls. This suggests that genetic factors may have been involved.

Auditory, visual, and motion stimulation. Hudak and Buckley (1961) reported that rats subjected to a combination of audiogenic stimuli, visual stimuli, and motion stress developed hypertension in excess of 150 mm Hg by the end of 28 weeks of exposure. It should be noted that the subject mortality rate was extremely high in this study.

Buckley, Kato, Kinnard, Aceto, and Estevez (1964), using the same procedure, examined the effects of saline, reserpine, or chlorpromazine injections on the hypertensive response. Systolic blood pressure rose from 132 mm Hg to 154 mm Hg over a 27 week period regardless of the type of drug given. These animals exhibited normal weight gain (100 percent) over the same period. Autopsy revealed damage to all portions of the adrenal glands in all groups and evidence of left ventricular hypertrophy in many animals. It is of interest to note that the mortality rate in the reserpinized group was three times that of the other two groups.

The absence of adequate controls in this study makes it difficult to evaluate the results. Campbell and Stanley (1964) have described in

detail the variety of alternative hypotheses which may be suggested in cases such as this.

Rosencrans, Watzman, and Buckley (1966) employed a well controlled design using this paradigm and confirmed and extended the previous findings. They reported that mean blood pressure rose from initial levels of 103 mm Hg to 145 mm Hg after 12 weeks of stress compared to a 12mm Hg increase in mean pressure in control subjects over the same period. The pressure continued to rise for 4 weeks even after termination of the stressors.

They noted that urinary catecholamine levels increased sharply in the stressed rats and gradually returned to control levels by the end of the eighth week; in fact, urinary catecholamine levels actually remained below control values for the remainder of the study in the stressed rats. A decrease in adrenal epinephrine (E) paralleled the increase in the urinary level of that catecholamine and thus the adrenal medulla was likely the source for the increased plasma levels. Only a slight decrease was seen in adrenal norepinephrine (NE) and thus it is likely that much of the increased urinary level was due to either increased peripheral turnover of NE or to poor specificity of the assay technique. Adrenal corticosterone content doubled after a single stress session but returned to control levels by the end of the eighth week as well. Plasma corticosterone levels increased in a similar pattern. It is important to note, however, that the corticosterone levels increased once again beginning at about the ninth week and resulted in significant elevations by the sixteenth week.

Rosencrans et al. (1966) concluded that the adrenal medulla was primarily involved during the acute phase of the stress response while the adrenal cortex was primarily involved during the chronic phase. They also argued that excessive plasma and tissue catecholamine levels are not involved in the chronic maintenance of the hypertension since the urinary levels were below those of controls after 8 weeks. They suggested instead that the vasculature might simply be hypersensitive to normal or subnormal levels of the catecholamines.

Although Rosencrans et al. (1966) used multiple t-tests in the analysis of their data, a procedure fraught with Type I error problems (Myers, 1972; Winer, 1971), the magnitude and consistency of the effects obtained do seem to confirm the hypertensinogenic effect of prolonged exposure to auditory, visual, and motion stimulation. The problems of high mortality and poor design in the earlier studies were corrected in this study.

Smookler and Buckley (1969, 1970) attempted to delineate more fully the biochemical processes involved in this hypertensive response. In the first experiment reported, rats developed a progressive elevation of pressure resulting in hypertension; the experimental subjects averaged 155 mm Hg systolic while the control subjects averaged only 115 mm Hg systolic. The peak pressure again was reached at the eighth week and the elevations remained for the full 20 weeks of observation. Serum corticosterone levels again rose sharply during the first 4 weeks of stress and then dropped below control levels. No significant alterations in brain NE or dopamine (DA) were obtained. No firm conclusions could be drawn concerning the biochemical mechanisms involved in the hypertension.

In the second experiment, Smookler and Buckley (1970) administered a-methyl-tyrosine (aMT), a reversible inhibitor of the rate limiting enzyme for catecholamine synthesis, to the rats daily during the stress period of 14 weeks. This was done in an attempt to assess the turnover rates for brain NE and DA.[3] The results indicated that a significant increase in turnover for brain NE occurred during the first 4 weeks of stress but disappeared by the sixth week. No such effect was obtained for brain DA. Rats receiving the stress and no drug exhibited the same blood pressure increase pattern obtained previously but subjects receiving the aMT did not display a hypertensive response.

Smookler and Buckley (1970) concluded that the acute phase of the stress response involved central sympathetic activation leading to increased release of ACTH (adrenocorticotropic hormone) from the anterior pituitary and therefore increased adrenal steroid secretion.[4] The aMT prevented the increase in the rate of synthesis of brain NE, thereby compensating for the effect of stress and preventing the hypertensive

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[3]Alpha-methyl-tyrosine blocks the hydroxylation of tyrosine, the rate limiting step in the synthesis of catecholamines. By administering this drug, Smookler and Buckley apparently hoped to prevent the synthesis of new norepinephrine or dopamine; subsequent measurements of the brain levels of these catecholamines would indicate the rate of activity of central sympathetic fivers. The lower the brain levels, the higher the activity would have been since no new catecholamines could be produced. Goodman and Gilman (1975) suggest caution in the interpretation of data of this sort.

[4]The finding of increased turnover of brain NE and the conclusion that stress results in central sympathetic activation is in conflict with recent work by Weiss, Glazer, and Pohorechky (1976). Weiss et al. reported a central noradrenergic deficit, particularly in forebrain and limbic structures, in a variety of stress paradigms.

response. The chronic phase involved a decrease of central activity and steroid levels with elevated blood pressure maintained by some unknown process. They also noted that aMT shortens the duration of the increased corticosteroid levels from 4 weeks to 2 and suggested that the full development of the time course of the acute phase may be a necessary prerequisite for the chronic phase of the hypertensive response.

Smookler, Goebel, Siegel, and Clarke (1973) attempted to determine if the peripheral sympathetic system served as the mediator for this hypertensive response. They utilized 6-hydroxydopamine (6-OHDA) to chemically produce peripheral sympathectomy. Animals receiving the combination of stresses with no drug treatment developed the same hypertension found earlier. Animals treated with 6-OHDA and receiving the stress did not develop elevated pressure. Animals receiving only 6-OHDA exhibited a decrease in pressure compared to controls. That the drug treatment did serve to eliminate peripheral sympathetic activity was demonstrated by the lack of response to thoracolumbar stimulation of sympathetic fibers. Injections of NE also demonstrated that there were no differences in responsivity of peripheral receptors after development of the hypertension. They concluded that the peripheral sympathetic nervous system must be intact for the hypertensive response to occur.

Summary

The studies cited in this section seem to establish that repeated presentation of auditory, visual, and motion stimuli serve as stressors and can induce a hypertension which remains for at least some time following stressor termination. However, the stressors must be presented for

a period of approximately 8 weeks to obtain this effect. The hypertension may be due to central sympathetic activation resulting in increased turnover of brain NE and increased production of adrenal corticosteriods. The peripheral sympathetic nervous system must be intact and functioning normally for this hypertension to develop, and dysfunction of this system does not seem to occur as a result of the elevated pressure. Hypersensitivity of adrenergic receptors is not responsible for the hypertension as shown by Smookler et al. (1973). Adrenal release of catecholamines does not appear to be important since (1) such release is at normal levels following 8 weeks of stress and (2) the adrenal glands are not affected by 6-OHDA but 6-OHDA prevents the hypertensive response.

Chronic Exposure to Psychosocial Stimulation

Henry, Meehan, and Stephens (1967) presented evidence to support their argument that blood pressure levels do not change with age in normal populations. They argue that brief cardiovascular responses to symbolic stimuli, repeated frequently over time, result in sustained cardiovascular dysfunctions. In an effort to demonstrate the validity of this position, Henry and his coworkers conducted a series of studies involving chronic exposure to psychosocial stimulation in mice.

Henry et al. (1967) reported that there was no change with age in blood pressure levels in control CBA mice observed over a 21 month period. Mixing of young adult males from different litters resulted in systolic pressures of approximately 150 mm Hg which persisted for up to 12 months (compared to 120 mm Hg for controls). Aggregation accomplished by doubling the number of mice normally housed together in standard boxes resulted in sustained elevations of systolic pressure up to 160 mm Hg for 12 months and

which persisted even after freedom of movement was restored. The chronic presence of a predator also increased systolic pressures to 152 mm Hg, an effect which could be prevented by pretreating the subjects with reserpine (in sharp contrast to the findings of Buckley et al., 1964).

Early social isolation for 3 months followed by the placement of 48 males and females in an interconnected box system resulted in systolic pressures of 180 mm Hg by 7 months, poor weight gain and evidence of gross interstitial nephritis in a few animals. The elevated pressure remained even following return to isolation for 3 months, although the levels were not quite so high (156 mm Hg in the males and 141 Hg in the females). Animals placed in the interconnected box system without prior social isolation did not exhibit the hypertensive response.

Henry, Ely, Stephens, Ratcliffe, Santisteban, and Shapiro (1971) reported that 4 months of social isolation followed by 6 months in the crowded chamber resulted in increased frequencies of interstitial nephritis, myocardial fibrosis, and arteriosclerotic degeneration of the aorta and coronary vessels. Henry, Stephens, Axelrod, and Mueller (1971) reported elevations in several enzymes involved in the production of catecholamines using similar procedures.

Ely and Henry (1974) isolated mice for 6 months and observed that subsequent placement in the crowded chamber resulted in systolic pressure of 157 mm Hg while control mice had pressures of only 135 mm Hg. Adrenal weights were significantly higher for the experimental subjects. The size of the changes in pressure and adrenal weight compensate somewhat for the use of multiple t-tests in this study.

Henry, Stephens, and Santisteban (1975) replicated the earlier reports and provided some new data regarding the possible mechanism for this hypertension. Systolic blood pressure rose to 150 mm Hg within 30 days for all animals in the interconnected box system who had been isolated for 3 months. Mice again isolated following 60 days in the box system exhibited a gradual return of systolic pressure to control levels. This was also true, although to a lesser extent, for animals returned to isolation following 5 months in the system. Animals maintained in the crowded box for 9 months showed very little return to baseline systolic pressure levels. There was no difference in body weight between experimental animals and their appropriate controls.

Autopsy revealed an increase in ventricular weight which appeared to be reversible until about 9 months of psychosocial stimulation. There was also a significant increase in the degree of arteriosclerosis of the aorta with increasing time spent in the box. Finally, evidence of myocardial fibrosis was found in the experimental animals only.

Henry et al. (1975) argued that the lack of difference in body weight indicated no serious metabolic deficiency in the members of the experimental colonies. They also argued that the elevations in pressure were not due to increases in somatomotor activity. They suggested that

> sources of exaggerated [physiological] activation are the repeated confrontations with agonistic behavior that are evoked by the deficient early socialization . . . [and may lead to] progressive resetting of baroreceptor controls and to structural changes in precapillary resistance vessels.

(p. 162). The repeated activations would apparently be the cause of the increase in the adrenal medullary catecholamine-synthesizing enzymes

(Henry, Stephens, Axelrod, and Mueller, 1971). The arteriosclerosis observed involved increases in mucopolysaccharides in smooth muscle in mice exposed to short periods of psychosocial stimulation; such increases in the wall-to-lumen ratio are apparently easily reversed. In animals exposed for long periods of time, the changes in the vessels become more severe and less reversible. Henry et al. (1975) suggested that this was the cause for the irreversibility in blood pressure elevations in subjects exposed for long periods of time. They argued that the hypertension observed in their mice closely followed the pattern seen in man.

Summary. The data reported by Henry and his coworkers seem to establish that their procedures will produce a hypertension that does not significantly subside even after months away from the stressor. Exposure to the stressor must last at least 9 months for this effect to be obtained. The changes in arterial structure and heart weight are very suggestive as causes for this nonreversibility.

Classical Conditioning Paradigms

The literature on classical conditioning of autonomic responses is vast (see Harris and Brady, 1974, for a review). However, the number of studies which have examined blood pressure is rather limited. The number of studies specifically devoted to hypertension is even more limited. This discussion will focus on these latter papers.

Shapiro and Melhado (1957) evaluated the effect of classical aversive conditioning procedures on blood pressure in dogs, although their study was designed primarily to evaluate the relationship between renal injury and the severity of hypertension. All subjects were given a figure-of-eight tie of the left kidney and right nephrectomy; all

surviving subjects subsequently developed hypertension. Heart weight and adrenal weight increased significantly over intact controls. Dogs subjected to classical aversive conditioning following the surgery developed hypertension twice as fast as the nonstressed dogs, had greater heart size and adrenal size increases and had much more severe damage to the intact kidney. The authors concluded that the psychological stress enhanced the effects of the renal injury and therefore may be involved in the etiology of human essential hypertension.

Shapiro and Melhado (1958) used two classical aversive procedures, one identical to that from Shapiro and Melhado (1957) and the other a complicated schedule involving presentation of the CS-UCS pairings on the average of once every 3.2 hours for 20 weeks. Shapiro and Melhado reported no difference between any of the experimental groups and their appropriate controls for blood pressure, heart weight, adrenal weight, thyroid weight, kidney weight, blood pepsinogen, body weight, or ulceration. The only exception was the inclusion of the data presented in their 1957 report. They concluded that stress is not involved as a causative agent in human essential hypertension.

Clearly, chronic hypertension did not result from these procedures. However, it is important to consider how stressful their procedures were. This point will be considered in greater detail in a later section.

Dahl, Knudsen, Heine, and Leitl (1968) used a strain of rats highly susceptible to hypertension due to surgical or pharmacological interventions. They reported that classical aversive conditioning procedures had no effect on blood pressure in any of the groups, although several of the groups developed high pressure as a result of salt loading.

They concluded that psychological stress was not involved in the etiology of hypertension. Very little information was given concerning methodological issues and subjects were run for only a few weeks.

Summary. The classical paradigm has clearly not been as fruitful as others used in experiments reported here. It is possible that different classical paradigms such as discrimination procedures, or more stressful designs, might produce different results.

Operant Conditioning Paradigms

Operant conditioning of blood pressure. Plumlee (1969) presented the first uncontaminated operant conditioning of blood pressure.[5] He reported that his monkeys displayed an increase in diastolic pressure in response to the discriminative stimulus. This response was sharp and very brief. No chronic elevations developed in the 7 to 10 weeks of the experiment and no renal damage was observed under the signaled avoidance procedure. Maximal elevations were on the order of 30 mm Hg.

Only one control animal, a yoked control, was included in the experiment. No statistical comparisons of the yoked pair were made, although it was clear from the data presented that the yoked animal did not respond to the discriminative stimulus after habituation. Normal elevations in pressure did occur in the yoked animal with the presentation

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[5] DiCara and Miller (1968) described operant conditioning of blood pressure in the curarized rat but that preparation has been severely criticized by many authors (e.g., Brener, Eissenberg and Middaugh, 1974; Howard, Galosy, Caebelein and Obrist, 1974; Middaugh, Eissenberg and Brener, 1975) and appears to be aphysiological. Any data from that preparation is therefore considered to be contaminated.

of the shock, however. Since the experimental subjects made the avoidance response with such reliability, the yoked-control received very few shocks and chronic pressure remained unchanged.

The yoked control procedure has been roundly criticized on the grounds that it biases the experiment in favor of the experimental animal (Church, 1964; Katkin and Murray, 1968). These criticisms, at least as they relate to negative reinforcement paradigms, have been adequately dealt with by others, however (e.g., Black, 1967; Crider, Schwartz and Shnidman, 1969) and have been partially retracted (Katkin, Murray and Lachman, 1969). Seligman (1969) has criticized the control procedure on the grounds that the yoked animal learns something other than control as a result of the elimination of the contingency present in the avoidance situation. Weiss (1971a) has argued that this is a reason to use the yoked procedure rather than to avoid it. The author considers the yoked procedure to be a treatment of considerable interest. While the yoked animal may well be learning something as a result of the independence of shock and responses, this is precisely what the experimental subject would be doing if it were not for the contingency and thus, the yoked subject not only serves as a good control for number and temporal pattern of shocks but also as a procedure for examining the effects of loss of control over an aversive condition. It should be noted that these comments are restricted to negative reinforcement paradigms; the comments of Church (1964) may well apply to other paradigms.

Benson, Herd, Morse, and Kelleher (1969) shaped squirrel monkeys to perform on a shock avoidance schedule in which a predetermined increase in blood pressure for a predetermined period of time avoided a shock and

turned on a safety signal. The safety signal remained on so long as the pressure remained elevated. The pressure requirement was gradually increased until mean pressures of 150 mm Hg were obtained compared to 120 mm Hg for control levels. Only a few weeks were required for this result. Reversing the contingencies led to progressive declines in the mean pressure until levels close to control values were obtained.

Benson et al. (1969) noted that very few shocks were given during the increase or pressor phase of the experiment and that no motor activity in excess of control levels occurred, thus eliminating those two competing hypotheses. They also noted that a large number of shocks were administered during the depressor phase of the experiment and that some time was required to get pressures back to control levels.

Harris, Findley, and Brady (1971) reinforced increases in diastolic blood pressure with avoidance of shock and the opportunity for panel pressing for food. The two baboons used in the study demonstrated diastolic elevations of 50 to 60 mm Hg for up to 5 minute periods. No controls were used in this study other than the within subject control built into the design. Pressures did not have to remain elevated very long (40 seconds) to provide time out periods and this may explain the short term nature of the results. Since no data were provided during the sessions or between sessions, no comment can be made about any chronic effects.

Sidman avoidance and concurrent blood pressure measurements. Sidman avoidance procedures differ from other operant avoidance procedures in a very important way. In the Sidman (1953) procedure, shock is presented to the subject either in single pulses or trains of pulses if the

subject does not make the avoidance response at a certain rate. There is no explicit warning signal. A subject on a Sidman 20 second schedule would have to respond once every 20 seconds to avoid all shocks; each response postpones the shock by 20 seconds. The delay of the shock following a response is termed the response-shock interval (R-S interval; e.g., in a Sidman 20 second schedule, the R-S interval is 20 seconds). The interval between shocks if no response is made is called the shock-shock (S-S) interval. The Sidman procedure is universally considered to be more stressful than signaled avoidance tasks.

Forsyth (1968, 1969) reported on the effects of prolonged exposure to Sidman avoidance schedules in the restrained rhesus. All experimental animals showed an initial increase in both systolic and diastolic blood pressure and heart rate compared to baseline levels and most maintained the elevations for 14 months. The control subjects showed no such difference. This study may be criticized on several grounds. The control subjects, few in number, received on the average only half the number of shocks received by the experimental subjects, raising questions concerning the adequacy of those controls. There was also considerable variability in post-operative recovery times and in pretraining periods, raising questions concerning the equality of groups at the beginning of the study. In addition, the number of subjects in each group was quite small, often only one (e.g., the control subject who received random shocks). Finally the analysis of the data involved the use of multiple t-tests, a procedure criticized earlier in this discussion.

Herd, Morse, Kelleher, and Jones (1969) reported elevations of 30 to 40 mm Hg in monkeys on a Sidman schedule for 4 to 11 months. Only

within subject controls were used in this study and thus the experimental treatment was confounded with such factors as history and maturation (Campbell and Stanley, 1964). Benson, Herd, Morse, and Kelleher (1970) replicated these findings and observed gross renal damage in the subject sustaining the highest pressures; however, the design problems present in the first study remain in the second.

Forsyth and Harris (1970) reported on changes in regional blood flow in the rhesus subjected to a Sidman schedule. They obtained evidence of increased cardiac output, heart rate, and decreased total peripheral resistance in response to that schedule. In addition, their results indicate that blood flow was shunted to the skeletal muscle and heart during stress at the expense of the gastrointestinal tract, the skin and the kidneys. Forsyth (1971) reported on changes in regional blood flow in the rhesus at various intervals during 72 continuous hours of Sidman avoidance. Blood pressure was significantly increased throughout the 3 day period over controls. This elevated pressure was due to increased cardiac output and heart rate in the first 4 hours of avoidance, to nonsignificant increases in cardiac output and total peripheral resistance by the end of 24 hours, and entirely to elevated total peripheral resistance at the end of 72 hours. Forsyth's (1971) design in this latter study was sound although the use of multiple t-tests is still to be questioned.

Anderson and Brady (1971, 1972, 1973) and Anderson and Tosheff (1973) reported gradual increases in pressure and decreases in heart rate in dogs during preavoidance periods up to 15 hours in length. There was

no control for diurnal cycles and Forsyth (1969) provides data indicating that such a cardiovascular pattern over a 15 hour period is normal in the rhesus. This at least suggests caution in interpreting the dog data. These authors also utilized multiple t-tests and subjected their raw data to a change score procedure of the type so sharply criticized by McCanne and Sandman (1975).

Findley, Brady, Robinson, and Gilliam (1971) failed to replicate the work of Forsyth (1969) or Herd et al. (1969); however, a large procedural difference did exist between the studies. Findley et al. (1971) used a Sidman 120 second schedule which is certainly not as severe as the Sidman 20 second schedule that was utilized by the earlier investigators. In addition, no controls for diurnal cycles were used, no control subjects were included, and both subject animals were interrupted from the schedule for periods of from 14 to 55 consecutive days with renal infections or hernia problems. The general health of the subjects seems open to question.

Corley, Shiel, Path, Mauck, and Greenhoot (1973) reported severe debilitation in squirrel monkeys after very brief exposure to a Sidman 40 second schedule. Severe bradycardia, various arrhythmias, including QRS segment lengthening and T-wave inversion, and ventricular arrest occurred in one subject (E-8) on the first day of an 8 hour daily program. Microscopic heart damage was found in most of the experimental animals. Corley, Mauck, and Shiel (1975) used the same schedule and reported that subjects yoked to the avoidance monkeys were generally in a state of physical collapse after at most 30 days. Severe brandycardia and, occasionally, ventricular asystole occurred in the avoidance animals.

Average blood pressure values before training were 147/109 mm Hg and after the training were 151/117 mm Hg. Microscopic degeneration of the heart was observed in all subjects, including those subjected to restraint only. Corley, Shiel, Mauck, Clark, and Barber (1977) reported myocardial degeneration in subjects exposed to 24 hour Sidman 40 second schedules but not in their yoked controls, a finding in surprising disagreement with data presented by Seligman, Maier, and Solomon (1971) (cf. below).

These results must be viewed with caution. It is highly unlikely that the effects described for one subject (E-8) in the 1973 report could be due to only one day on a Sidman 40 second schedule. This is particularly unlikely since no such damage was found in subjects after 72 continuous hours of a Sidman 20 second schedule (Forsyth, 1971). The T-wave inversion is indictive of mycardial ischemia and supports the alternative explanation that the general health of the subjects may well have been poor. Species differences are unlikely since squirrel monkeys have been used by several other investigators (e.g., Herd et al., 1969) who have reported no such profound observations. These results are also in strong conflict with other reports on other grounds. Blood pressure levels initially were quite high (cf. Benson et al., 1970; Herd et al., 1969) and changed very little (cf. Herd et al., 1969). Finally, the data from the 1977 paper seem to contradict that reported in the 1975 paper even though there were very few differences in the procedure.

Lawler, Obrist, and Lawler (1975) reported on changes in cardiovascular function during periods immediately preceding, during, and after Sidman avoidance conditioning. They reported elevated pressures during

training periods when signaled shock was gradually faded into the Sidman schedule and during the Sidman schedule itself. Preavoidance pressures appeared to be elevated due to increased total peripheral resistance and avoidance pressures due to increased cardiac output. Heart rate and stroke volume as well as aortic dP/dt also increased during avoidance. Lawler et al. (1975) pointed out that two of the four dogs in the study did not show the above effects; however, their suggestion that the individuality of the cardiovascular response may be related to personality differences has support elsewhere (e.g., Frolich, Tarazi, and Dustan, 1969; Shapiro and Horn, 1955). They contradicted Anderson and Brady (1971, 1972, 1973) and Anderson and Tosheff (1973) by reporting that no trends in any measure were observed during the pre-avoidance period. Only within subject controls were used.

Summary. While there is evidence of some pressure elevation as a result of direct operant procedures, there is disagreement as to the effects of Sidman avoidance procedures. The avoidance literature presents a variety of methodological issues and one cannot be certain of the true cardiovascular effects of either short term or long term exposure to such contingencies.

Conflict Paradigm

Friedman and Dahl (1975) reported blood pressure changes in rats subjected to a particularly stressful paradigm, one so different from those described above as to warrant special attention. Rats particularly susceptible to hypertention due to surgical or pharmacological intervention served as subjects (cf. Dahl et al., 1968). Subjects in the conflict

group were on a concurrent variable interval schedule for food and a variable ratio schedule for shock. The systolic blood pressure of these subjects scored above 170 mm Hg within the first week and remained elevated for the 16 weeks of the study. Subjects yoked to these conflict animals for food and shock also showed large pressure increases. The pressures of subjects yoked for food only or shock only did not differ significantly from nonshocked controls. Subjects removed from the schedules after 13 weeks and given an additional 13 week rest period displayed a gradual, although incomplete, recovery. A few of the subjects retained the elevated pressures throughout the recovery period.

Friedman and Iwai (1976) recently confirmed this finding. In addition, they reported that rats particularly resistant to hypertension due to surgical or pharmacological intervention did not develop elevated pressures after being exposed to the procedures described above.

The conflict paradigm clearly can have potent hypertensive effects; however, as the results of Friedman and Iwai (1976) underscore, the effect of the procedure may well depend upon the genetic makeup of the subjects. Further work is needed using this procedure.

Summary

Five paradigms have been considered in this section: (1) prolonged exposure to auditory, visual, and motion stimulation; (2) prolonged exposure to severe crowding; (3) classical aversive conditioning; (4) operant avoidance paradigms; and (5) prolonged exposure to a conflict paradigm. Of the five paradigms discussed, the crowding and conflict paradigms did seem to have some longterm hypertensive actions. Prolonged

exposure to auditory, visual and motion stimulation produced some elevations in pressure, but they were not as great. The classical conditioning paradigm provided little in the way of a hypertensive response. The data from operant avoidance paradigms were incomplete. What little long term work was reported had serious methodological problems. The data provided by Forsyth (1971), demonstrating that subjects display a hemodynamic pattern similar to that found in human essential hypertension, certainly demonstrate a clear need for further information concerning the long term effects of Sidman avoidance procedures. The positive findings of Herd et al. (1969), Forsyth (1969) and the negative findings of Findley et al. (1971) underscore the need for a well designed study to determine the true long term effects of such a procedure. One of the purposes of the experiment reported here was to provide such a study.

It is probably safe to assume that in each experiment reported above, the investigators involved assumed that the procedure utilized would be stressful for the subjects. Yet clearly most of the studies reported above, no matter how extreme the procedures used were, produced little in the way of a hypertensive response. Perhaps the procedures used were simply not sufficiently stressful to evoke a permanent alteration in cardiovascular function. A closer examination of the nature of stressful or aversive events and procedures is the topic of the next section.

F. RESEARCH RELATED TO THE EFFECTS OF STRESS AND THE SIGNIFICANCE OF THE COMPONENTS OF STRESS

The terms stress, stressor, psychological stressor, etc. have been used rather loosely; more precise meanings are necessary. Selye (1976) has provided acceptable meanings for stress ("the non specific response of the body to any demand") and stressor ("that which produces stress") (p.472). A psychological stressor in this framework is a psychological event or process resulting in a physiological dysfunction. This is to be distinguished from an aversive event which will be used here in the traditional sense. Thorndike (1911) laid the groundwork for this concept in his definition of a punisher as any stimulus which the subject does nothing to receive and everything to avoid. Skinner (1953) considered aversive events to be those which could serve as negative reinforcers or punishers; events which increase the probability of a behavior when removed following the occurrence of that behavior and which decrease the probability of a behavior when presented following the occurrence of that behavior.

Electric shock has generally been considered to be an excellent example of an aversive event and has frequently been used in paradigms intended to cause stress (as shown in the preceding section). However, Morse and Kelleher (1977) have recently described evidence which indicates that as noxious an event as electric shock does not always act as an aversive event. An analysis of these studies and other work related to the effectiveness of shock as an aversive stimulus seem appropriate. An

important question to be considered is whether behaviorally aversive events are necessarily effective as stressors.

Seligman, Maier and Solomon (1971), Catania (1971), and Seligman and Binik (1977) have reviewed the literature concerning aversive conditioning and have identified two components deemed significant: the predictability and the controllability of the aversive events. Seligman et al. (1971) have defined an unpredictable situation as one in which the probability of shock, given a shock signal, is equal to that of shock, given no shock signal. They have defined an uncontrollable situation as one in which the probability of a shock, given a response, is equal to that of a shock, given no response. The reviews these authors have presented were unanimous in concluding that unpredictable and uncontrollable events are more aversive than predictable and controllable events.

Human subjects reported that unsignaled shock situations were more distressing than signaled shock situations (Seligman et al., 1971). These subjects generally reported that the signal either allowed them to relax in the absence of the signal or to prepare for the shock when the signal was given. A large number of studies indicated that subjects will almost always choose predictable shock over unpredictable shock. This was true whether the shock was avoidable, escapable, or inescapable (e.g. Badia and Culbertson, 1972; Badia, Culbertson and Lewis, 1971; Lockard, 1963; Seligman and Binik, 1977; Seligman et al., 1971). Seligman et al. (1971) also reported that immediate shocks were preferred over delayed shocks. However, Hineline (1970) has shown that responding was learned and maintained when its only effect was to postpone the timing of a shock within a specified interval and even though it had no effect on overall

shock frequency. Seligman et al. (1971) also reported that response contingent shock was preferred to noncontingent shock.

Predictable shocks produced considerably less physiological distress than did unpredictable shocks as seen in a large number of studies which have reported considerably less ulceration in the signaled condition (e.g., Sawrey, 1961; Weiss, 1968, 1970, 1971a, 1971b, 1971c). Weight loss was greater in animals subjected to unsignaled shock. Weiss (1970) reported elevated body temperature, plasma corticosterone, and defecation, and greater suppression of food and water intake in rats given unpredictable shock compared to those given predictable shock in both restrained and freely moving subjects.

Uncontrollable shock can clearly have disruptive effects upon ongoing behavior (Seligman et al., 1971) but the effects of such shock in terms of stress are not as clear. Generally uncontrollability has been confounded with unpredictability. It is clear from data described by Morse and Kelleher (1977) that controllable shock need not necessarily be aversive. They described the work of several researchers who, over a period of time, have shifted subjects from shock avoidance schedules onto concurrent schedules of shock avoidance and variable interval response contingent shock. Gradually the shock avoidance component was faded out and the subjects would be left on only the response contingent shock schedule. Not only was responding maintained, but it took on the characteristic scallop shape of variable interval schedules. If the shock was temporarily omitted from the schedule, responding declined, only to be reinstated when the shock was reinstated. Certainly shock in these

cases did not meet the traditional requirements for an aversive event. The aversiveness, or lack thereof, of an event would depend apparently upon the schedule of presentation of the event and upon the behavioral history of the subjects.

One can look back to the procedures described in the preceding section which have been used in attempts to develop animal models for induced hypertension and see that they differed in terms of predictability and controllability of the aversive events used. For example, the classical aversive conditioning procedures used by Shapiro and Melhado (1957, 1958) used very infrequent shock presentations which were perfectly predictable although uncontrollable; these researchers reported no pressure elevations. On the other hand, Friedman and Dahl (1975) and Friedman and Iwai (1976) reported large elevations in special rat strains; these researchers used a conflict paradigm which was particularly effective. The predictability and controllability of two different stressors, shock and hunger, must be considered for their subjects. They had a perfect predictor of safety from shock, not responding, and a weak predictor of shock, responding. They also had a weak predictor of food, responding on a variable interval schedule, and an excellent predictor of hunger and potential starvation, not responding. These subjects were, for all practical purposes, fed only for responding on the variable interval schedule. These conflict subjects were faced with a very serious problem: (1) their perfect predictor of hunger was also a perfect predictor of safety from shock, (2) their predictor of shock was also a predictor of food, and (3) they could control shock and face starvation or control hunger and face severe shock but they could not do both at the same time.

This report seems to underline the importance of controllability or lack thereof in the face of good predictability.

Summary

Predictability and controllability appear to be important determinants of the stressfulness of an aversive situation. From the classical aversive conditioning experiments, it seems that perfectly predictable shock presentations, although not controllable, did not have stressful effects. It is at least suggested from the work described by Morse and Kelleher (1977) that controllable shock, although not clearly predictable, need not have stressful effects. The attention of researchers in this area should be drawn toward the use of paradigms in which uncontrollability and unpredictability operate simultaneously. These procedures would apparently produce the most stressful situations.

Two paradigms appear to be worth pursuing in light of these discussions. The conflict paradigm has been shown to have hypertensive effects in a special strain of rats particularly susceptible to hypertension due to surgical or pharmacological interventions. The procedure has also been shown to have no such effect on a strain bred to be resistant to such influences. This paradigm deserves further examination, particularly in normal strains. It also deserves closer attention in terms of the physiological events involved in the hypertensive response.

The second paradigm which deserves further attention is that of Sidman avoidance and yoked controls. Several of the many studies using these procedures have reported very promising and interesting results (e.g. Forsyth, 1971; Lawler et al., 1975). A major flaw in work using

this procedure is the exclusion of a study which exposed subjects to these procedures and monitored its physiological effects on a long term basis. The paradigm provides controllability and moderate predictability for the Sidman avoidance subjects while depriving both controllability and predictability to the yoked control subjects. One of the purposes of the study reported here was to evaluate the long term effects of such procedures.

G. OBJECTIVES OF THIS RESEARCH

This research had several objectives touching on several issues; (1) to determine if prolonged exposure to Sidman avoidance or yoked control procedures did in fact serve as a stressor and cause cardiovascular distress, (2) to determine the time course of development of any such cardiovascular effects, (3) to determine whether such effects, if found, were schedule induced or whether they were observed outside the avoidance situation, (4) to provide further information on the cardiovascular effects of providing some subjects with predictability and controllability of stressful events while preventing others such access, (5) to determine if prolonged exposure to these procedures had the same ulcerogenic effect that Weiss (1971a) had reported for intensive, short term exposure, and (6) most importantly, to move a step further in answering the question of whether environmental and/or psychological stressors could serve as the initiating mechanism in hypertension.

CHAPTER II

METHODS

A. SUBJECTS

Twenty-four naive male Long-Evans hooded rats were used as experimental subjects. Their average initial weight was 514 grams (*SD* = 41 grams). The general health of the subjects was monitored by maintaining daily weight records for each subject and by daily individual inspection for signs of disease.

B. APPARATUS

Home Cages

Subjects were housed in plastic cages with interior dimensions of 16 x 23 x 42 cm in groups of three until they were used in the study. At that time, each subject was housed in a separate cage of the same dimensions. Each cage was fitted with a grated lid equipped with a water bottle and standard rat chow for ad lib water and food. Wood shavings were used as bedding. Each cage was cleaned at least once per week.

Experimental cages

Each subject was assigned to one experimental cage constructed of clear plexiglass following the descriptions given by Weiss (1971a, 1971b, 1971c). A 10 cm wheel was positioned to facilitate turning by the subject. Such wheel turns were used as the required response for shock avoidance. The subject's tail extended through a 1 cm hole from the rear wall of the

cage. A wooden washer (8mm thick with an outer diameter of 2.5 cm and inner diameter drilled to fit) was slipped onto the tail and moved to a point 2 to 3 cm from the base. This washer was attached to the tail using Dermacell tape and served as a stop, preventing the subject from pulling the tail into the cage.

Three of these experimental cages were placed in each of four large wooden sound-isolated boxes equipped with a house light and speaker centered on the inside of the lid. The light was a standard 24 vdc light powered by a 12 vdc source for dim and diffuse illumination. The speaker served to present the subjects with 87 db white noise. Each box was independently ventilated. The three cages within the box were separated by partitions which prevented visual contact but allowed sound and light from the speaker and house light to pass evenly to the three cages. Each of the large boxes was equipped with a smoked plexiglass window for observation of the subjects. The four large boxes were placed in a sound-isolated, electrically shielded room which measures 1.8 m by 2.7m. This room will hereafter be called the running room.

Behavioral Programming Equipment.

A KIM-1 microprocessor (MOS Technologies, Inc.) was programmed to control all aspects of the behavioral schedules including the timing of the response-shock intervals, shock-shock-intervals, duration of the shock, delivery of shocks, counting of responses, counting of failures to avoid, and counting of total shocks delivered for each of 12 subjects simultaneously (Lawler and Murray, 1978; Murray and Lawler, 1978). Output of the behavioral data was accomplished via linkup between the KIM-1 and an LA30 DECwriter (Digital Equipment Corporation). A separate "gray"

noise generating system, designed by the author, was used to make extraneous noise in the running boxes.[6] All the programming equipment was housed in a room adjoining the running room.

Tail Shock System

Tail shock electrodes were constructed by sewing a 2.5 cm by 1.6 cm section of steel braid to a 1.6 cm wide velcro cuff made by sewing together two 2.5 cm opposing sections of velcro. A flexible insulated wire was soldered to one end of the braid; the other end was attached to a standard male banana plug for connection to banana plug recepticles located in the wall of the wooden running box.

A separate constant current shock delivery system was provided for each subject (Murray and Lawler, 1978). A large series current limiting resistor was used to deliver a tightly controlled current to the tail. The shock duration was controlled by the KIM-1 and the shock intensity was controlled by setting the value of individual potentiometers in series with the shock source and the subject.

Indirect Cardiovascular Monitoring Equipment

Systolic blood pressure was monitored regularly in all subjects using a Narco Bio-Systems model 7211 electrosphygmograph coupler connected to a Narco pneumatic pulse transducer. The transducer was used in conjunction with a tail cuff (outside length 34 mm, inside diameter 13mm) supplied by Narco Bio-systems. The coupler was housed in a Narco model PMP-4A polygraph equipped with solid state model 7070 channel amplifiers.

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[6]The term "gray" noise is used because the noise generator was not a true "white" noise generator as the term is used in engineering circles. The signal approximated a true white noise signal and was quite satisfactory for use to mask other sounds.

Direct Cardiovascular Monitoring Equipment

The chronically implanted polyethylene cannula (cf. below) for each subject was connected to a Narco Bio-systems RP 1500 pressure transducer which fed directly into the Narco polygraph equipped with four solid state model 7070 channel amplifiers and four solid state model 7172 strain guage couplers, providing continuous polygraph tracings of all blood pressure signals. All direct pressure monitoring equipment except the transducers was housed in the room adjoining the running room and was connected to the experimental cages via cables.

C. PROCEDURE

Assignment of Subjects

One subject from each of the three experimental conditions (cf. below) was run in each of the four wooden boxes at the same time. As a result, subjects were considered at the same time as belonging to a given condition, and to a triplet. Subjects were therefore randomly assigned to triplet-condition combinations prior to being introduced to the study.

Experimental Conditions

Subjects assigned to the Sidman condition were placed in a Sidman avoidance paradigm (Sidman, 1953). Subjects were required to turn the wheel in the front wall of the cage one-quarter turn within 20 seconds of the last response in order to avoid shock. When the 20 second response-shock interval elapsed without a response, alternating current shock of a 0.2 seconds duration was delivered through the tail shock electrodes every 1.8 seconds until a response was made. Subjects were shaped onto the schedule by using a gradually increasing shock intensity and permitting the subjects to auto-shape. The shock intensity was set a 0.05 ma on the

first day and was stepped up whenever the subject received ten shocks in a row without responding. The schedule of current increments used is given in the appendix. On the second day, the shock intensity was initially set at the second step of the schedule. On the third and fourth days, the shock intensity was initially set at the third step of the schedule. On the fifth and each day thereafter, the initial shock intensity was set at the fourth step of the schedule, 0.2 ma. In all cases, whenever the subject received 10 shocks in a row without making a response, the shock intensity was stepped up the next level on the shock current intensity schedule.

Subjects assigned to the yoked condition were yoked to the Sidman subject in the same triplet. Thus, these subjects received the same duration and intensity of shock at the same time the Sidman subject received it. However, responses by yoked animals had no effect on the timing of shock presentations.

Subjects assigned to the nonshock control condition were placed in the same type of experimental cages housed in the same large wooded boxes as the other members of the triplet. These subjects thus received all stimuli received by the other subjects including attachment of shock electrodes, but did not receive shock.

Scheduling of Triplets

Due to various logistical problems staggered starts were used for the eight triplets. Two triplets were started each week for two weeks. This procedure resulted in only one triplet coming due for recording during any given session on any given week (cf. the section on direct cardiovascular measurement precedures). It also resulted in no more than three

subjects coming due for surgery on any given day. These triplets were run for 11 weeks on schedule and then subjected to surgery (cf. the surgical procedures section below), given a week to recover, and subjected to direct cardiovascular recording for one week. At that time, the entire sequence was repeated.

Training Session Procedures

Training sessions were run five days per week and lasted three hours. An additional hour was required to prepare the subjects and equipment for the session and one half hour to remove them afterwards. Weekends were reserved for indirect pressure measurements and surgery as needed. Training sessions were run in the afternoons or evenings. All triplets were run at the same time.

Each daily session began with an equipment check. The microprocessor system was thoroughly tested before the subejcts were brought up from the animal facility. Each subject, in turn, was weighed and had a wooden washer of the appropriate size attached to his tail as described earlier. The subject was then placed in the appropriate experimental cage. After all subjects were in place, all tails were rubbed vigorously with a gauze pad soaked in ethyl alcohol to clean the 2 to 3 cm of skin just caudal to the washer.

At this time, the tails of the subjects were taped to the sides of the experimental cages so as to prevent the subjects from rotating in their cages. Pilot work indicated the extremely disruptive nature of such turning and also indicated that the taping procedure was effective in preventing it.

Shock electrodes were attached as follows. Gauze strips, cut in 1.6 cm widths and 5 cm long, were moistened in a normal saline solution and placed over the steel braid of the shock electrodes. The electrodes were then placed around the base of the tail in the region cleaned with alcohol Care was taken to prevent the two electrodes from shorting due to physical contact or saline running across the skin between them. The distance between the two electrodes varied from day to day and from subject to subject. It was determined empirically each day by measuring the resistance across the electrode placement. The electrodes were adjusted until the resistance across the placement was below 550 Kohms and above 5 Kohms The current limiting series resistance was typically on the order of 2 Mohms, creating a worst case ratio of 3.6:1. Pilot work indicated that the tail resistance dropped to a maximum of 15 to 20 Kohms following the delivery of several shocks, thereby increasing the worst case ratio 10:1, a value high enough to ensure a constant current shock source.

The electrode placement resistance for each subject fell within the limits described above, the series resistances were adjusted such that the total load resistance across the shock source for each subject was equal to the initial value prescribed for that particular day; the table of initial shock current and load resistance values is given in the appendix. The ventilation fans in the wooden boxes were then started and the box house lights turned on. White noise signalled the onset of the three hour training session and termination of that noise signalled the end of the session.

During the session, the electrode resistances, and thus shock currents, were changed only when the experimental subject in a triplet failed to respond in the face of 10 consecutive shocks. As described above, this resulted in an increase of shock current stepwise via lowering the current limiting resistance. The currents for both experimental and yoked members of the triplet were adjusted at the same time.

At the end of the three hour session, the KIM-1 automatically terminated the schedules and the subjects were returned to their home cages. The equipment used in the training session was then cleaned.

Indirect Blood Pressure Measurement Procedures

Beginning at the end of the fourth week on schedule, systolic blood pressure measurements were made on each subject using the tail plethysmographic equipment described above.[7] All such measurements were made on Saturday mornings, and in cages quite different from the experimental cages. The pressure measurements were made in a different random order each week.

In turn, each subject was placed in a Narco Bio-systems Rat Holder, a cylindrical plastic cage mounted on a flat platform. An aluminum base located immediately beneath the cylindrical cage evenly distributed heat generated by two high wattage resistors located in the flat base of the device. Small plastic partitions could be placed in either end of the cylinder to prevent forward and backward movement on the part of the

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[7]Delays in receiving the tail plethysmographic equipment from Narco-Bio-systems resulted in being unable to collect data from some groups for the first three weeks.

subject. Temperature of the aluminum base was monitored using a remote temperature meter (Yellow Springs Instrument Co., Inc. model 43TD). The thermistor for the device was taped to the aluminum base. The temperature of the base was controlled by varying the current passed through the resistors with a Narco Bio-systems Rat Holder Temperature Control Unit modified by the author so that two holders could be used simultaneously. Pilot work had indicated that each subject had to be placed on the base heated to 39-43° C for 10 to 15 minutes before acceptable signals could be obtained. One subject was thus allowed to "warm up" while measurements were being made on another. While the first pair of subjects were being prepared for cuff measurements, the system was calibrated using the standard operating instructions for the ESG Coupler Type 7211 (Narco Bio-systems). The system was calibrated such that 40 mm Hg pressure was represented by a 1 cm pen deflection.

On each measurement day, three good measurements were recorded on the polygraph per subject. Often 15 or 20 readings were made before 3 acceptable readings were obtained. A reading was acceptable if the baseline after the reading agreed with the baseline prior to the reading, and if the reading was generally noise free. The principle source of noise was movement artifact. In addition to the three systolic determinations, a 6 second sample was taken to determine heart rate.

Surgical Procedures

After 11 weeks exposure to the training sessions, each subject was implanted with a cannula constructed by joining a 5 cm section of PE 10 polyethylene tubing (Clay-Adams) to a 20 cm section of PE 90 tubing; the tip of the PE 10 was beveled to assist in the insertion into the target

vessel. The construction and implantation procedures are similar to those described elsewhere (e.g., Forsyth and Baireuther, 1967; Herd and Barger, 1964; Still, Pradham and Whitcomb, 1956; Still and Whitcome, 1956). A brief description of the surgical procedure is given below.

Under sodium pentobarbital anesthesia (1mg/kg body weight) a 1 cm incision was made in the base of the neck. A second 1 cm incision was made in the flank of the subject on the left side 2 cm below the rib cage and along the lateral midline. The cannula was drawn under the skin from the incision at the neck to the incision in the side. A 2 cm incision was made along the abdominal midline, exposing the abdominal cavity. The abdominal aorta in the region of the renal arteries was exposed for a distance of approximately 5 mm moving posterior to the renal artery. A trocar made of 20 ga stainless steel tubing was then passed from the abdominal cavity to the site of the lateral incision by one of two routes. In the first 12 subjects, the cannula passed through the psoas muscle just anterior to the left kidney. In the second 12 subjects, the cannula passed through the abdominal wall immediately beneath the lateral incision and into the abdominal cavity well below the left kidney.

For subjects with the anterior entry, a narrow channel was opened under the renal artery and vein on the anatomical left side. The tip of the cannula was carefully passed through the channel; prior molding of the cannula resulted in the cannula pushing out against the psoas muscle rather than against the artery and vein. In addition, the molding caused the cannula to lie flat against the muscle wall and parallel to the aorta. The junction between the PE 90 and PE 10 was tied to the psoas muscle as close to the aorta as possible and approximately

5 mm posterior to the renal vein; the tie was loose at this point and tightened later.

For subjects with the posterior entry, the cannula was molded such that the PE 90 curved up toward the junction between the left renal vein and aorta and then sharply back in a posterior direction. This resulted in the PE 10 section lying parallel to the aorta. The junction between the PE 90 and the PE 10 was tied to the psoas muscle as close to the aorta as possible and approximately 5 mm posterior to the renal vein; the tie was loose at this point and tightened later.

With the cannula positioned, a 2 cc syringe equipped with a blunt tipped 20 ga hypodermic needle was attached to the externalized cannula tip; the syringe was filled with a USP saline solution containing 1000 units/ml sodium heparin. The cannula was then anchored with 000 silk to the fascia at the neck incision and the incision closed with 00 silk, in addition; the side incision was closed with 00 silk.

With the cannula positioned, a small section of the exposed aorta was cleaned of some of the fascia and membraneous material covering it. A small puncture was then made using a 27 ga needle. A cotton swab was placed over the puncture upon removal of the needle and mild pressure applied for several minutes, until a thin clot formed over the hole. With the clot in place, the beveled tip of the cannula was checked to be sure that only 8-10 mm of the cannula would be inserted and then the cannula was inserted downstream. The suture anchoring the cannula was drawn tightly such that the cannula was pulled into the aorta up to the PE 10-PE 90 junction. This assured that the cannula would not be dislodged even though a very short section was inserted. The total length of the small bore PE 10 tubing was typically 8-10 mm.

The cannula was tested for blood flow and then filled with part of the USP saline solution containing the sodium heparin in the attached syringe. The externalized section of the PE 90 was then plugged with a section of 20 ga stainless steel wire. The fascia around the exposed aorta was sutured in place with 0000 gut and the abdominal incision closed with 00 silk. The subject was given a prophylactic dose of 60,000 units of procaine penicillin IM. Subjects were observed closely for 1 week postop and the penicillin treatment continued for a total of 3 days. The cannulae were flushed daily with a normal saline solution containing 1000 units/ml sodium heparin.[8] Care was taken only to put as much fluid into the cannula as was necessary to refill the tube.

Direct Cardiovascular Measurement Procedures

At the end of 4-7 days postop recovery, the members of each triplet were given special treatment. Direct recording sessions were of approximately 90 minutes duration, although preliminary and followup treatment generally lasted several hours in addition.

On the day in which a triplet was used in recording, the three subjects were brought into the running room and in turn gently restrained in a towel. A clamp was placed on the tip of the cannula and the plug removed. A 25.4 cm connector made of PE 90 and housed in a tight steel spring for protection was attached to the end of the cannula. The

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[8]Ether was used to lightly anesthetize members of all triplets during the flushing procedure on the first two days following surgery. It was deemed necessary to protect the incisions. No ether was used within 48 hours of recording sessions.

connector had previously been filled with a normal saline solution containing 1000 units/ml sodium heparin. The connector was then plugged and the subject placed in the appropriate experimental cage.

A separate pressure transducer was prepared for each member of the triplet and placed in a foam rubber holder attached to the partitions in the wooden boxes. (The foam rubber was used to moderate movement vibration.) The spring on the connector was suspended by a rubber band such that it formed an arch with one end in the rat and the other end hanging near the transducer. Enough slack was allowed such that the subject would move freely without crimping the cannula. The tranducer was positioned to be at the level of the heart.

After the normal training session preparations had been made, including attaching the shock electrodes and adjusting the current intensity, the recording system was calibrated using standard operating instructions for the Serain Gage Coupler Type 7172 (Narco Bio-systems). A 40 mm Hg pressure was indicated by a 1 cm pen deflection. The transducers were then carefully connected to the PE 90 connectors. Flushing of catheters was repeated if necessary. When all available signals were acceptable (i.e., had a pulse pressure of at least 30 mm Hg and clear sign of a dichrotic notch), the KIM-1 was started to initiate the session and the white noise turned on. Continuous polygraph records were obtained of all signals and instances of shock indicated with the event marker. Recording continued for approximately 90 minutes with occasional interruptions only when absolutely necessary due to loss of the signal.

When the recording session was over, the subjects were disconnected from the transducers and carefully removed from the experimental cages, the

connectors removed and the plugs reinserted in the cannulae, and the transducers were rechecked for calibration on the polygraph.

Autopsy Procedures

All subjects were sacrificed using chloroform and their stomachs removed for examination for lesions. The stomachs were split and rinsed gently to remove all food material and stored in saline for later examination. Examination of the aorta for signs of damage and confirmation of cannula placement was made in each subject. Gross examination was also made for condition of the kidneys and other tissues.

Data Analytic Procedures

The indirect blood pressure records were read blind by three observers. The three readings for each subject on each weekly record by each observer were averaged and these scores averaged across observers to obtain a single score per subject per week. The same procedure was followed for the indirect heart rate data. Only after the final values were obtained were the scores matched with the identity of the subject.

The direct blood pressure records were read by examining a 4 second sample from each of 60 1 minute sections of the polygraph tracings. The 1 minute sections were consecutive where possible. The 4 second segments were the first 4 seconds of the 1 minute interval unless the quality of the record was poor.

The direct heart rate records were read by counting the number of systolic events occurring during the first 10 seconds of each 1 minute interval used in the direct blood pressure readings. These values were then multiplied by 6 to obtain estimates of 1 minute heart rates.

Stomachs were pinned out in wax dissection trays and examined for gross lesions. All lesions observed were measured for diameter and the locations were noted. The stomach examinations were conducted blind.

Due to the equipment malfunctions and unexpected disruptions in the daily routines, some data were not collected under the response and shock variables. All data were available for all cardiovascular parameters, however. The missing scores in the response and shock variables were replaced using procedures adapted from Meyers (1972) and similar to those described by Winer (1971) and Dayton (1970). The basic technique involved assigning arbitrary values for all missing scores and sequentially computing a value for each missing score using formulae which minimized contributions to interaction effects. The procedures were programmed on a DEC PDP 11/05 (Digital Equipment Corporation) computer by the author. The program continued the replacement procedure until the values computed in each iteration converged.

All data collected were subjected to repeated measures analysis of variance under the appropriate schema with the exception of the lesion data. Prior to conducting the ANOVAs, the data were tested for conformity to certain assumptions underlying the statistical model (Winer, 1971). Jennings and Wood (1976) have recently pointed out the uncomfortably high incidence of reports in this field which did not include tests of these assumptions and which as a result may have included many false findings of significance. Of particular importance to the analyses conducted were the assumptions of homogeneity of the variance-covariance matrices for all level of the between subject factor combinations. A more complete description of these procedures is given in the Results Chapter.

CHAPTER III

RESULTS

All data were subjected to repeated measures analyses of variance appropriate for the design under which they were collected. Further tests were used as needed. The data will be considered in terms of the dependent variables which were included.

A. BEHAVIORAL AND BODY WEIGHT DATA

Response Data

The summary table from the analysis of variance performed on the response data is presented in Table 1. The only effect which achieved significance was Groups. A Tukey A multiple comparisons test indicated that each group mean differed significantly from each other group mean ($P < .05$). Figure 1 depicts the Groups by Weeks interaction, which while itself not statistically significant, clearly shows the main effect of Groups. The shape of the curve is not surprising: the animals subjected to Sidman avoidance procedures responded at a high and stable rate ($\overline{X}$ = 2645 responses per 3 hour session), those subjected to yoked control procedures responded at a stable but lower rate ($\overline{X}$ = 1238 responses per 3 hour session), and those subjected to control procedures responded at a very low and stable rate ($\overline{X}$ = 204 responses per 3 hour session).

It should be noted that a generally unfamiliar column appears in the summary table in Table 1 as in all such tables, that for df'. This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance

Table 1. Analysis of Variance Summary Table for Response Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	264193727.58	2		132096863.79	29.81[b]
Replications	6176426.91	1		6176426.91	1.39
Groups by Replications	3103101.35	2		1551550.68	0.35
Subjects Within Groups by Replications	79766024.36	18		4431445.80	
Weeks	2399044.93	10	4	239904.49	1.76
Groups by Weeks	4715275.39	20	7	235763.77	1.73
Replications by Weeks	1556311.34	10	4	155663.13	1.14
Groups by Replications by Weeks	4515315.76	20	7	225765.79	1.65
Subjects by Weeks Within Groups by Replications	24576798.68	180	65	136537.77	

[a]This term refers to the corrected degress of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

[b]$P < .05$.

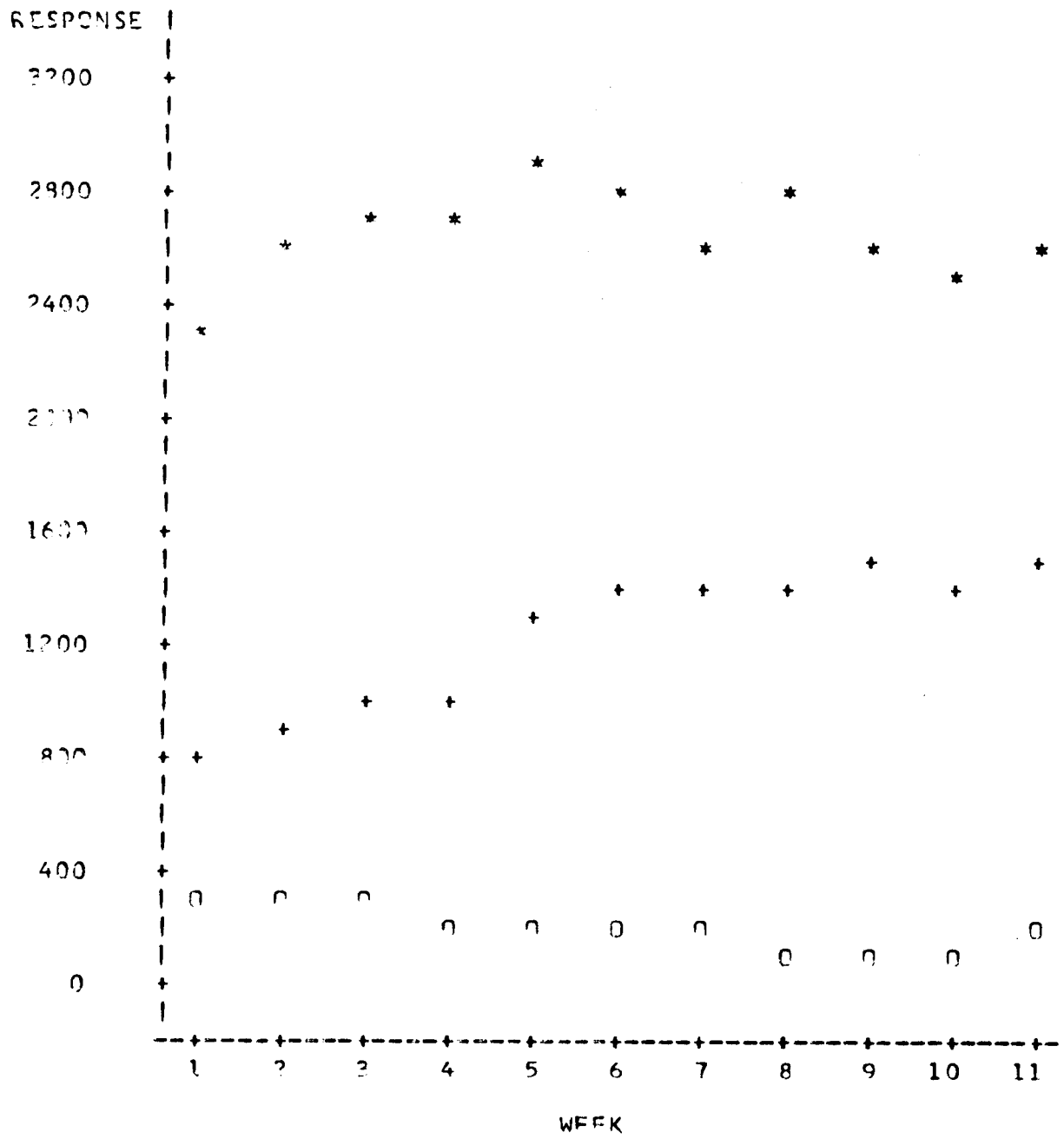


Figure 1. Responses plotted for groups as a function of weeks.

* = Experimental Group
+ = Yoked control Group
o = Nonshock control Group

matrices as described by Winer (1971, p. 523). Winner and others (e.g., Jennings and Wood, 1976; Myers, 1975) have argued that for the sampling distribution of the F ratio for within-subject effects to fit the F distribution with the expected degrees of freedom, the variance covariance matrices associated with those effects must fit a certain pattern. Winer has presented Box's test (Winer, 1971, p. 595-597) which can be used to determine if the matrices are acceptable. The use of this test is fairly easy since it is available in generally accessable statistical computer packages, e.g., SAS•76 (Barr, Goodnight, Sall and Helwig, 1976; Helwig, 1977). However, in instances when the determinant of one or more of the variance-covariance matrices is zero, one is unable to complete that test. Winer offers an alternative procedure in the form of the Geiser-Greenhouse conservative test (Winer, 1971, p. 530); however, this test is often unacceptably conservative. A third alternative is to compute the Geisser-Greenhouse correction factor "e" (Winer, 1971, p. 523). Jennings and Wood (1976) have also suggested the use of this correction procedure. This procedure adjusts the nominal degress of freedom downward as required by the degree of heterogeneity of the variance-covariance matrices. Since this "e" has as its lower bound the value suggested by the Geisser-Greenhouse conservative test, it is typically higher and thus yields a more powerful test. The author has prepared software based on SAS•76 procedures which generates the needed matrices and computes the correction factor "for any repeated measures design."[9] The simplicity of the program and the availability of the language enhance the attractiveness of this

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[9]This program is currently in preparation for submission for publication.

alternative. Indeed, the procedure ought to supplant the need to make Box's test at all in many cases.

The corrected degrees of freedom will be given in all analysis of variance summary tables. The mean squares presented in those tables result from the use of the normal degrees of freedom. The adjusted df are used only in the selection of the critical F value in the F tables to be used for a given test (Winer, 1971, p. 281).

Shock Data

Table 2 presents the results of the analysis of variance performed on shock data. The only effect approaching significance was Weeks whose F ratio had a probability only slightly greater than .05 ($_{.05}F_{4,21}=2.84$). Since a decline over weeks had been expected in this variable, Figure 2 is included to show that such a decline, although not statistically significant, did in fact occur.

Body Weight Data

Table 3 presents the results of the analysis of variance performed on body weight data. Three significant effects were obtained: the Replication by Weeks interaction and each of those two main effects. Since the interaction was significant, tests of simple main effects were required prior to evaluation of the main effects (Winer, 1971; pages 232-236). The interaction may be most clearly seen in Figure 3.

Table 4 presents the results of the analysis of simple main effects for Replications. Since the statistical procedures involved were rather complicated, some attention will be given them at this time. The procedures derive from Winer's discussion for this topic (pages 529-531). To test

Table 2. Analysis of Variance Summary Table for Shock Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Replication	392.29	1		392.29	0.00
Subjects Within Replications	588534.18	6		98089.03	
Weeks	187424.49	10	4	18742.45	2.83
Replications by Weeks	73745.55	10	4	7374.66	1.11
Subjects by Weeks Within Replications	397638.11	60	21	6627.30	

[a]This term refers to the corrected degress of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (c.f. Winer, 1971, page 523).

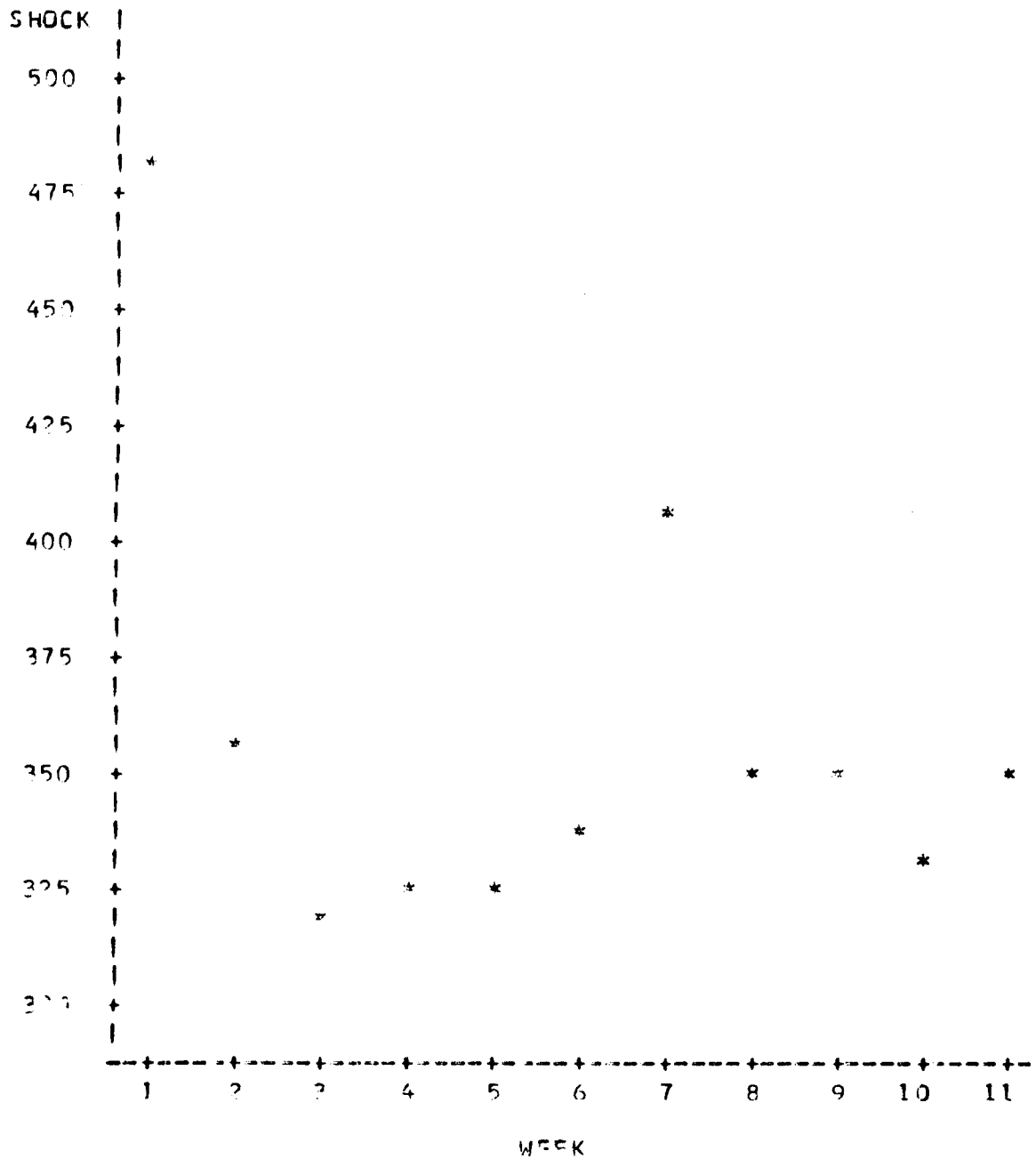


Figure 2. Shocks plotted as a function of weeks.

Table 3. Analysis of Variance Summary Table for Weight Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	22180.26	2		11090.13	0.60
Replications	166413.01	1		166413.01	9.05[b]
Groups by Replications	54988.31	2		27494.15	1.05
Subjects Within Groups by Replications	330885.38	18		18382.52	
Weeks	90256.86	10	2	9025.69	114.51[b]
Groups by Weeks	1185.63	20	4	59.28	0.75
Replications by Weeks	23436.46	10	2	2343.65	29.73[b]
Groups by Replications by Weeks	487.00	20	4	24.35	0.31
Subjects by Weeks Within Groups by Replications	14187.99	180	37	78.82	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

[b]$P < .05$.

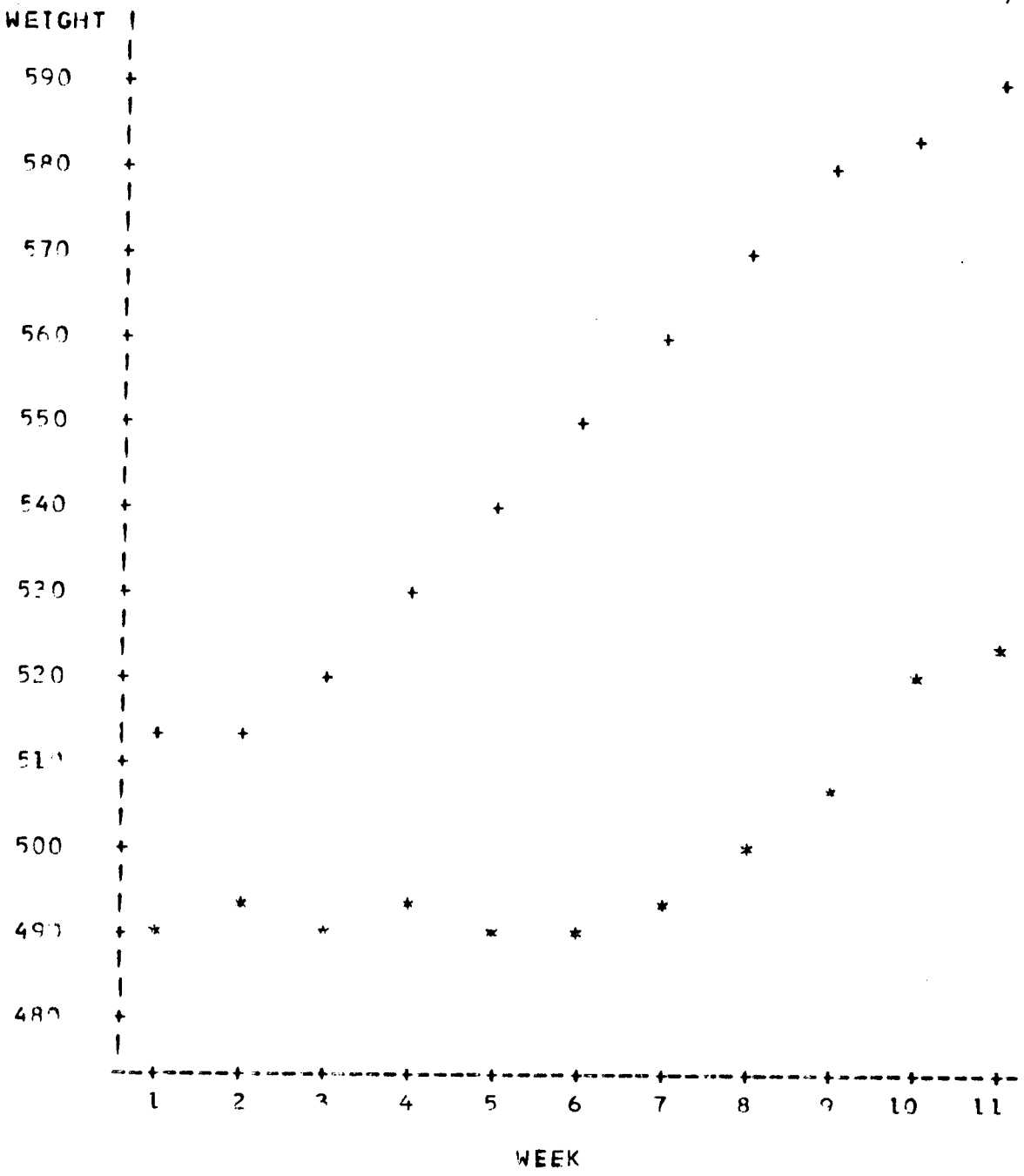


Figure 3. Body weight plotted for replications as a function of weeks.

* = Replication 1
\+ = Replication 2

Table 4. Analysis of Variance Summary Table for the Simple Main Effects of Replications at 11 Levels of Weeks for Body Weight Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Replications at Week 1	3504.17	1		3504.17	2.01
Replications at Week 2	2412.02	1		2412.02	1.38
Replications at Week 3	4896.33	1		4896.33	2.81
Replications at Week 4	7357.00	1		7357.00	4.22
Replications at Week 5	14084.42	1		14084.42	8.08[b]
Replications at Week 6	21026.00	1		21016.00	12.06[b]
Replications at Week 7	24588.80	1		24588.80	14.11[b]
Replications at Week 8	30659.20	1		30659.20	17.59[b]
Replications at Week 9	30487.88	1		30487.88	17.49[b]
Replications at Week 10	24003.38	1		24003.38	13.77[b]
Replications at Week 11	26840.28	1		26840.28	15.40[b]
Subjects Within	345073.37[c]	198		1742.80[d]	

[a]This term refers to the adjusted degrees of freedom obtained using the Satterthwaite procedure described in the text (cf. Winer, 1971, pages 530-531).

[b]$P < .05$.

[c]The subjects within replications term is the sum of the subjects within groups and the weeks by subjects within groups terms from the original analysis as described in the text.

[d]The Satterthwaite procedure calls for use of the original degrees of freedom in determining the mean square even though they are not used in testing the F ratio.

the simple main effects of Replications is to conduct a sample one way analysis of variance on Replications at each level of Weeks. The error term used in any one way analysis of variance is of course Subjects Within. In this type of design what would normally be considered different subjects are actually weeks and so the Subjects Within term is computed by combining the Subjects Within Groups by Replications sum of squares and Subjects by Weeks Within Groups by Replications sum of squares terms from the original data analysis. The degrees of freedom for this computed Subjects Within term are obtained by combining the degrees of freedom for the two terms taken from the original analysis. These values are the normal df 180 and 18. The mean square for Subjects Within in Table 4 was obtained by dividing the computed Subjects Within sum of squares by 198.

Winer (1971) further complicates the situation by pointing out that since the computed Subjects Within mean square is an average of nonhomogeneous sources of variance, the F ratio formed with the Replications effect mean square is not distributed as F with the nominal degrees of freedom. He describes Satterthwaites' procedure for correction of this problem by adjusting the degrees of freedom for the Subjects Within term. This procedure was followed after being adapted for the design used here. Thus the 180 df were adjusted downward to 20. Inspection of the F ratios presented in Table 4 reveals that Replications were significant for all weeks beyond the fourth week. In all cases, the body weight value for Replication 2 exceeded that for Replication 1.

Table 5 presents the results of the analysis of simple main effects for Weeks. Clearly the Weeks effect is strong in both Replications. It

Table 5. Analysis of Variance Summary Table for the Simple Main Effects of Weeks at Two Levels of Replications for Body Weight Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Weeks at Replication 1	17019.05	10	2	8509.53	4.88[b]
Weeks at Replication 2	96674.26	10	2	48337.13	27.74[b]
Weeks by Subjects Within Groups by Replications	14187.99	180	37	1742.80[c]	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

[b]$P < .05$.

[c]The error term for this analysis comes from the original analysis.

should be noted that the error term used in these tests was the same as used in the overall test for Weeks (cf. Table 3, page 73).

The Tukey A multiple comparisons test performed on Weeks means at Replication 1 showed Week 11 to be significantly different from all other weeks but Week 10. Week 10 was found to be significaty different from all but Week 9 and Week 11. Week 9 was found to be significantly different from Weeks 1, 6, 5, and 3. No other weeks differed significantly.

The Tukey A multiple comparisons test performed on Weeks at Replication 2 confirmed what is clearly seen in Figure 3, which shows the strong and stable gain in body weight over weeks. Week 4 differed from 1 and 2. Week 5 differed from 1-3. Week 6 differed from 1-4. Week 7 differed from 1-5. Week 8 differed from 1-6. Weeks 9 and 10 differed from 1-7. Week 11 differed from 1-8. Weeks 9, 10, and 11 did not differ significantly from each other.

B. CARDIOVASCULAR DATA

Tail Cuff Blood Pressure Data

Table 6 presents the results of the analysis of variance performed on the blood pressure data obtained using the tail cuff plethysmographic technique. The only significant effect was Replications. This effect is somewhat visible in the Replications by Weeks interaction shown in Figure 4. The two Replications differed on the average by only 6.1 mm Hg (129.9 mm vs 135.0 mm Hg). The group means are plotted by weeks in Figure 5.

Tail Cuff Heart Rate Data

Table 7 presents the results of the analysis of variance performed on the heart rate data obtained using the tail plethysmographic technique.

Table 6. Analysis of Variance Summary Table for Tail Cuff Blood Pressure Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	55.01	2		27.51	0.11
Replications	1782.42	1		1782.00	7.11[b]
Groups by Replications	619.34	2		309.67	1.24
Subjects Within Groups by Replications	4510.09	18		250.56	
Weeks	218.62	7	4	31.23	0.22
Groups by Weeks	1764.24	14	8	126.02	0.89
Replications by Weeks	1098.70	7	4	156.96	1.11
Groups by Replications by Weeks	2312.91	14	8	165.21	1.17
Subjects by Weeks Within Groups by Replications	17768.16	126	76	141.02	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

[b]$P < .05$.

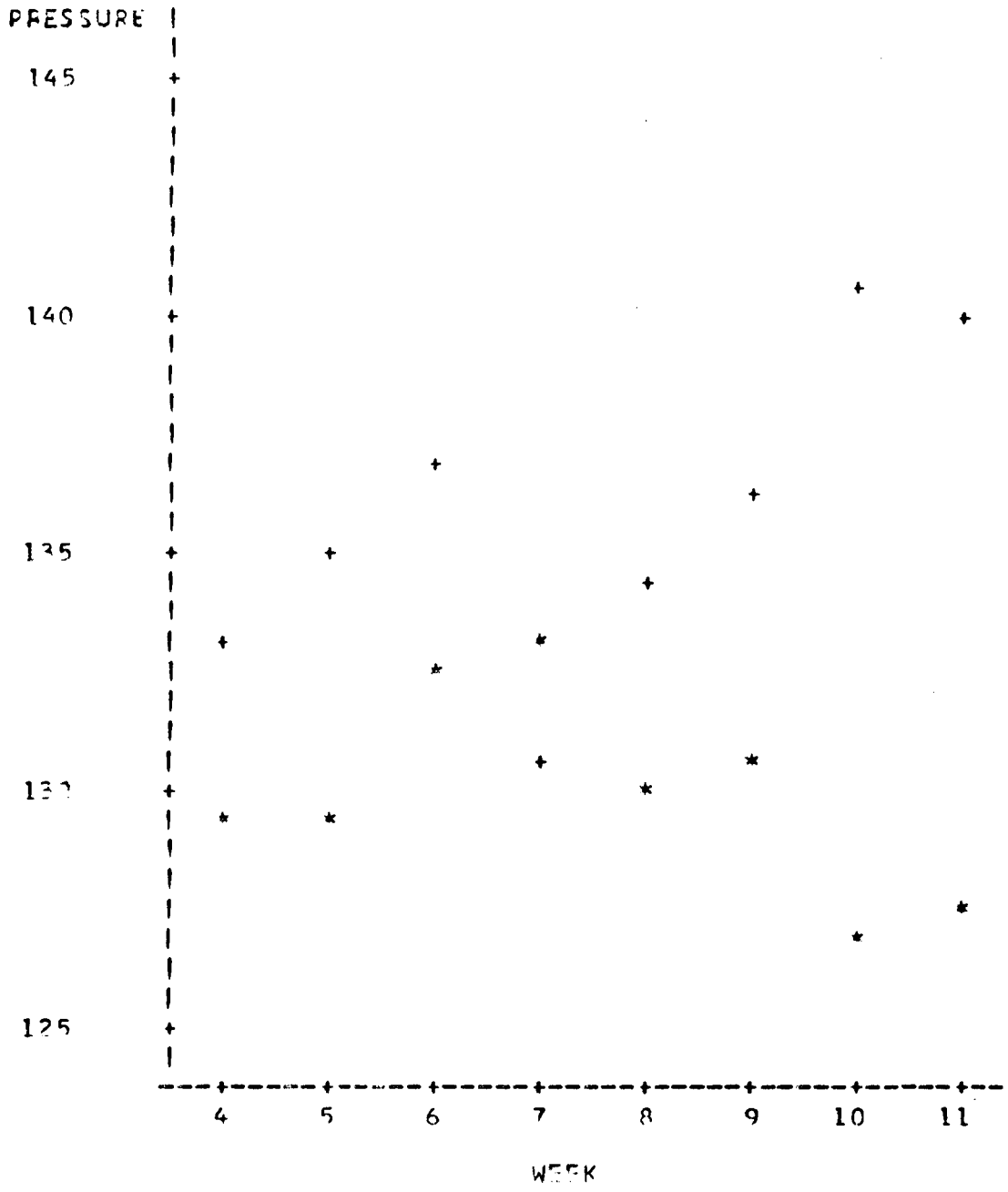


Figure 4. Tail cuff blood pressures for replications plotted as a function of weeks.

* = Replication 1
\+ = Replication 2

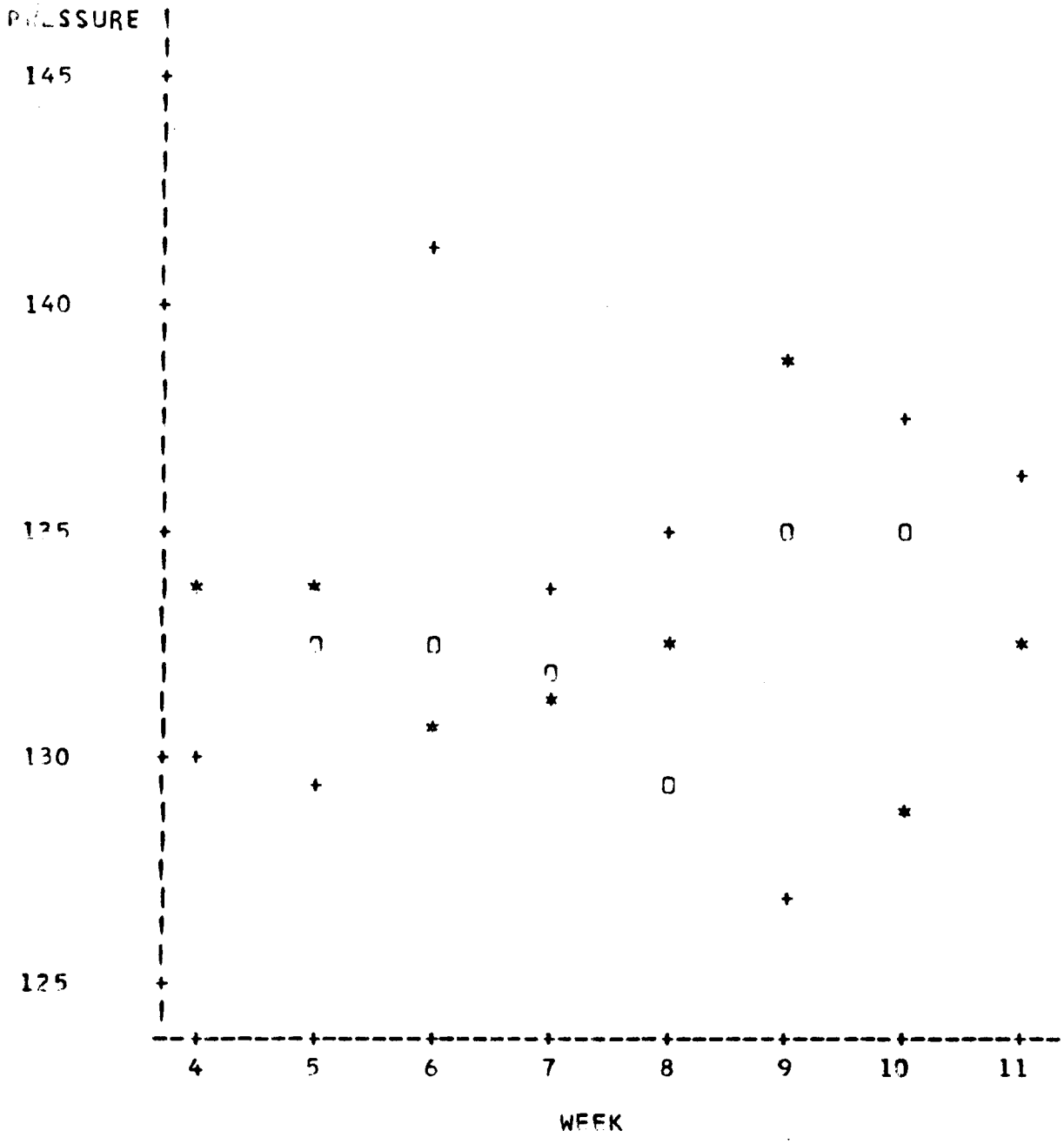


Figure 5. Tail cuff blood pressures plotted for groups as a function of weeks.

* = Experimental Group
\+ = Yoked control Group
o = Nonshock control Group

Table 7. Analysis of Variance Summary Table for Tail Cuff Heart Rate Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	41687.28	2		20843.64	2.89
Replications	142245.19	1		142245.19	19.71[b]
Groups by Replications	7349.16	2		3674.58	0.51
Subjects Within Groups by Replications	129916.94	18		7217.61	
Weeks	9440.40	7		1348.63	1.73
Groups by Weeks	6235.89	14	10	445.42	0.57
Replications by Weeks	9551.23	7	5	1364.46	1.75
Groups by Replications by Weeks	10518.18	14	10	751.30	0.96
Subjects by Weeks Within Groups by Replications	98209.56	126	92	779.44	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

[b]$P < .05$.

The only significant effect was Replications. This effect is clearly seen in the Replications by Weeks interaction shown in Figure 6. The two Replications differed by an average of 54.5 bpm (344.3 vs 398.8 bpm). Figure 7 demonstrates an apparent difference between the heart rates of the yoked control group and those of the other two groups; however, this difference did not achieve statistical significance (F=2.89, df=2,18).

Directly Measured Systolic Blood Pressure Data

Table 8 presents the results of the analysis of variance performed on the systolic blood pressure data obtained during direct recordings. While none of the effects proved statistically significant, Figure 8 indicates a decline in systolic pressure during the first 16 minutes on the schedule which was followed by a progressive return to the initial levels. This pattern held for all three groups.

Directly Measured Diastolic Blood Pressure Data

Table 9 presents the results of the analysis of variance performed on the diastolic blood pressure data obtained during direct recordings. Again, none of the effects proved statistically significant. The biphasic pattern seen in the systolic blood pressure data is shown in Figure 9; it is less clear in the diastolic pressure, however.

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[10] Direct recordings were obtained on 20 of 24 subjects. The other four subjects either had no signal due to poor cannula placement or such a weak signal as to make them unsuitable. Data from 18 of those 20 subjects were used in the analysis. Since an equal number of subjects from each group was desired for the analysis, good data from one experimental and one yoked control subject were not included in the analysis.

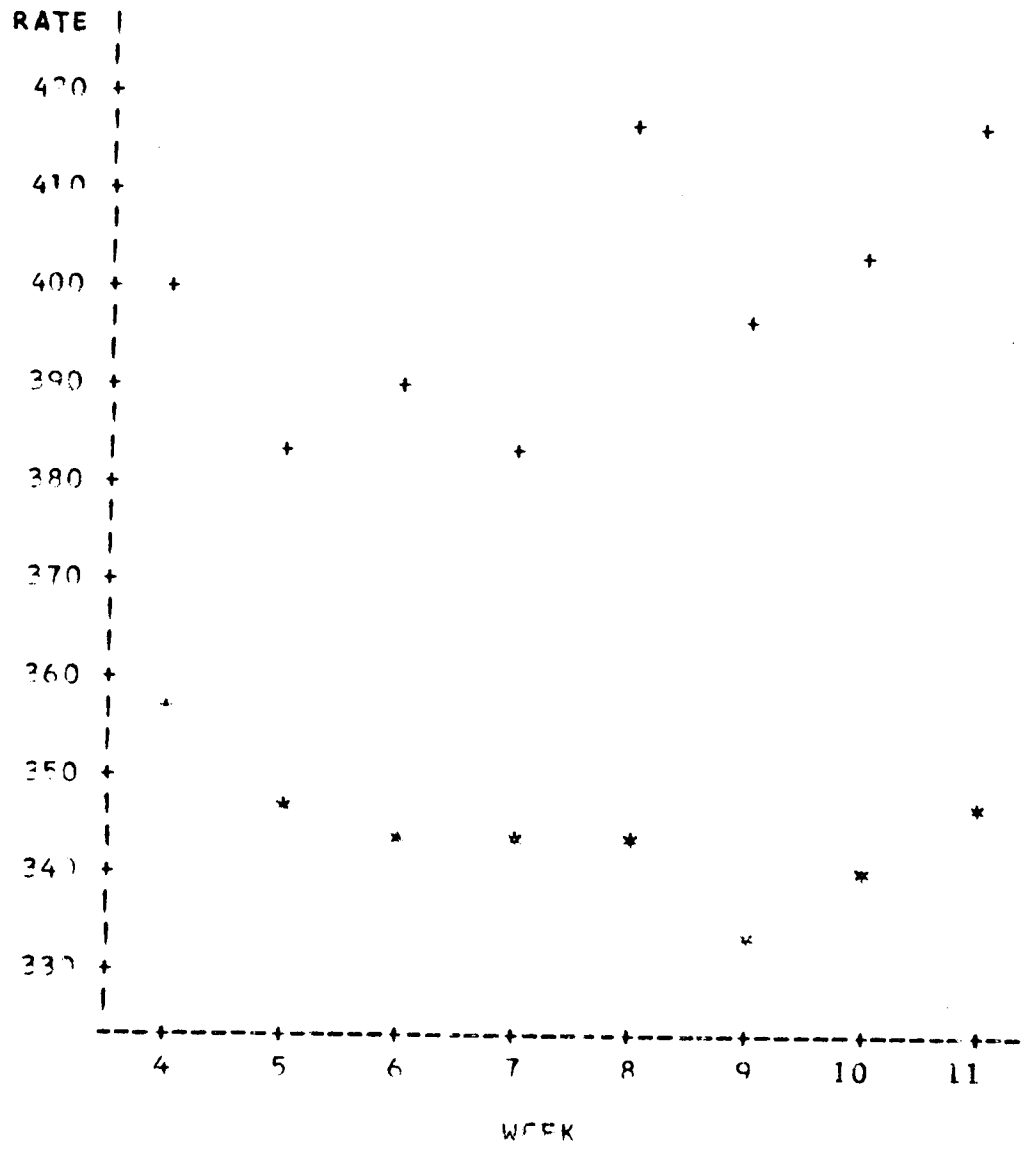


Figure 6. Tail cuff heart rates plotted for replications as a function of weeks.

* = Replication 1
\+ = Replication 2

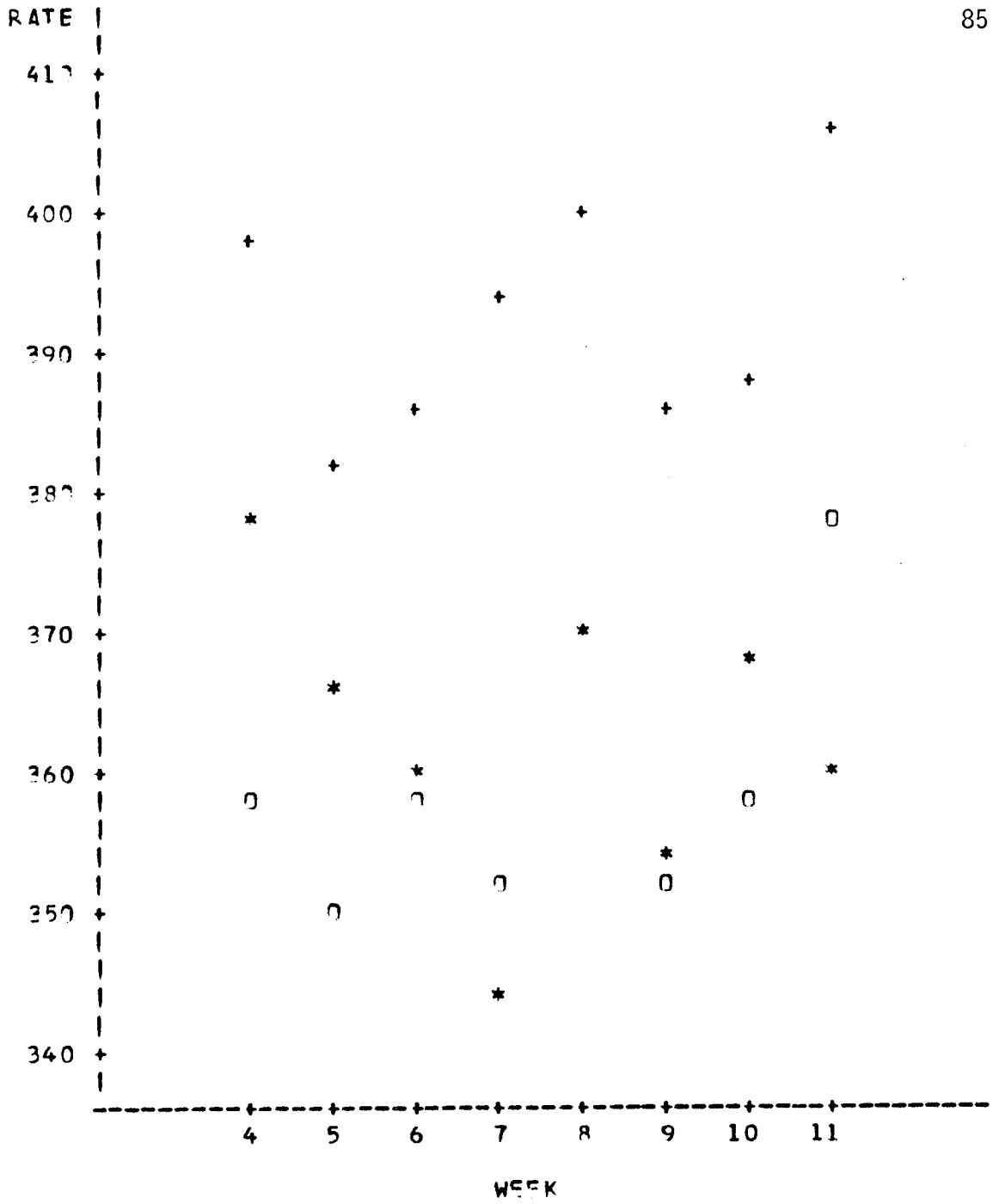


Figure 7. Tail cuff heart rates plotted for groups as a function of weeks.

* = Experimental Group
\+ = Yoked control Group
o = Nonshock control Group

Table 8. Analysis of Variance Summary Table for Direct Systolic Blood Pressure Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	925.61	2		462.81	0.81
Subjects Within Groups	8533.21	15		568.88	
Blocks	618.96	11	5	56.27	2.30
Groups by Blocks	564.30	22	9	25.65	1.05
Subjects by Blocks Within Groups	4043.58	165	71	24.51	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

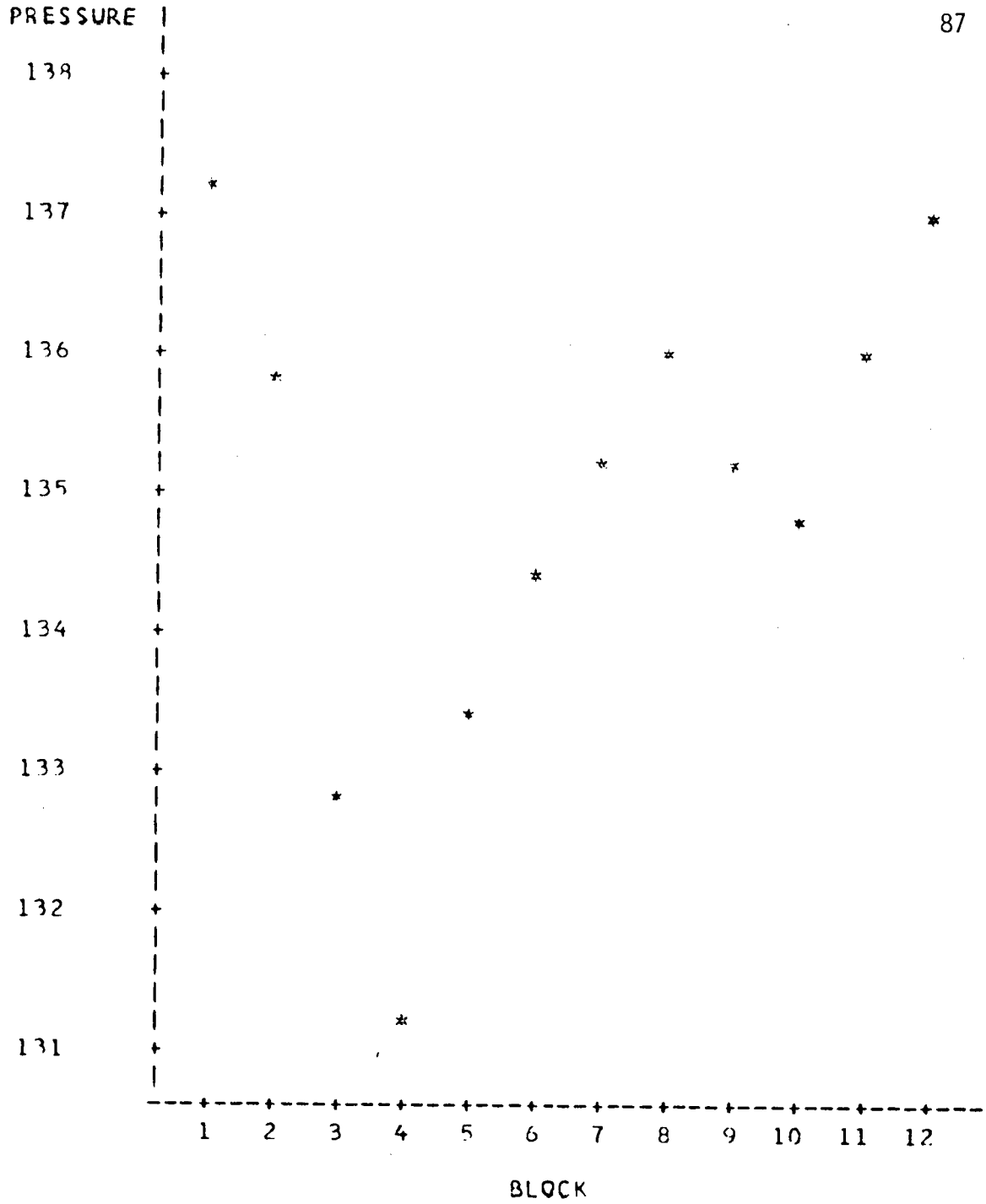


Figure 8. Direct systolic blood pressure plotted as a function of five minute blocks.

Table 9. Analysis of Variance Summary Table for Direct Diastolic Blood Pressure Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	449.71	2		224.85	0.32
Subjects Within Groups	10683.96	15		712.26	
Blocks	318.18	11	4	28.96	1.80
Groups by Blocks	319.17	22	8	17.78	1.10
Subjects by Blocks Within Groups	2659.34	165	59	16.12	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

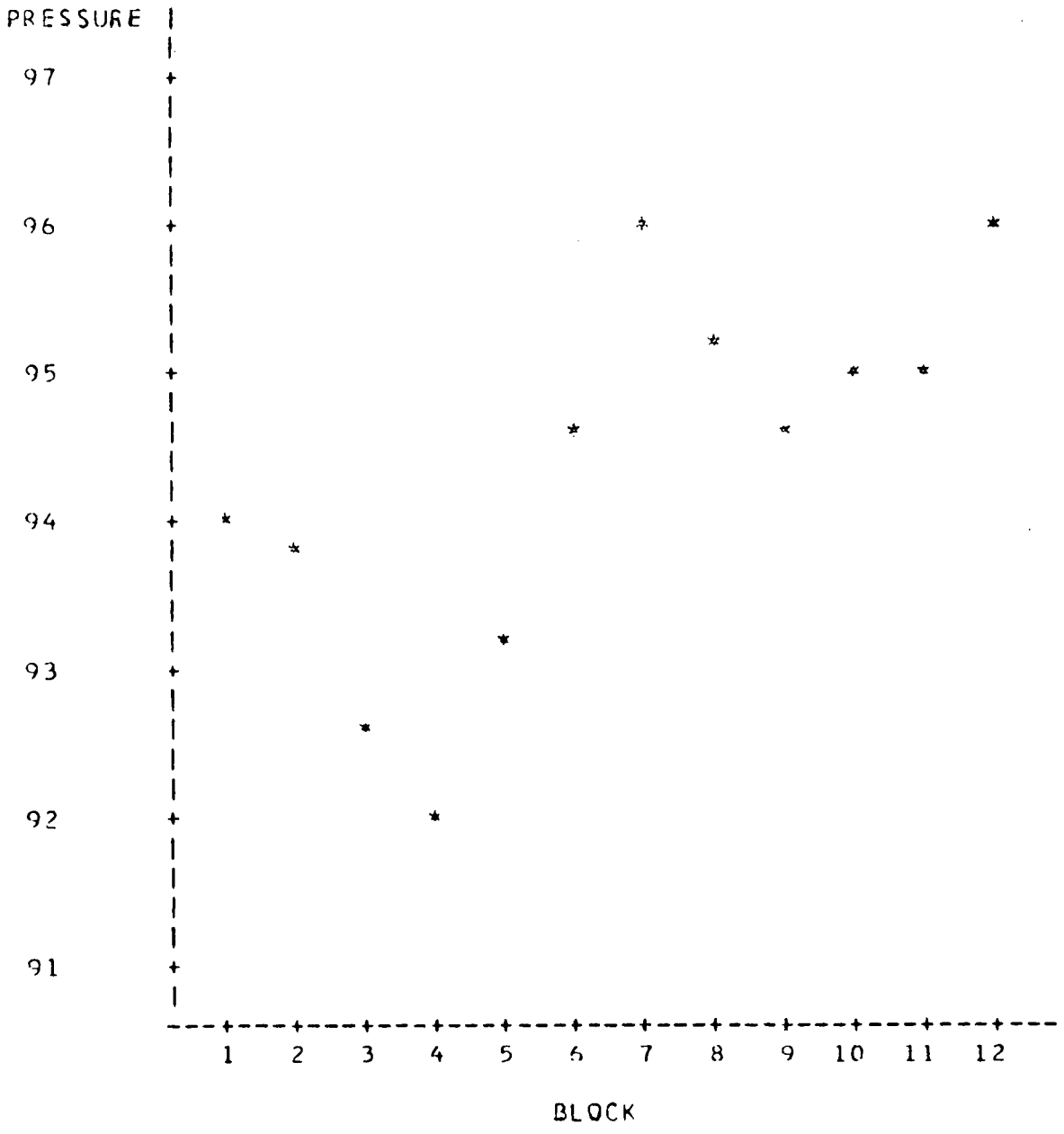


Figure 9. Direct diastolic blood pressure plotted as a function of five minute blocks.

Direct Heart Rate Data

Table 10 presents the results of the analysis of variance performed on the heart rate data obtained during direct recordings. Again, none of the effects proved statistically significant. Figure 10 demonstrates the absence of any biplasic trend.

D. ULCERATION DATA

Signs of ulceration were found in only four of the 24 subjects used in the study. The ulceration was minimal and therefore the data were not analyzed further.

Table 10. Analysis of Variance Summary Table for Direct Heart Rate Data

Source of Variation	Sum of Squares	df	df'[a]	Mean Squares	F
Groups	38322.44	2		19161.22	1.88
Subjects Within Groups	152477.92	15		10165.19	
Blocks	5017.32	11	4	456.12	1.19
Groups by Blocks	5398.31	22	8	245.38	0.64
Subjects by Blocks Within Groups	63143.31	165	57	382.69	

[a]This term refers to the corrected degrees of freedom obtained using the Geisser-Greenhouse correction factor for heterogeneity of variance-covariance matrices as described in the text (cf. Winer, 1971, page 523).

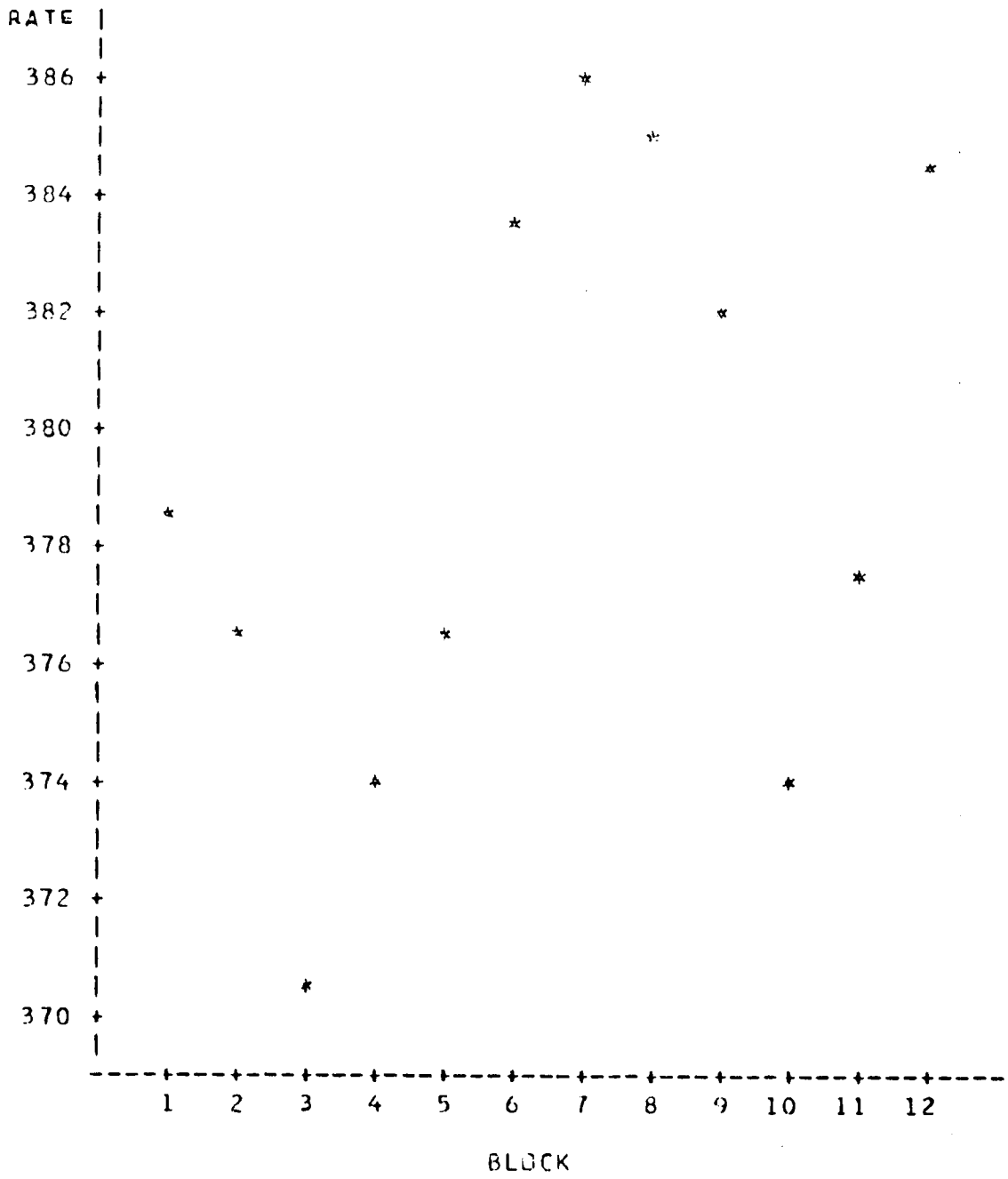


Figure 10. Direct heart rate plotted as a function of five minute blocks.

CHAPTER IV

DISCUSSION

While the cardiovascular data are the data of interest in this presentation, the behavioral and body weight data presented certain interesting findings. These data will be considered separately.

A. BEHAVIORAL AND BODY WEIGHT DATA

It is clear from the results of the analysis of response data that the behavioral procedures used had the expected behavioral effects. It is not particularly of interest to dwell on data confirming once again that Sidman (1953) was right. The response data and shock data do however indicate just that.

The body weight data provide a note of interest. The main effect of Replications and the Replications by Weeks interaction effect were not expected when the experiment was planned. In part, the replication effect may be due to a difference in initial weight and age of the subjects used in the two Replications. The subjects were purchased approximately three months apart and ordered in order to begin initiation into the study at the same age and weight. Unfortunately, the subjects ordered for the second Replication arrived at the proper weight but approximately two weeks early. By the time they were initiated into the study their average weight was greater than that of the first Replication population (as seen in Figure 3, page 74). While this fact may contribute to the Replications main effect, it does not explain it entirely for the Replications were not

significantly different during the first 4 weeks (as seen in Table 5, page 77). Replications were significant as a main effect only for the last 7 weeks.

The Replications by Weeks interaction may provide an explanation for the shape of the Weeks curve for Replication 1 (see Figure 3, page 74). The weight of the subjects was stable until the seventh week during the first Replication. Beyond the seventh week the slopes of the curves for the two Replications are similar. The timing of the change in the slope of the body weight curve for Replication 1 coincides dramatically with the timing of a procedural change made during that Replication. At the end of the fifth week (fourth week for half of the subjects in the Replication) of running, it was observed that the animals were literally chewing through the brass bars which had been used to form the spokes of the running wheels in the experimental cages. In fact, several animals had almost cut the eighth inch solid brass bars in half. This phenomenon was totally unexpected. A week passed before a rapidly placed order for stainless steel bars could be filled and the replacement bars installed. Little was thought of the incident until the weight charts began to show the coincidence between the removal of the brass and the rapid weight gain. Analysis of the weight charts by subjects confirmed that the weight gain in each case began on the day that the stainless steel rods were introduced. It is impossible to draw any firm conclusions as to cause and effect but the coincidence is very suggestive.

Setting the "brass effect" aside for a moment, the steady and gradual increase in body weight seen in the second Replication and in the

later portion of the first Replication mimics that reported by Friedman and Dahl (1975) in their subjects yoked for shock alone.

B. CARDIOVASCULAR DATA

The data reported here show an absence of any cardiovascular effect due to prolonged exposure to Sidman avoidance, yoked control, or nonshock control procedures in which all subjects were similarly restrained. This finding was consistent across three cardiovascular indices measured using two very different techniques. The data would suggest that such prolonged exposure has no hypertensive effect. This finding is in conflict with the reports of Forsyth (1969) and Herd et al. (1969) who described a hypertensive response in monkeys subjected to long term Sidman avoidance. The finding is consistent with those of Findley et al. (1971), who used a paradigm similar to Forsyth (1969) and Herd et al. (1969) but did not obtain any pressure elevations, and Friedman and Dahl (1975) who found no pressure elevation in subjects placed in a yoked shock condition similar to that used in the present study.

The reports by Forsyth (1969) and Herd et al. (1969) were criticized earlier for several methodological reasons. Much of that criticism revolved around the issues of control groups and statistical analyses. Both laboratories had reported gradual elevations in blood pressure in two species of monkey (rhesus and spider) and no such rise in the controls used. Despite the methodological criticisms made earlier, the shape of the curves reported by Forsyth and Herd et al. showing the elevations in pressure for their experimental animals was not questioned. The issues

raised involved the lack of an adequate comparison group rather than the validity of those curves. Their subjects displayed an elevation in pressure. However, the data described here did not show elevations in any of the groups. The results presented here simply differ from those presented by Forsyth and Herd et al. Procedural variations may account for certain of the differences and species differences may account for others.

Forsyth (1969) and Herd et al. (1969) subjected their animals to 12 hours of avoidance per day for 10 to 14 months. The elevations in pressure became apparent at about the fourth or fifth month. Yet both studies used monkeys as subjects. It was reasoned that rats subjected to similar procedures should show a response, if any was to be shown, in a much shorter time due to the differences in life span. It was also reasoned that the rats should show the effect with a briefer exposure to the avoidance paradigm. Thus the subjects in this study were exposed to the avoidance schedule for 3 hours per day for 3 months. It is important to recall that the only laboratories which had used rats as subjects had seen hypertensive responses in less than 2 weeks (Friedman and Dahl, 1975) and 8 weeks (e.g., Henry et al., 1975) respectively. In spite of what appeared at the time to be good reasoning, it is possible that these procedural differences may account for part of the discrepancy.

The issue of species differences should also be considered. Findley et al. (1971) subjected baboons to procedures similar to those used by Forsyth (1969) and Herd et al. (1969): 12 hours of avoidance per day for approximately 1 year. They observed no hypertensive response. The species used in the present study was rat and again no hypertensive response

was observed. The validity of the findings described here is supported in part by Friedman and Dahl (1975) who reported no elevation in pressure in subjects in a condition similar to the yoked control condition used in this study. Their species was also rat. Friedman and Dahl also suggested that genetic factors should be considered when approaching the question of psychological stress and hypertension, and their arguments were extended by Friedman and Iwai (1976). Their concerns about genetics were not specifically for interspecies differences but their arguments can logically be extended to include such differences. It is possible that the species used may in part determine the cardiovascular effects of these procedures.

One final issue should be discussed concerning the discrepancy between the findings of Forsyth (1969), Herd et al. (1969) and the present study. The suggestion concerning genetics above and that of procedural differences prior to that have merit; however, the author is reluctant to attribute the entire difference to those two factors. A third possibility exists. Both of the earlier studies used chronic restraint in the form of primate chairs. The subjects were placed in the chairs after catheter implantation and kept there for the duration of the study (over one year). Forsyth and Baireuther (1967) have shown that such restraint is not in and of itself stressful (i.e., it does not cause a rise in blood pressure). In the studies by Forsyth (1969) and Herd et al. (1969) no controls were included for a possible interaction between the effects of the chronic restraint and those of the avoidance schedule. While the 1967 paper does seem to control for a main effect of restraint, the interaction

exists as a possible cause for the pressure elevations rather than the avoidance schedule itself. The present study did not use chronic restraint.

Other issues also deserve attention. As described earlier, it was expected that the unpredictability and uncontrollability of the yoked control condition would make that condition particularly aversive and therefore likely to have stressful effects on the subjects placed in it. Clearly no physiological stress occurred. Friedman and Dahl (1975) reported a similar finding, although it was in their special rat strain. Their finding, coupled with the present one, would seem to suggest that unpredictability and uncontrollability may not be as important as previously thought, at least in terms of stress.

It is important to recall that much of the work concerning physiological stress produced by unpredictable and uncontrollable shocks involved intensive but short term aversive procedures. For example, Weiss (1971a) exposed rats to either Sidman avoidance, yoked control or restraint only control procedures for 48 continuous hours. All subjects were food and water deprived. He found ulceration in the avoidance and yoked control groups but primarily in the yoked control group. The almost total absence of ulceration and other signs of physiological stress in the present study would suggest that prolonged exposure to these procedures differs greatly in its impact upon the subject than such short term but very intense exposure. The food deprivation is also likely to have been important in Weiss's findings. His emphasis on the significance of unpredictable and uncontrollable aversive events may not be applicable to prolonged exposure to such events.

The clear findings of physiological stress in subjects exposed to short term unpredictable and uncontrollable events and the apparent lack of such stress in subjects exposed to such events long term suggests that subjects may adapt to such aversive events over time. Such adaptation would clearly have survival value. This possibility would seem to greatly reduce the significance of psychological stress in the etiology of such diseases as hypertension.

Another possibility exists, however. Consider the paradigm used in the study reported here. Shocks were administered to subjects (yoked controls) as (on average) 350 discrete events. Each shock was intended to be uncontrollable and unpredictable. But upon observing the subjects during a daily session, one could see that shocks were not delivered as 350 discrete and totally unpredictable events. Rather, they were delivered in bursts of generally 5 to 10 shocks in rapid order: this because the Sidman avoidance subject responded in a manner so as to produce this particular pattern. Rather than 350 discrete events, there were perhaps 35 to 70 bursts of shock. The probability of shock given shock was quite high and therefore most of the shocks were predictable. When one considers that the 35 to 70 bursts were delivered over a 3 hour period, one sees that the shock was actually delivered at a rate of one burst every 2.6 to 5 minutes. That is not very frequent shock. One is left with a primarily predictable shock that is infrequent in what was intended to be a totally unpredictable and uncontrollable shock situation. The way that the individually unpredictable shocks were scheduled (by the Sidman avoidance subject) altered the way in which the shocks impacted upon the yoked subject.

This interpretation leaves open the possibility that uncontrollable and unpredictable shocks may have important effects on subjects. If one agrees with this interpretation, the uncontrollable and unpredictable condition has still not been used on a long term basis. This is particularly true if, in the work of Friedman and Dahl (1975), the yoked shock subjects received shock in the same sort of clustered pattern. Further work is needed in this area.

Certain aspects of the data require further consideration. It is clear from the curves in Figures 4 and 6 (pages 80 and 84) that there was a Replication effect in both the blood pressure and heart rate from tail cuff recordings. This effect was not expected in either case. A possible explanation comes from the fact that two different persons were involved in conducting the tail cuff measurements, and the two were involved primarily in the two different Replications. Perhaps some idiosyncracy in procedure on the part of one or the other of these persons contributed to the difference.

Another aspect of the data calling for further consideration is the form of the variance-covariance matrices for repeated measures factors. As described earlier, the F ratios obtained in the analyses of the data were tested using adjusted degrees of freedom. Many F values which would have been statistically significant using the nominal degress of freedom were not found to be significant when tested with the adjusted values. This finding seems to reaffirm Jennings and Wood's (1976) observation that the failure to evaluate the form of the variance-covariance matrices may lead to an inflated number of findings of significance. The data gathered have demonstrated again the need to make corrections for the matrices.

Several areas of possible future research seem open. The possibility that the condition of unpredictable and uncontrollable shock has still not been applied to subjects long term requires that this be done. The effects of such aversive events in terms of the production of stress will remain obscured until this is done. The analysis presented here raises questions concerning the generalizability of short term effects obtained in this condition.

Certainly the paradigm of conflict used by Friedman and Dahl (1975) deserves further attention. Not only is further work needed in analyzing the significant components of the aversive paradigm used, but also more detailed work is needed showing what is happening physiologically during the hypertensive response. As more and more data concerning the physiology of human essential hypertension become available, the burden on the animal researcher to demonstrate the relevance of his particular animal model to the human disorder increases.

The burden of proof for a relationship between psychologically aversive events and hypertensive disease remains on the psychophysiologist. The relationship is not yet established.

LIST OF REFERENCES

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Alexander, F. *Psychosomatic Medicine*. New York: Norton, 1950.

Anderson, D. E., and Brady, J. V. Preavoidance blood pressure elevations accompanied by heart rate decreases in the dog. *Science*, 1971, *172*, 595-597.

Anderson, D. E., and Brady, N. V. Differential preparatory cardiovascular responses to aversive and appetitive behavioral conditioning. *Conditioned Reflex*, 1972, *7*, 82-96.

Anderson, D. E., and Brady, J. V. Prolonged preavoidance effects upon blood pressure and heart rate in dogs. *Psychosomatic Medicine*, 1973, *35*, 4-12.

Anderson, D. E., and Tosheff, J. G. Cardiac output and total peripheral resistance changes during preavoidance periods in the dog. *Journal of Applied Physiology*, 1973, *34*, 650-654.

Badia, P., and Culbertson, S. The relative aversiveness of signaled vs unsignaled escapable and inescapable shock. *Journal of the Experimental Analysis of Behavior*, 1972, *17*, 463-471.

Badia, P., Culbertson, S., and Lewis, P. The relative aversiveness of signaled vs unsignaled avoidance. *Journal of the Experimental Analysis of Behavior*, 1971, *16*, 113-121.

Barr, A. J., Goodnight, J. H., Sall, J. P. or Helwig, J. T. A User's Guide to SAS•76. Raleigh, North Carolina: SAS Institute Inc., 1976.

Benson, H., Herd, J. A., Morse, W. H., and Kelleher, R. T. Behavioral induction of arterial hypertension and its reversal. *American Journal of Physiology*, 1969, *217*, 30-34.

Benson, H., J. A., Morse, W. H., and Kelleher, R. T. Behaviorally induced hypertension in the squirrel monkey. *Circulation Research*, 1970, *26* and *27*, 121-126. (Supplement 1).

Birkenhager, W. H., and Schalekamp, M.A.D.H. *Control Mechanisms in Essential Hypertension*. Amsterdam: Elsevier Scientific Publishing Company, 1976.

Black, A. H. A comment on yoked control designs. Technical Report No. 11, September 1967, McMaster University, Department of Psychology.

Braunwald, E. Regulation of the circulation. *The New England Journal of Medicine*, 1974, *210*, 1124-1125.

Brener, J., Eissenberg, E., and Middaugh, S. Respiratory and somatomotor factors associated with operant conditioning of cardiovascular responses in curarized rats. In P. A. Obrist, A. H. Black, J. Brener, and L. V. DiCara (Eds.), *Cardiovascular Psychophysiology*. Chicago: Aldine, 1974.

Buckley, J. P., Kato, H., Kinnard, W. J., Aceto, M.D.G., Estevez, J. M. Effects of reserpine and chlorpromazine on rats subjected to experimental stress. *Psychopharmacologia*, 1964, *6*, 87-95.

Campbell, D. T., and Stanley, J. C. *Experimental and quasi-experimental designs for research*. Chicago: Rand McNally College Publishing Company, 1964.

Cannon, W. B. *Bodily changes in pain, hunger, fear and rage*. New York: Appleton, 1923.

Catania, A. C. Elicitation, reinforcement, and stimulus control. In R. Glazer (Ed.), *The nature of reinforcement*. New York: Academic Press, 1971.

Church, R. M. Systematic effects of random error in the yoked-control design. *Psychological Bulletin*, 1964, *62*, 122-131.

Corley, K. C., Mauck, H. P., and Shiel, F. O'M. Cardiac responses associated with "yoked chair" shock avoidance in squirrel monkeys. *Psychophysiology*, 1975, *12*, 439-444.

Corley, K. C., Shiel, F. O'M., Mauck, H. P., Clark, L. S., and Barber, J. H. Myocardial degeneration and cardiac arrest in squirrel monkey: physiological and psychological correlates. *Psychophysiology*, 1977, *14*, 322-328.

Corley, K. C., Shiel, F. O'M., Path, M. R. C., Mauck, H. P., and Greenhoot, J. Electrocardiographic and cardiac morphological changes associated with environmental stress in squirrel monkeys. *Psychosomatic Medicine*, 1973, *35*, 361-364.

Crider, A., Schwartz, G. E., and Shnidman, S. On the criteria for instrumental autonomic conditioning: a reply to Katkin and Murray. *Psychological Bulletin*, 1969, *71*, 455-461.

Dahl, L. K., Knudsen K. D., Heine, M., and Leitl, G. Hypertension and stress. *Nature*, 1968, *219*, 735-736.

Davis, J. O., and Freeman, R. H. Mechanisms regulating renin release. *Physiological Reviews*, 1976, *56*, 1-56.

Dayton, C. M. *The design of educational experiments*. New York: McGraw Hill Book Company, 1970.

DiCara, L. V. and Miller, N. E. Instrumental learning of systolic blood pressure responses in curarized rats: dissociation of cardiac and vascular changes. *Psychosomatic Medicine*, 1968, *5*, 489-494.

Dustan, H. P., Tarazi, R. C., and Bravo, E. L. Physiologic characteristics of hypertension. *The American Journal of Medicine*, 1972, *52*, 610-622.

Eich, R. H., Cuddy, R. P., Smulyan, H., and Lyons, R. H. Hemodynamics in labile hypertension: a follow-up study. *Circulation*, 1966, *34*, 200-307.

Ely, D. L., and Henry, J. P. Effects of prolonged social deprivation on murine behavior patterns, blood pressure, and adrenal weight. *Journal of Comparative and Physiological Psychology*, 1974, *87*, 733-740.

Esler, M., Julius, S., Zweifler, A., Randall, O., Harburg, E., Gardiner, H., and DeQuattro, V. Mild high-renin essential hypertension: neurogenic human hypertension? *The New England Journal of Medicine*, 1977, *296*, 405-411.

Farris, E. J., Yeakel, E. H., and Medoff, H. S. Development of hypertension in emotional gray norway rats after air blasting. *American Journal of Physiology*, 1945, *144*, 331-333.

Feigel, E. O. Physics of the cardiovascular system. In T. C. Ruch and H. D. Patton (Eds.), *Physiology and biophysics: circulation, respiration and fluid balance*. Philadelphia: W. B. Saunders Company, 1974.

Findley, J. D., Brady, J. V., Robinson, W. W., and Gilliam, W. Continuous cardiovascular monitoring in the baboon during long term behavioral performances. *Communications in Behavioral Biology*, 1971, *6*, 48-59.

Fletcher, P. S., Korner, P. I., Angus, J. A., and Oliver, J. R. Changes in cardiac output and total peripheral resistance during development of renal hypertension in rabbit: lack of conformity with autoregulation theory. *Circulation Research*, 1976, *35*, 633-639.

Folkow, B., Hallback, M., Lundgren, Y., and Weiss, L. Structurally based increase of flow resistance in spontaneously hypertensive rats. *Acta Physiologica Scandinavica*, 1970, *79*, 373-378.

Forsyth, R. P. Blood pressure and avoidance conditioning. *Psychosomatic Medicine*. 1968, *30*, 125-135.

Forsyth, R. P. Blood pressure responses to long term avoidance schedules in the restrained rhesus monkey. *Psychosomatic Medicine*, 1969, *31*. 300-309.

Forsyth, R. P. Regional blood-flow changes during 72-hour avoidance schedules in the monkey. *Science,* 1971, *173,* 546-548.

Forsyth, R. P., and Baireuther, R. Systematic arterial blood pressure and pulse rate in chronically restrained rhesus monkeys. *American Journal of Physiology,* 1967, *212,* 1461-1463.

Forsyth, R. P., and Harris, R. E. Circulatory changes during stressful stimuli in rhesus monkeys. *Circulation Research,* 1970, *26* and *27,* I13-I20. (Supplement 1).

Friedman, R., and Dahl, L. K. The effect of chronic conflict on the blood pressure of rats with a genetic susceptibility to experimental hypertension. *Psychosomatic Medicine,* 1975, *37,* 402-416.

Friedman, R., and Iwai, J. Genetic predisposition and stress-induced hypertension, *Science,* 1976, *193,* 161-162.

Frolich, E. D., Tarazi, R. C., and Dustan, H. P. Hyperdynamic beta-adrenergic circulatory state. *Archives of Internal Medicine,* 1969, *123,* 1-7.

Geber, G. L., and Klevans, L. R. Central nervous system modulation of cardiovascular reflexes. *Federation Proceedings,* 1972, *31,* 1245-1252.

Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *Journal of Experimental Medicine,* 1934, *59,* 347-379.

Goodman, L. S., and Gilman, A. *The pharmacological basis of therapeutics.* New York: Macmillan Publishing Co., Inc. 1975.

Guyton, A. C., Coleman, T. G., Cowley, A. W., Manning, R. D., Norman, R. A., and Ferguson, J. D. A Systems approach to understanding long-range arterial blood pressure control and hypertension. *Circulation Research,* 1974, *35,* 159-176.

Guyton, A. C., Coleman, T. G., Cowley, A. W., Scheel, K. W., Manning, R. D., and Norman, R. A. Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension. *The American Journal of Medicine,* 1972, *52,* 584-594.

Guyton, A. C., Coleman, T. G., and Granger, H. J. Circulation: overall regulation. *Annual Review of Physiology,* 1972, *34,* 13-46.

Harris, A. H., and Brady, J. V. Animal learning--visceral and autonomic conditioning. *Annual Review of Psychology,* 1974, *25,* 107-133.

Harris, A. H., Findley, J. D., and Brady, J. V. Instrumental conditioning of blood pressure elevations in the baboon. *Conditioned Reflex,* 1971, *6,* 215-226.

Helwig, J. T. SAS Supplemental Library User's Guide. Raleigh, North North Carolina: SAS Institute, Inc., 1977.

Henry, J. P., Ely, E. L., Stephens, P. M., Ratcliffe, H. L., Santisteban, G. A., Shapiro, A. P. Role of psychosocial factors in the development of arteriosclerosis in CBA mics: observations on the heart, kidney, and aorta. *Atherosclerosis,* 1971, *14,* 203-218.

Henry, J. P., Mehan, J. P., and Stephens, P. M. The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. *Psychosmatic Medicine,* 1967, *29,* 408-432.

Henry, J. P., Stephens, P. M., Axelrod, J., and Mueller, R. A. Effect of psychosocial stimulation on the enzymes involved in the biosynthesis and metabolism of noradrenaline and adrenaline. *Psychosomatic Medicine,* 1971, *33,* 227-237.

Henry, J. P., Stephens, P. H., and Santisteban, G. A. A model of psychosocial hypertension showing reversibility and progression of cardiovascular complications. *Circulation Research,* 1975, *36.* 156-164.

Herd, J. A. Overall regulation of the circulation. *Annual Review of Physiology,* 1970, *32,* 289-312.

Herd, J. A., and Barger, A. C. Simplified technique for chronic catheterization of blood pressure. *Journal of Applied Physiology,* 1964, *19,* 791-792.

Herd, J. A., Morse, W. H., Kelleher, R. T., and Jones, L. G. Arterial hypertension in the squirrel monkey during behavioral experiments. *American Journal of Physiology,* 1969, *217,* 24-29.

Hineline, P. H. Negative reinforcement without shock reduction. *Journal of the Experimental Analysis of Behavior,* 1970, *14,* 259-268.

Howard, J. L., Galosy, R. A., Gaebelein, C. J., and Obrist, P. A. Some problems in the use of neuromuscular blockade. In P. A. Obrist, A. H. Black, J. Brener, L. V. DiCara (Eds.), *Cardiovascular Psychophysiology.* Chicago: Aldine, 1974.

Hudak, W. J., and Buckley, J. P. Production of hypertensive rats by experimental stress. *Journal of Pharmacological Science,* 1961, *50 263-264.*

Jennings, J. R., and Wood, C. C. The e-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology,* 1976, *13,* 277-278.

Jose, A., Crout, J. R., and Kaplan, N. M. Suppressed plasma renin activity in essential hypertension. *Annals of Internal Medicine,* 1970, *72,* 1-15.

Julius, S., and Esler, M. Autonomic nervous cardiovascular regulation in borderline hypertension. *The American Journal of Cardiology*, 1975, *36*, 685-696.

Kannel, W. B., McGee, D., and Gordon, T. A general cardiovascular risk profile: the Framingham study. *The American Journal of Cardiology*, 1976, *38*, 46-51.

Kannel, W. B., Schwartz, M. J., and McNamara, P. M. Blood pressure and risk of coronary heart disease: the Framingham study. *Diseases of the Chest*, 1969, *56*, 53-43.

Katkin, E. S., and Murray, E. N. Instrumental conditioning of autonomically mediated behavior: theoretical and methodological issues. *Psychological Bulletin*, 1968, *70*, 52-68.

Katkin, E. S., Murray, E. N., and Lachman, R. Concerning instrumental autonomic conditioning: a rejoinder. *Psychological Bulletin*, 1969, *71*, 462-466.

Kirchheim, H. R. Systemic arterial baroreceptor reflexes. *Annual Review of Physiology*, 1976, *56*, 100-176.

Korner, P. I. Integrated neural cardiovascular control. *Physiological Review*, 1971, *51*, 312-367.

Laragh, J. H. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *The American Journal of Medicine*, 1973, *55*, 261-274.

Lawler, J. E., Obrist, P. A., and Lawler, K. A. Cardiovascular function during preavoidance, avoidance, and postavoidance in dogs. *Psychophysiology*, 1975, *12*, 4-11.

Lawler, J. E., and Murray, D. M. A software program for the control of aversive conditioning schedules using the KIM-1 microprocessor. *Psychophysiology*, 1978, *15*, 292. (Abstract).

Levy, R. L., Hillman, C. C., and Stroud, W. D. Transient hypertension: its significance in terms of later development of chronic hypertension and cardiovascular-renal diseases. *Journal of the American Medical Association*, 1944, *126*, 829-833.

Linden, R. J. Function of nerves of the heart. *Cardiovascular Research*, 1972, *6*, 605-626.

Lindquist, E. F. *Design and analysis of experiments in education and psychology*. Boston: Houghton Mifflin Company, 1956.

Lockard, J. S. Choice of a warning signal or no warning signal in an unavoidable shock situation. *Journal of Comparative and Physiological Psychology*, 1963, *56*, 526-530.

Mahl, G. F. Physiological changes during chronic fear. *Annuals of the New York Academy of Science*, 1953, *56*, 240-249.

McCanne, T. R., and Sandman, C. A. Determinants of human operant heart rate conditioning: a systematic investigation of several methodoligical issues. *Journal of Comparative and Physiological Psychology*, 1975 *88*, 609-618.

Medhoff, H. S., and Bongiovanni, A. M. Blood pressure in rats subjected to audiogenic stimulation. *American Journal of Physiology*, 1945, *143*, 300-305.

Middaugh, S., Eissenberg, E., and Brener, J. The effects of artificial ventilation on the cardiovascular status and on heart rate conditioning in the curarized rat. *Psychophysiology*, 1975, *12*, 520-526.

Mitchell, J. R. Renin-aldosterone profiling in hypertension. *Annals of Internal Medicine*, 1977, *87*, 596-612.

Moorse, W. H., and Kelleher, R. T. Determinants of reinforcement and punishment. In W. K. Honig and J. E. R. Standdon (Eds.) *Handbook of Operant Behavior*. Englewood Cliffs, New Jersey: Prentice-Hall, Inc. 1977.

Murray, D. M., and Lawler, J. E. A KIM-1 microprocessor interface for aversive conditioning applications using multiple subjects. *Behavior Research Methods and Instrumentation*, 1978, *10*, 334-339.

Myers, J. L. *Fundamentals of experimental design*. Boxton: Allyn and Bacon, Inc., 1972.

Page, I. H., and McCubbin, J. W. The physiology of arterial hypertension. In W. F. Hamilton (Ed.), *Handbook of Physiology* (Circulation, Sec. 2, Vol. 3). Washington, D. C.: American Physiological Society, 1975.

Pickering, G. Hypertension. Definition, natural histories and consequences. *The American Journal of Medicine*, 1972, *52*, 570-583.

Plumlee, L. Operant conditioning of increases in blood pressure. *Psychophysiology*, 1969, *6*, 283-290.

Rosencrans, J. A., Watzman, N., and Buckley, J. P. The production of hypertension in male albino rats subjected to experimental stress. *Biochemical Pharmacology*, 1966, *15*, 1707-1718.

Ross, G. The regional circulation. *Annual Review of Physiology,* 1971, *33,* 445-478.

Sagawa, K., Kumada, M., and Schramm, L. P. Nervous control of the circulation. In A. C. Guyton (Ed.) *Cardiovascular Physiology.* Baltimore: University Park Press, 1974.

Sawrey, W. Conditioned responses of fear in the relationship to ulceration. *Journal of Comparative and Physiological Psychology,* 1961, *54,* 347-348.

Scherr, A. M. Carotid and aortic regulation of arterial blood pressure. *Circulation,* 1977, *56,* 521-528.

Seligman, M. E. P. Control group and conditioning: a comment on operationism. *Psychological Review,* 1969, *76,* 484-491.

Seligman, M. E. P., and Binik, Y. M. The safety signal hypothesis. In H. Davis and H. M. B. Hurwitz (Eds.), *Operant-Pavlovian Interactions.* Sommerset, N. J.: John Wiley and Sons, 1977.

Seligman, M. E. P., Maier, S. F., and Solomon, R. L. Unpredictable and uncontrollable aversive events. In F. R. Brush (Ed.), *Aversive conditioning and learning.* New York: Academic Press, 1971.

Selye, H. A. The general adaptation syndrome and diseases of adaptation. *Journal of Clinical Endocrinology,* 1946, *6,* 117.

Selye, H. A. *The Stress of Life.* New York: McGraw-Hill Book Co., 1976.

Shapiro, A. P., and Horn, P. W. Blood pressure, plasma pepsinogen, and behavior in cats subjected to experimental production of anxiety. *Journal of Nervous and Mental Disease,* 1955, *122,* 222-231.

Shapiro, A. P., 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,* 619-623.

Shapiro, A. P., and Melhado, J. Observations on blood pressure and other physiologic and biochemical mechanisms in rats with behavioral disturbances. *Psychosomatic Medicine,* 1958, *20,* 303-313.

Sidman, M. Avoidance conditioning with brief shock and no exteroceptive warning signal. *Science,* 1953, *118,* 157-158.

Skinner, B. F. *The pathogenesis of hypertension.* In E. Schlittler (Ed.), *Antihypertensive agents.* New York: Academic Press, 1967.

Smith, O. A. Reflex and central mechanisms involved in the control of the heart and circulation. *Annual Review of Physiology*, 1974, *36*, 93-123.

Smookler, H. H., and Buckley, J. P. Effect of drugs on animals exposed to chronic environmental stress. *Federation Proceedings*, 1970, *29*, 1980-1984.

Smookler, H. H., Goebel, K. H., Siefel, M. I., and Clarke, D. E. Hypertensive effects of prolonged auditory, visual and motion stimulation. *Federation Proceedings*, 1973, *32*, 2105-2110.

Still, J. W., Pradham, S. N., and Whitcomb, E. R. Direct measurements of aortic blood pressure in unanesthetized rats. *Journal of Applied Physiology*, 1956, *8*, 575-576.

Still, J. W., and Whitcomb, E. R. Technique for permanent long-term intubation of rat aorta. *Journal of Laboratory and Clinical Medicine*, 1956, *18*, 152-154.

Thorndike, E. L. *Animal Intelligence*. Fascimile of 1911 Edition) Darien, Conn.: Hafner Publishing Company, 1970.

Tobian, L. A viewpoint concerning the enigma of hypertension. *American Journal of Medicine*, 1972, *52*, 595-609.

Vatner, S. F., and Braunwald, E. Cardiovascular control mechanisms in the conscious state. *The New England Journal of Medicine*, 1975, *293*, 970-976.

Weiss, J. M. Effects of coping responses on stress. *Journal of Comparative and Physiological Psychology*, 1968, *65*, 251-260.

Weiss, J. M. Somatic effects of predictable and unpredictable shock. *Psychosomatic Medicine*, 1970, *32*, 397-408.

Weiss, J. M. Effects of coping behavior in different warning signal conditions on stress pathology in rats. *Journal of Comparative and Physiological Psychology*, 1971a, *77*, 1-13.

Weiss, J. M. Effects of punishing the coping behavior in different warning signal and conditions on stress pathology in rats. *Journal of Comparative and Physiological Psychology*, 1971b, *77*, 14-21.

Weiss, J. M. Effects of coping behavior with and without a feedback signal on stress pathology in rats. *Journal of Comparative and Physiological Psychology*, 1971c, 77, 22-30.

Weiss, J. M., Glazer, I. H., and Pohorechky, L. A. Coping behavior and neurochemical changes: an alternative explanation for the original "learned helplessness" experiments. In G. Serban and A. Kling (Eds.) *Animal Models in Human Psychobiology*. New York: Plenum Press, 1976.

Winer, B. J. *Statistical principles in experimental design*. New York: McGraw-Hill Book Company, 1971.

Woodbury, D. M. Physiology of body fluids. In T. C. Ruch and H. D. Patton (Eds.), *Physiology and biophysics: circulation, respiration and fluid balance*. Philadelphia: W. B. Saunders Company, 1974.

Zanchetti, A. S. Neural regulation of renin release: experimental evidence and clinical implications in arterial hypertension. *Circulation*, 1977, *56*, 691-698.

APPENDIX

Table A1. Shock Current Increment Schedule

Increment No.[a]	Series Resistance (ohms)	Shock Current (ma)
1	5,000,000	0.085
2	4,000,000	0.106
3	3,000,000	0.141
4	2,000,000	0.212
5	1,500,000	0.283
6	1,300,000	0.326
7	1,100,000	0.386
8	1,000,000	0.425
9	900,000	0.472
10	850,000	0.500
11	800,000	0.531
12	750,000	0.566
13	700,000	0.607
14	650,000	0.653
15	600,000	0.708
16	550,000	0.772
17	500,000	0.850
18	450,000	0.944
19	400,000	1.062
20	350,000	1.214

[a]The shock current was incremented stepwise as described on pages 57 and 58.

VITA

The author was born in Forest City, Arkansas on September 17, 1951. His family traveled widely in the southeast and midwest and he attended schools in Tennessee, Texas and Ohio. He attended Denison University where he received his B.A. in Psychology in 1973. The University of Tennessee was selected for graduate school because of the work of Jasper Brener, then in Knoxville. After the departure of Dr. Bener and his successor, Ethel Eissenberg, the author began work with James E. Lawler who subsequently served as the director of his dissertation research.

Immediately upon successful completion of his oral examination, the author became engaged to Paula Jane Denman and began preparations for their move to the University of Minnesota where he will begin his work as a NIMH post doctoral fellow in the fall of 1978.