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THE EFFECT OF ACUTE AVOIDANCE AND CHRONIC CONFLICT SCHEDULES ON THE BLOOD PRESSURE AND HEART RATE OF RATS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

R. Allan Buchholz

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ABSTRACT

It has been repeatedly demonstrated that the severity of physiological responses to psychological stress depends to some extent upon the *predictability* and *controllability* of the subject's environment (Mason, 1968; Seligman, Maier, and Soloman, 1971; Weiss, 1968; 1971 abc). Obrist, Langer, Grignolo, Sutterer, Light, and McCubbin (1977) propose that certain qualities of psychological stress appear to be important in evoking circulatory changes similar to those observed in some hypertensive individuals, pointing to the controllability of the stressor, or lack of it, as one such characteristic. In an effort to elucidate the role of psychological stress in the etiology of hypertension, the present research sought to further determine how variation in these stimulus properties, controllability and predictability, affect cardiovascular responses to psychological stress.

The study utilized 48 normotensive rats, half assigned to an acute avoidance condition and half to a chronic conflict condition. Within each condition, animals were assigned to one of three groups: experimental, yoked, or nonshock control. Rats in the acute avoidance situation were subjected to a signalled shock avoidance schedules 3 hours/day for 3 weeks. Chronic conflict animals were also subjected to 3 weeks of signalled avoidance, followed by an additional 8 weeks exposure to an avoidance-avoidance conflict schedule. During signalled avoidance, the experimental animals in each condition, acute and chronic

were required to make a wheel turning response in order to avoid a train of shock pulses delivered simultaneously to both themselves and their yoked partners. In the chronic conflict phase, the experimental animals had to continue to perform the wheel turning response in order to avoid the series of shocks, but were punished for each response by delivery of a single shock.

Weekly *indirect* blood pressure measurements indicated that for all animals systolic blood pressure (SBP) increased while heart rate (HR) declined during the 3 weeks of signalled avoidance conditioning. Measurements taken in the last week of signalled avoidance demonstrated a divergence in SBP levels between groups. Yoked animals exhibited higher SBP's than either experimental or control rats. All animals in the chronic conflict condition showed a significant rise in SBP over the course of the experiment. However, both the experimental and yoked groups under this condition displayed significantly higher SBP's than did the control group when averaged over all weeks of stress. In addition, experimental and yoked animals were found to have significantly more hypertensive SBP readings (SBP > 150 mm Hg) than controls during weekly indirect blood pressure assessment.

Direct recording of systolic and diastolic (DBP) blood pressures and heart rate during the terminal session for the acute avoidance condition indicated that SBP and DBP for both experimental and yoked rats rose above pre-avoidance levels at avoidance onset. Heart rate

increased only in the experimental animals. Both SBP and DBP remained elevated throughout the session and during post-avoidance only in yoked rats. Heart rate, systolic, and diastolic blood pressure in the experimental rats declined gradually throughout the session, reaching post-avoidance values that were below those observed during pre-avoidance. No significant changes were observed in the control group.

The hemodynamic responses of the experimental animals exposed to chronic conflict, unlike those displayed by experimental animals in signalled avoidance, were more similar to blood pressure responses displayed by their yoked companions. Systolic and diastolic pressures for both groups increased at conflict onset and remained elevated throughout the session and during post-conflict. Heart rate increased significantly only in the yoked rats and remained elevated for most of the session, returning to baseline levels during post-conflict. No changes in either blood pressure or heart rate were observed in the control group.

The data are discussed in respect to the role of control and prediction in the production of psychological stress and its influence on the cardiovascular system.

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CHAPTER I

INTRODUCTION

Essential or primary hypertension is a physiological condition in which the arterial blood pressure of an individual is elevated by some undetermined mechanism(s). The detection and treatment of this condition is important because of its relationship to the increased risk of cardiovascular disease and cerebrovascular accident, two leading causes of death (Kannel, Schwartz, and McNamara, 1969). However, the classification of what level of blood pressure is or is not hypertensive has been a topic of much debate. The World Health Organization in 1960 defined hypertension as 160/95 mm Hg or above. Normotension was defined as pressures below 140/90 mm Hg. Individuals whose blood pressure fell between these limits were left unclassified, but have since been described as having "borderline hypertension" (Julius, 1977). The purpose of these divisions was to provide the physician with a guideline for making decisions concerning the level of pressure at which treatment should begin.

Pickering (1968, 1972) argues, however, that the dividing line between hypertension and normotension is an arbitrary decision and that there is no evidence to support such a distinction. He contends that the relationship between blood pressure and mortality is a quantitative rather than qualitative one; "the higher the pressure, the worse the prognosis" (1972, p. 570). Variations in blood pressure, which occur throughout the day for a normotensive individual, may at times be at

hypertensive levels. In contrast, individuals categorized as hypertensive may have pressures that range well into the so called normotensive area (Pickering 1977; Birkenhager and Scalekamp, 1976). Obviously, determination of a hypertensive state could well depend upon the conditions in which pressure is recorded. Zanchetti and Bartorelli (1977) refer to data by their group that show that during sleep blood pressure in patients with essential hypertension can be reduced to normotensive levels.

Kannel (1976), referring to data from the longitudinal Farmingham Study, supports the Pickering viewpoint. He suggests that the abnormalities that promote cardiovascular disease are more a matter of degree than of kind. The *level* of both systolic and diastolic pressure are good predictors of future cardiovascular disease. The notion that diastolic pressure alone is responsible for the consequences of hypertension, e.g., coronary heart disease, a common misconception, has not been borne out by the Framingham data. Indeed, it has been suggested that lability of blood pressure, even in normotensive ranges, may be an identifying characteristic of persons prone to developing hypertension. Kannel suggests that "it is not hypertension that predisposes to vascular disease but the degree of elevation of blood pressure, there being no discernable critical 'hypertensive' value" (p. 274).

If it is the case that essential hypertension is a disease of quantity and not quality, then it follows logically that the factor(s) involved in its initiation and maintenance are most likely an exaggeration or attenuation of some existing mechanism(s) of blood pressure regulation.

It is, therefore, also a disease of regulation (Page, 1974). Two primary mechanisms of blood pressure regulation are the kidney and the nervous system, both the autonomic and central divisions. Because of their importance in blood pressure control, it is quite likely that a disruption of either or both systems could play a major role in the development and maintenance of essential hypertension.

The Kidney and Hypertension

After the discovery by Goldblatt in the mid-1930's that hypertension could be produced by narrowing of the renal arteries, the kidney was looked to as the potential key to unlocking the mystery of essential hypertension. A substantial amount of research since that time has indeed shown that alterations of renal function and activation of a renal pressor system can lead to hypertension.

It has been known for quite some time that disease of or damage to the renal parenchyma, the functional portion of the kidney, is associated with elevations in blood pressure concomitant with sodium and water retention, undoubtedly contributing to the rise in pressure. We shall discuss the role of such renal dysfunction in hypertension, but first it must be pointed out that the kidney can contribute to hypertension in ways other than by fluid retention and volume expansion. It is now well known that reductions in blood flow to the kidney, for whatever reason, are detected by an intrarenal stretch receptor and lead to release of renin into the blood stream (David and Freeman, 1973). Renin acts upon a substrate (angiotensinogen) in the plasma of the blood to form angiotensin I. Angiotension I is then acted upon by a converting enzyme to form angiotension II, the most potent vasopressor substance

known (Reid, Morris, Ganong, 1978). This conversion occurs primarily in the pulmonary circulation. Angiotension II, hereafter referred to as angiotensin, acts almost selectively upon the precapillary resistance vessels leading to vasoconstriction and increased blood pressure. The hemodynamic pattern induced by angiotensin is similar to the one seen in established hypertensives: increased resistance to blood flow (Folkow and Neal, 1971). Angiotensin also has both direct and indirect effects on sodium retention, as well as direct and indirect excitatory effects on the peripheral and central nervous systems. With such multifarious influences, it seems only natural that it should attract a great deal of interest as a potential mechanism involved in hypertension, particularly of renal orgin.

It has been repeatedly demonstrated in several species that narrowing of one renal artery with a removable clip, while leaving the opposite kidney untouched, leads to a rise in blood pressure. The severity of the hypertension is proportional to the amount of blood flow restriction (Carretero and Romero, 1977). This form of hypertension (referred to as two-kidney Goldblatt hypertension) seems to involve a different pathogenic mechanism than the hypertension involving one renal artery constriction and removal of the contralateral kidney (one-kidney Goldblatt hypertension). In the two kidney form, pressure rises initially without any salt or water retention (Tobian, 1975). It seems generally agreed upon that the early rise in blood pressure in this form of hypertension is due to the vasoconstrictor action of angiotension (Carretero and Romero, 1977; Tobian, 1975). Tobian (1972) calls this direct pressor effect a

prohypertensive function of the kidney. Angiotensin, as was mentioned earlier, also has an effect on both the peripheral and central nervous system (Zanchetti and Bartorelli, 1977; Tobian, 1972). Peripherally, it enhances norepinephrine (NE) release from both the sympathetic nerve endings and the adrenal medulla. Centrally, it appears to act at the area postrema, an area devoid of a blood-brain barrier, to enhance sympathetic outflow and inhibit parasympathetic activity. The combined results of these effects would be to reinforce angiotensin's own pressor action by further increasing total peripheral resistance (TPR) and by augmenting cardiac output (CO), thus increasing blood pressure even further. At the same time, the untouched kidney, in an attempt to compensate for the rise in pressure, increases sodium and water excretion. This promotes a reduction in extracellular fluid volume (ECFV) which in turn reduces plasma volume and therefore blood pressure. However, as demonstrated in sheep who show a loss of ECFV, the animals still become hypertensive (Tobian, 1975). This supports the role of the renin-angiotensin system in the early pressure increases in two-kidney Goldblatt hypertension.

Angiotensin acts directly upon the adrenal cortex to release a second hormone, aldosterone (Laragh, Baer, Brunner, Buhler, Sealy, and Vaughn, 1972). Adlosterone acts on the proximal portion of the renal tubules to increase reabsorption of sodium, and therefore water, by the kidney. This, combined with the direct action angiotensin has on sodium retention by the kidney, leads eventually to extracellular fluid volume expansion and increased blood volume, which precipitates further increases

in pressure. As volume expands and pressure rises, renin release is suppressed and plasma renin level declines toward normal. This occurs during the chronic phase of two-kidney Goldblatt hypertension (Carretero and Romero, 1977). If perfusion pressure to the kidney decreases due to renal arteriolar damage, renin release would again rise. This is exemplified in the malignant stage of hypertension (DeQuattro, Campanese, and Antonaccio, 1976).

In the one-kidney Goldblatt preparation, there appears to be much less dependence on the vasoconstrictor effects of angiotensin and more emphasis on sodium and water retention. As long as exchangeable sodium is available, this remains true (Tobian, 1975). This is probably due to the greater effect of reduced perfusion pressure on sodium retention in the clipped kidney, in the absence of the contralateral kidney. However, sodium depletion can transform the volume dependent, one-kidney hypertension into a renin dependent hypertension (Gavras, Brunner, Vaughn and Laragh, 1973). Carretero and Romero (1977) report evidence from several studies demonstrating that both one and two-kidney Goldblatt hypertension are reversible. In the one-kidney preparation, removal of the renal artery clip leads to an immediate reduction in pressure. The excessive fluid volume is reduced by the increased output of the kidney. Upon removal of either the arterial constriction or the clipped kidney *early* in two-kidney Goldblatt hypertension, pressure recedes to normal levels. However, in chronic renal hypertension, removal of the arterial clamp and contralateral kidney are necessary to achieve normal blood pressure levels. It is suggested that the untouched kidney is responsible for maintaining the hypertension, even after the original

cause, the arterial constriction, is removed. Vascular damage to the contralateral kidney (untouched) may have occurred because of the increased load placed on it. The clipped kidney on the other hand, was protected from the elevated pressure head by the renal artery constriction. It is apparent that structural changes in the systemic vasculature are not responsible for maintaining this form of hypertension, even in the chronic phase.

Tobian (1972) pointed out that in humans with longstanding hypertension due to renal artery stenosis, vascular thickening is extensive, but removal of the constriction leads to normalization of both pressure and peripheral resistance. These findings are important because they oppose the long revered notion that increased TPR in the systemic circulation is responsible for the maintenance of most forms of hypertension, including essential hypertension. It also points out that hypertension induced initially by a renal vasoconstrictor mechanism will not persist if the original cause is removed, unless there has been renal artery damage or altered kidney function. That is, the kidney, if *uncompromised*, will in the long run compensate for any pressure rise by increasing the sodium and water output, as in the case of reversed chronic one-kidney Goldblatt hypertension.

The concept of the kidney as being paramount in long term control of blood pressure has been adamantly espoused by Guyton and his colleagues (1969, 1970, 1972, 1977). Guyton (1977) proposes a series of concepts which removes the emphasis placed on increased peripheral resistance per se as the mechanism of sustained hypertension. He instead proposes that all conditions that cause hypertension do so by disruption of the

balance between salt and fluid intake and the capacity of the kidneys to excrete water and sodium. A disturbance of the fluid volume control mechanism that shifts the equilibrium toward retention of sodium and water will in turn expand the extracellular fluid volume. Extracellular fluid volume has a direct effect on the filling of the circulatory system with blood volume, which Guyton (1977) calls "paramount in the long term control of arterial pressure" (p. 586). He points out though, that hypertension does not mean there is necessarily an excessive blood volume. In fact, most essential hypertensives show a contracted plasma volume with a normal extracellular fluid volume (Frohlich, 1977; Schalekamp, Birkenhager, and Lever, 1977).

Central to Guyton's theory of pressure regulation is the phenomenon of pressure diuresis. As the arterial pressure rises the kidneys compensate by increasing fluid and salt excretion. This will in turn reduce extracellular fluid and intravascular volume thereby reducing pressure. Pressure will continue to decline until a point is reached at which fluid intake will exactly balance fluid output. The principal factor determining the level of pressure at which intake and output are balanced is the functional capability of the kidneys to excrete fluid and electrolytes (Guyton, Scheel, Manning, and Norma, 1972). Anything that alters the "state" of the kidneys will alter the pressure-diuresis relationship requiring greater pressures in order to maintain fluid balance.

Several studies have shown that alterations in the functional capacity of the kidneys lead to a condition that requires an elevated

pressure to equilibrate fluid intake and output (Guyton, Coleman, Bower, and Granger, 1970; Guyton, Coleman, Fourcade, and Navar, 1969). They induced hypertension in dogs by partial nephrectomy and salt and water loading. Under these conditions hypertension, due to volume expansion, occurs quite rapidly. Expansion of ECFV leads to increased blood volume and greater venous return. Through the Frank-Starling mechanism, CO is increased and blood pressure rises. Initially peripheral resistance is reduced, probably due to baroreceptor reflexes. Over several days or weeks, however, constant over-perfusion of the tissues caused by the elevated cardiac output elicits a marked vasoconstriction due to the phenomenon of autoregulation. This in turn increases TPR and leads to reductions in CO. The increased pressure induces pressure diuresis and a reduction of ECFV to normal or near normal levels. However, because of the reduced renal mass the renal function curve has shifted to a level requiring an elevated blood pressure in order to maintain fluid balance. Any move to reduce pressure will lead to re-expansion of fluid volume and its sequalae (Tobian, 1975). Increased peripheral resistance is shown to be a by-product of hypertension and not its cause, a notion previously mentioned. In the long run, fluid balance has been achieved, but at the expense of increased arterial blood pressure.

It has been argued that the renal-fluid volume theory of hypertension requires an intrinsic renal dysfunction in order to initiate hypertension (Frohlich, 1977). Folkow and Neal (1971) state that there is no evidence for a renal "trigger" mechanism, but do not deny the possible role of the kidney in the long term maintenance of hypertension. Guyton certainly suggests that renal impairment must be present for

hypertension to persist, but whether this implies an intrinsic renal defect is unclear. Guyton et al. (1977, 1972) propose that renal function may be altered through action by other systems, thereby shifting the pressure diuresis curve to a higher level. Fluid balance will then regulate blood pressure at a higher pressure level.

Exemplary of the mechanisms that can alter renal function are the autonomic and central nervous systems. Renal artery vasoconstriction created by increased sympathetic activity can reduce blood flow to the kidney and evoke a series of renal compensatory actions. Excitation of the renin-angiotensin system by central augmentation of the sympathetic innervation of the kidney is another means by which the functional capabilities of the kidney may be altered (Zanchetti and Bartorelli, 1977). The important role the nervous system plays in normal blood pressure regulation and its ability to alter the "state" of the kidneys make it a prime candidate for consideration as a mechanism involved in the development and maintenance of essential hypertension.

The Nervous System and Hypertension

In discussing the etiology of essential hypertension, one must bear in mind that there appears to be no anatomical abnormality or structural pathology at the onset of the disease. Indeed, the patient seems quite normal upon casual inspection, except for the fact that he/she has elevated arterial blood pressure. Essential hypertension is asymptomatic in its uncomplicated form, sometimes referred to as benign, essential hypertension. The term benign, however, carries the connotation of harmless, which *any form* of hypertension is not, and should be deleted in any reference to hypertension.

As Page (1949) points out, hypertension is a disease of regulation, with many factors involved in the "mosaic" of blood pressure control. We have discussed one such factor with respect to the kidney. Another mechanism of pressure control is most certainly the nervous system.

Arterial blood pressure is a hemodynamic variable that is the end result of the interaction of several other hemodynamic variables (Dustan, Tarazi, and Bravo, 1972). The state of arteriolar resistance, contractility of the myocardium, heart rate, venous distensibility and rate of filling of the heart are all factors that can influence the level of the blood pressure. Each of these in turn is influenced by the sympathetic division of the autonomic nervous system, which in turn is acted upon by the central nervous system. It is therefore apparent that the nervous system plays an integral role in the regulation of arterial blood pressure.

The prominent role the nervous system, in particular the sympathetic division, plays in normal cardiovascular function, suggests that any aberration in hemodynamic equilibrium may be initiated by the nervous system. Frohlich (1977) suggests several ways in which altered adrenergic function may increase blood pressure:

> We have speculated that this abnormality could be initiated by some alteration in adrenergic function mediated through the central nervous system, by altered catecholamine metabolism, by amplification of adrenergic and catecholamine function (e.g., through sodium metabolism), or by adrenergic receptor abnormalities. Indeed, even the increased formation and release of renin with consequent generation of angiotensin II might perpetuate further the abnormality through stimulation of certain medullary centers in the brain (p. 42).

Many experimental models of hypertension have been developed and the role of the nervous system explored in each.

Doba and Reis (1973), have recently discovered that bilateral electrolytic lesions of the nucleus tractus solitarius (NTS) in the medulla of rats, centrally deafferentates the baroreceptors and leads to acute fulminating hypertension, ending in frank pulmonary edema and death. Systemic administration of 6-hydroxydopamine (6-OHDA) which functionally destroys the sympathetic nervous system failed to block pressure rise without adrenalectomy. Intracisternally injected 6-OHDA blocked the development of NTS hypertension (Doba and Reis, 1974). The authors concluded that central disruptions of baroreceptor reflexes leads to hypertension due to increased vasoconstriction mediated by augmented sympathetic outflow to the α-adrenergic receptors of the vasculature.

Two other forms of experimental hypertension also demonstrate involvement of the sympathetic nervous system. Rats treated with the steriod desoxycorticosterone acetate (DOCA) and salted loaded, develop hypertension over a period of weeks (DeChamplain and van Ameringen, 1972). Treatment of this form of hypertension by immunosympathectomy, adrenalectomy, and intravenous 6-OHDA, prevented or reversed its development (DeChamplain, 1977). The investigators suggested that the mechanism responsible for the hypertension is a combined hyperactivity of the sympathetic nervous system and the adrenal medulla. Experimental renovascular hypertension has also been shown to be inhibited or reversed by combined chemical peripheral sympathectomy and adrenalectomy, or central sympathectomy, respectively (Chalmers, 1975). The link between the kidneys and the central nervous system may well lie in the action of angiotensin on the medullary vasomotor centers (Chalmers, 1975; Zanchetti and Bartorelli, 1977).

A common notion among early proponents of neural models of hypertension and human hypertension was that the baroreceptors of the carotid sinus and aortic arch may play a significant role in the development of hypertension. McCubbin and Ferrario (1977) cite several studies demonstrating the production of experimental hypertension by sinoaortic deafferentation. Cowley, Liard, and Guyton (1973), using baroreceptor-denervated dogs, found that indeed many times throughout a 24 hour period blood pressure rose to extreme levels, but it also fell to levels below normal. The basic effect of baroreceptor-denervation was to increase blood pressure variability. This seems to indicate that the primary function of the baroreceptors is to minimize daily fluctuations in blood pressure. As for the role of the baroreceptors in hypertension, although resetting and decreased sensitivity have been demonstrated in essential hypertension (Sleight, 1972), they seem to be a result of and not the cause of hypertension. At best the baroreceptors seem to play a permissive role in essential hypertension.

The sympathetic nervous system does appear to participate in various forms of hypertension induced by physiological intervention. It is also intimately involved in a more natural genetic model of hypertension, that of the spontaneously hypertensive rat (SHR). Some have suggested that the spontaneously hypertensive rat is the most appropriate model of essential hypertension in humans, and therefore it is being thoroughly investigated.

The development of hypertension in SHR is characterized by an augmented CO, elevated heart rate (HR), increased myocardial contractility

and greater TPR (Pfeffer and Frohlich, 1973). With age, cardiac output and heart rate decline while resistance increases. There is also evidence of altered baroreceptor function (Frohlich, 1977). This is a similar hemodynamic pattern to that of borderline hypertension and mild essential hypertension in humans (Julius and Esler, 1975). Pfeffer, Frohlich, Pfeffer, and Weiss (1974) treated young SHR with parasympathetic and beta-adrenergic blocking agents in an attempt to elucidate the mechanisms involved in the augmentation of these hemodynamic variables. In agreement with Hallback and Folkow (1974), they found that in SHR there appears to be reduced parasympathetic but increased beta-adrenergic influences on cardiac performance in the SHR, as suggested by a failure to normalize cardiac index until both systems were blocked. In addition, reduction of CO and HR by long term treatment with beta blockade in young SHR failed to impede the rise in blood pressure. Similar treatment initiated from birth also failed to prevent hypertension in SHR (Pfeffer, Pfeffer, Weiss, and Frohich, 1977). These findings are at odds with those of Weiss (1974) and Folkow, Hallback, Lundgren, Sivertsson and Weiss (1973). They found beta-blockade both prevented the pressure rise and reduced it to normal levels, if allowed to develop, in the early phases of hypertension in SHR. Hallback and Folkow (1974) also reported SHR to have lower resting HR than normal controls, contrary to Pfeffer et al. (1973, 1974, 1977). Two different beta blocking drugs were used however, and the differing results may be due to the nonspecific properties of one drug over the other. The latter group of researchers suggest that the hyperdynamic circulation is not essential to the elaboration of

hypertension in SHR, but reflects a general increase in sympathetic outflow to the cardiovascular system. Judy, Watanabe, Henry, Besch, Murphy, and Hockel (1976), using direct neural recording, support the concept of an augmented sympathetic outflow in the SHR.

Hallback and Folkow (1974) suggest that the circulatory pattern in SHR is consistent with the hemodynamic changes observed during stimulation of the hypothalamic defense area. They found that the SHR tend to show both an exaggerated neurogenic discharge and blood pressure response to even mild alerting stimuli. These exaggerated "defense" responses, consistent with the generally heightened sympathetic outflow are thought to contribute to the development of hypertension. SHR isolated from any environmental perturbations from an early age, show a reduced pressure rise compared to nonisolated SHR (Hallback and Weiss, 1977).

Folkow and Rubinstein (1966) argue that repeated episodes of heightened sympathetic discharge, due to emotional facets of everyday life, may act as a trigger mechanism and lead to an increased functional load on the cardiovascular system, resulting in a gradual development of hypertension in predisposed individuals. They found that intermittent stimulation of the hypothalamic defense area, which increased blood pressure and heart rate without concomitant behavioral changes, elicited a gradual rise in mean blood pressure over a period of several weeks. The pressure fell to normal levels when stimulation was stopped for two weeks, but *immediately* rose to previously elevated levels when stimulation was reinstated. These pressure rises were in an inherently normotensive strain of rats. The authors concluded that intermittent stimulation of

the hypothalamic defense area can elevate pressure, but once the trigger mechanism is removed pressure returns to normal as long as there is only a mild degree of induced hypertension.

In a more recent series of studies Folkow and co-workers (Folkow, Hallback, Lundgren, Sivertsson, and Weiss, 1973; Folkow, Hallback, Lundgren, and Weiss, 1970a,b) have reported that the systemic resistance vessels of SHR demonstrate a restructuring due to the increased pressure load placed on them. This vascular restructuring is due to medial hypertrophy of the vascular smooth muscle, resulting in as much as 50 percent increase in resistance, even at maximal vasodilation. Thus an increased wall thickness to lumen ratio exist. Because the vascular smooth muscle encroaches on the vessel lumen, and because vascular contractions originate from the outer most muscle layer (Folkow and Neal, 1971, p. 574), the entire wall mass is pushed towards the lumen, narrowing it even more than would occur with comparable stimulation for contraction in a normal vessel. They report no increase in sensitivity or reactivity in the smooth muscle to injections of norepinephrine, i.e., the threshold for contraction is normal. However, for any stimulation above threshold there is greater narrowing of the vessel lumen. This is so because for any given shortening of the contractile elements the flow resistance will increase more with an increased wall to lumen ratio. There is no increase, however, in basal vascular tone. They have also demonstrated vascular adaptation to increased pressure loads in renal hypertensive rats, but to a much less extent. Folkow et al. (1973) suggest that a genetic predisposition may be necessary for the vessels to respond with medial hypertrophy and increased resistance to flow when

faced with increased functional pressure rises. This may account for the failure to demonstrate persistent elevations in the nongenetically select strain of rats. The transition from elevated cardiac output to increased peripheral resistance as a mechanism for sustained increases in blood pressure involves such vascular adaptation in the SHR.

For many years it has been thought that the primary mechanism sustaining essential hypertension is an overall increase in total peripheral resistance. How then are the findings in SHR of elevated cardiac output and augmented adrenergic drive related to established hypertension in humans? As was mentioned earlier, the hemodynamic pattern in human labile hypertension (blood pressure occasionally ranging into hypertensive levels, i.e., borderline hypertension) is strikingly similar to that of the SHR, and also that associated with stimulation of the hypothalamic defense area. Many borderline hypertensives exhibit an elevated CO and HR with TPR at a normal level (Julius and Esler, 1975). They also demonstrate an elevation in plasma catecholamine levels, a finding also reported for essential hypertensives (Julius and Esler, 1975; DeQuattro and Miura, 1973). Elevated plasma catecholamines (primarily norepinephrine) are suggestive of increased sympathetic drive to the heart and blood vessels. Indeed, excessive catecholamine (urinary) responsiveness has been reported in borderline hypertension when patients are subjected to acute mental stress or physical maneuvers evoking sympathetic reflex mechanisms (Nestel, 1969; Esler and Nestel, 1973). Dustan et al. (1972) report that the blood pressure rise during the Valsalva maneuver (increased intrathoracic pressure due to forced

expiration against a closed glottis) is often exaggerated but may be reduced by pharmacological suppression of sympathetic nervous system activity.

Both cardiac output and heart rate are elevated in many, but not all borderline hypertensives. Julius and Esler (1975) and Frohlich (1977) cite research which indicates combined usage of pharmacological autonomic blocking agents, propranolol and atropine, leads to a normalization of cardiac function in the borderline hypertensive individual. With full autonomic cardiac blockade, cardiac output fell into a normal range. The necessity of blocking both the sympathetic (propranolol) and parasympathetic (atropine) divisions of autonomic innervation to achieve normal cardiac output and heart rate led to the conclusion that in borderline hypertensives displaying increased cardiac output, there is augmented sympathetic and reduced parasympathetic control of the heart. This is exactly the finding reported in early SHR hypertension. Julius and Esler (1975) described this condition as "hyperkinetic" borderline hypertension.

Total peripheral resistance is in the normal range in hyperkinetic borderline hypertension with the patient at rest. However, the level of total peripheral resistance has been described as being inappropriate for the level of cardiac output (Julius and Esler, 1975). Normal compensatory reflexes would usually adjust total peripheral resistance to a lower level when cardiac output rises, thus preventing a rise in blood pressure. The normal but inappropriate peripheral resistance in many borderline hypertensives is maintained by increased alpha adrenergic tone, as revealed by a normalization of blood pressure, due to reductions in peripheral resistance by administration of phentolamine, an alpha blocking drug (Esler, Julius, Randall, Ellis, and Kashima, 1975).

In some patients with hyperkinetic borderline hypertension, there exist an increased central pulmonary blood volume (Frohlich, 1977). Reductions in venous distensibility, via increased sympathetic tone, may cause a redistribution of venous blood from the periphery to the central capacitance vessels. This may contribute to increased cardiac filling with blood. The increased filling of the heart, via the Frank-Starling mechanism, may contribute to the elevated CO, especially when combined with increased contractility due to neural sources.

These findings in borderline hypertension have led to the conclusion that both an exaggerted sympathetic outflow, involving both alpha receptors in the periphery and cardiac beta receptors, and reduced para-sympathetic inhibition exist in many of these individuals (Julius and Esler, 1975). They also conclude that the primary locus of abnormal autonomic regulation is in the integrative areas of the medulla. It is additionally suggested, higher centers in the brain, such as the hypothalamic defense area, may also contribute to the autonomic neural aberration.

As has been indicated, established essential hypertension involves a substantially increased total peripheral resistance. Critical then in demonstrating a relationship between hyperkinetic borderline hypertension and essential hypertension is the transition from a state of intermittent elevations in blood pressure involving augmented cardiac output to a state of sustained hypertension involving increased total peripheral resistance.

Eich, Cuddy, Smulyan, and Lyons (1966) reported on observations of several hypertensive individuals over several years, that involved a

variety of hemodynamic changes. Patients who initially had elevated cardiac outputs showed a reduction in output to normal, while total peripheral resistance rose. Patients with low or normal CO initially, demonstrated increased TPR, with this pattern remaining unchanged overtime. In a recent paper Weiss, Safar, London, Simon, Levenson, and Milliez (1978) offer supporting evidence that borderline hypertension may represent the initial stages in the development of fixed hypertension. A homogenous population of male hyperkinetic borderline hypertensives was followed over a period of 47 months. Initially, blood pressure was significantly elevated compared to control subjects, as was cardiac index (cardiac output related to total body surface area). Peripheral resistance however although slightly higher, was not significantly different from controls. Cardiac output in the borderline hypertensives was correlated with heart rate at the beginning of the study. Systolic blood pressure increased significantly in the borderline hypertensives from the first to the second measurement at the end of 47 months. Both cardiac output and heart rate decreased significantly, while total peripheral resistance rose significantly. The initial correlation between heart rate and cardiac output disappeared on the second measurement although blood volume and cardiac output were found to be normal. This suggests a transition from neural to volume control of cardiac output. The authors relate this to the finding that in normotensives, cardiac output is under predominant neural control, while in hypertensives volume factors seemed to dominate cardiac output. This study supports the concept of a transition from a borderline to a permanent hypertension by increases in vascular resistance and declining cardiac output.

The question remains as to the mechanisms involved in the rise of total peripheral resistance and decline in cardiac output. Guyton et al. (1969, 1970, 1972, 1977) have continually postulated the phenomenon of autoregulation (vasconstriction due to over perfusion of the tissues) as the mechanism causing the rise in resistance. Two arguments may be mounted against this concept. First several studies (for references see Birkenhager and Schalekamp, 1976) have demonstrated a direct relationship between cardiac output and oxygen consumption in borderline hypertension. This would contradict the idea that the increased perfusion of the tissues was unwarranted. Secondly, the time course of autoregulation, as amply demonstrated by Guyton, is a period of a few weeks in both experimental preparations and anephric humans. The rise in peripheral resistance in hypertension however, is of a much more gradual nature, requiring months and years to develop.

Folkow et al. (1970 a,b; 1973), as previously mentioned, have demonstrated a vascular restructuring in the SHR. This involves the hypertrophy of the vascular smooth muscle which in turn narrows the luminal diameter of the vessel. Tobian (1972) reported additionally, that the arterioles in hypertension are water logged, containing increased sodium and water concentrations. This in turn decreases the vascular distensibility and may serve to increase peripheral resistance. Thus, vascular changes may account for a great deal of the increase in peripheral resistance. Sivertsson and Olander (1968) found that the hand vessels of hypertensive men showed an increased resistance to flow even at maximal dilation. Esler, Julius, and Randall (1975) report that in many borderline

hypertensives administration of phentolamine, an alpha adrenergic blocker produced little change in peripheral resistance. This suggests that even in the early stages of hypertension, the normal but inappropriate total peripheral resistance may be maintained by nonneurogenic factors.

Concommitant with the rise in total peripheral resistance is a decline in cardiac output. The rising afterload (blood pressure) the heart must face certainly contributes to a reduction in cardiac output. Two other factors may also be involved. Plasma volume has been consistently found to be reduced in established hypertension (Frohlich, 1977). This occurs in the presence of normal extracellular fluid volume (Schalekamp, Birkenhager, and Lever, 1977). Frohlich (1977) and Dustan et al. (1972) reported a decreased ratio of plasma volume to interstitial fluid volume, suggesting a pressure induced migration of intravascular fluid into the interstitium. Such a reduction in blood volume would decrease cardiac filling and hence contribute to a decreased cardiac output.

Julius, Randall, Esler, Kashima, Ellis, Bennet (1975), have found that in borderline hypertension involving normal cardiac output, the appearance of normalcy of the output obscures altered autonomic control. In these patients they found that after complete cardiac autonomic blockade with propranalol and atropine there was a reduced cardiac output and stroke volume compared to normals, but central blood volume was normal. These findings suggested that mechanisms other than cardiac filling were responsible for the reduced stroke and cardiac outputs. These patients demonstrated a reduced response in terms of heart rate and cardiac output to infusions of the beta adrenergic agonist isoproterenol when compared to normals. Diastolic pressure changes, indicative of the

drug's peripheral effect, were similar in patients and normals. The patients also demonstrated lesser increases in heart rate during atropine infusions than did controls. This latter finding implies reduced vagal restraint. The authors conclude that the reduced parasympathetic inhibition maintains the appearance of normal cardiac function in the face of a decreased cardiac response to sympathetic stimulation and venous filling. They speculate that borderline hypertensive individuals with normal cardiac output may have had excessive sympathetic stimulation for a longer period of time and become somewhat refractory to it. In essence, they suggest a "cardiac autoregulation" of cardiac output to normal values. Pfeffer, Pfeffer, and Frohlich (1976) cite research indicating a similar decrease in responsiveness to exogenous sympathetic stimulation occurs in young SHR. Thus, the reduction in cardiac output observed during the suggested transition from borderline to permanent hypertension may come about in several ways.

The Kidney and Nervous System--An Integration

It has been amply demonstrated that the nervous system plays a prominent role in various forms of experimental and human hypertension. Increased sympathetic drive, modulated by suprabulbar centers, can increase cardiac output and total peripheral resistance resulting in increased blood pressure. Increases in pressure load may induce adaptive changes in the resistance vessels that further increase the resistance to blood flow and raise pressure. Guyton et al. (1969, 1970) however, maintain that elevations in blood pressure cannot persist without involvement of the kidney. For any rise in pressure the kidney will compensate

by increasing fluid output. Thus, a functional alteration is required to limit the kidney's compensatory activity. The nervous system can certainly induce such changes. Vasoconstriction of the renal arteries will reduce renal blood flow. Zanchetti and Bartorelli (1977) cite several studies showing that the sympathetic nerves can directly cause release of renin from the juxtaglomerular cells of the renal afferent arterioles. This in turn increases angiotensin levels in the blood, and associated with this angiotensin's effects on the nervous system and kidney. They also report evidence demonstrating direct sympathetic innervation of the proximal tubules of the nephron. Stimulation of these nerves increased sodium and water retention by the kidney.

The etiology of essential hypertension may well involve both neural and renal mechanisms, combined with a genetic predisposition toward developing hypertension. Brown et al. (1977) have postulated a model for the development of hypertension that indeed involves both mechanisms. They suggest that hypertension is the result of two mechanisms which by themselves are incapable of sustaining a hypertensive state. A sequalae of events is postulated involving first an elevation in blood pressure due to neural mechanisms, followed by a transition to hypertension dominated by the kidney and vascular restructuring.

Numerous researchers indicate that one of the primary factors involved in triggering the increased neural activity is environmental or psychological stress (Brown et al., 1977; Julius and Esler, 1975; Pickering, 1972, 1968; DeQuattro and Miura, 1973; Folkow and Rubinstein, 1966). Brod (1971), reporting on his earlier work, found that severe mental stress evoked a circulatory pattern in *normotensive* individuals

similar to that of borderline hypertensives and also that associated with the defense reaction; increased cardiac output; elevated heart rate; renal, splanchnic, and cutaneous vasoconstriction; and muscular vasodilation. Folkow and Rubinstein (1966) suggested that an increased functional load on the circulatory system created by the intermittent elicitation of the defense reaction by daily life stresses, may in time lead to a gradual rise in pressure.

Pickering (1968) has maintained there is a strong genetic component in human essential hypertension. Folkow et al. (1973) have suggested that similar to the SHR, the genetic component may be a predisposition of the vessels to react to an average increase in functional load by hypertrophy of the vascular smooth muscle. This contributes to elevations in pressure by increased resistance to flow. Guyton's theory (1977) would maintain however, that such rises in pressure would be compensated for by the kidney. Folkow, Gothberg, Lundin, and Rickstein (1977) have reported that structural changes occur in the preglomerular vessels of the kidney in SHR. These changes are of the same nature as those observed in the systemic circulation. Such vascular changes could create the means by which alteration in kidney function would come to dominate the hypertensive state. The nervous system though, undoubtedly continues to contribute to the hypertension as demonstrated by significant reduction in blood pressure, in all forms of hypertension, with the administration of anti-adrenergic drugs (Zanchetti and Bartorelli, 1977; Page, 1974; Tobian, 1972).

The implication of environmental and psychological factors as a means of modifying autonomic nervous system outflow, and hence cardiovascular function, has been repeatedly made. The exact parameters of

behavior that induce such changes are as yet unclear. In the next chapter we will discuss the role of psychological stress in the development of hypertension.

CHAPTER II

PSYCHOLOGICAL STRESS AND HYPERTENSION

Reactions by humans to alterations in their environment may involve complex physiological changes (Benson and Gutmann, 1974). The interaction between environmental factors and the relation of behavior to these factors is of importance because of the potential role each may play in the etiology of human disease states. As previously mentioned, the relationship between the environment and elevations in blood pressure are of particular interest because of the increased morbidity and mortality associated with any persistent elevation in pressure (Kannel, Schwartz and McNamara 1969; Kannel, 1976).

The uncertainty of the outcome of daily events, lack of appropriate behavior to deal with daily interactions, and the failure to adjust to environmental changes may be very stressful on the individual, potentially leading to elevation of arterial pressure. That human behavior patterns are related to cardiovascular disease is becoming an increasingly substantiated finding (Glass, 1977). One approach to investigating the etiology of essential hypertension is through manipulation of the individual's environment. The feasibility and ethics of such manipulation in humans limits their potential as research subjects. The development of an animal model of hypertension induced by alterations in the environment or adjustments in behavior seems appropriate. Unpredictable and uncontrollable changes in the environment may be sufficiently stressful

to the point of participating in the development of cardiovascular disease, in particular hypertension.

As suggested by Folkow and Rubinstein (1966), intermittent perturbations in cardiovascular function may serve as a triggering mechanism for hypertension. To this end, a variety of environmental manipulations have been utilized in an attempt to cause chronic increases in blood pressure. Farris, Yeakel, and Medhoff (1945) found that in Norway rats showing high emotionality in an open field test (evidenced by the amount of exploratory behavior), blood pressure rose when they were presented with intermittent blasts of air. Rats showing low emotionality and nonstressed high emotionality rats showed no changes in pressure.

Smookler and Buckley (1969) and Perhach, Ferguson, and McKinney (1975) reported that a regime of visual, auditory, and motion stimuli presented for 4 hours/day, 3 days/week to a normotensive strain of rats led to systolic pressures of 150 mm Hg by the end of 8 weeks and they remained elevated through the remaining 12 and 4 weeks of stress, respectively. Perhach et al. found blood pressure remained elevated for 20 weeks after the last stress session. Buckley and Smookler found that administration of alpha methyltyrosine, which blocks the synthesis of norepinephrine, prevented the rise in pressure evoked by the noxious stimulation. Brain norepinephrine levels were depleted by 70 percent of pre-stress, suggesting a dampening of central sympathetic activity was responsible for the suppression of the pressor response.

Classical Conditioning

Less successful in producing elevations in blood pressure have been studies utilizing classical (Pavlovian) conditioning and non-contingent shock techniques. Shapiro and Melhado (1957), subjected rats to 6 hour stress sessions 3 days per week. During the session, a pattern of tone (CS) paired with shock (UCS) was presented every 30 seconds for three one hour periods alternating with CS presentation alone for three one hour periods. Stress sessions for 24 weeks under these conditions failed to elicit any persistent elevation in pressure. When combined with a 1-kidney Goldblatt preparation, stress appeared to speed up the development of hypertension.

Acute pressure elevations have been demonstrated in dogs using a classical conditioning paradigm. Dykman and Gantt (1960) reported pressor responses during typical aversive classical conditioning sessions, however pressure fell to normal with termination of the session. They found that even after a 13 month rest period one dog's pressor response was fully present upon the first presentation of the old CS alone. They suggested that persistence of the pressor response to the CS over such a long period of time, may provide a frame work for the development of a model of human hypertension. That is, the pressor response, although no longer warranted, appears to be due to a fixed behavior pattern. This may explain why individuals become hypertensive over a life time. Dahl, Knudsen, Heine, and Leitl (1968), failed to demonstrate rises in pressure with either noncontingent shock or aversive classical conditioning, even when using a specially bred strain of rats genetically predisposed toward

becoming hypertensive. Salt ingestion in these rats produces severe elevations in pressure. These investigators warned against the implication of "stress" as a causal factor in hypertension. Indeed, the failure of classical conditioning techniques to evoke long term elevation in blood pressure may be due to the inability of the stressor to become generalized outside the specific condition of CS presentation.

In recent years there has been a trend toward the use of three basic types of psychological stress paradigms in studying behaviorally induced changes in the cardiovascular system: forced overcrowing and territorial conflict; strict operant schedules, including both appetitive and aversive conditioning; induction of psychological uncertainity utilizing both appetitive and aversive conditioning.

Territorial Conflict and Overcrowding

The elicitation of the defense reaction has been reported to be one of the more significant ways in which environmental stressors can induce changes in cardiovascular function. Abrahams, Hilton, and Zbrozyna (1960) were the first to demonstrate that cardiovascular changes induced by hypothalamic stimulation were *concomitant* with radical behavioral changes in the cat, consisting of hissing, claw extension and attack, as reported previously by Hess and Brugger (Zanchetti and Bartorelli, 1977). Stimulation of the posterior hypothalamus, besides producing the above behavioral changes, leads to increases in blood pressure, cardiac output, and heart rate, mediated by the sympathetic nervous system. There is also a redistribution of cardiac output away from

viscera, toward the sketetal muscles. This latter phenomenon appears to be due to sympathetic cholinergic vasodilation in cats or dogs, as it can be blocked by atropine.

Zanchetti (1977) cites several studies by his group which used a model of natural behavioral conflict to study its effects on the cardiovascular system. Cats were implanted with flow probes and catheters for monitoring various hemodynamic functions. These animals were then confronted with another cat whose behavior could be manipulated via an electrode implanted in the hypothalamus. Stimulation through the electrode evoked attack behavior. It was assumed the attacking cat would elicit the defense reaction and its hemodynamic concomitants, much as direct hypothalamic stimulation does. They found however, that unlike direct stimulation, rises in blood pressure were small, and different patterns of heart rate, cardiac output, and regional circulation were present depending on the behavior exhibited by the defending cat. If the defending cat fought only with the forepaws, while laying down, or remained immobile there was little change in blood presssure, heart rate slowed, and vasoconstriction was present in both the hindlimbs and viscera. Muscular vasodilation, the sine qua non of the defense reaction, only occurred in what Zanchetti calls supportive fighting, i.e., when hindlimb movement was involved. Blood pressure rose somewhat at the onset of supportive fighting, but only after prolonged fighting did there appear to be any marked elevation. Zanchetti (1977) suggests there are two hemodynamic patterns that may accompany emotional behavior, one for immobile confrontation, the other being characteristic of "emotional movement" or the classic defense reaction.

During acute conditions like those used by Zanchéttis group, blood pressure changes are mild and of short duration. If such a stiuation, conspecific confrontation, were to occur many times throughout an animal's life, however, they may be of sufficient intensity to increase the average pressure load presented to the resistance vessels, leading ultimately to vascular adaptation and elevations in pressure. Zanchetti's data, indicating that prolonged fighting elevates pressure, supports this contention. Folkow et al. (1973) have indicated the increase in functional load initially, need only be of a few millimeters mercury to result in vascular restructuring.

Prolonged and constant conspecific interaction in mice, raised in isolation, or forced overcrowding among siblings, have both been shown to elevate blood pressure to hypertensive levels (Henry, Meehan, and Stephens, 1967; Ely and Henry, 1974; Henry, Stephens, and Santisteban, 1975). Henry et al. (1967) found that when mice (siblings), used to living in fairly close contact, were forced to live in half the normal cage space they showed mean systolic pressure levels of 160 mm Hg. This pressure level was sustained for a period of 9 months. When placed back into normal living space, restoring freedom of movement, pressures declined slowly but failed to return to control levels. Other similar experiments in this report, found that mixing males from different litters or promotion of territorial conflict between mixed males and females that had previously been isolated, led to comparable blood pressure elevation. The intensity of fighting was found not to be directly related to pressure elevation. Forced crowding in siblings produced less severe fighting in mixed litter males, but provoked equivalent pressure changes. Socially

deprived females, who showed little overt fighting or aggressive behavior also demonstrated significant blood pressure elevation. Alexander (1974) using socially deprived rats placed in a population cage of interconnecting boxes, found similar but less dramatic pressure changes. Dominant males, who had more opportunity for confrontations, demonstrated the highest systolic pressures.

Henry, Stephens, and Satisteban (1975) reported that placing female and male mice, raised in isolation, together in an interconnecting box system with a central food source, induced fighting and territorial conflict. Systolic pressure in *males* rose significantly and progressively over an initial 21 day period. Groups of animals placed in such conditions for up to 6 months showed sustained elevations in pressure throughout this period, but when placed back into isolation pressure declined towards normal. If psychosocial stress was maintained beyond 6 months, blood pressure remained at hypertensive levels even after return to isolation. Increases in heart weight (hypertrophy), presence of aortic atherosclerosis, and myocardial fibrosis were reported in mice maintained under these conditions beyond 6 months. The authors conclude that an augmented sympatho-adrenal medullary axis may have contributed significantly to the circulatory dysfunction.

The progression of the disease state may be quite similar to humans. Return to isolation before 6 months (approximately 1/4 the life span of a mouse) led to reductions in blood pressure, indicating that no permanent morphological changes had occurred to maintain the hypertension. As the exposure to the stress condition occupied greater and greater

portions of the animal's life span, the more severe and irreversible the pathophysiology. This is as in humans, where the insidious nature of the hypertension makes it difficult to be aware of, and pathology gradually becomes more severe. The findings by Henry's group support the postulate that intermittent emotional behaviors, if occurring often enough and over a sufficiently long period of time, may contribute, via the sympathetic nervous system, to the development of hypertension and cardiovascular disease similar to that observed in humans.

Operant Schedule Control of Behavior

Operant conditioning schedules that exert strong, continuous control over an animal's behavior also induce persistent increases in mean arterial blood pressure (Herd, Morse, Kelleher, and Jones, 1969). Squirrel monkeys implanted with arterial catheters for blood pressure monitoring, were trained to avoid electric shock on either a fixed ratio or fixed interval schedule. The schedules required the subjects to press a key upon presentation of an S^D (light), the fixed ratio schedule demanding 30 responses in 30 seconds to turn off the S^D for 1 minute, while the fixed interval schedule required a single response within 15 seconds after the S^D had been on for a period of 2 to 4 minutes. Failure to meet these criteria resulted in a single shock repeated every 15 seconds until a response was made or 10 shocks given. During sessions subjects were restrained in a primate chair, but were returned to individual cages after termination of daily 1-3 hour sessions. Early in training many shocks were administered, but little change in blood pressure was observed. As training progressed fewer shocks (more efficient responding) were

given and blood pressure began to rise. Eventually four of six monkeys had elevated mean blood pressures; one subject on the fixed ratio and all three animals on the fixed interval schedule. Continuous 24 hour monitoring of blood pressure indicated that the pressure increments presisted throughout the day, as well as during the session.

It has been suggested that high rates of responding (exercise effect) and the application of electric shock may be responsible for the observed increases in blood pressure in these animals. However, pressure rose to its highest levels during the latter phases of training when responding was more efficient and few noxious stimuli were given. Only one subject, on the fixed ratio schedule, exhibited any stong correlation between responding (high rates) and increases in pressure. Additionally, the fact that pressure remained elevated even in the home cage mitigates against the idea of response rate induced increases in blood pressure.

Benson, Herd, Morse, and Kelleher (1969, 1970) in subsequent studies found that monkeys first trained to avoid shock by key pressing but subsequently required to maintain mean pressure levels at a set criterion, 10-15 mm Hg above baseline with additional increments over sessions, eventually exhibited persistent pressure elevations without physical responding. This additionally, argues against an exercise effect. These pressure changes (30-40 mm Hg mean pressure) required several months to develop. The authors concluded that strict schedule control of behavior is the primary factor for inducing pressure elevations under these conditions. It is also maintained that the terminal events involved in the schedule, e.g., shock, are less important than the rate

and patterning of schedules, as exemplified by the greater ability of the fixed interval schedule to evoke pressor responses. Similar patterns of heart rate and blood pressure change have been reported using a fixed ratio schedule for food (Kelleher, Morse, and Herd, 1976). Anderson and Brady (1972) found comparable changes in heart rate and pressure with dogs on a variable interval schedule for food, as compared to an unsignalled shock avoidance task. Pressure and heart rate differences between the two schedules did exist, however, during pre-periods each day. Thus, changes in circulatory patterns may be induced by schedules using pleasurable, as well as noxious stimuli for the terminal event. These findings increasingly support the concept of strict schedule control as the variable of primary importance in behaviorally induced elevations in blood pressure.

Large increases in blood pressure have also been reported using schedules which combine food reward and shock avoidance to control behavior (Goldstein, Harris, and Brady, 1977a,b; Harris, Gilliam, Findley, and Brady, 1973). Baboons were required to maintain specified levels of diastolic blood pressure in order to gain food and to avoid shock. After 2 or 3 months under these conditions the subjects exhibited pressure elevations of 30-40 mm Hg and maintained these levels during 95 percent of the 12 hour trials. During the 12 hour conditioning-off periods pressure declined to basal levels. Perhaps longer exposure to this type of schedule would produce sustained elevations in pressure outside the stress session. Nevertheless, these studies, as in the case of Herd et al. (1969), support strong schedule control over an animal's behavior as a means of producing elevation in arterial blood pressure, at least within daily stress sessions.

Findley, Brady, Robinson, and Gilliam (1971), using an alternating food reward-shock avoidance schedule, failed to observe any long term changes in blood pressure. Under these conditions however, shock was not contingent upon the subject's responding. This finding is perhaps not surprising in light of the failure of classical conditioning studies and noncontingent shock presentation to evoke elevations in blood pressure (Shapoir and Melhado, 1957; Dahl et al., 1968).

Lawler, Obrist, and Lawler (1975), using an unsignalled (Sidman) shock avoidance paradigm, reported that blood pressure elevations were observed only in dogs whose behavior was under strong schedule control. Of related interest to this was the finding (Herd, Kelleher, Morse, and Grose, 1977) that animals who were poor discriminators during stress sessions were more likely to exhibit the highest pressure levels. That is, these animals responded at rates sufficiently high to avoid most noxious stimuli, but responded during time-out periods as well as S^D periods. Nathan (1977) comments that experience has shown that in poor discriminators, or rather before discrimination is well established, blood pressure elevations are observed, but as training proceeds and discrimination improves, pressure is somewhat reduced in time-out periods as compared to intertrial periods. Lawler et al. (1975), also report reductions in blood pressure late in training, as opposed to early training. These findings suggest that the uncertainty of the environment, as indicated by the subject's behavioral performance, may be an important contributor to elevations in blood pressure.

Behavioral Schedules Promoting Psychological Uncertainty

The concept of an environment, lacking in predictability and controllability, as being highly stressful can be applied to investigations into the role of psychological factors in the etiology of hypertension. As just reviewed, several studies using very predictable and controllable schedules are capable of consistently producing within session pressure elevations, although few have reported sustained elevations in blood pressure. This may be due to the duration of exposure to these schedules, or it may be that because they are predictable, and cardiovascular responses fail to generalize outside the conditioning session. Two previously mentioned studies (Lawler et al., 1975; Anderson and Brady, 1972) used an unsignalled shock avoidance paradigm to evaluate psychological influences on the cardiovascular system. Although Sidman avoidance schedules are cyclic, and therefore somewhat predictable, they are also unsignalled and create a climate of psychological uncertainty.

Previous studies involving unsignalled avoidance schedules have primarily investigated the effects of acute exposure to such a schedule, on the order of days or weeks, and then for only brief periods at a time (1-2 hours/day) (Lawler et al., 1975; Anderson and Brady, 1971, 1973; Anderson and Tosheff, 1973). Prolonged exposure of animals to Sidman avoidance schedules have been reported in only one study (Forsyth, 1969). Rhesus monkeys, performing on schedules requiring responses every 5, 7, or 20 seconds in order to avoid unsignalled shock, were kept on daily 12-16 hour sessions for period lasting from 7 to 12 months. Initially,

blood pressures rose slightly but then declined below control levels during the second and third months. During the fourth month pressures began to rise again with final systolic pressures in the 150 mm Hg range, a rise of approximately 20-25 mm Hg. Diastolic pressures rose 15-20 mm Hg. Whether these results are due to strong schedule control over behavior or the uncertainty of the task is unknown. As yet, no studies have been performed using this type of long term schedule and utilizing yoked controls to determine the effect of being able to cope or not cope on changes in cardiovascular function. This also holds true for studies utilizing predictable schedules, i.e., yoked subjects have not been run.

Weiss (1971a,b,c), in an elegant series of studies on the effects of stress in the gastro-intestinal tract found that the ability to cope effectively, even in uncertain situations, is very important in determining the extent of physiopathology. Animals exposed to stressful schedules, but not able to cope effectively (yoke subjects), developed greater ulceration. These findings suggest that had yoked animals been used in previous studies on stress and cardiovascular function, they may have exhibited pressure elevations even greater than those of the coping animals.

Obrist, Langer, Grignolo, Sutterer, Light, and McCubbin (1977) reported that elicitation of the beta-adrenergic hyperdynamic state in normotensives similar to that observed in some borderline hypertensives occurred only in stress situations requiring a coping response, and then only if the response criterion (reaction time) provided occasional success

in avoiding the noxious stimulus. If the response was either too difficult or too easy the beta-adrenergic hemodynamic pattern was not evoked. Obrist, Howard, Lawler, Sutterer, Smithson, and Martin (1972b) also reported that coping attempts in a classical conditioning paradigm occurred concomitantly with an augmented sympathetic outflow, which was lost when the dogs gave up coping attempts. Obrist et al. (1977) indicated additionally, that hyper- or hypo-reactivity in a given stress situation failed to be predictive of reactivity in any other forms of stress employed. That is, subjects who were maximally reactive in terms of systolic pressure during an avoidance task failed to be differentiated from other subjects when stressed by a cold pressor test or by viewing a pornographic film.

An apparent contradiction seems to be present based on the hypothesis Weiss (1971a) has put forward, i.e., that coping should ameliorate the pathogenic process induced by stress, and the findings of Obrist et al. (1977), that coping behavior evokes blood pressure elevations via a beta-adrenergic hemodynamic pattern. Resolution may come about by the fact that although coping was possible in Obrist's studies, it was not always effective. A residual amount of uncertainty may therefore exist, evoking the beta-adrenergic state. Indeed, when coping was too easy or not possible all uncertainty was removed from either condition, i.e., subjects were always able to avoid or never able to avoid shock, and the beta-adrenergic state was *not* elicited. The ability both to predict and control one's environment (removal of uncertainty) appear to be important determinants of physiological responses to behavioral stress.

Friedman and Dahl (1975) and Friedman and Iwai (1977) exposed rats, genetically predisposed to becoming hypertensive after salt ingestion, to a conflict stress. Experimental animals were shaped to bar press for food on a variable interval 52 second schedule. An electric shock was programmed to occur on the average for every eight responses. Several yoked conditions were used to control for food and shock presentation, as well as a nonstressed control group. In the 1975 study subjects were kept on a low salt diet during the experiment. The experimental subjects in the approach (food)--avoidance (shock) conflict, a highly uncertain situation, showed rises in systolic pressure within the first two weeks of stress and sustained indirectly measured systolic pressures of 160-170 mm Hg during the 26 week course of the experiment. Subjects in the yoked-food and shock condition, an unpredictable and uncontrollable situation, had increases in systolic pressure almost as severe as the experimental animal, both groups significantly higher than any other group. These pressure elevations however, were not of the magnitude seen when the same strain of rats were fed a 4 or 8 percent salt diet. Even when the same stress condition is combined with mild salt diet (2 percent), pressure increases are reported less than in those observed with high salt diets (Friedman and Iwai, 1977). However, several subjects allowed a post treatment recovery period continued to exhibit raised pressure levels (Friedman and Dahl, 1975). The investigators concluded that the psychological stress (at least in the form used) does contribute to rises in blood pressure, but it is doubtful that stress alone is capable of producing hypertension. They emphasize that genetic and environmental interactions may be a potent factor in causing hypertension.

A recent study by Falk, Tang, and Foreman (1977) explored an unusual form of schedule controlled behavior leading to elevations in pressure when combined with unilateral nephrectomy and salt loading. The schedule is one in which the experimental animal is in a predictable but *uncontrollable* environment. Exaggerated and chronic behavior patterns were induced by means of a restricted food schedule that induces exaggerated drinking behavior in rats. Experimental subjects were food deprived and received food only during a single 5 hour period each day. Food was delivered on a fixed interval 90 second schedule. *No response* requirements were demanded for food presentation. Control subjects received the same quantity of food in a single presentation. All animals were mononephrectomized and saline was the only available drinking fluid. The latter conditions predisposed animals toward hypertension but in and of themselves did not lead to hypertension. Both groups were equated for fluid intake. Over the course of one year the experimental, but not the controls, became hypertensive. The authors suggested that hypertension may have been due to volume expansion although no determination of this was made. Greater body weight in the experimental animal could be indicative of such volume expansion; however, no data concerning this variable were presented. One might hypothesize that the *uncontrollability* of the animal's environment, not the schedule per se, acting in concert with the physiological biasing, were responsible for the eventual rise in blood pressure.

It appears that the stimulus qualities of certain environmental conditions are important in determining just how stressful a situation

is to the subject. Predictability and controllability of the environment are ostensibly important variables in evoking changes in cardiovascular function. Further investigation of these parameters may lead to an optimum model of psychological stress induced hypertension.

Hemodynamic Patterns During Psychological Stress

Several studies have monitored more than blood pressure and heart rate responses to stressful stimuli. Blood pressure elevations during psychological stress periods, at least initially, appear to be due to increased cardiac output with reduced total peripheral resistance (Forsyth and Harris, 1970; Forsyth, 1971; Anderson and Tosheff, 1973; Lawler et al., 1975). During prestress periods however, TPR maintains pressure with a slightly reduced CO. The transition in hemodynamic variables that maintain elevated blood pressure before and during stress have been observed in monkeys (Forsyth and Harris, 1970) and dogs (Anderson and Tosheff, 1973; Lawler et al., 1975).

Forsyth (1971), using radioactive microspheres to determine regional blood flows found that in a 72 hour continuous stress session, increased blood pressure was initially maintained by increased cardiac output, with reduced resistance. During the first 20 minutes of stress the major portion of the increased CO was distributed to the skeletal muscles and liver. During the course of the experiment there was a gradual decline in cardiac output and rise in resistance. By the end of the session blood pressure elevation was maintained exclusively by TPR, as CO was at baseline levels. Heart rate also declined over the session, suggesting activated baroreceptor reflex mechanisms due to

increased pressure. Changes in organ resistance to blood flow were similarly significantly changed in the opposite direction: blood flow was increased to the heart, spleen and liver, at the expense of the kidneys, skeletal muscle, and GI tract. Brain blood flow was unchanged. The increase in skeletal muscle resistance was primarily responsible for the overall increased resistance. This appears to be a microcosm of the changes suggested in the transition from borderline to essential hypertension. The selective contributions of stress versus fatigue in the changing hemodynamic pattern were not assessed.

Herd et al. (1977) used pharmacological techniques in an attempt to assess the relative contribution of each division of the autonomic nervous system to the blood pressure and heart rate increases observed in animals under strict schedule control. They found that phentolamine, an alpha adrenergic blocker, reduced absolute pressure levels and increased heart rate, the latter effect apparently due to inherent cardiac stimulating effects of the drug. Episodic changes in blood pressure during responding were still present. Doses of propranolol known to reduce cardiac output in the squirrel monkey had no effect on pressure but dramatically reduced heart rate. Episodic changes in heart rate associated with responding were still present, although slightly reduced in magnitude. Atropine eliminated the episodic heart rate increases. The failure of propranolol to effect reductions in blood pressure may be due to the fact that both beta-1 and beta-2 adrenergic receptors were blocked. The fall in cardiac output combined with a slight reduction in beta-adrenergic vasodilation could allow vasoconstriction to compensate

reflexly and maintain pressure. Elevations in mean blood pressure may, however, typically be maintained by alpha vasoconstriction in this species. Use of a cardiac specific beta blocker would obviate this question. Tonic heart rate increases are probably due to beta adrenergic activity while episodic changes are primarily of vagal origin. The phasic changes in blood pressure, concomitant with responding, are of an undetermined origin according to the authors. Combined alpha and beta blockade was not used.

Goldstein et al. (1977) also used pharmacological agents to determine the physiological processes subserving operantly conditioned blood pressure increases in baboons. Beta-blockage, again using propranolol, slightly reduced baseline heart rate and blocked tachycardia at session onset, but had no effect on blood pressure. Alpha blockade (phentolamine or phenoxybenzamine) lowered baseline pressure but failed to prevent blood pressure increases at session onset. The maximum pressure level attained was reduced, but the magnitude of the change was comparable. Combined alpha and beta blockade prevented the tachycardia but not the pressure rise. The increase in pressure, although slightly reduced in magnitude, was still significant (18-20 mm Hg). As Herd et al. (1977) suggest, these investigators also attributed the change in blood pressure under combined alpha and beta blockade to nonadrenergic functions such as parasympathetically mediated changes in contractility. One fails to see how vagal alterations in contractility could effect such increases in pressure. Vagal stimulation in the anesthetized dog produces a 5 percent reduction in contractility (Furnival, Linden, and Snow, 1970). Even if full vagal restraint were

present and release occurred, it is doubtful that a 5 percent increase in contractility would produce a 20 mm Hg rise in blood pressure. The findings of Herd et al. (1977) and Goldstein (1977) are consistent with adrenergic participation in cardiovascular alterations due to psychological stress.

Anderson and Brady (1971, 1973) and Anderson and Tosheff (1973) report that dogs trained on a 20 second Sidman avoidance schedule show a differential heart rate and blood pressure pattern when pre-avoidance and avoidance periods are compared. They found that over the course of one hour pre-avoidance period heart rate slowed while blood pressure rose. This pattern may be representative of the baroreceptor reflex. With the commencement of the avoidance period, further increases in blood pressure were accompanied by a marked tachycardia. Anderson and Tosheff (1973) determined that the pressure rise in pre-avoidance was due to increased total peripheral resistance while cardiac output sustained the elevations in pressure during avoidance periods. Peripheral resistance fell during avoidance but remained elevated 15 percent above the level observed at the start of pre-avoidance. Lawler et al. (1975) confirmed the findings concerning blood pressure control during pre-avoidance and avoidance but failed to observe a patterned change in blood pressure, heart rate, and cardiac output during pre-avoidance. They suggest that this pattern may emerge only after numerous conditioning sessions. Lawler's dogs had many fewer sessions than those of Anderson and Tosheff (1973).

Anderson, Yingling, and Brady (1976) have recently investigated cardiovascular responses during pre-avoidance and avoidance with and without beta-adrenergic blockade. During pre-avoidance the cardiovascular changes typically observed in the intact dog were unaltered by beta blockade with propranolol. This finding is consistent with the previous results indicating pressure increases were due to vasoconstriction, while heart rate slowing was of vagal origin. Propranolol failed to prevent the blood pressure rise with the initiation of avoidance behavior. Only the tachycardia usually observed at session onset was attenuated. The rise in heart rate that did occur was apparently due to vagal release. One would expect that if cardiac output were maintaining the elevated pressure during avoidance, then reductions in this parameter by pharmacological intervention would at least attenuate the pressure rise. As previously mentioned though, propranolol has peripheral as well as cardiac effects, e.g., inhibition of vasodilation. Anderson et al. (1976) correctly suggest that compensatory increases in resistance, due to inhibition of opposing vasodilator receptors, may continue to maintain the elevated pressure in the face of the reduced cardiac output. It is to be noted that no direct measurements of cardiac output or peripheral resistance were made. Forsyth (1976) measured both cardiac output and peripheral resistance in monkeys during similar stress sessions. Beta blockade did lead to an unopposed increase in resistance during stress, while cardiac output was significantly attenuated. The continued use of a nonspecific beta blocker in the pharmacological analysis of cardiovascular response during stress seems of little value. Compensatory

changes in other hemodynamic variables continue to obscure the mechanisms one is trying to elucidate.

Similarly, Anderson and Brady (1976), using alpha blockade under conditions similar to those mentioned above, found cardiovascular responses that would appear to be contradictory to their previous findings concerning hemodynamic changes in pre-avoidance and avoidance sessions, i.e., failure of pressure to rise at avoidance onset during alpha blockade. One would expect at least some rise in pressure, even during alpha blockade, if cardiac output is primarily responsible for such increases during avoidance behavior. The authors suggested that the side effects of the drug may have been partly responsible for their results. Judicious selection and application of pharmacological agents is imperative if they are to be of benefit in revealing the mechanisms responsible for cardiovascular function during behavioral stress.

We have reviewed some of the approaches taken in the study of behavioral stress and its relationship to hypertension. There appears to be at least one common denominator in terms of mechanism involved in the mediation of behavioral stress and hemodynamic disruption, the sympathetic nervous system. We have seen that sympathetic outflow either to the myocardium (beta adrenergic) or vasculature (alpha adrenergic) can produce elevations in blood pressure. Such elevations are usually compensated for by reflex changes in other parts of the circulation. A good example of this is the baroreceptor reflex, i.e., slowing of the heart, and peripheral vasodilation due to vagal inhibition of sympathetic outflow. Recent findings by two groups

involved in behavioral-cardiovascular research suggest that this reflex mechanism may be altered in the course of psychological stress.

Herd et al. (1977) have demonstrated that the baroreceptor reflex is less sensitive during stress sessions. They found that reflex slowing of the heart due to drug induced elevations in pressure was on the order of 20-30 beats per minute less in the responding phase of a conditioning session as opposed to the time out phase. Goldstein et al. (1977) also report a change in sensitivity of the baroreceptors during operant stress sessions. However, they found that rather than the baroreceptors being less sensitive during stress they were instead simply more sensitive during the conditioning off periods. It is not at all clear as to the reason for these changes. It is apparent though, that the behavioral, and therefore psychological, manipulation may lead to alteration in sympathetic neural outflow, thus participating in the control of cardiovascular function

Research of Related Interest

Researchers dealing with other physiological systems (endocrine, gastrointestinal), as well as complex behavior patterns, have suggested that the ability of an animal to predict and control its environment is important to its psychological and physiological well being (Mason, 1968; Seligman, Maier, and Solomon, 1971; Weiss, 1968, 1971a,b,c). Several theories have been generated to explain the role predictability and controllability play in altering an animal's behavior and physiology.

Weiss (1971a,b,c) has proposed a theory to account for the gastrointestinal pathology (ulcers) induced by certain types of behavioral manipulations. Weiss found that, when triplets of animals,

one escape/avoidance, one yoked shock, and one nonshock control, were exposed to either signalled or unsignalled shock avoidance conditioning, the yoked animals in either situation consistently showed greater ulceration than either the avoidance/escape or nonshock control animals. In addition, the avoidance/escape animals in the signalled condition ulcerated less than avoidance/escape animals in the unsignalled condition. Turning of a small wheel served as the instrumental response. Weiss suggests that the ulceration seen in any animal exposed to a stressful situation is dependent upon two factors: (1) the ability of the animal to make an effective coping response and (2) the amount of positive relevant feedback produced by these responses. Relevant feedback is defined as any stimulus *not* associated with the stressor, in this case electric shock. If an animal responds at a high rate, with these responses producing little relevant feedback, ulceration will be severe. If, however, relevant feedback is high, little or no ulceration will occur regardless of response rate. In turn, little or no responding also produces little ulceration, regardless of the feedback given. Thus, Weiss proposes that the yoked inescapable shock animals showed more ulceration than the other groups because they responded at a higher rate, and these coping attempts were ineffective in producing positive relevant feedback. More simply, high rates of responding with no feedback produce severe ulceration. The avoidance/escape animals had an effective coping response, while the nonshock controls never experienced the stressor, and therefore ulcerated less. The avoidance/escape animals in an unsignalled avoidance condition have greater ulceration than

avoidance/escape animals in a signalled condition because the latter group has greater predictability of the stressor and subsequent absence of stimuli associated with the stressor, thus providing greater relevant feedback when a response is made. In essence, Weiss has said that the more predictable and controllable a situation, the greater the relevant feedback produced by coping responses, therefore reducing the stressfulness of the situation.

Seligman (Seligman and Binik, 1977; Seligman, Maier and Soloman, 1971) has offered a somewhat similar hypothesis known as the safety signal hypothesis. This hypothesis has been utilized to explain why animals choose signalled noxious stimuli over unsignalled aversive events. When a signal reliably indicates absence of the aversive event, the animal is removed from a fearful condition for as long as the safety signal is present, or in other words the absence of any stimulus associated with the aversive event. The safety signal hypothesis explains Weiss' findings by proposing that the avoidance/escape animal presents itself with a safety signal whenever it avoids or escapes shock, whereas the yoked animal has no *dependable* safety signal and therefore ulcerates more severely. The dependability of the safety signal has been shown to be an important variable in reducing stress (Badia, Harsh, Coker, and Aboott, 1976). Thus, using much the same approach as Weiss, with different terminology, the safety signal hypothesis is concerned with predictability and controllability of the stressor. However, Seligman and Binik (1977) have suggested that Weiss' theory is needlessly elaborate and his findings on ulceration can be explained by the more parsimonious safety signal hypothesis.

Both the safety signal hypothesis and relevant feedback hypothesis can again be utilized to explain the *acute* effects of exposure to a conflict situation, with similar predictions for each. Weiss (1971b) found that in an acute conflict situation (24 hours), where the avoidance-escape subject had to produce a single shock to avoid a train of shock pulses, an avoidance-avoidance condition, the avoidance rat had much more severe ulceration than its yoked partner. Weiss explained this finding using the relevant feedback theory, saying the avoidance animal was punished for a response that had previously been rewarded by avoidance of shock, and thus received *negative* feedback. Because it kept responding, but at a reduced rate, it received a great deal of negative feedback, a very stressful situation. Seligman and Binik (1977) suggested that the avoidance animal, having lost its dependable safety signal, is in a state of chronic fear, and therefore ulcerates more severly than the yoked animal.

Up to this point, the two hypothesis being discussed in relation to the effects of predictability and controllability of a stressor on the physiology and behavior of an animal, have had very little divergence in predictions about the effects of a stressful situation. The only apparent difference being in the terminology and the parsimony of one over the other. However, a situation is herein proposed which leads to different predictions from each of these theories. Prolonged exposure, as opposed to the previously used acute presentations, to an avoidance-avoidance conflict situation, with the same noxious stimulus used for both parts of avoidance, varying only in amount, would lead to very different predictions from the safety signal and relevant feedback

hypotheses. An example of such a situation and the different predictions is as follows. Subjects would be conditioned to press a panel or turn a wheel to avoid a train of shock pulses, a typical avoidance paradigm. After stable performances are attained, a single shock is made contingent upon the avoidance response, i.e., the animal is now punished for making the avoidance response. Avoidance of the train of shock pulses is, however, still contingent upon making the required response. In other words, the animal will now have to respond and receive a single shock in order to avoid several shocks. This paradigm would be maintained over several weeks. During the initial period of transition to the conflict situation, we would expect to see greater blood pressure elevations in the avoidance animals than in their yoked partners. This is based upon Weiss' (1971b) finding of greater ulceration in the avoidance animal during acute exposure to a conflict situation. Over time though the two theories would make different predictions about the effects of the task upon behavior and possibly physiology. The relevant feedback theory would continue to predict greater physiological and psychological disruption in the avoidance animal. Negative feedback (production of the stressor) would be produced by the subject, leading to a highly stressful situation. The safety signal hypothesis might predict though, that over time the single shock given after a response would come to act as a safety signal, indicating a period free from several shock pulses, i.e., the single shock would indicate a period of lower shock density.

Sidman (1962) and Herrnstein and Hineline (1966) have shown that animals will learn to respond to reduce overall shock frequency even

when their response neither avoids nor escapes shock. Lambert, Bersh, Hineline, and Smith (1973) found that rats will learn to press a bar and receive a single shock in order to avoid five more shocks, a situation very similar to the one proposed above. Neffinger and Gibbon (1975) also reported that many animals will continue to respond even when the probabilities of receiving a shock are identical for responding or failure to respond. These findings lend some credence to the idea that given sufficient time, animals taught to avoid shock, then punished for that response, will again respond or continue to respond in order to reduce overall shock frequency, therefore reducing the stressfulness of the situation.

Statement of the Research Problem

Psychological stress has been consistently implicated as playing at least a contributory role in the production of essential hypertension. Animal and human studies have suggested that the stimulus parameters used in various behavioral manipulations are important in determining the amount of physiological change that occurs in respect to such manipulations. In particular, the predictability and controllability of an animal's environment appear to be two critical stimulus qualities that determine just how stressful a situation is. Research in other physiological systems has demonstrated the importance of psychological continuity, brought about by increased predictability and controllability, in maintaining physiological homeostasis.

Systematic research on the influence stimulus qualities such as predictability and controllability have on the cardiovascular system is just beginning. To that end, the present research was undertaken to

further elucidate the role of prediction and control in producing psychological stress, the ultimate goal being the development of an optimum model of stress induced hypertension.

The present study utilized systematic manipulation of the controllability and predicability of a noxious stimulus, shock, via an avoidance-avoidance conflict situation (similar to the one described in the Research of Related Interest section) to determine how changes in these variables affect the cardiovascular system in rats. These subjects were used because of their short life span, thus reducing the time that may be required to produce significant changes in the blood pressure of these animals through exposure to a stressful environment.

Both yoked and nonshock controls were used. The former, a means by which to study the effect being unable to make a coping response (loss of control) may have on the blood pressure of animals. The latter, to control for simply being in a restraint apparatus.

The following were specific questions of interest in this study.

1. Does a signalled shock avoidance task produce elevations of blood pressure in avoidance or yoked animals?
2. If pressure changes have occurred, does an abrupt change to conflict type stress produce further increases in pressure?
3. If pressure changes have not occurred during the avoidance task, does imposition of the conflict cause any alteration in pressure?

4. Are the pressure changes, if any, similar in magnitude to changes produced by other behavioral paradigms? How do they compare to changes produced by physiological intervention?
5. Will there be a persistence of the blood pressure elevations when response contingencies are not in effect?
6. Will there be initial differential blood pressure responses between avoidance and yoked subjects? Will these differences persist?
7. Does prolonged exposure to the conflict stress differ in its effect on blood pressure from that of the acute exposure?
8. In what way may the changes in blood pressure that may be observed in the above conditions be related to the hypotheses suggested by Weiss (relevant feedback) and Seligman (safety signal)?

CHAPTER III

METHODS

Subjects

Forty-eight normotensive, male Long-Evans rats (Blue Spruce Farms, Altamont, New York) served as subjects in the experiment. Animals weighed between 300-400 grams at the commencement of the study and weights were recorded daily for the duration of the experiment. All subjects were allowed a minimum one-week adaption period after arrival from the supplier. Animals were housed in the Animal Facility of the Walter's Life Sciences Building, University of Tennessee, Knoxville.

Apparatus

Home Cages. Subjects were housed in standard laboratory cages. A grated lid allowed ad libitum access to food and water. All subjects were housed three to a cage until utilization in the experiment, at which time they were housed individually. Cages were maintained by animal facility employees under the supervision of the author.

Experimental Cages. Subjects were housed in small, individual, rectangular cages during the experimental sessions. The cages, constructed of plexiglass, were 28.0 cm x 8.5 cm x 7.0 cm in size and mounted on a 5.1 cm platform. A hinged lid allowed the subject to be easily placed into and removed from the apparatus.

In each cage a wheel, mounted on an axle beneath the cage floor protruded 3.5 cm into the cage at a position 15.3 cm from the rear and

5.0 cm from the front of the enclosure. The wheel consisted of two .6 cm thick plexiglass disks, 7.6 cm in diameter, attached at the perimeter to one another by 12 equally spaced 5.1 cm x .5 cm stainless steel bars. A 1/4 wheel turn tripped a microswitch located beneath the floor of the cage and was the required response for avoidance of electric shock. The subject's tail extended through a 1.2 cm wide slot in the rear of the cage, allowing a 1.9 cm wooden disk with a .9 cm center hole to be slipped on and taped in place at a point approximately 1 cm from the base of the tail. This prevented the animal from turning around in the cage, and from reaching and disturbing its shock electrodes.

Three individual cages, one each for the avoidance, yoked, and nonshock control animals, hereafter called a triplet, were positioned in a large wooden box. Each large box was sound attenuated and equipped with house light, speaker, and ventilation fan. One way windows in each large box allowed unobtrusive observation of the subjects. Four such boxes were located in a 2 x 3 x 2.5 meter room.

Programming Equipment. A KIM-1 microprocessor system, (MOS Technology) with appropriate interfacing (Murray and Lawler, 1978) and software (Lawler and Buchholz, 1979), controlled the scheduling and duration of stimulus presentations, i.e., tones (CS) and shocks, independently, for all four large boxes. The microprocessor system was located adjacent to the room used to run the animals. The KIM-1 system also detected and processed all appropriate behavioral data, to be detailed elsewhere, for each subject in a given experimental session. A hard copy of the behavioral data for all animals was output on a LA-30

DECwriter (Digital Equipment Corporation) at the end of each session.

Cardiovascular Monitoring Equipment. Blood pressure and heart rate (HR) were monitored in each subject using both indirect (noninvasive) and direct recording techniques. Noninvasive physiological monitoring utilized two restraining cages with heating strips and a Narco Biosystems electrosphygmomanometer system (Model 7211), with pneumatic pulse transducer and tail cuff in conjunction with a Narco-Biosystems Physiograph (Model PMP-4A), to determine systolic blood pressure (SBP) and HR.

Direct systolic and diastolic blood pressure (DBP) and heart rate were monitored in chronically catheterized subjects via Narco Biosystems RP-1500 pressure transducers, each connected to a solid state strain gage coupler (Model 7172) and amplifier (Model 7070) housed in the Physiograph. The polygraph provided continuous tracings of each subject's blood pressure. The amplified pressure signal was fed into a blood pressure digitizing circuit, designed in our laboratory (Lawler, Murray, Buchholz, Culver, Cox, and Kirby, 1978). The digitizer is designed to track the DC voltage output of the polygraph amplifier and, via a sample and hold technique and comparator circuit, detect peaks (systolic pressure) and troughs (diastolic pressure). When either a peak or trough is detected, a sample command is given to the Datel-DAS 16 8 channel, 10 bit, analog to digital converter (ADC), housed in the digitizer unit. The ADC then converts the voltage for the given pressure into digital form which is then stored in the appropriate accumulator for either systolic or diastolic pressure. In addition, each time a systolic peak is detected, a single count is also placed in the heart rate accumulator. Depending

on which has been detected, a peak or trough, the process is then reversed to find the next appropriate portion of the cardiac cycle, a peak if a trough has last been noted and vice-versa.

The accumulation process continues until a preset recording interval (as determined by the experimenter via thumbwheel switches has elapsed. At this point, off-line determination and paper print out of recording interval, total number of heart beats (heart rate if recording interval is 1 minute), and mean systolic and diastolic pressures occur. Because this routine is performed off-line by the digitizer, there is no loss of incoming data. The digitizer sequences through four input channels, changing to the next channel at the end of a recording interval and upon reaching the end of the fourth recording interval returns to the first input channel. Three channels were used for recording of blood pressure from each of the three animals housed in one of the large boxes. This instrument has been demonstrated to be accurate within 1 mm Hg of blood pressure read directly from the polygraph record.

Procedure

Group Assignment. The 48 subjects were randomly assigned to one of two groups designated as acute conflict or chronic conflict conditions. Within each condition, the animals were further randomly assigned to one of eight sets of three rats each, called triplets. There were a total of 16 triplets in the experiment, 8 for each group. Each member of the triplet was randomly selected to be in one of three groups: (1) avoidance-escape subject--has control over the frequency and duration

of shock and tone presentations; (2) yoked subject--receives same frequency and duration of all stimuli presented to the avoidance animal but has no control over their presentation; (3) nonshock control subject--subjected to same conditions as yoked subject except it receives no shock. Church (1964) has criticized the use of yoked control designs in behavioral research. The present experiment did not utilize the yoked control design as described by Church because the yoked subjects were, in fact, a specific condition that were studied and not a control group at all (Weiss, 1971a). Yoked subjects lacked any control over their environment and allowed a comparison of the physiological and behavioral reactions in groups with and without a viable coping response. The nonshock subjects served as a control for the effects of tone presentation and restraint.

Avoidance-Escape Training. Each triplet of animals regardless of group assignment (acute or chronic conflict) received 1-1/2 hours of training over a 2 day period on an avoidance-escape schedule prior to commencement of daily stress sessions. During this time the conditions for each animal in a triplet were the same as in the daily stress session, the single exception being the use of a method of successive approximation to teach the avoidance animal the appropriate avoidance response, a 1/4 wheel turn. A 2000 Hz, 75 db tone (CS) was presented 5 seconds before shock occurred and remained on until a response was made. Shock was administered via tail electrodes in pulses .2 seconds in duration with a shock-shock interval of .8 seconds. The shock density for avoidance and yoked animals was constant and equal because of the use of fixed

tail electrodes set up in a parallel circuit and combined with the use of a constant current shock source. Shock intensity started at .2 ma each day and was adjusted as necessary to levels sufficient to maintain behavioral performance. Shock intensities never exceeded .65 ma and typically were in a range between .3-.4 ma. During the training period, a response at any time by the avoidance animal terminated any stimulus present, tone or shock, and postponed the next CS presentation for 10 seconds. The yoked animal received the same number and duration of all stimuli presented to the avoidance animal, but had no control over them. The nonshock animal received only the CS presentations. Timing parameters for tone and shock presentation and methods of adjustment for shock intensity remained the same throughout the experiment except where changes are noted.

Daily Stress Sessions. Subsequent to the avoidance-escape training period, each triplet was subjected to stress sessions on a daily basis, 5 days a week, Monday through Friday. Because of equipment limitations not all subjects were run at the same time of day. Four triplets at a time were run in one of three daily sessions: morning, afternoon, or early evening. A triplet starting the experiment in a given period of the day, morning, afternoon, or evening, remained on that schedule for the duration of the experiment. Time and equipment limitations necessitated the running of all acute conflict triplets during the morning session, while half the chronic conflict group ran in the afternoon session and half in the evening session.

All daily stress sessions were 3-1/2 hours in duration. The first 15 minutes of the session were designated a prestress period. After having a wooden disk taped on its tail, each member of a triplet was placed in the appropriate individual cage. After shock electrodes were attached to the tails of the avoidance and yoked animals, the door of each large box was closed and the subjects remained in the darkened, sound attenuated chamber for the duration of the prestress period. The number of responses made by each subject during this time was recorded by the KIM-1 system. At the end of the 15 minute prestress period the behavioral data were output in hardcopy form on the DECwriter.

Commencement of the 3 hour stress period was signalled by turning on a 12 volt house light in each box. An 87 db white noise was also turned on in the room containing the large boxes in order to mask any extraneous noise that might have disrupted an animal's performance. At the end of the stress period the white noise was turned off and each box was again darkened. All behavioral data were output in hard copy form. This was followed by a 15 minute poststress period with conditions identical to that of the prestress period. Again, responses made during this time were recorded by the microprocessor system and output when the period was over. These conditions held for all subjects throughout the experiment except where changes are noted.

Avoidance-Escape Phase. After avoidance-escape training was completed all subjects in both the acute and chronic conflict groups were run for 3 days on the same signalled avoidance-escape schedule

utilized during training. During these 3 days software programming of the KIM system only allowed recording of behavioral data during the 3 hour stress period. The pre and post stress periods were in effect, however, no behavioral data were collected during these periods. This 3 day phase allowed the avoidance subjects to stabilize their performance before implementation of the next, more difficult phase of the experiment.

Signalled Avoidance Phase. Following the 3 day avoidance-escape phase, triplets in both groups of subjects were run for an additional 10 days on a signalled avoidance stress paradigm. During this phase, all stimulus conditions and timing parameters were the same as in the escape-avoidance section, except the opportunity to escape shock was eliminated and failure of the avoidance animal to respond during the first 5 seconds after CS onset led to the administration of five inescapable shocks. The five shocks were presented over a 5 second period, each shock .2 seconds in duration. The CS was then terminated with the last shock and the next CS presentation was at least 10 seconds away. Again, a response by the avoidance animal at any time other than during the presentation of the inescapable shock postponed the next CS presentation for 10 seconds.

Behavioral data were collected for each of the four triplets in a given daily session during pre and post stress periods as well as the stress period. These data consisted of: (a) the number of responses by each member of each triplet during the pre and post periods; (b) the number of responses by each animal during the stress period

that occurred at any time other than during the five inescapable shocks (designated as responses before shock); (c) the number of responses by each subject during the inescapable shock (designated as responses during shock); (d) the number of CS presentations; (e) the number of failures to avoid shock for each avoidance animal. Multiplication of the failures to avoid shock by five provided the total number of shocks for each triplet in a given stress session.

Conflict Phase. At the end of the second week of straight avoidance conditioning, the third week overall, triplets belonging to the acute conflict group were then implanted with aortic catheters for direct blood pressure and heart rate recording. Upon recovery from surgery each triplet was exposed to one more day of straight signalled avoidance stress, followed by 2 days on a conflict schedule. During each of these days direct monitoring of SBP, DBP, and HR was performed.

The conflict schedule used exactly the same stimulus and timing parameters found in the avoidance phase except that whenever the avoidance animal made criterion response, regardless of whether the CS was on or not, a single shock pulse, .2 seconds in duration, was given. The avoidance response, however, was still required to postpone the train of five shocks that followed 5 seconds after CS onset. Thus, the avoidance animal was required to respond in order to avoid a train of five shocks as before, but was then punished for making such a response, i.e., a single shock was contingent upon performance of the

avoidance response. Also as in the other phases, the avoidance response terminated the CS, if present, and postponed its next presentation for 10 seconds. Yoked subjects continued to receive the same stimuli presented to the avoidance animal. Direct monitoring of blood pressure and heart rate thus occurred during one day of sinalled avoidance and two days of conflict for the acute conflict group. The acute conflict subjects received a total of three weeks of avoidance stress, with an additional three days of physiological monitoring. The acute conflict subjects were then sacrificed and gross visual inspection of the viscera was performed to determine the presence of infection or notable pathology.

Following completion of the avoidance phase, the chronic conflict group was placed on the conflict schedule described above. The chronic conflict triplets remained on this schedule for eight more weeks, making a total of 11 weeks of stress sessions for this group: 1 week of avoidance, 2 weeks signalled avoidance, and 8 weeks of conflict. A summary of the conditioning schedules for both the chronic and acute conflict groups is depicted in Table 1. As indicated in the table, one half of the subjects in each group participated in the experiment at different times than did the remaining half.

Surgery. At the appropriate stage in the experiment each animal was implanted with an indwelling aortic catheter. Due to time restrictions, the catheterization procedure was staggered over a 4 day period (Monday-Thursday), for each set of four triplets. Catheterizations were performed on one triplet per day (see Table 2). All subjects had at least 3 days

Table 1

Time Table of Events for Each Replication in the Acute and Chronic Conflict Groups

Groups	WEEKS 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Acute																	
Rep 1 (n=12)	T	A	A	S	R												
Rep 2 (n=12)						T	A	A	S	R							
Chronic																	
Rep 1 (n=12)	T	A	A	C	C	C	C	C	C	C	C	S	R				
Rep 2 (n=12					T	A	A	C	C	C	C	C	C	C	C	S	R

T = Training/Avoidance-Escape.

A = Avoidance.

C = Conflict.

S = Surgery.

R = Recording.

Table 2

Surgery and BP Recording Schedules for any
Four Sets of Triplets

	DAYS										
*Triplets	M	T	W	TH	F	S	S	M	T	W	TH
1	S	-	-	-	R	R	R				
2		S	-	-	-	R	R	R			
3			S	-	-	-	-	R	R	R	
4				S	-	-	-	-	R	R	R

- Recovery

S Surgery

R Recording

* Designates any four Triplets that might be used and does not refer to any specific set of triplets.

of recovery before direct recording sessions began.

Under sodium pentobarbital anesthesia (50 mg/kg), 2.5-3.0 cm midline incision was made in the abdominal wall of the rat, exposing the abdominal cavity. Fascia were separated to the depth of the aorta at the branching of the left renal vein. A catheter, consisting of 20 cm of PE 90 tubing joined to a 18 mm section of PE 10 tubing, was passed down the back of the neck through a subcutaneous cancel and through the left body wall. The catheter was then anchored to the psoas major back muscle approximately 3 mm lateral to the aorta.

A 3 mm section of the aorta, just inferior to the left renal vein, was cleaned of excess connective tissues and a single puncture made with a 27 guage needle. Direct pressure with a cotton tipped applicator was applied until clotting occurred, a matter of a few minutes. The catheter was then filled with heparinized saline (500 units/cc). Approximately 1.5 cm of PE 10 was then inserted through the puncture into the vessel in a downstream position. The catheter was tested for blood flow, rinsed and filled with heparinized saline. A 20 gauge stainless steel obturator was then inserted into the PE 90 end of the catheter. Fascia was laid in place over the aorta and the muscle wall of the abdomen closed with 4-0 gut followed by the closure of the skin with 3-0 silk. The PE 90 end of the catheter was then anchored at the base of the neck. Each subject then received a 60,000 unit injection (IM) of procaine penicillin (300,000/cc), followed by additional prophylactic treatments for two more days.

Upon recovery from surgery and prior to recording, each rat had its catheter flushed on a daily basis. For the first two days,

each animal was lightly anesthetized with ether and the catheter plus was removed for determination of patency. The catheter was cleared of any clots by normal blood flow, then flushed with .15cc of heparinized saline (500 units/cc). After checking to ensure no air bubbles were present in the catheter, the obturator was repositioned. The remaining daily flushings occurred *without* the use of ether. Instead, the animals were gently held by the experimenter and the procedure continued as stated above.

Equipment Calibration. (a) Electrosphygmograph (ESG)--Calibration of the ESG for *indirect* blood pressure recording was done according to procedures recommended by the manufacturer. Thirty minutes prior to a recording session the channel amplifier and ESG were turned on and allowed to stabilize. After setting the channel pen to an appropriate baseline, the ESG was balanced and the 0-200 mm Hg pressure range selected for recording purposes. The pressure/range sensitivity was then set via the channel amplifier variable control and the Internal Calibrate switch to equal 40 mm Hg/cm pen deflection. The channel amplifier filter was set at the 30 Hz position throughout the recording process. The ESG calibration was checked between subjects by use of the Internal Calibration switch.

(b) Strain Gage Coupler--At least 30 minutes prior to a daily *direct* blood pressure recording session, the polygraph channel amplifiers, strain gage couplers, and blood pressure digitizer were turned on and allowed to stabilize. The RP-1500 pressure transducers were filled with sterile isotonic saline while ensuring that no air bubbles were

trapped in the dome. The transducers were then secured at heart level to the exterior of each animal's experimental cage and connected to the strain gage couplers. Upon establishment of an appropriate baseline for each channel, the Record switches on the strain gage coupers were turned on and the transducers were allowed to stabilize for a minimum of 20 minutes before being calibrated.

The following is representative of the calibration procedure for each strain gage coupler. The channel amplifier Gain control was set to a 20mV/cm position and a digital multimeter, on a millivolt setting, was connected to the auxillary output of the amplifier. The strain gage was then balanced to a zero millivolt reading. Next, the sensitivity of the strain gage was adjusted such that a 2-1/2 cm pen deflection was equivalent to a pressure of 100 mm Hg. The strain gage balance was again examined and readjusted to a zero millivolt reading when necessary. The voltage equivalent for a pressure of 100 mm Hg was determined via the digital multimeter and recorded for each channel for use in the calibration of the blood pressure digitizer. An additional 10-20 minutes was allowed for stabilization of the strain gage, followed by re-examination of the Balance and Sensitivity controls prior to commencement of a recording session. Each channel amplifier's calibration was checked per manufacturer's instructions at the beginning of each week of direct blood pressure recording.

(c) Blood Pressure Digitizer--Subsequent to the calibration of the polygraph, the blood pressure digitizer was calibrated. The auxillary output of each channel amplifier was connected to the inputs

of the BP digitizer. With the digitizer in the Calibrate mode, the Continue switch was depressed followed by a reset command. This placed the first channel into a sampling condition. The Offset potentiometer on the digitizer was adjusted until the least significant bit (LSB) of the ADC was on 50 percent of the time. Each of the 10 binary bits of the ADC was represented by a front LED. The digitizer was allowed to sequence through and print out the value for each channel twice. During this time, the offset of each channel was noted and adjustments, if necessary, were made by rezeroing the balance on the strain gage coupler. The printer output for systolic pressure was zero for each channel under these conditions.

Once the offset for each channel was adjusted such that the LSB was on half of the time and the printout for systolic pressure was zero, the gain was selected via a second front panel potentiometer. With the digitizer again in a sampling state and reset to the first channel, the Internal Calibrate switch on the strain gage coupler was depressed presenting a voltage input to the digitizer equal to a 100 mm Hg pressure signal. A 100 mm Hg pressure was represented by a decimal 200 on the front panel LEDs, i.e., the LEDs representing 128, 64 and 8 were on. Adjustments were made with the Gain control until this LED pattern was displayed. The digitizer was then allowed to sequence through each channel several times to ensure that the printer output was 100 for systolic pressure. The balance of the strain gage and the digitizer offset were redetermined and the digitizer switched from the calibrate to the record mode. The transducers were then connected to each animal and the recording session was started.

Physiological Monitoring. (a) Indirect Method--Indirect systolic blood pressure was recorded on a weekly basis for each rat. One week prior to commencement of the training period a baseline systolic blood pressure and heart rate were determined for each animal using the equipment previously described. Subsequent pressure recordings were made after completion of the last stress session of each week. Indirect pressures were recorded a minimum of one hour after the animals were removed from their experimental cages and placed back in their home cages.

Two subjects at a time were placed one each in two small restraining cages containing heating elements. The animals were gently heated to produce vasodilation in the tail so as to allow the Korotkoff sounds to be detected by the pneumatic pulse transducer taped to the tail. Systolic pressure and heart rate were recorded first on one rat then the other. A 6 second strip of pressure pulsations was taken for determination of HR. This was followed by three successive determinations of SBP. The entire process for each animal took just under 10 minutes. Approximately 2 hours were needed to record pressures from the entire set of triplets, for each daily session. Blood pressure and heart rate determinations were completed on each member of a triplet before progressing to the next triplet. The first triplet to be recorded from each week was rotated sequentially from first to last. That is, each triplet in the acute conflict group was in each position, 1-4, once over the 4 weeks in which recordings were made. Each triplet in the chronic conflict group was in each position three times over the 12 weeks in which recordings were made.

(b) Direct Method--After recovery from surgery, direct blood pressure and heart rate recordings were made from one triplet at a time. As presented in Table 2, page 68, recordings were never made on more than two triplets on any given day. Each triplet was monitored during the usual 15 minute pre and poststress periods; however, a triplet was exposed to only 1 hour of stress during which time physiological data were collected. The reduction in the duration of the stress session was due to the difficulty often encountered in maintaining patent catheters, without the use of an infusion pump, for much more than 1-1/2 hours. Each triplet was monitored for three consecutive days.

On recording days each member of a triplet had its catheter tested for blood flow and flushed with heparinized saline (500 units/cc). Each rat was then placed in its individual cage and the catheter was connected to the appropriate pressure transducer. The polygraph and blood pressure digitizer were calibrated prior to the stress session. The criteria for an adequate pressure signal were a pulse pressure of at least 30 mm Hg and the presence of a dichrotic notch.

Blood pressure and heart rate were monitored for 15 seconds of each minute by the digitizer circuit; continuous recordings were made on the polygraph. Thus, a representative sample of blood pressure and heart rate was provided for each subject for each minute of the prestress, stress, and poststress periods. When digitized records were lost or suspect due to equipment malfunction, data were obtained by direct reading of the polygraph records, covering intervals comparable to those sampled by the digitizer. At the end of a recording session

the catheter in each animal was flushed and refilled with heparinized saline and the subject returned to its home cage.

CHAPTER IV

RESULTS

Body Weight

Body weight for the avoidance, yoked, and control animals in the acute group increased progressively over the three week period in which they were in the experiment (Figure 1). The analysis of variance indicated a significant week main effect, F (2, 42) = 32.74, $p < .05$. Post hoc analysis using the Tukey HSD[1] showed week 3 body weights for all groups to be significantly larger than either weeks 1 or 2 body weights.

Chronic group body weights also rose monotonically over the 11 week period in which they were observed (Figure 2). The analysis of variance indicated a significant week main effect, F (10, 210) = 277.29, $p < .05$. Post hoc analysis indicated that body weights in weeks 1 and 2 were significantly less than all other weeks except each other. Body weights for weeks 3, 4, and 5 were significantly less than weeks 6-11 but not significantly different from each other. Weeks 6-8 were significantly different from each week subsequent to them. Week 9 body weight was significantly less than week 11 only. No difference existed between body weight for weeks 10 and 11. No replication effects were found for either the acute or chronic group.

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[1]All post hoc comparisons used the Tukey HSD test and were at $p < .05$ unless otherwise noted.

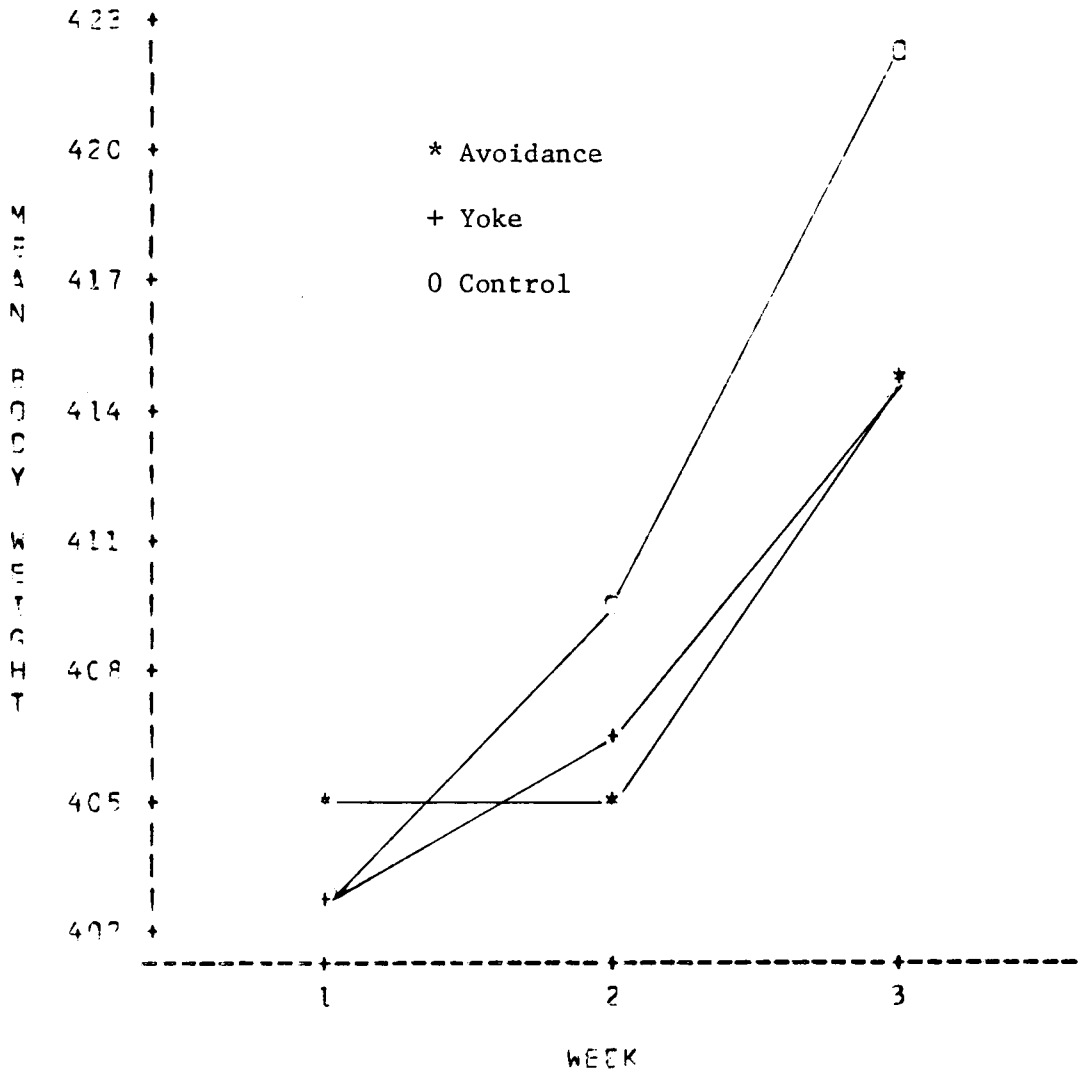

Figure 1. Mean Body Weight in Grams for the Acute Group During Avoidance-Escape and Signalled Avoidance.

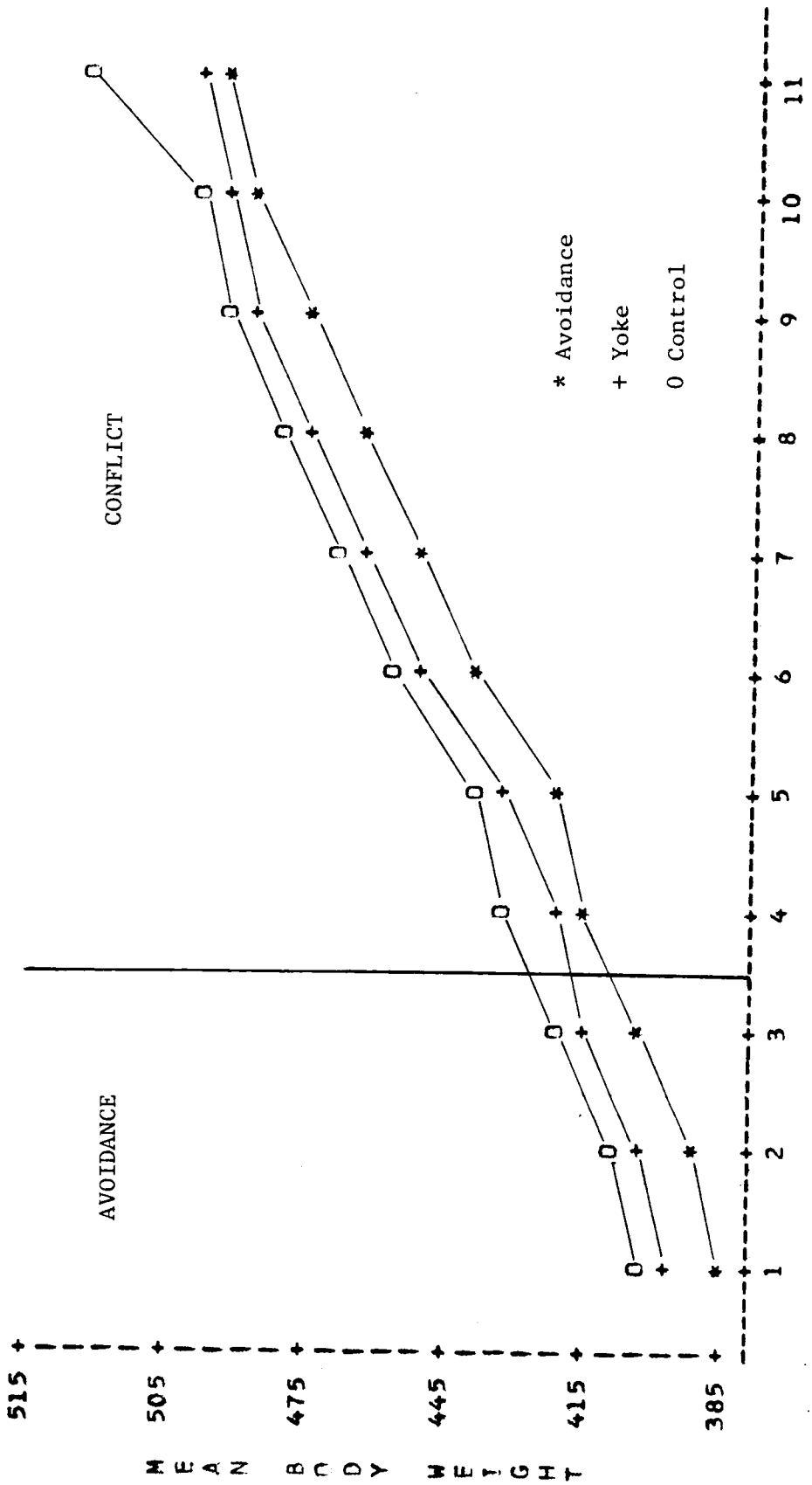

Figure 2. Mean Body Weight in Grams for the Chronic Group During Avoidance and Conflict.

Behavioral Data Days 1-3 Avoidance-Escape

Because treatment conditions were identical during this period and analysis of variance failed to reveal any main effects due to conditions or replications, the data for the acute and chronic groups were combined. The avoidance animals showed a daily decline in failures to avoid shock during the avoidance-escape phase, as shown in Figure 3. The analysis of variance revealed a significant days effect using the Geisser-Greenhouse conservative degress of freedom F (1, 30 = 5.26. $p < .05$. Comparison of the means in the follow up analysis indicated that on days 2 and 3 there were significantly fewer failures to avoid shock by the avoidance animals than for day 1. Although no significant differences were revealed by the analysis of variance, Figure 4 indicates that an almost identical decline in mean number of shocks over days 1-3.

Total mean responses were significantly different for the avoidance, yoke, and control conditions, F (2, 45) = 21.27, $p < .05$. Follow-up analysis indicated that the avoidance animals responded significantly more than either yokes or controls during the initial stress sessions. Yoked animals also responded significantly more than did controls. The mean number of 1/4 wheel turns were 3904, 2163, and 843 for avoidance, yoked, and controls respectively. No main effects due to replication were found to be significant in any of the above analyses.

Behavioral Data Weeks 2 and 3, Signalled Avoidance

The analysis of variance failed to reveal significant main effects due to replications or conditions (acute-chronic) on any variable during

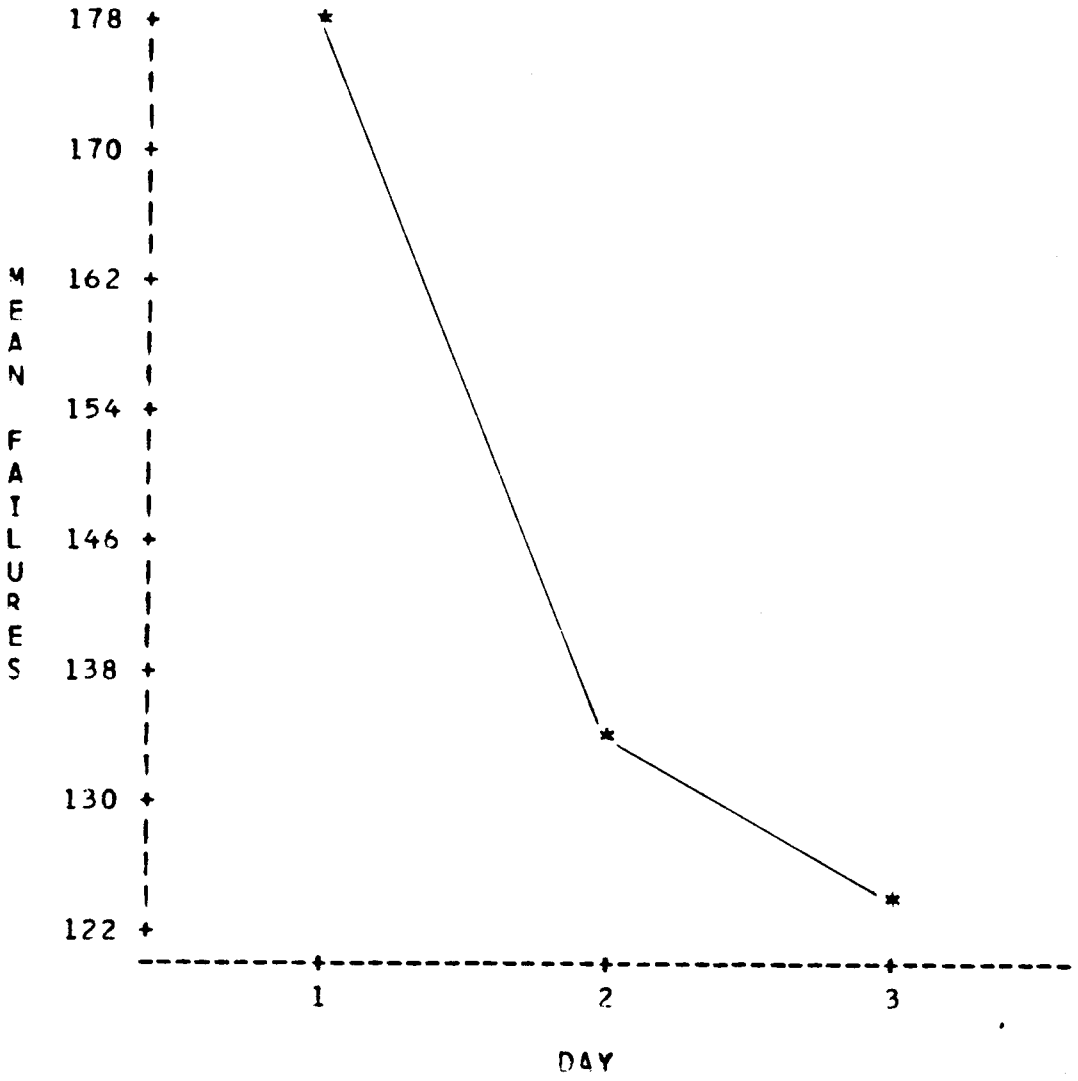

Figure 3. Mean Failures to Avoid Shock by the Avoidance Animal During Avoidance-Escape. Means Represent Combined Acute and Chronic Groups

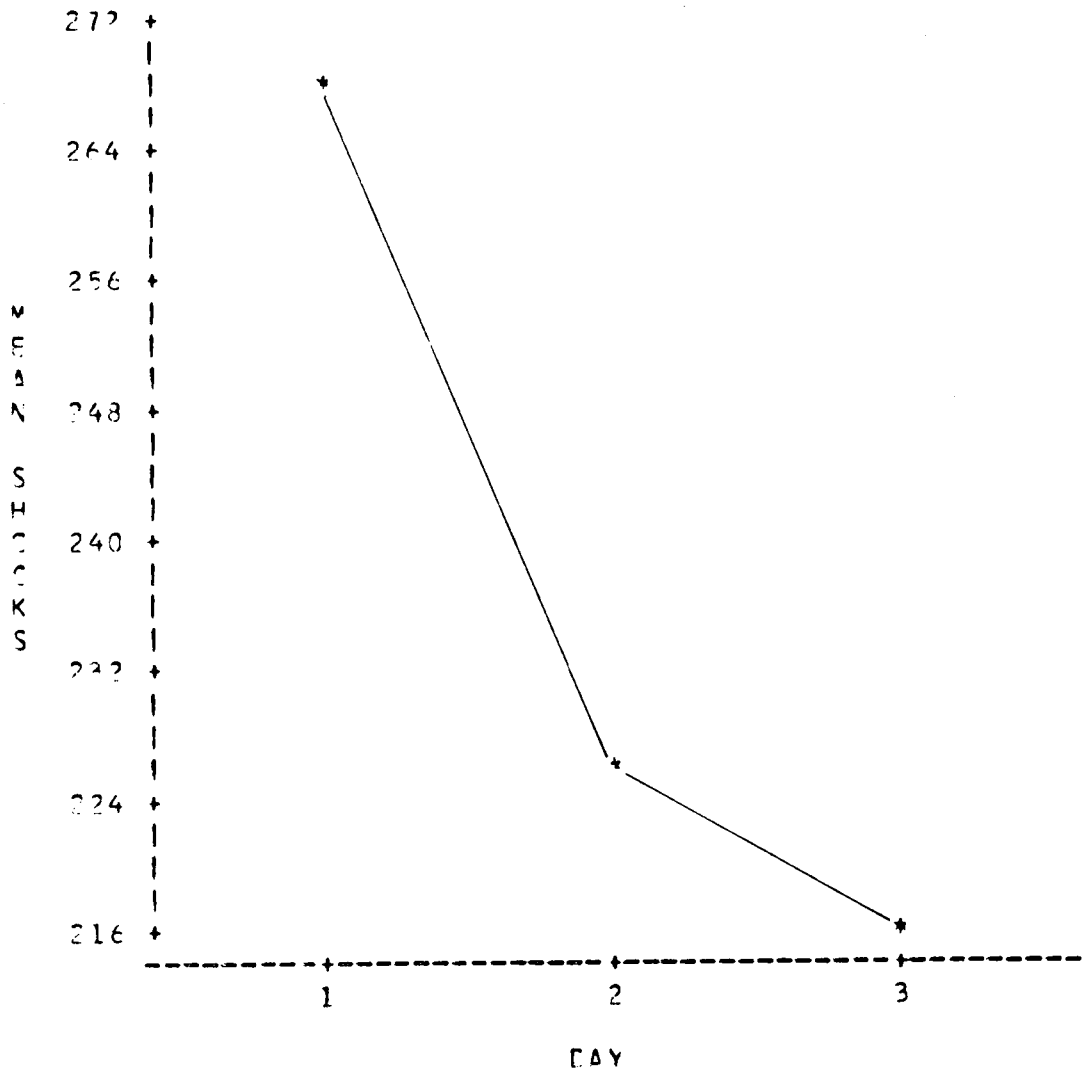

Figure 4. Mean Number of Shocks Received by the Avoidance and Yoked Animals During Avoidance-Escape. Means Represent Combined Acute and Chronic Groups.

the signalled avoidance phase. Therefore it was considered appropriate to combine the data across conditions. This was done because treatment was identical for the acute and chronic groups during this phase of conditioning.

Figure 5 shows the continued daily decline in failures to avoid shock by the avoidance animal. A significant day effect was found, $F\ (4, 67)$[2] $= 2.71$, $p < .05$.

Post hoc analysis indicated that on days 4 and 5 at the start of the signalled avoidance phase avoidance subjects failed to avoid shock significantly more often than on day 13, the end of signalled avoidance. This is indicative of a typical learning curve.

With the commencement of the signalled avoidance phase behavioral data were collected not only during the stress sessions but during both the pre-and post-stress periods. It was found that during this phase of conditioning, avoidance and yoked animals responded significantly more often than did controls in both the pre-and post-stress periods $F\ (2, 45) = 4.98$, $p < .05$.

Responses during the stress session were recorded as occurring at any time other than during shock presentation, defined as responses before shock, or during shock presentation, called responses during shock. There was a significant group $F\ (2, 45) = 21.27$, $p < .05$, effect

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[2]The degrees of freedom in this analysis were corrected for variations in the variance-covariance matrix by the Geisser-Greenhouse epsilon and adjustment precedure as recommended by Jennings and Wood (1976) and Winer (1971).

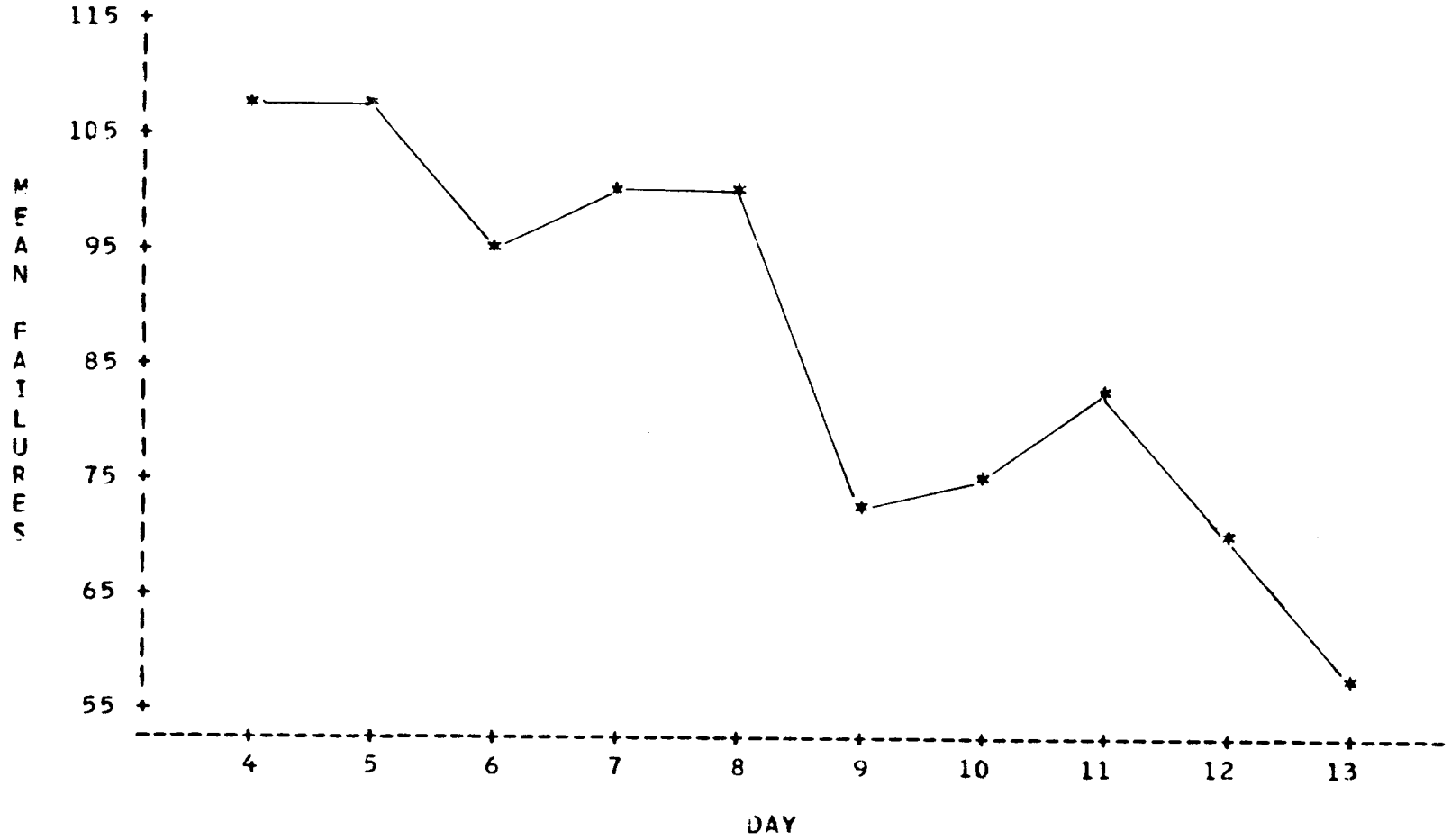

Figure 5. Mean Failures to Avoid Shock During Signalled Avoidance. Means Represent Combined Acute and Chronic Groups.

for responses before shock. Figure 6 indicates that responding during the second week of signalled avoidance increased slightly from the first week for all groups, with more dramatic increase in the avoidance animal's responses. The group by week interaction was marginal $p < .08$. Group comparisons indicated that the avoidance animals responded significantly more than either the yoke or control subject. There was no statistical difference between the yoke and control subjects.

Responses made during shock presentation by the avoidance and yoked animals showed a substantial fall from the first to the second week of signalled avoidance (Figure 7). Group F (2, 45 = 11.69, $p < .05$, and week F (1, 45) =14.18, $p < .05$ main effects, and the group by week interaction, F (2, 45) = 3.28, $p < .05$ were all significant. Tests of simple main effects indicated that the avoidance, but not the yoke or control subjects, decreased responding significantly from week 2 to week 3, F (1, 45) = 10.86, $p < .05$, and week 3 F (2, 67) = 5.01, $p < .05$. Post hoc analyses of the simple main effects indicated that for weeks 2 and 3, the number of responses made during shock by the avoidance and yoke subjects was significantly greater than the control group, but not significantly different from each other.

Behavioral Data for Weeks 3 and 4--Transition from Avoidance to Conflict

The data presented in this section are only from the chronic group represent the behavioral response to the transition from signalled avoidance to conflict. No main effects due to replication (running half the group at a later point in time than the other half) were found for any of the variables analyzed in this section.

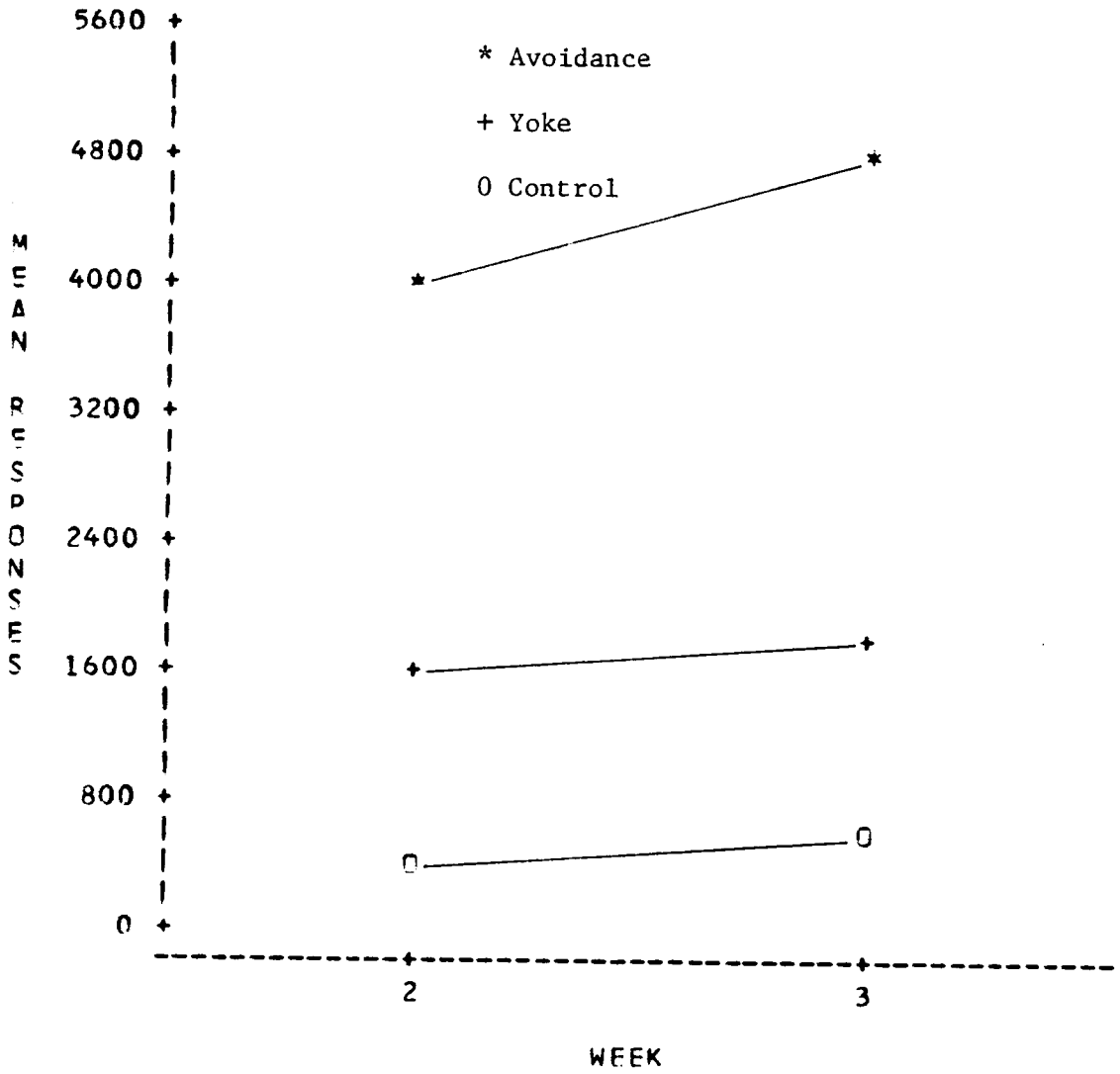

Figure 6. Mean Responses Before Shock During Signalled Avoidance. Means Represent Combined Acute and Chronic Groups.

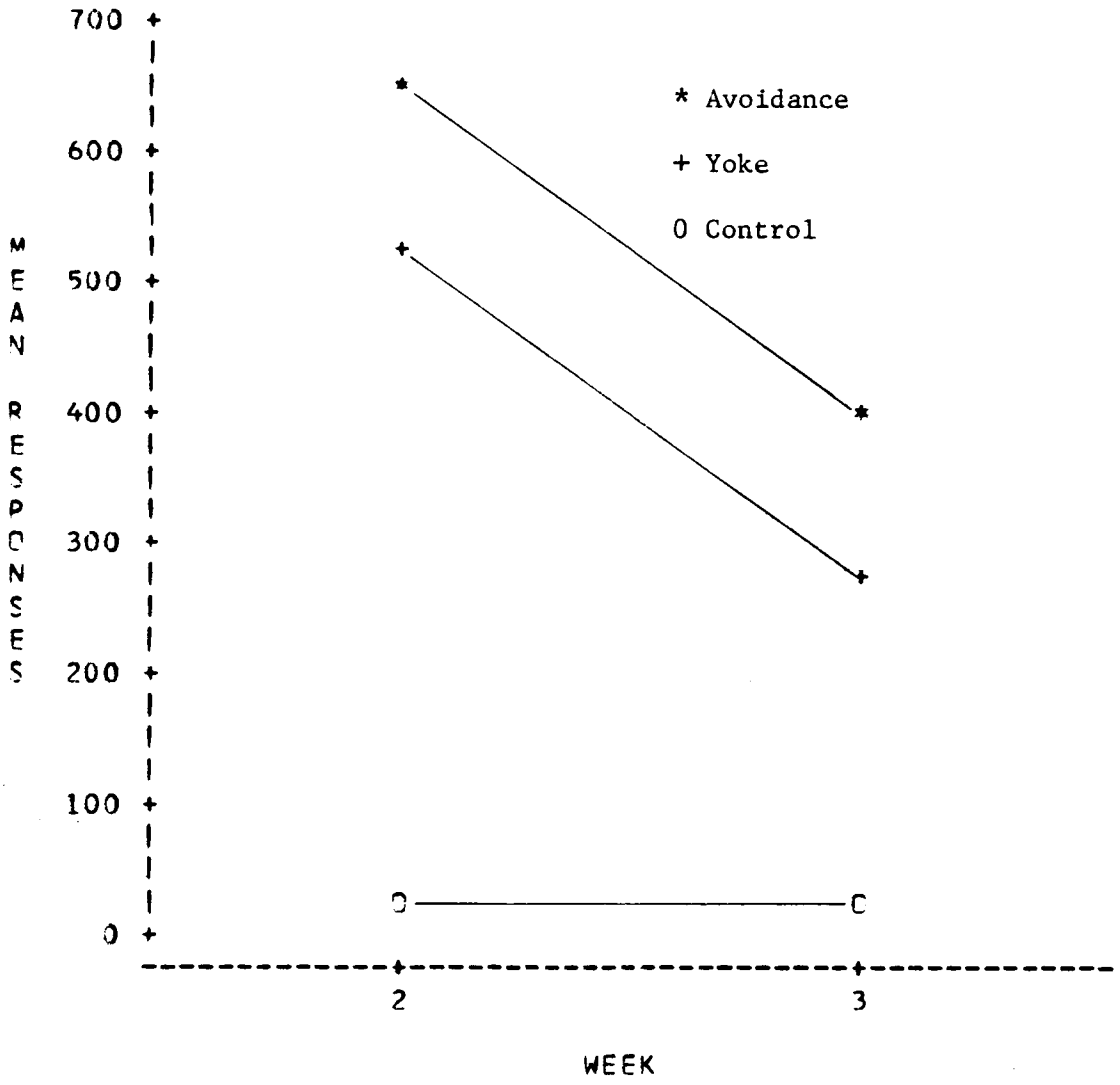

Figure 7. Mean Responses During Shock for the Signalled Avoidance Phase. Means Represent Combined and Chronic Groups.

As was expected the transition from avoidance to conflict disrupted the performance of the avoidance animal. Figure 8 represents the day by day performance of the avoidance animal during the last week of avoidance and the first week of conflict. A dramatic increase in failure to avoid shock occurred on the first conflict day followed by a more gradual increase in failures throughout the week. A significant day effect was present, F (2, 13)[3] = 4.18, $p < .05$. Post hoc analysis found the fourth day of conflict (day 17) to be significantly different from all 5 days of avoidance. Days 16 and 18 showed significantly more failures to avoid shock than days 10 and 13 of avoidance.

No differences were found in the amount of responding during either the pre or post periods. Responses made before shock (Figure 9) continued to show a group main effect, F (2, 21) = 11.25, $p < .05$, and the group by week interaction was significant, F (2, 21) = 3.71, $p < .05$. Tests of simple main effects were applied to determine the meaning of the interaction effect. A group effect was found to be significant for week 3 F (2, 21)[4] = 12.94, $p < .05$, and for week 4, F (2, 21)[5] = 8.24, $p < .05$. Follow up analysis on each week indicated that on week 3 the number of responses made by the avoidance animals was significantly greater than either the yoked or control group's, who did not differ. The depression

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[3]The mean square error used in these test represented the pooled error terms of the within and between group factors and degress of freedom as per the Satterthwaite procedure (Winer, 1971, p 530).

[4]See footnote 3.

[5]See footnote 3.

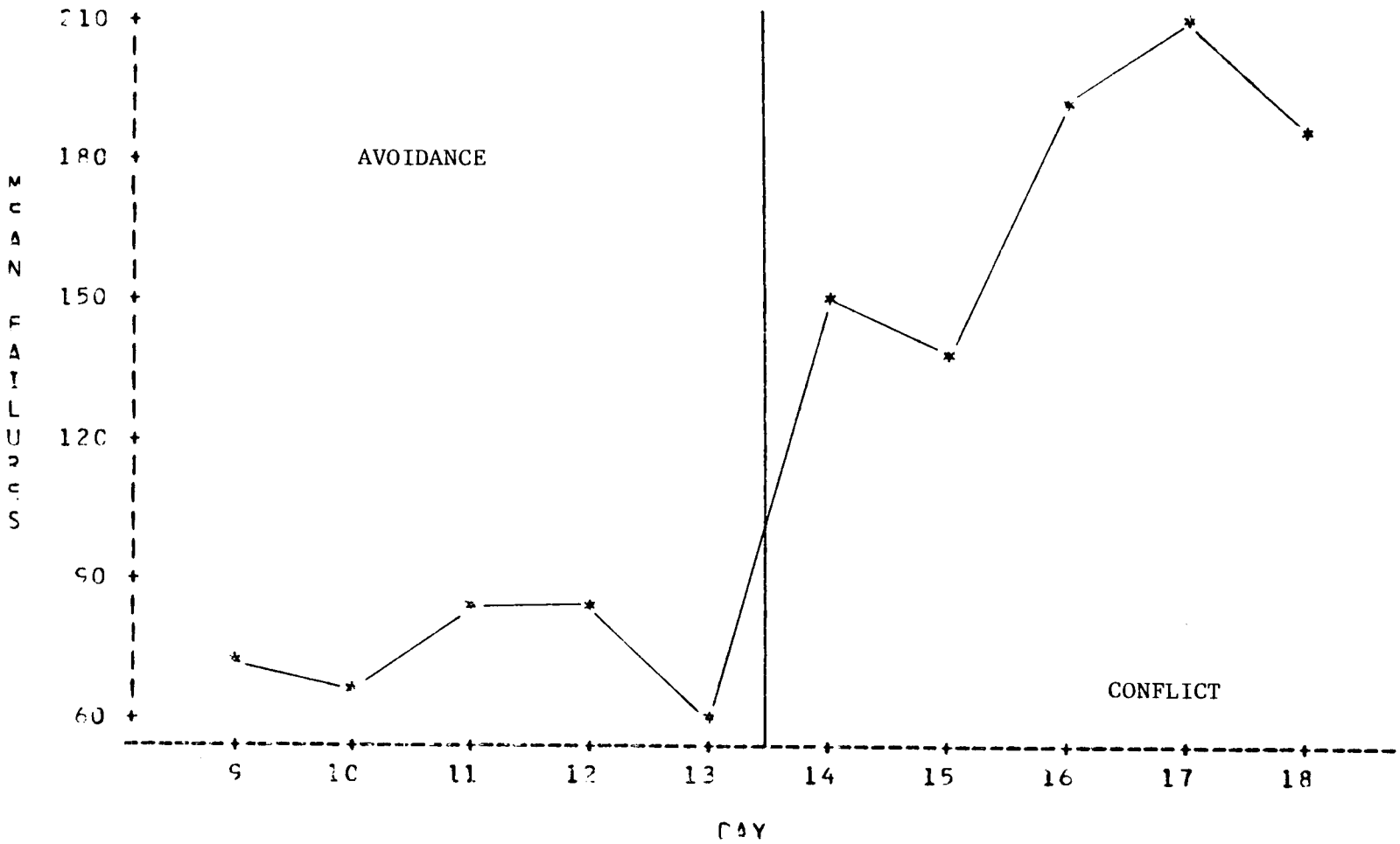

Figure 8. Mean Failure to Avoid Shock by the Avoidance Animal of the Chronic Group During the Last 5 Days of Signalled Avoidance and the First 5 Days of Conflict.

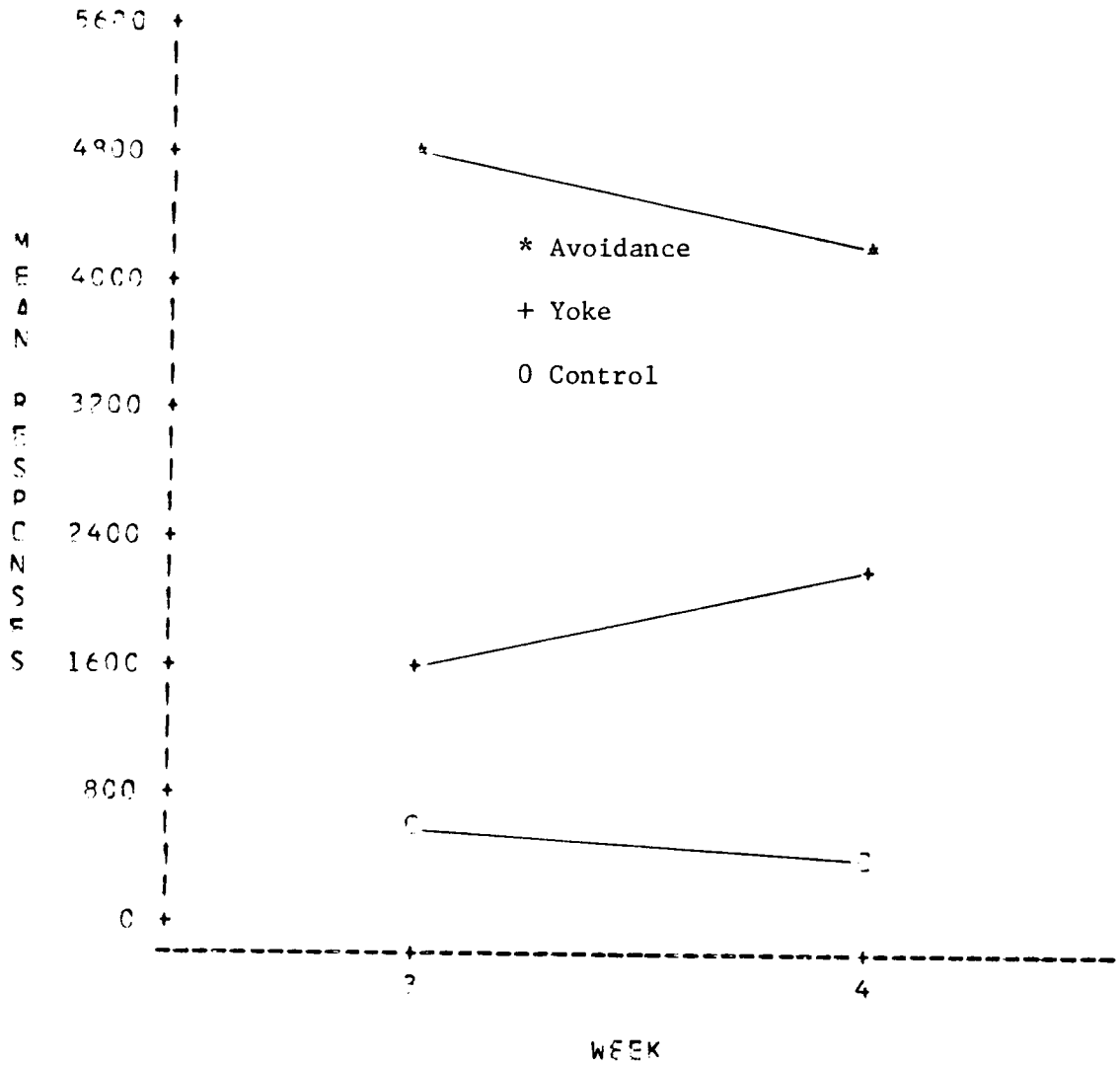

Figure 9. Mean Responses Before Shock by the Chronic Group for the Last Week of Signalled Avoidance and the First Week of Conflict.

in the avoidance animal's responding and increases in the yoke's respondong during week 4 led to a significant difference only between avoidance and control animals.

Figure 10 shows responses during shock for the transition from avoidance to conflict. Despite what appears to be a classic interaction between the avoidance and yoked animals, analysis of variance revealed only a significant group effect, F (2, 21) = 6.10, $p < .05$; the interaction was not even marginal. Both avoidance and yoked subjects responded more during shock than did controls, $p < .05$.

Behavioral Data Weeks 2-11, Avoidance and Chronic Conflict

The long term effect of conflict on the avoidance animals' performance is presented in Figure 11. There was an abrupt distruption of performance with a very gradual but continuous decline during conflict, as indicated by a significant weeks effect, F (2, 14)[6] = 4.55, $p < .05$. A Tukey HSD post hoc test found that from week 5 on, all other weeks had significantly more failures to avoid shock than did the last weeek of signalled avoidance, week 3. Weeks 9, 10, and 11 also had significantly poorer shock avoidance performance than in the first week of signalled avoidance, week 2. No differences existed within the conflict weeks or within the avoidance weeks.

Both week, F (9, 189)[7] = 3.15, $p < .05$, and group, F (2, 21) = 4.19, $p < .05$, effects were found to be significant in respect to the amount of responding in the pre-and post-stress periods over the course

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[6] See footnote 2.

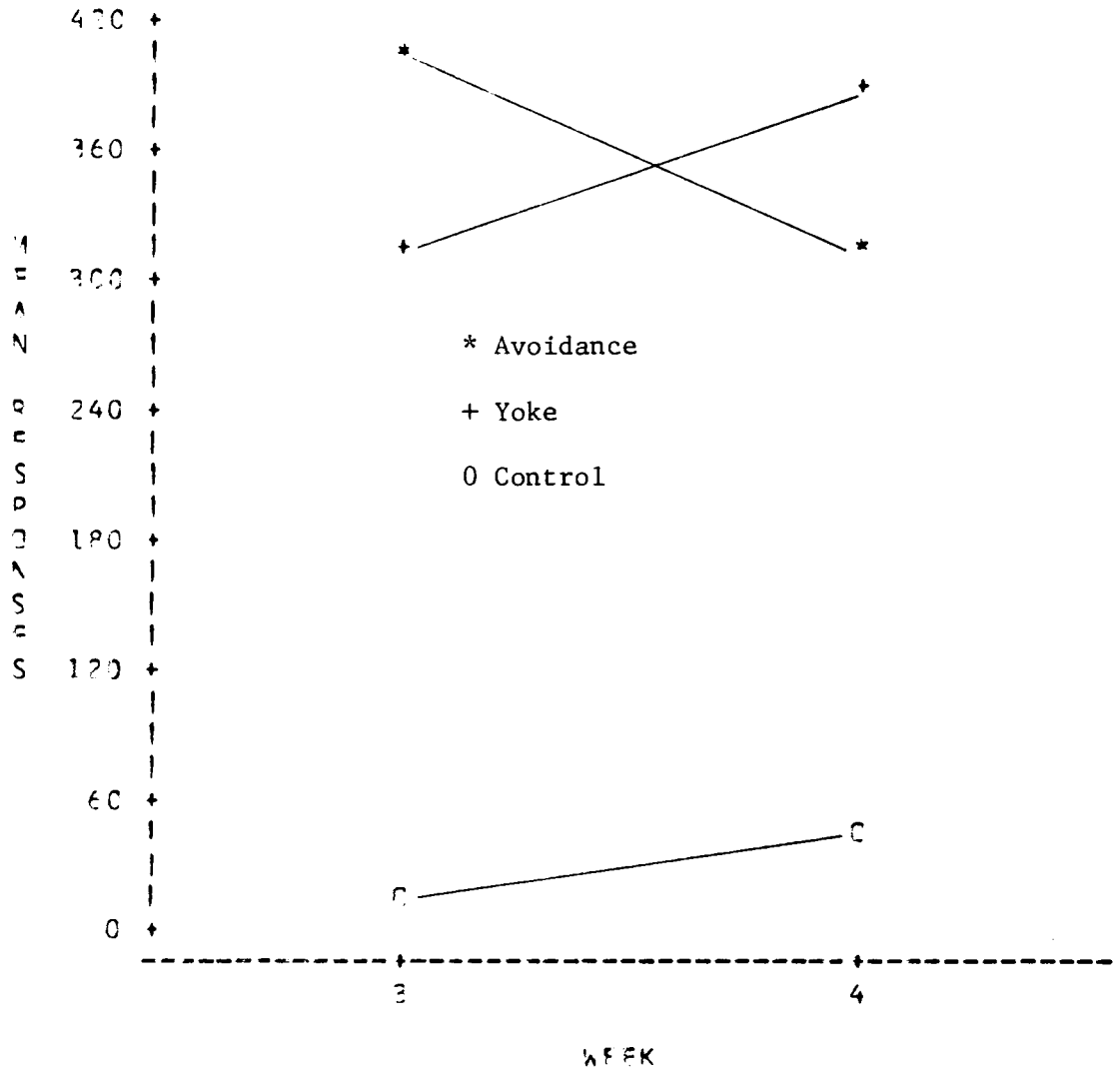

Figure 10. Mean Responses During Shock by the Chronic Group for the Last Week of Signalled Avoidance and the First Week of Conflict.

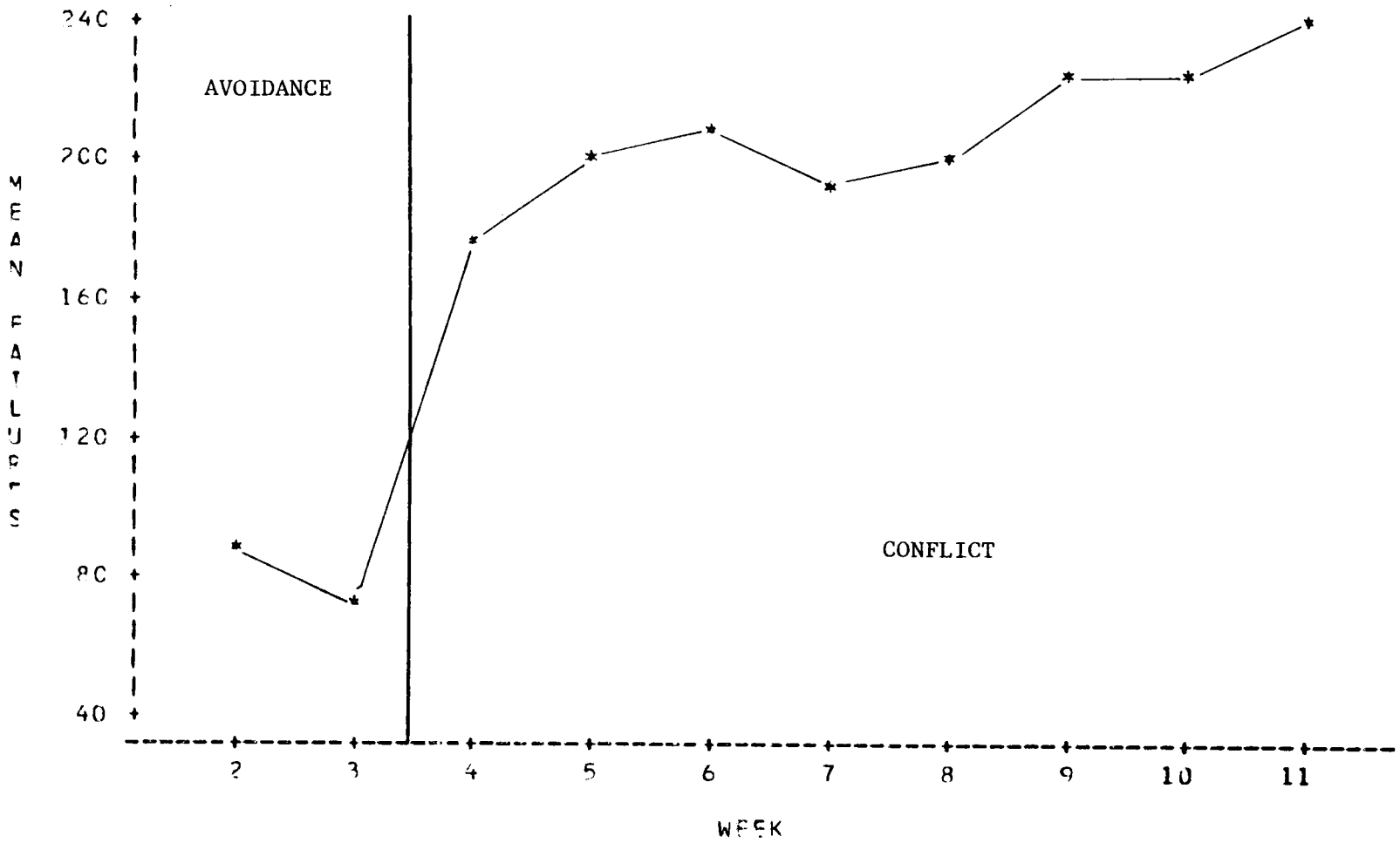

Figure 11. Mean Failures to Avoid Shock by the Avoidance Animal During Signalled Avoidance and Conflict for the Chronic Group.

of the study. Weeks 7, 8, 10, and 11 of the conflict phase, had significantly more total responding than did week 2, the first week in signalled avoidance, $p < .05$. Week 10 also had more overall responding than the last week of signalled avoidance, week 3, $p < .05$. Post hoc analyses indicated that despite a gradual rise in responding over weeks by the yoked group, only the avoidance and control groups showed significant differences in responding during both pre- and post-periods. The avoidance animals showed the greatest activity, the controls the least.

Responding before shock (Figure 12) over the avoidance and conflict phase continued to exhibit significant group differences, F (2, 21) = 8.41, $p < .05$. The group by week interaction failed to reach conventional levels of significance with adjusted degrees of freedom,[8] $.05 < p < .1$. Comparisons between group means indicated that responses before shock were significantly higher only for the avoidance group when compared to the control animals.

Group differences also persisted throughout conflict for responding during shock, F (2, 21) = 4.27, $p < .05$. A group by week interaction was found not to be significant after adjustment in the degrees of freedom.[9] A change in the group response pattern is demonstrated in Figure 13. With the onset of conflict, yoked subjects responded the greatest amount during shock, whereas avoidance animals showed higher

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[7] See footnote 2.

[8] See footnote 2.

[9] See footnote 2.

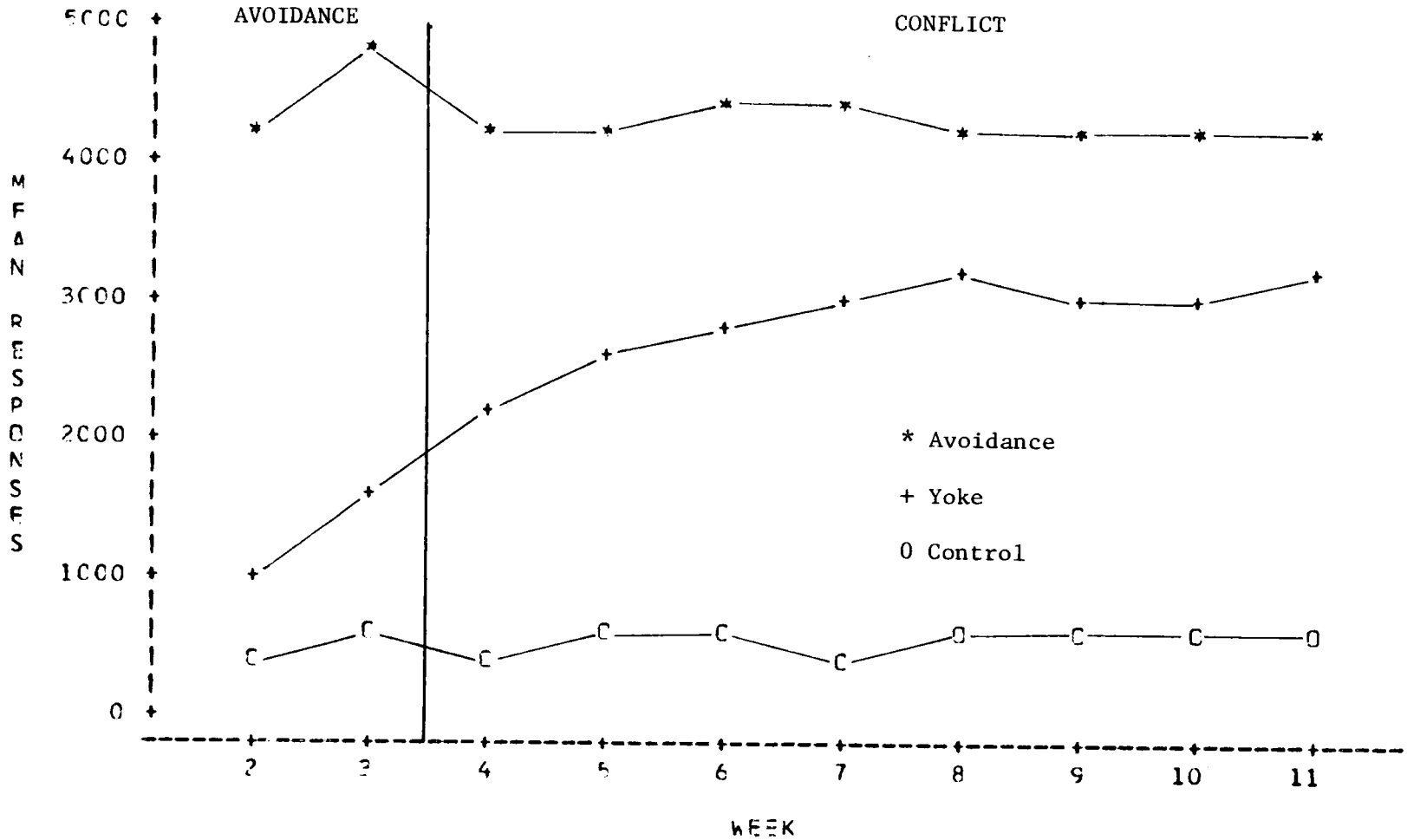

Figure 12. Mean Responses Before Shock by the Chronic Group During Signalled Avoidance and Conflict.

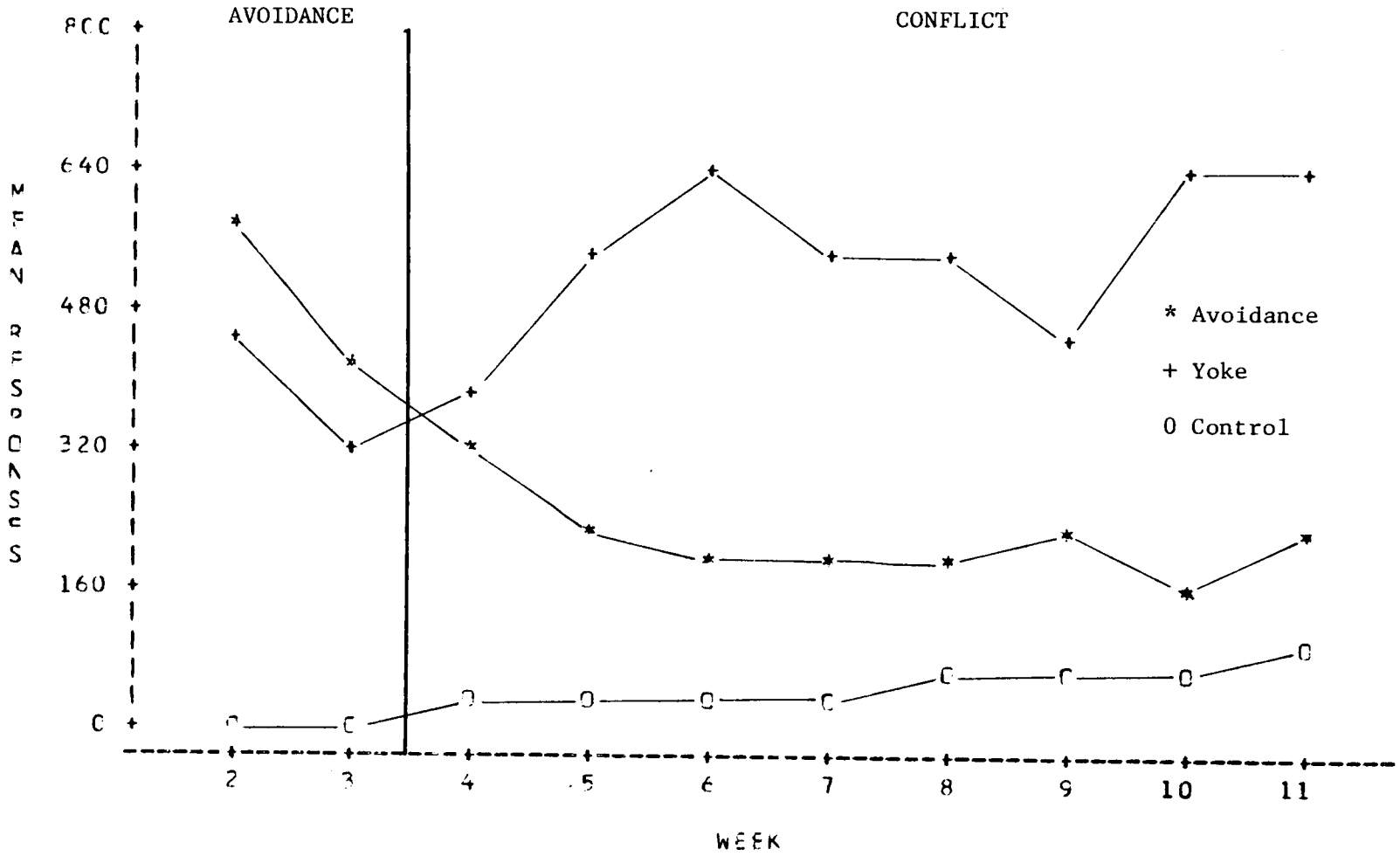

Figure 13. Mean Responses During Shock by the Chronic Group During Signalled Avoidance and Conflict.

levels in the signalled avoidance phase. Yokes, however, were significantly different only from control animals. No statistical difference was present between the avoidance and control subjects. The findings are exactly the opposite of those for the avoidance phase.

Indirect Blood Pressure and Heart Rate Data

Indirect blood pressure and heart rate data for baseline and avoidance conditioning were combined for the acute and chronic groups. As previously mentioned, when animals had been under the same experimental treatment and no significant differences were found due to conditions (acute vs. chronic), it was considered appropriate to collapse across conditions, and thus increase the power of the analyses.

Upon first exposure to the tail cuff procedure for determining indirect heart rate and blood pressure all animals exhibited tachycardia (Figure 14). Subsequent weekly measurements were accompanied by significant reductions in heart rate, F (1, 45) = 5.35, $p < .05$ (Geisser-Greenhouse conservative degrees of freedom). Weeks 3 and 4 showed significantly lower heart rates than those of week 1. A marginal difference was present between week 1 and 2, $.05 < p < .1$. There were no differences between weeks 2-4, nor were there any significant group differences.

Significant systolic blood pressure elevations occurred in all groups (Figure 15) during exposure to signalled avoidance, as demonstrated by significant weeks main effect, F (1, 45) = 17.73, $p < .05$ (Geisser-Greenhouse conservative degrees of freedom). Pressure levels were significantly higher for all groups during the three weeks of

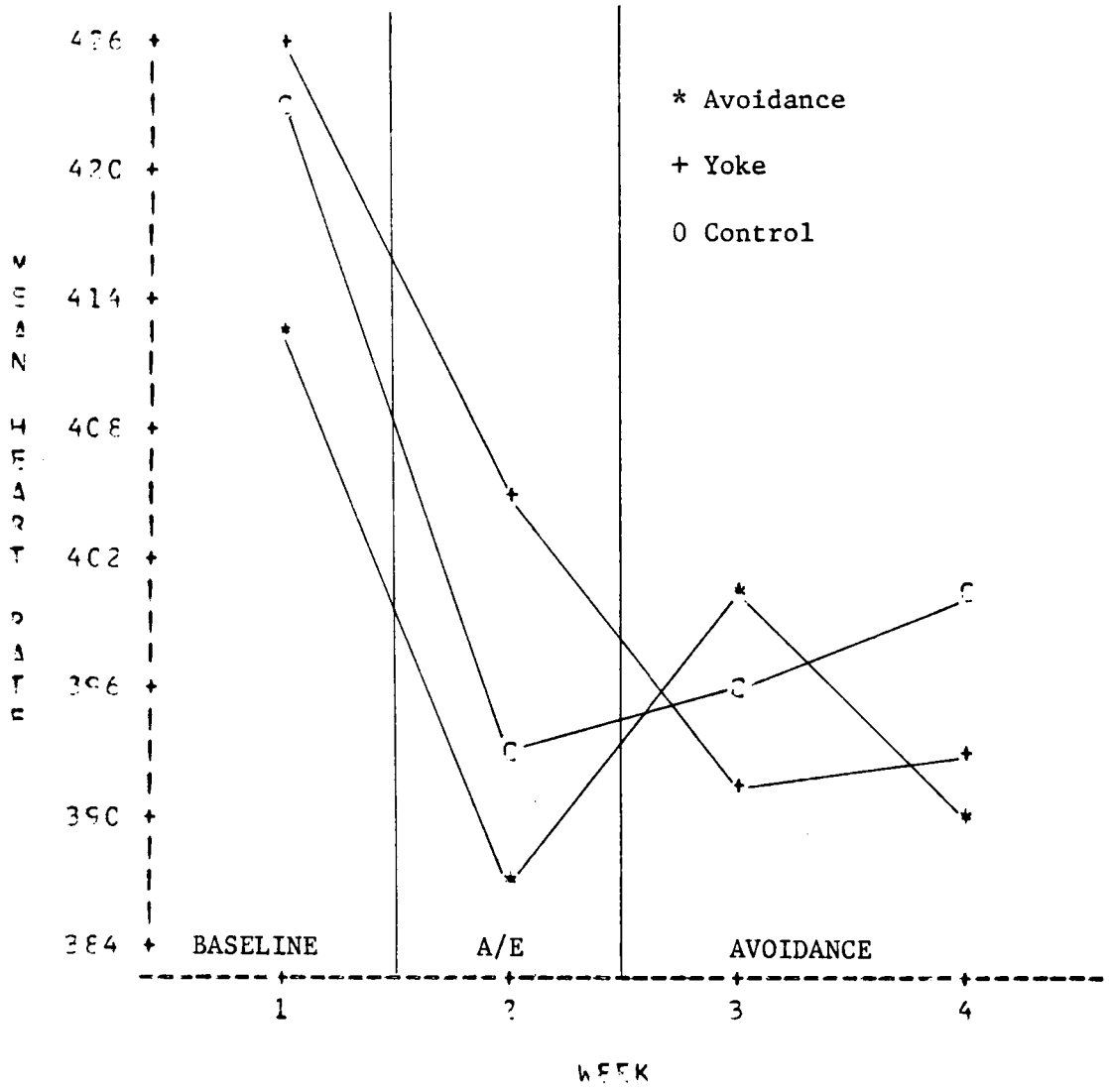

Figure 14. Mean Indirect Heart Rate (BPM) During Baseline Measurement (wk 1), Avoidance-Escape (wk 2) and Signalled Avoidance (wks 3 and 4). Means Represent Combined Acute and Chronic Groups.

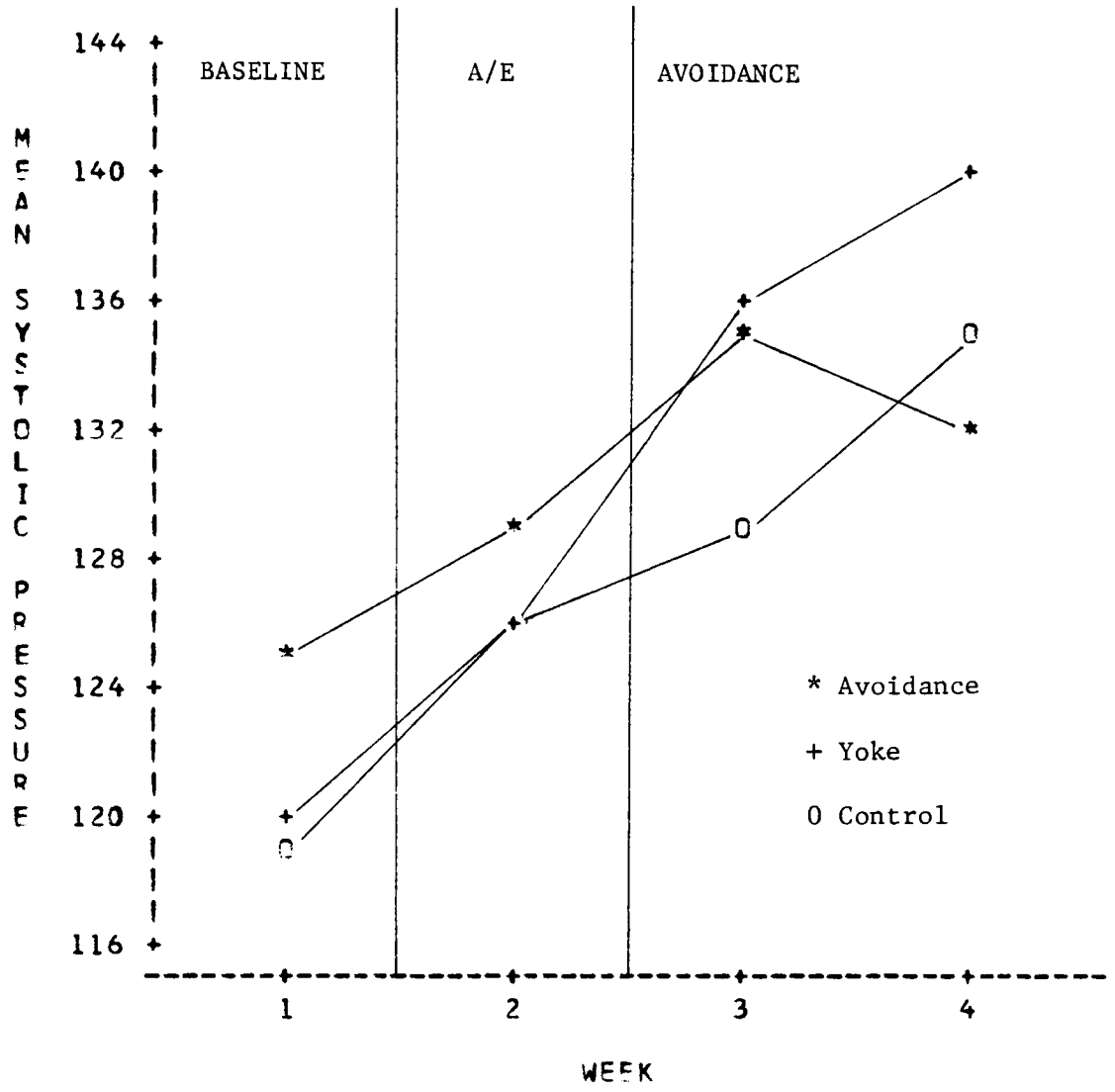

Figure 15. Mean Indirect Systolic Blood Pressure (mm Hg) During Baseline Measurement (wk 1), Avoidance-Escape (wk 2), and Signalled Avoidance (wks 3 and 4). Means Represent Combined Acute and Chronic Groups.

signalled avoidance, as compared to baseline levels. Pressure levels for all groups were higher in weeks 3 and 4 than in the first week of conditioning. No changes occurred from week 3 to week 4.

Changes in the systolic blood pressure of animals exposed to chronic conflict are shown in Figure 16. Significant group, F (2, 21) = 3.59, $p < .05$, and week, F (1, 21) = 10.90, $p < .05$, main effects were revealed by the analysis of variance. A post hoc analysis of the group effect failed to differentiate between the groups when a Tukey HSD test was used. This is a fairly conservative aposteriori test. Duncan's multiple range test, a more liberal test than the Tukey HSD, did uncover group differences, $p < .05$. Both the avoidance and yoked groups displayed significantly higher mean systolic pressures across all weeks than the control group. Mean systolic pressure for the avoidance, yoked, and control groups respectively, across all weeks were 139, 193, 132 mm Hg. However, the mean systolic pressures for the terminal session were 146, 146, and 134 mm Hg for avoidance, yoke, and control groups.

The Follow up analysis on the week main effect indicated that baseline pressures for all subjects were significantly lower than pressures in all but the first week of conditioning. Pressures for all subjects during the first week of conditioning were significantly lower than during weeks 4 and 7-12, all conflict schedule weeks. Group pressures in the second week of avoidance conditioning (week 3 in Figure 16) were lower than during weeks 8 and 9, again both conflict schedule weeks. Finally week 6, the second week of conflict, was significantly lower than weeks 8-10 and week 12.

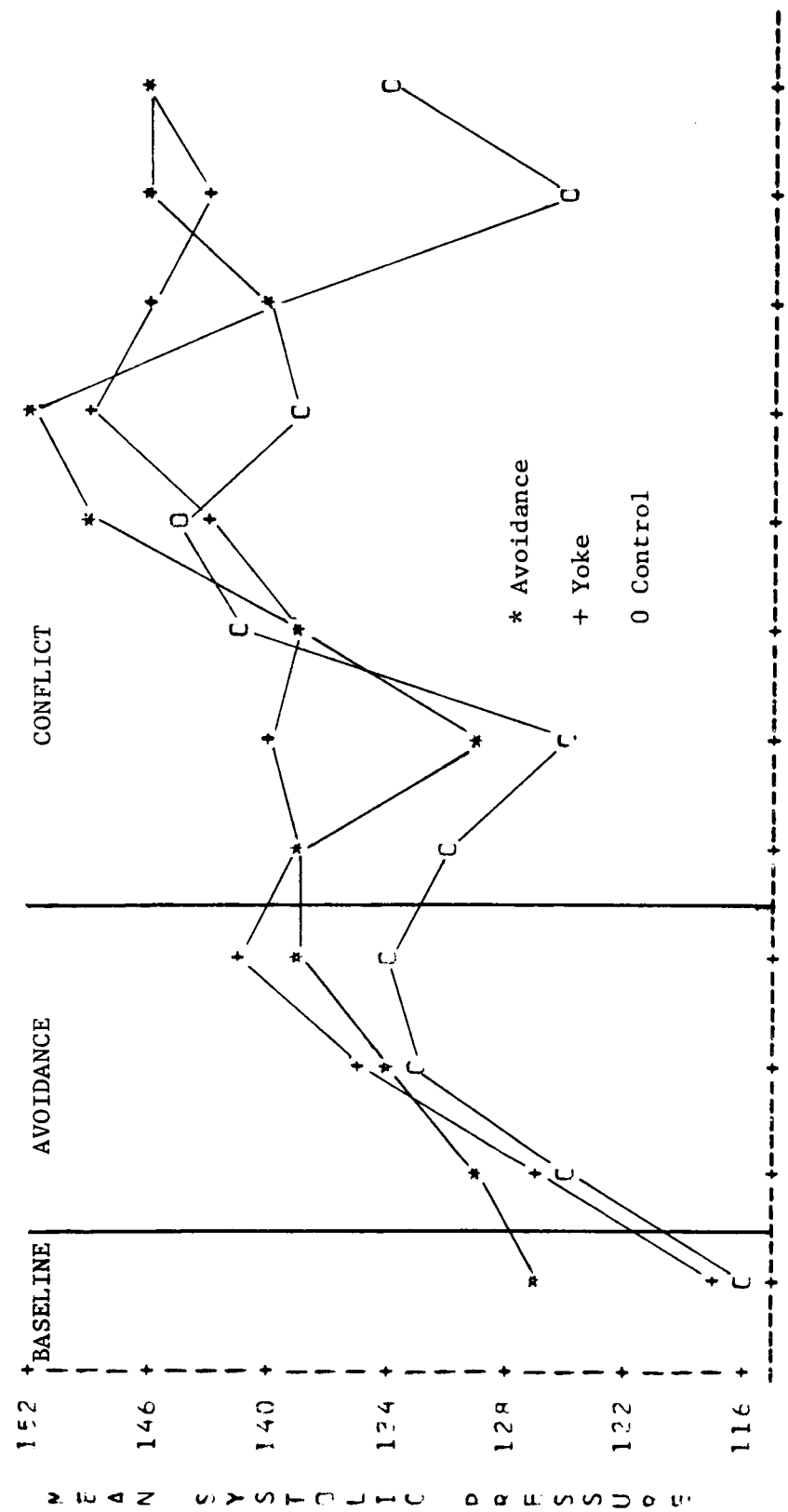

Figure 16. Mean Indirect Systolic Blood Pressure (mm Hg) for the Chronic Group During Baseline, Avoidance and Conflict.

The frequency and significance of hypertensive pressure readings for each group of animals, avoidance, yoked, and control, during the 8 weeks of conflict was determined by use of 2 x 3 chi-square contingency table. With the criterion for the hypertensive reading set at 150 mm Hg, a significant difference in the frequency of hypertensive readings was found between the groups, $X^2 = 11.74$, $p < .05$. Thirty-four percent of the systolic pressure determinations in the avoidance group and 38 percent in the yoke group were equal to or above 150 mm Hg. Only 13 percent of the readings reached this level in the control animals. When the criterion was shifted to 140 mm Hg, consistent with the low end of the borderline hypertension range, 67 and 59 percent of the avoidance and yoked pressure readings were equal to or above this level. The control animals displayed pressure levels in this range half as often, i.e., 30 percent of the time, as avoidance or yoked subjects. These differences are significant $X^2 = 20.05$, $p < .05$ (see Table 3).

Direct Blood Pressure and Heart Rate Data

The data reported in this section are from a single 1-1/2 hour avoidance or conflict session: 15 minutes pre-avoidance (conflict) 60 minutes avoidance and, 15 minutes post-avoidance

Acute Group--Heart rate. The failure to maintain patent catheters in 6 animals precluded collection of blood pressure and heart rate data from these subjects. In addition, a seventh animal was lost due to accidental ether overdose during its first daily catheter flushing following surgery. The following data from the acute group are based upon 6 avoidance, 5 yoked, and 6 control animals.

Table 3

Frequency and Percentage of Indirect SBP Readings for the Chronic Conflict Group During the Conflict Phase for Two Criterion Levels of Hypertension: SBP≥150 mm Hg and SBP≥140 mm Hg

	SBP (mm Hg)			SBP (mm Hg)		
Group	<150	≥150	%≥150*	<140	≥140*	%≥140*
Avoidance	42	22	34	21	43	67
Yoked	40	24	38	26	38	59
Control	56	8	13	45	19	30
	$X^2 = 11.749$ $p<.05$			$X^2 = 20.05$ $p<.05$		

The heart rate changes observed via direct blood pressure monitoring during a single avoidance session following surgery are shown in Figure 17. It is apparent that the heart rate pattern during the pre-avoidance, avoidance, and post-avoidance periods are different for each group. This is substantiated by a significant block by group interaction, F (5, 70) = 3.45 $p < .05$, and a significant block main effect F (10, 70) = 6.07, $p < .05$. A test of simple main effects indicated heart rate in the avoidance animals changed significantly over the course of the session, F (5, 70)[10] = 10.1, $p < .05$. Post hoc comparisons showed that the heart rate during the post-avoidance period was significantly lower than at all other times before or during the session. The changes in heart rate exhibited by the yoked group failed to reach significance at the .05 level, $05<p<.1$. The control group showed no systematic changes throughout the session. Comparison of the pre- and post-avoidance heart rates for the avoidance, yoked, and control groups demonstrated a significant period effect, F (1, 14) = 11.09, $p < .05$, and period by group interaction, F (2, 14) = 7.99, $p < .05$. Tests of the simple main effects indicated that the heart rate for the avoidance group was significantly lower in post-avoidance as compared to the pre-avoidance rate, F (1, 14) = 9.35, $p < .05$. Neither the yoked nor the control groups showed any difference in heart rate from pre- to post-avoidance.

Systolic blood pressure--The stolic pressure of the avoidance and yoked groups increased by 8-10 mm Hg at avoidance on (Figure 18). The yoked group sustained the pressure rise throughout the session as

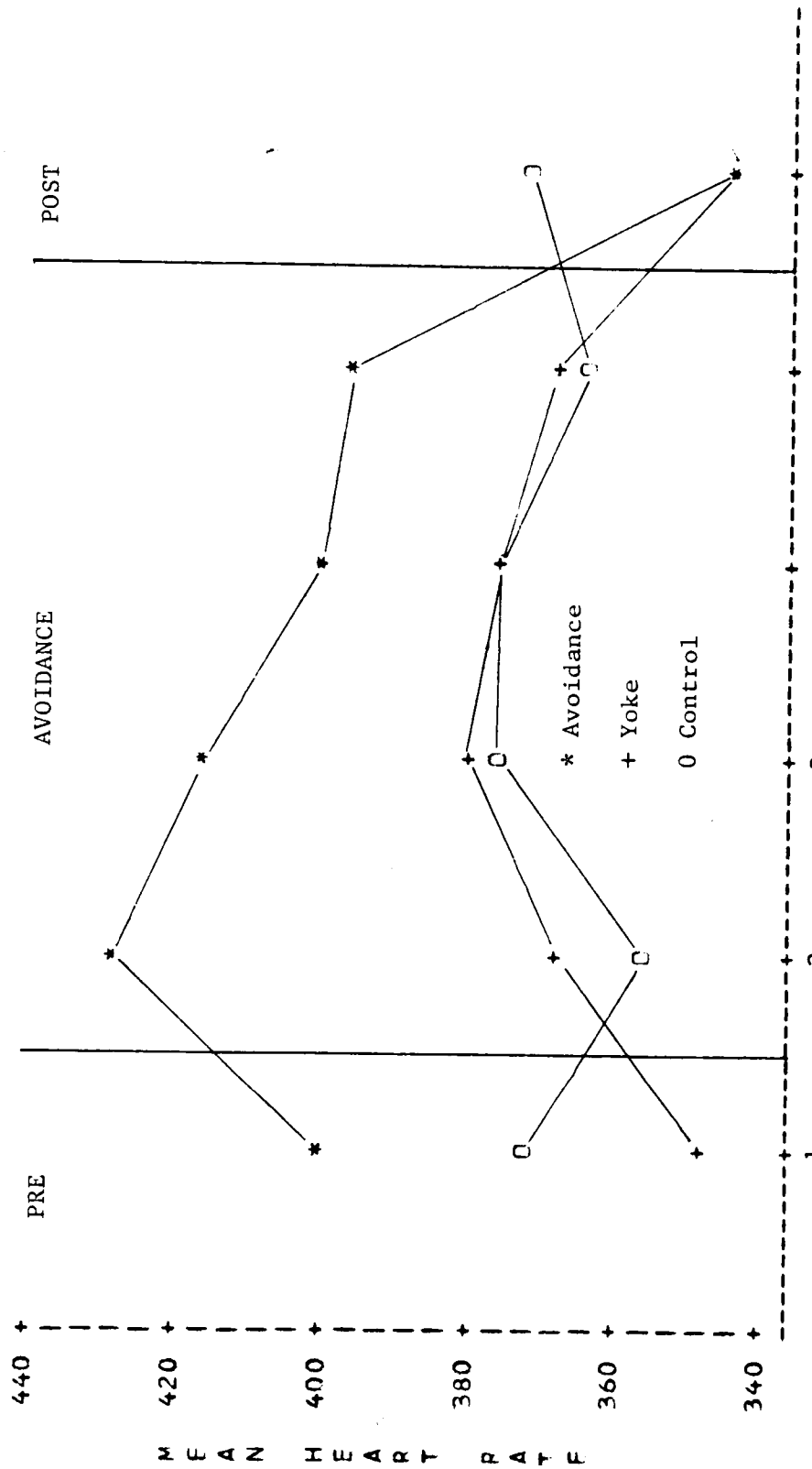

Figure 17. Mean Direct Heart Rate (BPM) During Pre-Avoidance, Avoidance, and Post-Avoidance Periods for the Acute Group. Each Block Represents 15 Minutes.

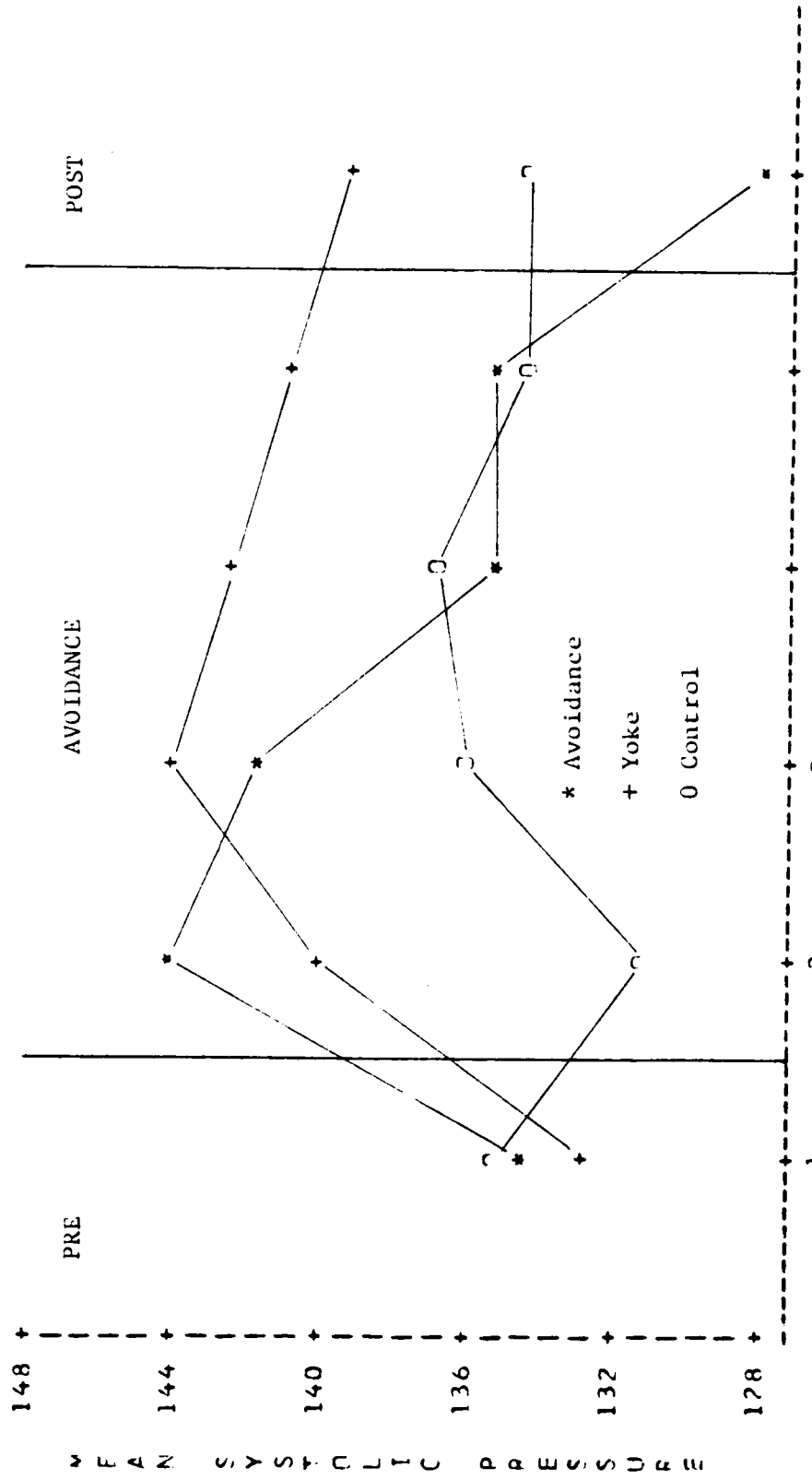

Figure 18. Mean Direct Systolic Blood Pressure (mm Hg) During Pre-Avoidance, Avoidance, and Post-Avoidance Periods for the Acute Group. Each Block Respresents 15 Minutes.

well as during post-avoidance. The avoidance group systolic pressure on the other hand, graually declined toward pre-avoidance levels by the end of the session, and fell below pre-avoidance levels during post-avoidance. These changes were reflected in the significant block effect, F (5, 70) = 4.25, $p < .05$. Significant changes in systolic pressure over the duration of the session were found in both the avoidance and yoked groups, F (5, 70) = 6.75, $p < .05$, respectively. Comparison of the means by Tukey HSD test indicated that the mean systolic pressure of the avoidance group during the first 15 minutes of avoidance was significantly higher than both pre- and post-avoidance, as well as the last half of avoidance. Post hoc analysis of the yoked group's mean systolic pressure revealed that the pressure levels reached during the middle two 15 minute blocks of avoidance were significantly higher than pre-avoidance pressures in the yoked group. They were not, however, different from any other 15 minute block, indicating that pressure rose significantly and was sustained at the increased level.

Diastolic blood pressure--Figure 19 represents the changes in diastolic pressure for the avoidance, yoked, and control groups during an avoidance session. The analysis of variance showed a significant main effect for block, F (5, 70) = 3.71, $p < .05$, and blocks by groups, F (10, 70) = 2.31, $p < .05$. Simple main effects tests indicated there was a significant change in diastolic pressure for the avoidance group over the course of the session, F (5, 70) = 3.99, $p < .05$. The Tukey HSD test indicated that the pressure levels for the first 30 minutes of avoidance were significantly higher than during post-avoidance for this group.

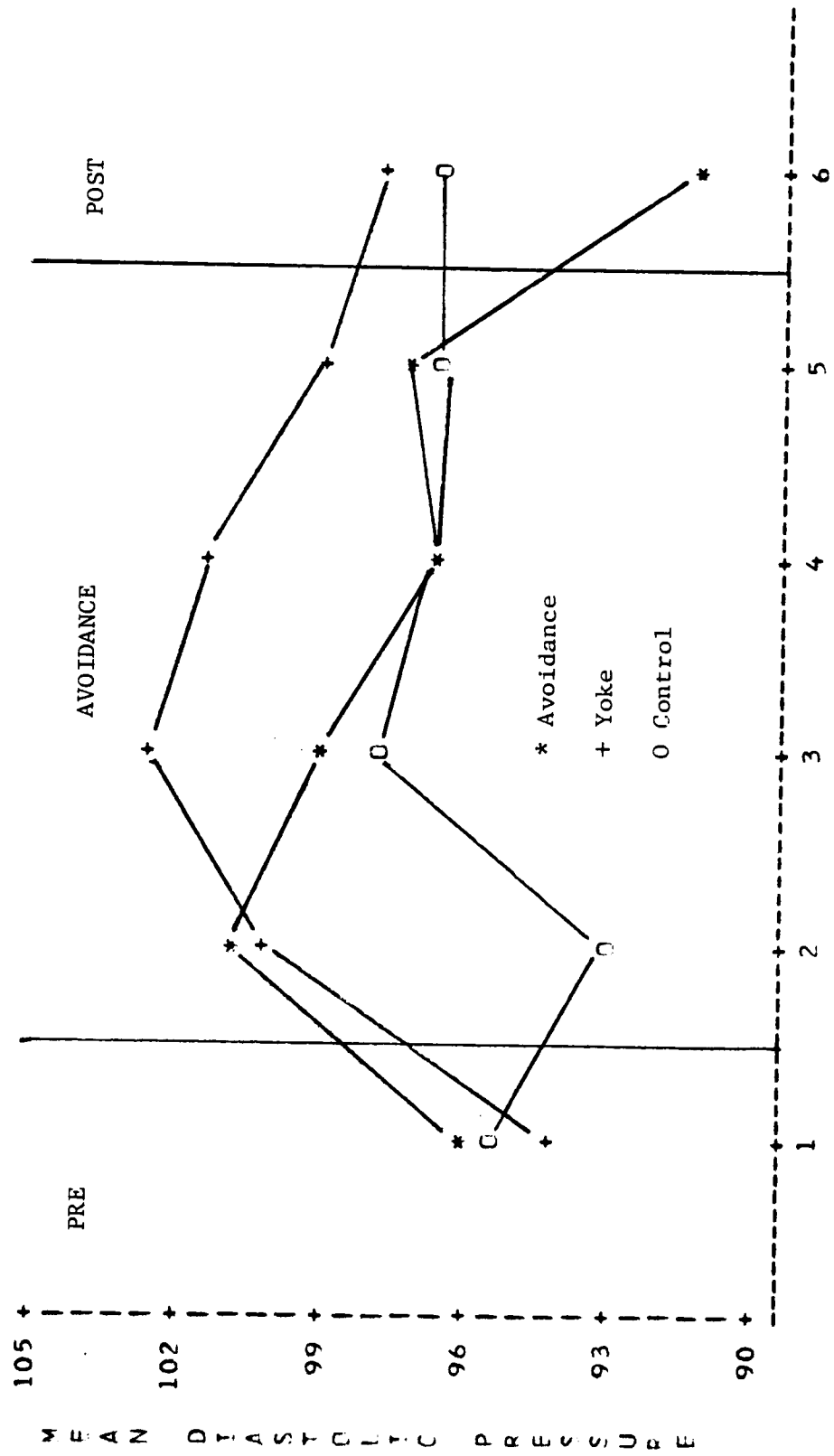

Figure 19. Mean Direct Diastolic Blood Pressure During Pre-Avoidance, Avoidance and Post-Avoidance for the Acute Group. Each Block Represents 15 Minutes.

The yoked subjects also showed a significant change in diastolic blood pressure during the avoidance session, F (5, 70) = 3.90, $p < .05$. Pressure rose to a peak during the second 15 minutes of avoidance, which was significantly higher than the pre-avoidance diastolic pressure. The control group's remained at pressure levels no different than pre-avoidance levels.

Behavioral data during direct monitoring--An analysis of variance was conducted on the response rates of each group with the direct monitoring of blood pressure during the avoidance session. Significant group and period main effects were found, F (2, 14) = 13.59, $p < .05$ and F (2, 28) = 24.12, $p < .05$, respectively. The period by group interaction for response rates was also significant, F (4, 28) = 14.43, $p < .05$. Tests of simple main effects on the group variable, revealed a significant group difference in response rates during the avoidance period, F (2, 14)[11] = 40.57, $p < .05$. Subsequent analysis indicated that avoidance group had a significantly higher response rate than either the yoked or control subjects. A simple main effects test on the period factor for the avoidance group showed a significant difference in response rate over pre-avoidance, avoidance, and post-avoidance. Post hoc tests indicated that responding by the avoidance group is most rapid during the avoidance session (Figure 20).

Chronic Group

The data reported in this section are based on a single conflict session during which direct monitoring of blood pressure and heart rate occurred. Only one avoidance subject failed to maintain a patent catheter,

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[10] See footnote 3.

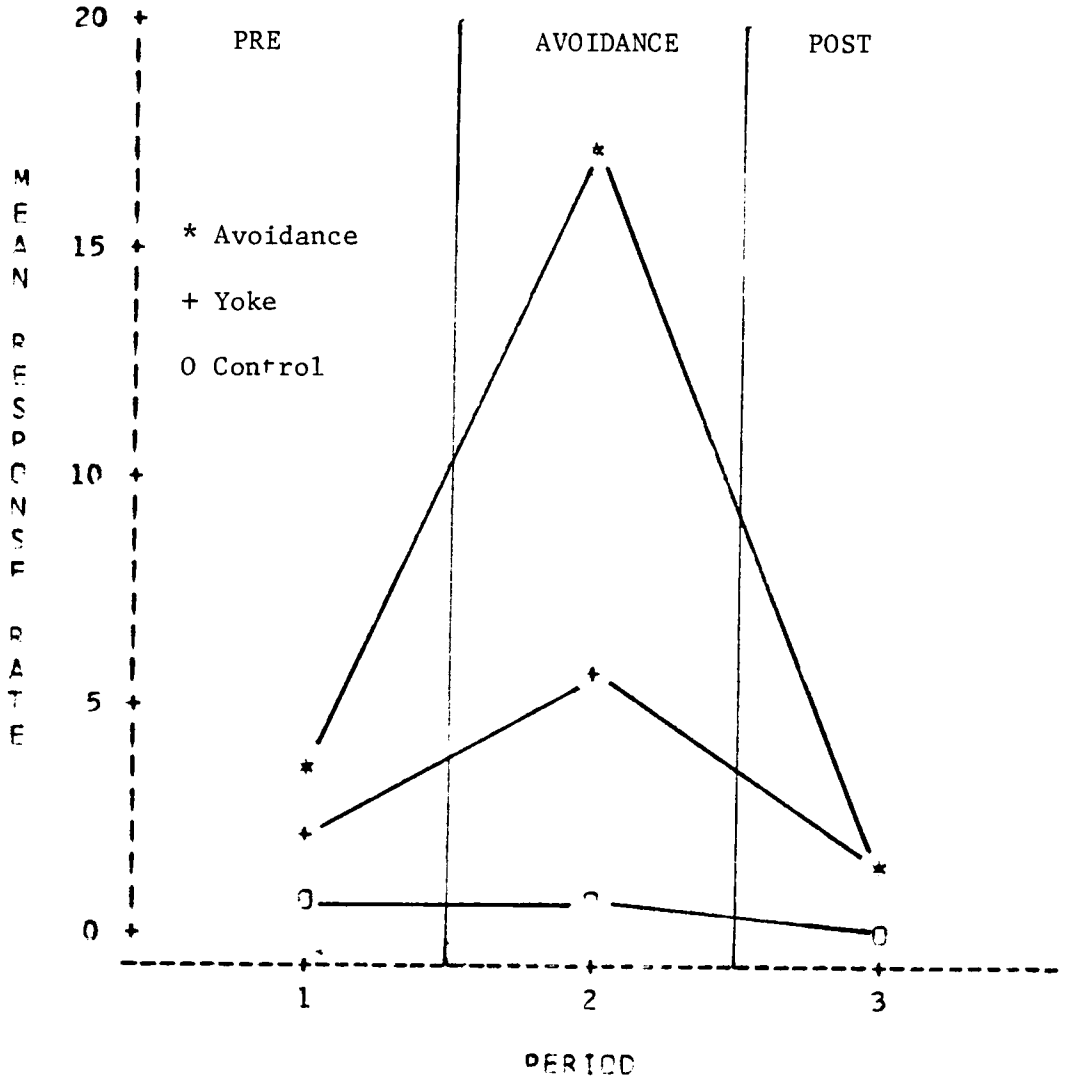

Figure 20. Mean Response Rates During Direct Blood Pressure Recording for the Acute Group.

thus yoked and control groups have 8 subjects each, while the avoidance group has 7 subjects.

Heart rate--As observed in the acute subjects on an avoidance schedule, the avoidance and yoked groups on a conflict schedule respond with tachycardia upon commencement of the stress session, Figure 21. The analysis of variance showed both a block and block by group interaction F (5, 100) = 5.37, $p < .05$ and F (10, 100) = 2.84, $p < .05$, respectively. The group main effect for heart rate was marginally significant $.05 < p < .06$. Simple main effects tests on the blocks variable were significant only for the yoked subjects, F (5, 100) = 9.48, $p < .05$. Post hoc comparisons showed that heart rate in the yoked subjects during the first 45 minutes of conflict was significantly elevated over pre- and post-conflict levels. The heart rate during the first 15 minutes of conflict was, in addition, also significantly higher than the last 15 minutes of conflict for this group. The increase in the heart rate of the control animals during the third 15 minute block was not significant (Figure 21).

Systolic blood pressure--Both the avoidance and yoked subjects demonstrate a dramatic rise in systolic pressure with the initiation of the conflict session (Figure 22). The block main effect and block by group interaction were both significant, F (5, 100) = 5.73, $p < .05$ and F (10, 100) = 2.20, $p < .05$. Tests of simple main effects indicated that only the yoked group showed a significant change in systolic pressure over the conflict session, F (5, 100) = 7.45, $p < .05$. The avoidance group showed marginally significant changes in systolic pressure, $.05 < p < .1$. Comparison of block means showed a significant pressure rise

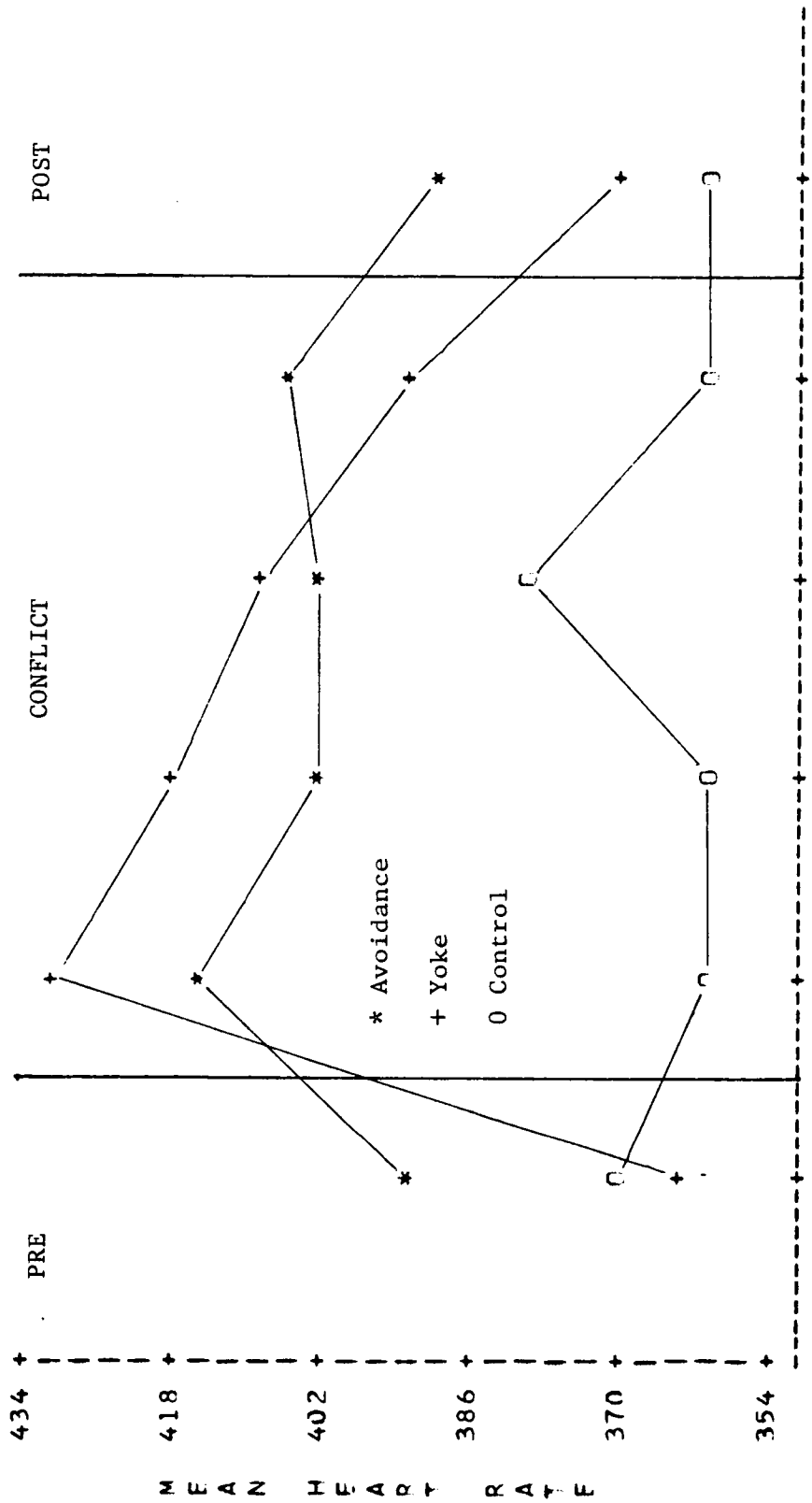

Figure 21. Mean Direct Heart Rate (BPM) During Pre-Conflict, Conflict, and Post Conflict Periods for the Chronic Group. Each Block Represents 15 Minutes.

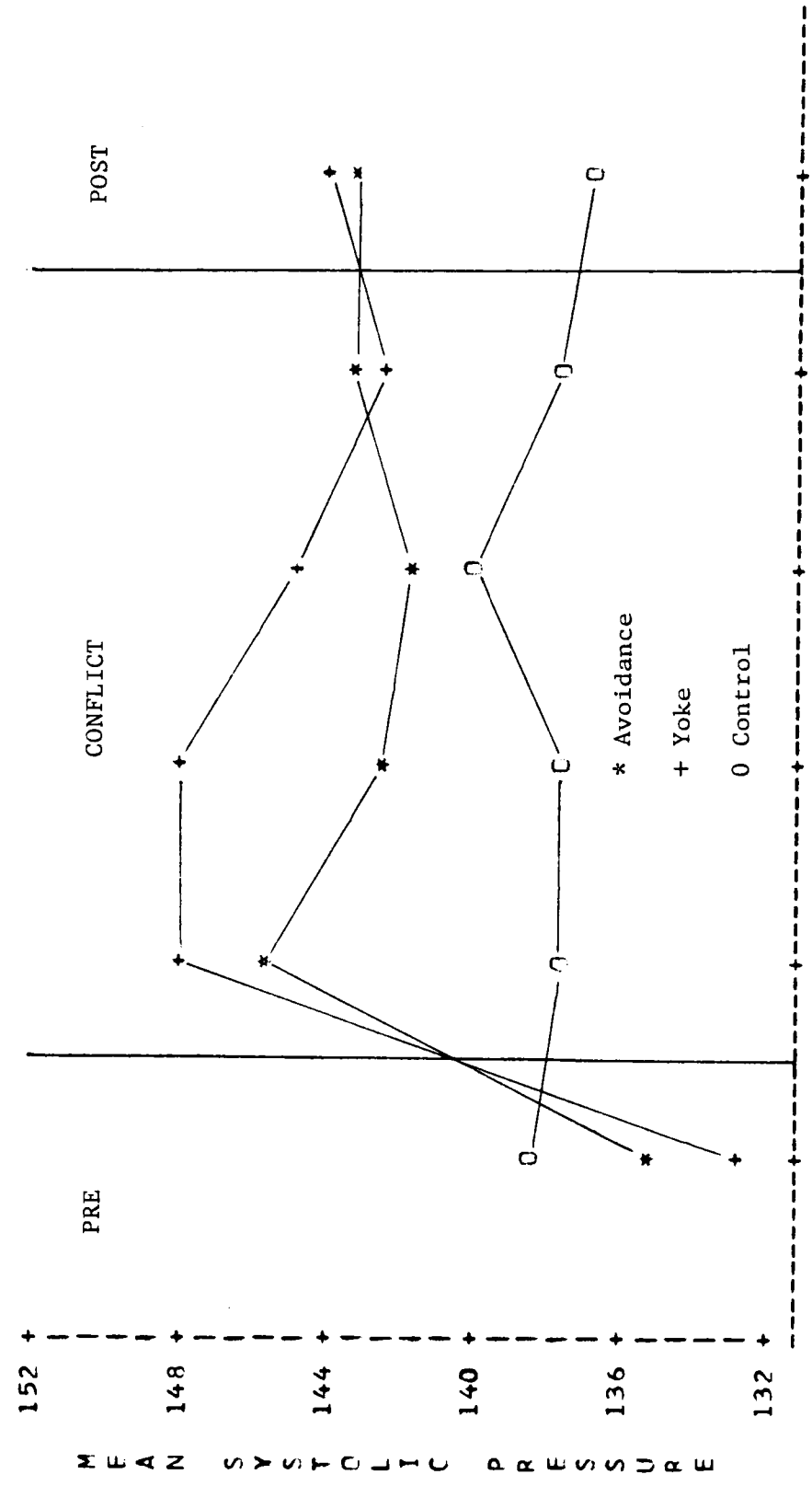

Figure 22. Mean Direct Systolic Blood Pressure (mm Hg) During Pre-Conflict, Conflict, and Post-Conflict Periods for the Chronic Group. Each Block Represents 15 Minutes.

in the yoked animals at the onset of conflict, and the pressure remained significantly elevated for all but the last 15 minutes of the conflict period. Pressure rose again in post-conflict to levels that were significantly different from pre-conflict systolic pressure. Systolic pressure in the control group remained stable across all periods. Comparison of pre- and post-conflict systolic pressures showed a significant period effect, F (1, 20) = 7.42, $p < .05$, indicating systolic pressure for both the yoked and avoidance subjects was higher in the post-conflict period (see Figure 22).

Diastolic blood pressure--Significant block and group by block effects were present for diastolic pressure, F (5,100) = 4.69, $p < .05$ and F (10, 100) = 2.29, $p < .05$. Significant changes in diastolic blood pressure occurred only in the yoked group, as indicated by simple main effects test, F (5, 100) = 6.55, $p < .05$. Diastolic pressure for the first 30 minutes of conflict was significantly higher than during pre-conflict in the yoke group (Figure 23). No other changes in diastolic pressure, for any group, were found to be significant.

Response rate data--As in the acute subjects response rate data were recorded for each group in the conflict condition during direct monitoring of blood pressure and heart rate. Significant differences in response rate between groups and across periods were present.

Post hoc analyses revealed that avoidance and yoked groups responded at significantly higher rates than did the control group. In addition, the avoidance group responded at a significantly higher rate than did the yoked subjects. Post hoc analysis of response rate across periods

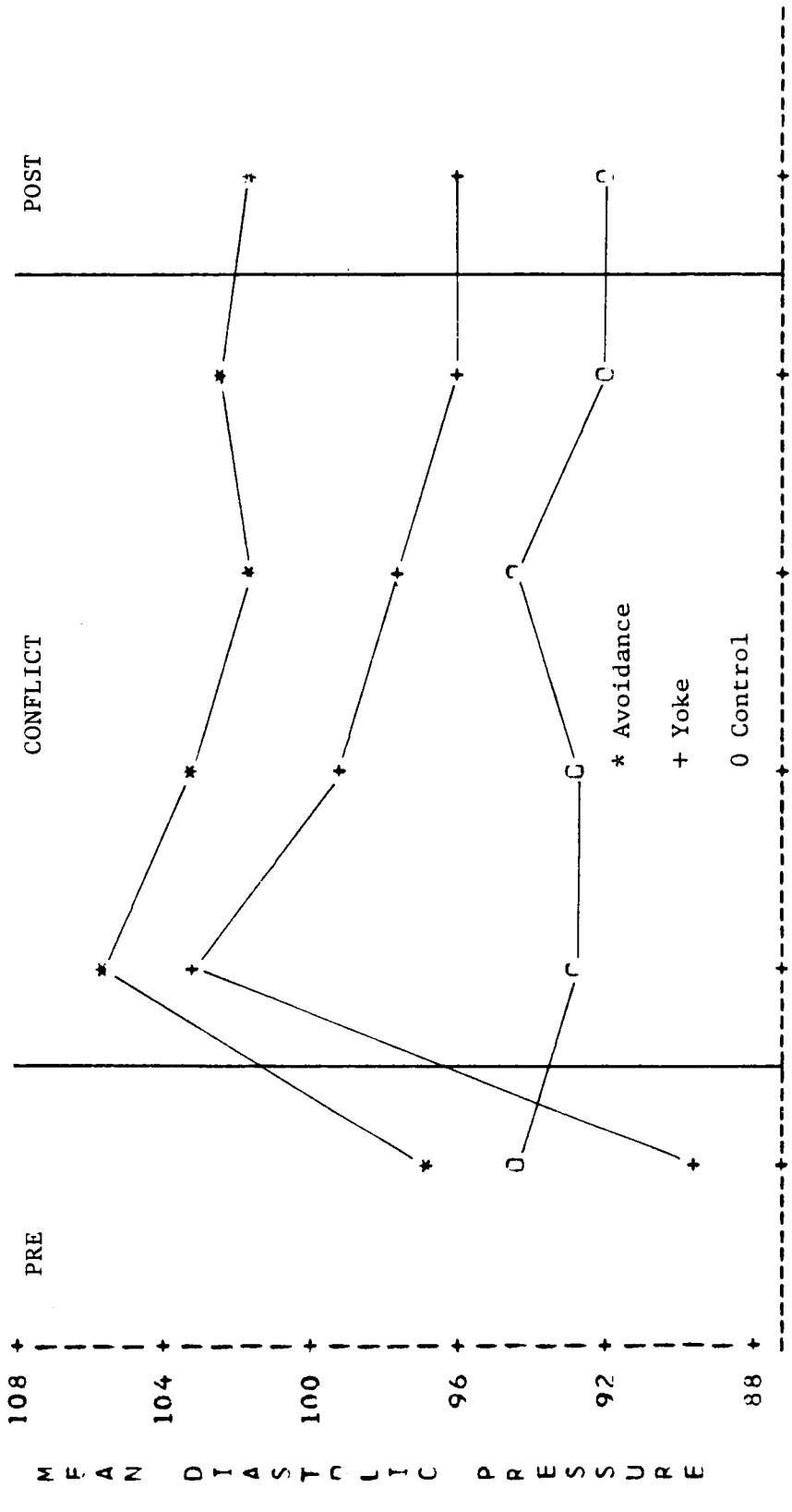

Figure 23. Mean Direct Diastolic Blood Pressure (mm Hg) During Pre-Conflict, Conflict, and Post-Conflict Periods for the Chronic Group. Each Block Represents 15 Minutes.

indicated greater responding for all groups during the conflict period (Figure 24).

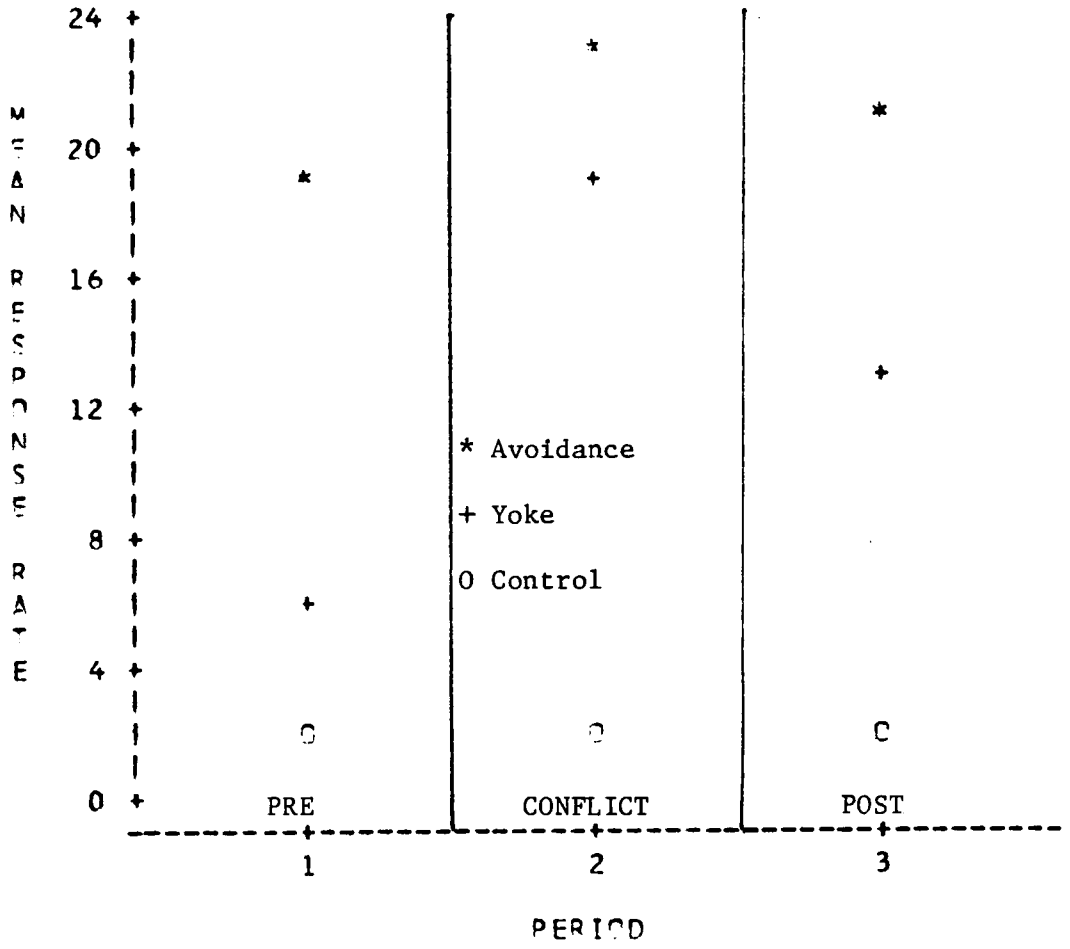

Figure 24. Mean Response Rates During Direct Blood Pressure Recording for the Chronic Group.

CHAPTER V

DISCUSSION

The purpose of this study was to investigate how changes in the predictability and controllability of an animal's environment may effect its cardiovascular system, in particular blood pressure. Short term exposure to a signalled avoidance schedule was employed to determine what difference may exist in the cardiovascular responses of animals able to predict and control their environment (avoidance group) and those able to predict but not control or effectively cope with their environment (yoked group). Additionally, it was of interest to see how reductions in the level of controllability of the environment would effect subjects who initially had substantial control. This was done by the imposition of a conflict situation in place of a signalled avoidance paradigm.

The behavioral data for the avoidance/escape and signalled avoidance phases of the present study indicate that the avoidance group learned to perform the required avoidance response. This was evidenced by the significant reductions in failures to avoid shock by the avoidance group. Additionally, the avoidance group sustained a higher level of activity than either yoked or control groups. This was due to the demand placed on this group to respond in order to avoid shock. The ability to make an effective coping response apparently elicited greater coping behavior.

Although no significant group differences in *indirectly* determined blood pressure or heart rate were found during the short term avoidance phase, the significant rise in pressure for all groups indicates that simply being restrained, as well as having to perform, may be somewhat stressful. The indirect mean systolic pressure at the end of signalled avoidance, shows a trend suggesting that being able to cope effectively does reduce stress. This is evidenced by the display of higher systolic pressure in the yoked group, unable to cope, as opposed to the avoidance group, Figure 15, page 98. The differences in pressure are not large (approximately 10 mm Hg), nor are the absolute pressure levels startling, but the implication for the loss of control as means of producing stress is present. This trend is supported by the findings during direct recording of blood pressure throughout an avoidance session.

The hemodynamic patterns assessed by direct means during signalled avoidance were different for the avoidance and yoked groups. The avoidance group showed significant increases in systolic pressure with avoidance onset. Heart rate and diastolic pressure also rose but not significantly. Over the course of the session all three variables decreased in similar fashion (Figure 17, page 104, Figure 18, page 105 and Figure 19, page 107), and fell below pre-avoidance levels during the post-avoidance period. A similar finding was reported by Lawler et al. (1975). The changes from avoidance onset to post-avoidance were significant for all three hemodynamic variables. Indeed, post-avoidance heart-rate was significantly lower than pre-avoidance levels in the avoidance group. The striking similarity in the direction of response by both systolic and diastolic pressure and heart rate is noteworthy.

The yoked animals, on the other hand, showed no significant change in heart rate throughout the session. Both diastolic and systolic pressures rose significantly above pre-avoidance levels and remained elevated across the session and in post-avoidance.

The gradual decline in blood pressure and heart rate in the avoidance group across the session, as opposed to the sustained increases in pressure for the yoked, may be due to a reduction in stress created by the ability to cope effectively with the situation. On the other hand the initial elevation in all three variables for this group may reflect an exercise response. The avoidance animal usually responded more rapidly at the onset of avoidance than at later stages (personal observation). The reductions in pressure and rate across the session may have been due simply to a reduced rate of responding. The post-avoidance fall in pressure and rate below pre-avoidance levels may have been due to a metabolically induced vasodilation and increased vagal restraint of the heart. However, in the chronic conflict condition, the avoidance group had pre-conflict pressure levels comparable to those of the acute avoidance group during pre-avoidance (Figure 18, page 105, Figure 19, page 107, Figure 22, page 112, Figure 23, page 114) but had a response rate during this period higher than that observed in the avoidance group during the avoidance period. This would argue against a differential exercise effect as being responsible for the avoidance group's hemodynamic pattern.

A second possibility consistent with the data is that responding became more efficient, as the session progressed, i.e., improved

controllability and predictability, which led to reductions in stress. The yoked group however, remained in an uncontrollable environment, and thus experienced a greater amount of stress; hence, sustained increases in blood pressure.

The mechanisms responsible for the hemodynamic patterns of the avoidance and yoked groups were not evaluated. However, some speculation might be made based on the relationship between pressure and rate for each group. As previously noted, there was a striking similarity in the pattern of change in systolic and diastolic pressure and heart rate for the avoidance group. All three variables changed in the same direction and showed remarkably similar rates of decline across the session (see Figure 17, page 104, Figure 18, page 105, Figure 19, page 107). In the yoked group, pressure increased without significant changes in heart rate, and remained elevated during post-avoidance while heart rate was at pre-avoidance levels. The pressure increases in the avoidance group also occur more rapidly than in the yoked group. One might suggest that the increases in pressure in the avoidance group are due to an augmented cardiac output, as reflected in the increased heart rate. This would be consistent with the findings of Anderson and Tosheff (1973) and Lawler et al. (1975), who found that increases in pressure at avoidance onset were maintained by increased cardiac output. The yoked group pressure increases may be vasoconstrictor induced. This would be consistent with the findings of Zanchetti (1977) who found peripheral vasoconstriction in instances of emotional behavior concommitant with physical immobility. As evidenced by the very low response rate during

post-avoidance, Figure 20, page 109, and sustained increase in pressure, the yoked subjects may have been in the emotional state described by Zanchetti, including its associated vasoconstriction.

The behavioral data related to the chronic conflict animals, is indicative of disruption in performance, and at least some loss in control for the avoidance group with the onset of conflict. In addition, the heightened behavioral activity that evolved in the yoked animals across the weeks of conflict may have been due to a reduction in the predictability of the stressor, possibly elicting renewed and more vigorous coping behavior.

The indirect blood pressure data demonstrated significantly increased mean systolic pressure in both the avoidance and yoked animals exposed to chronic conflict. In addition, there was substantially higher incidence of hypertensive blood pressure readings in the avoidance and yoked conflict animals than for controls. Although the pressure-elevations are modest to say the least, Folkow et al. (1973) have suggested that only modest elevations in the functional load faced by the vasculature, may be needed to induce vascular change, and thus enhance the development of permanent hypertension.

The indirect systolic pressures from the final conflict session showed mean systolic pressure of 146, 146, and 134 respectively for the avoidance, yoked and control subjects. However, the pre-conflict pressures recorded by direct means were on the order of 10 mm Hg lower than the indirect pressures. Because the indirect pressures were always recorded after the session it may be more appropriate to compare them to the post-conflict direct systolic pressure. When this is done, the

mean pressures determined for each group are much more similar to the indirect systolic pressure: 142, 143, 137 for direct post-conflict pressures in the avoidance, yoked, and control groups.

The findings on the effects of chronic exposure to conflict on systolic blood pressure would seem to suggest that a single shock delivered upon each avoidance response may come to serve as a safety signal. Inspection of Figure 16, page 100, shows that systolic pressures for the avoidance group in the conflict condition were elevated above those of the yoked group during weeks 4 and 5 of conflict (weeks 8 and 9 overall), followed by a decline in pressure by the end of the experiment to levels comparable to those attained by the yoked group. Although these elevations in pressure were modest and not significant, this pattern of tonic blood pressure response was observed in both replications of the avoidance animals run under these condition. That is, even though half the avoidance animals were run subsequent to the other half, the same blood pressure response pattern emerged for each set of avoidance animals The data therefore tend to support the safety signal hypothesis (Seligman and Binik, 1977) in respect to the type of blood pressure response produced by exposure to chronic conflict.

The direct heart rate and blood pressure patterns after prolonged conflict showed some interesting differences from those observed for avoidance, yoked, and control animals during signalled avoidance. The heart rate changes in the avoidance and yoked groups during avoidance were reversed after prolonged conflict. In the avoidance phase only the avoidance group showed a significant increase in heart rate at the

onset of the stress session. This was followed by a gradual decline to below pre-avoidance levels. In conflict, the *yoked* subjects exhibit a marked increase in heart rate (70 bpm) followed by a gradual fall to the prestress level. The pre- and post-conflict heart rates for the yoked animals appeared to be quite similar to the yoked animals in the acute signalled avoidance condition. The avoidance animal in each condition also had similar pre-stress heart rates, although no statistical comparison has yet been made. However, the avoidance animals in the conflict task showed no significant change in rate during stress or in post-conflict periods, whereas the acute avoidance animals showed a significant decline in heart rate, with a significantly decreased rate in post-avoidance.

The yoked animals in conflict showed significant increases in systolic and diastolic pressure with the onset of the stress session. As in the acute avoidance condition, the yoked subjects sustained these increased pressures across the session, including post-avoidance. The avoidance group in conflict only achieved marginally significant increases in systolic pressure. However the pattern of pressure change for both systolic and diastolic pressure was substantially altered. The avoidance animals no longer show reductions in pressure to pre-stress levels. Increases in both diastolic and systolic pressure, although not significant, were sustained throughout conflict and in post-conflict. Their pressure patterns resembled those of the yoked group. The response rates for the avoidance group were higher in pre-and post-conflict than during signalled avoidance. One might argue that the sustained pressure in

post-avoidance was an artifact of the higher response rate in that period. However, the response rate in pre-conflict was nearly the same as in post-conflict, yet the mean systolic pressure for the avoidance group in pre-conflict was 135 mm Hg but 143 mm Hg during post-conflict. The lower pressure in pre-conflict at a similar response rate to that of post-conflict fails to support an exercise effect.

The results of this study are in agreement with earlier findings reported by Hokanson, DeGood, Forrest, and Brittain (1971) and DeGood (1975) in that the availability of an effective avoidance or coping response appears to reduce arousal during performance on a shock avoidance paraidgm, as reflected by tonic blood pressure and heart rate responses. They are however, at odds with the findings of Obrist et al. (1977), Obrist, Gaebelein, Teller, Langer, Grignolo, Light, and McCubbin (1978), and Manuck, Harvey, Lechleiter, and Neal (1978). The latter studies have reported that the avoidability of a coping response in an aversive reaction time task (Obrist et al. 1977, 1978) or on a cognitive task under conditions of threat and perceived control (Manuck, et al. 1978) produced heightened blood pressure and heart rate responses as compared to other types of stressful situations, including having no control over the aversive stimulus.

In agreement with Manuck et al. (1978) and Obrist et al. (1978), it seems unlikely that physical exertion can account for the types of responses observed in either their studies or the present research. It is not yet clear why the subjects having control in their studies exhibit

greater and more persistent increases in systolic blood pressure and heart rate than do yoked subjects, while just the opposite is found in our research. Difference in species (human versus rats) and the type of task utilized may be two possible explanations, but as yet have not been explored. The duration of exposure to the stress may also provide another possible explanation for the discrepancy in results.

Cardiovascular measurements were taken only during one session of relatively brief duration in both the Obrist and Manuck studies. Cardiovascular monitoring during stress in the present study occurred after many days of conditioning. Therefore, the strigent demands of coping during an initial exposure to stress may indeed be more arousing to the avoiding rather than the yoked subject. This hypothesis receives some support from a recent report by Light and Obrist (1978), who found greater increases in SBP from pre-stress levels in avoidance as compared to yoked subject.

Both Obrist et al. (1978) and Manuck et al. (1978) indicate that such changes in blood pressure and heart rate are observed only under response conditions which are difficult in nature. When responding is too easy, or too hard the cardiovascular responses are reduced in magnitude and duration. It is possible this same circulatory pattern for avoidance animals may have been present during the initial training periods of the present study, when effective coping was more difficult. As conditioning progressed and coping became easier for the avoidance animals, the magnitude and persistence of their cardiovascular responses were reduced in comparison to those of the yoked animals. Recording

of hemodynamic responses in both groups during the first exposures to a signalled avoidance schedule would obviate this question. Until that time the answer remains clouded.

The loss of control by the avoidance animals in the conflict condition appears to be primarily responsible for their changes in blood pressure and heart rate responses. Coping under these conditions became more demanding although not impossible, and may have evoked the type of circulatory response observed by Obrist and Manuck under their conditions of difficult responding.

Yoked animals during the signalled avoidance phase were in a somewhat predictable situation. With commencement of the conflict schedule, there was a further loss of predictability for these animals This may have been responsible for the slight increases in systolic blood pressure levels for this group over those demonstrated during signalled avoidance (see Figure 18, page 105 and Figure 20, page 109). The greater change in blood pressure responses exhibited by the avoidance group exposed to conflict however, implies that the loss of control experienced by this group had a more substantial impact on the cardiovascular system than did the loss of predictability experienced by their yoked partners. Further research will help to clarify this issue.

The blood pressure changes observed in this study have been relatively modest. The use of an inherently normotensive strain of rats may have been responsible for such modest changes (Folkow and Rubinstein, 1966). The findings in the present study are none the less intriguing. It may help in the future to combine the manipulation of stimulus

qualities (predictability and controllability) with a predisposing factor in order to produce larger magnitude changes in pressure. It is to be remembered though, that the process of hypertension is insidious in nature and may start in fact with modest elevations in pressure, i.e., borderline hypertension.

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He was married to Gail Estrade in June 1974. They are possessed by one black cat, Samantha. Allan likes being outdoors whether at the ocean or the mountains. He enjoys playing tennis and basketball. Consumption of good food and wines, combined with the company of close friends, are high on the list of favorite activities.

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