THE EFFECT OF PHYSICAL TRAINING ON THE DEVELOPMENT OF SALT-INDUCED HYPERTENSION IN DAHL SENSITIVE MALE RATS

by

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THE EFFECT OF PHYSICAL TRAINING ON THE DEVELOPMENT OF SALT-INDUCED HYPERTENSION IN DAHL SENSITIVE MALE RATS

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Abstract

The aim of this study was to determine the effect of an aerobic training program on the development of blood pressure changes in male Dahl sensitive (DS) rats on two dietary regimens. All rats were given an initial treadmill education period of 10 days, after which the animals were randomly divided into four groups on two diet regimens. The groups were: Normal Chow Nontrained (NCN), Normal Chow Trained (NCT), High Salt Nontrained (HSN), and High Salt Trained (HST). The normal chow groups received Purina 5001 rodent chow in meal form; the high salt groups received normal chow supplemented with sodium chloride (36 grams NaCl per 964 grams chow). Tap water was provided ad libitum. Trained groups ran on a rodent treadmill at 26.4 m/min at a 5 percent grade for increasing lengths of time, beginning at 7.5 min. per day and reaching 115 min. per day by the end of the 12th week. Direct blood pressure measurements were performed under halothane-nitrous oxide anesthesia after the 4th, 8th, and 12th weeks of the training program.

The training program resulted in significantly lower systolic and diastolic blood pressures ($p < 0.0001$) in both the trained groups as compared to their nontrained counterparts. The training also resulted in significantly slower heart rates and significantly greater relative heart weights than the nontrained groups. Nontrained groups attained greater body weights than the trained groups. Mechanisms involved in the

differences observed were not investigated. The results indicated that physical training acted in some way to reduce the development of salt-induced hypertension in DS male rats on two dietary salt regimens.

Dedication

To Theresa my lover and friend,

This thesis our lifestyle did bend,

We ran all the rats,

I did all the stats,

Now it's finished, we've done it,

THE END.

Acknowledgements

After an experiment of this type, I have many people to thank. First I thank my senior supervisor Marg Savage for her unending guidance, support, and of course (constructive ?) criticism. The lessons I learned "in getting the job done" were invaluable in all respects.

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Lastly I thank my wife Theresa who always kept me going. We made it <u>together</u>!

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A. INTRODUCTION

Up to one fifth of the world's population has been classified as having hypertension. When hypertension has been defined as blood pressure above 160 mm Hg systolic and/or 95 mm Hg diastolic, from 8 to 18 percent of adults have been labelled hypertensive (WHO, 1978). In general, the higher the arterial pressure, either systolic or diastolic, the greater the cardiovascular morbidity and mortality (WHO, 1978).

Depending on the severity of hypertension, as defined by the degree of elevation of the arterial blood pressure, different cardiovascular complications result. Mild hypertension (90-104 mm Hg diastolic) has been primarily associated with increased atherosclerosis. Some of the major complications associated with moderate hypertension (105-114 mm Hg diastolic), have included: increased atherosclerosis, hemorrhagic stroke, congestive heart failure, dissecting aortic aneurysm, and malignant hypertension. Untreated severe hypertensives (115 mm Hg and over diastolic) generally succumb to one of the above mentioned complications (Fries, 1978).

Epidemiological studies have isolated several factors highly correlated to the incidence of hypertension. The World Health Organization (1978) named the following as associated with the occurrence of hypertension: age, race, heredity, weight, the intake of sodium chloride (salt), protein, alcohol, demineralized water, exercise, and psychosocial factors. In addition the WHO (1978) made some "conjectural recommendations" for the prevention of primary (essential) hypertension. These

included: control of salt intake, regular physical activity, control of weight, and the avoidance of prolonged adverse psychological and social conditions.

Epidemiologic studies have emphasized the major role of sodium chloride (salt) consumption in the prevalence and possible prevention of hypertension. Many studies have investigated the relationship between sodium chloride and blood pressure. The presence of genetic predispositions to the hypertensogenic effects of dietary salt has been identified both in animals (Dahl, Heine, and Tassinari, 1962), and in humans (Kawasaki, 1978; Fujita, 1980). It has been suggested that nine to twenty percent of the human population are genetically susceptible to salt-induced hypertension (Tobian, 1979). This postulated genetic predisposition combined with the high level of salt consumption of the modern diet, could be a cause in a large portion of those afflicted with the disease.

The use of experimental animal models has become prominent in hypertension research. Several experimental models of hypertension have been developed (Yamori, 1979). The use of animal models provides several experimental advantages:

1. control of the type and severity of the hypertension,
2. control of the drugs and diet,
3. control of age,
4. control of the number of subjects,
5. control of experimental methods increased.

The variety of experimental models available has allowed the selection of an appropriate model for an experiment based on

previously documented characteristics. Genetic models of hypertension have proven particularly useful as many similarities between rat models and human forms of hypertension have been identified (Yamori, 1979).

A unique experiment designed to prove the existence of a genetically determined predisposition to salt-induced hypertension was performed by L.K. Dahl and his group in the early 1960's (Dahl, Heine, and Tassinari, 1962). Susceptibility and resistance to salt-induced hypertension was selected for by inbreeding Sprague-Dawley rats. The inbreeding of genetically susceptible (sensitive) and resistant rats continued for three generations by which time a definite separation of two distinct strains was apparent; a sensitive strain, which developed fulminating hypertension when placed on a high sodium chloride diet, and a resistant strain, which showed no blood pressure elevation on the same diet. The experiment not only proved the existence of a genetic predisposition to the hypertensogenic effects of salt, but has also provided valuable models for the study of salt hypertension: the Dahl Sensitive (DS), and Dahl Resistant (DR) rats.

In addition to the control of salt intake, the WHO also recommended physical activity in the prevention of primary hypertension (WHO, 1978). Large surveys have shown definite correlations between increased physical activity and lower blood pressure. Montoye and others (1972), surveyed 1700 males over 16 years of age and found that more active men had significantly lower systolic and diastolic blood pressure than more sedentary

men from the same community. Gyntelberg (1977) reported similar results from a study of 5,249 males.

When human subjects have been placed on physical training programs a variety of results have been reported. A general reduction of blood pressure due to training has been reported by several groups (Boyer and Kasch, 1970; Kiveloff and Huber, 1971; Choquette and Ferguson, 1973; Sannerstedt and others, 1973; Bonanno and Lies, 1974; Khomanzink and others, 1978), whereas nonconclusive results have been reported by others (Johnson and Grover, 1967; Hanson and Nedde, 1970). Studies on human subjects in this area have often been complicated by the variability of symptoms and severity of the hypertensive subjects. Most recent research has, therefore, moved towards the use of experimental models of hypertension.

Physical training studies have been performed on several of the hypertension models including: models of genetic, surgical, and pharmacological origin. The most common model used has been the spontaneously hypertensive rat (SHR). With rats as with humans, results have been inconclusive. Overall, the results have suggested that certain forms of training were effective to a limited degree in reducing resting systolic blood pressure. In a recent study Dahl strain females were utilized and preliminary results indicated a substantial systolic blood pressure normalization effect resulting from a treadmill running program (Shepherd, 1981).

A contentious area in the study of blood pressure responses to training in the rat has been the almost exclusive use of

indirect blood pressure measurement. This type of measurement in the rat involves heating, confinement, and often anesthesia, to obtain a measurable pulse in the rat tail. Considerable criticism, particularly with regard to the heating and stress involved, has been made against this indirect method (Bunag, McCubbin, and Page, 1971). Repeated direct blood pressure measurement in a physical training study has yet to be attempted. As a result, only limited data are available on diastolic blood pressure levels which have not been measured indirectly. Several human studies have shown diastolic pressure modification due to training to be particularly responsive (Boyer and Kasch, 1970; Choquette and Ferguson, 1973; Bonnano and Lies, 1974). However the almost exclusive use of indirect measurement, in most rat studies, has left an area of doubt in the results of most hypertensive rat studies obtained up to now.

Aim

The aim of this study was to investigate the effects of physical training on the blood pressure of the DS male rat. Physical training as a modifier of hypertension has been studied in several other rat models, but not in detail in the DS male rat.

The Dahl rat model offered unique characteristics (Folkow, 1977), which with respect to physical training have only partially been explored (Shepherd, 1981). As the DS model is not spontaneously hypertensive, but rather susceptible when induced by dietary sodium, the intensity of the induced hypertension may be partially controlled by the amount of sodium in the diet

(Dahl and others, 1968). The present study investigated two dietary sodium levels, therefore two intensities of hypertension induction, in response to physical training. This served, not only to indicate whether training had an effect on blood pressure, but also at which levels the effect was significant.

Additional physiological and structural data were collected and analyzed to assess differences between the trained and nontrained DS male rat. These included: body weight, food intake, anesthetized heart rate, and wet heart and kidney weights. Blood, kidney, aorta and muscle samples were also collected for later endocrine and histological examination.

The method of repeated direct blood pressure measurement employed in this study had not been previously reported in a physical training study. The feasibility of this method was investigated in the present study.

B. REVIEW OF LITERATURE

Physical training and salt have both been implicated in the pathogenesis of hypertension. The effects of both these parameters have been studied independently. However, little research has been performed on the effect of physical training on salt-induced hypertension. The effect of salt and physical training on blood pressure has, therefore, been reviewed separately in this chapter. Blood pressure measurement methods in small animals have also been reviewed.

For the past two decades several authors have suggested the use of physical exercise or training as an approach to the treatment of hypertension. Although a considerable amount of research has been conducted on the effect of physical training on blood pressure, direct proof of the efficacy of physical exercise in the control of blood pressure has not yet been demonstrated either in human or in animal model experiments.

The study of hypertension has been greatly facilitated by the use of animal models which are similar in some ways to human hypertension. The Dahl rats are of specific interest as they have been developed to be susceptible or resistant (two strains) to salt-induced hypertension (Dahl and others, 1962). Several lines of research have demonstrated characteristics in human hypertension similar to those found in the salt-induced hypertension of the Dahl rats (Fries, 1976; Tobian, 1979).

Salt and Hypertension

Salt or more specifically the sodium ion has become an integral part of the diet of modern man. Salt has been used as a

flavour enhancer and preservative without regard for the potential damage which has been shown to result from excess consumption. Recent research has helped to point out the potential detrimental effects of salt.

A strong case against the ad libitum consumption of salt has developed. Even as far back as the Egyptian era, the priests abstained from salt consumption claiming salt would lead to melancholy, and that abstinence would keep their souls free of perturbations (Weinsier, 1976). More recently, in the past century, emphasis has focused on the role of salt in the pathogenesis of hypertension. Despite many advances in hypertension research the role of salt has remained prominent. As was stated by Page (1974),

> It is ironic that one of the earliest subjects of concern in the treatment of hypertension at the turn of the century was none other than salt and water!

Studies like those of Kempner in the 1940's, showing blood pressure reductions in human hypertensives due to a low sodium diet (Kempner, 1948), have encouraged research in this area.

Evidence gathered in the past thirty years has shown the role of salt to be of major if not paramount importance in the course of hypertension. Investigators have approached this area from several directions including: epidemiological, genetic, hemodynamic, and pharmacological studies (Fries, 1976).

Early epidemiological studies showed that many unacculturated populations had a very low incidence of hypertension. In addition, it was found that blood pressure did not rise with age as was found in western cultures (Meneely and

others, 1953; Dahl and Love, 1954). The low incidence of hypertension was found to correlate with a low dietary salt intake (Dahl and Love, 1954). Later authors studied the blood pressure of the people of the Solomon Islands. Two communities similar in all respects except that one community cooked primarily with sea water the other with fresh water were observed. It was found that, in addition to the cooking water difference, the daily salt consumptions and the blood pressure were quite different. The community that cooked their food in salt water had a 10 percent incidence of hypertension whereas the fresh water cooking was associated with a virtual absence of hypertension (Page, Danion, and Moellering, 1974).

Canadian authors reported a similar situation (Fodor, Abbott, and Rusted, 1973). Two populations on the island of Newfoundland, one coastal and one inland, were found to be very different with respect to the incidence of hypertension. The coastal community had 2 to 3 times the frequency of hypertension. It was found that age and somatotype were not different between the communites, but that dietary salt intake on the coast was considerably greater. Genetic factors could not be ruled out as another source of difference between the communities.

Large intakes of sodium have been associated with an increased incidence of hypertension. It was found that some communities in northern Japan habitually consumed 425 mEq of sodium per day (Takehashi, 1957; Sasaki, 1961). These areas of Japan were shown to have a very high incidence of hypertension

and stroke.

Blood pressure responses were observed in normotensives subjected to extreme dietary salt intakes (up to 1500 mEq per day) over a short period of time. Results showed an increase in blood pressure (Murray and others, 1978). In addition it has been shown that a high salt intake negates the effects of diuretic drugs (benzothiadiazines) in reducing blood pressure (Winer, 1961).

Studies of low dietary salt levels have also been shown to correlate inversely with the incidence of hypertension. When the intake of sodium has been very low, less than 30 mEq per day, there was essentially no hypertension. At slightly higher levels, that is 30 to 60 mEq per day, the incidence of hypertension has remained below 3 percent (Tobian, 1980). In contrast sodium intakes between 90 and 200 mEq per day, as has been commonly found in western societies, have often failed to show a strong correlation with blood pressure levels (Kannel and Dawber, 1973; Simpson, 1979).

Recent work has been able to classify hypertensives based on their responses to dietary salt and diuretic therapy (Kawasaki, 1978; Fujita and others, 1980). It is of interest that the hypertensive response to salt loading has not required the presence of kidneys. Anephric patients, when salt loaded, demonstrated different blood pressure responses based on their previous blood pressures. Previously hypertensive patients developed high blood pressure when salt and water loaded, whereas anephric patients who were previously normotensive

remained normotensive (Onesti and others, 1975).

The variety of results, particularly in the middle range of salt consumption, lead investigators to look at the role of genetic predisposition to the effects of dietary salt. Work in this area lead to the postulate that 9 to 20 percent of people were genetically susceptible to essential hypertension. The susceptible individual would have to restrict salt intake to less than 60 mEq per day to remain normotensive and prevent subsequent hypertensive complications (Tobian, 1980).

In addition to epidemiologic and experimental findings in humans, the effect of dietary salt on blood pressure has also been noted in several different animals including: chickens (Lenel and others, 1948), rats (Sapirstein, Brandt, and Drury, 1950; Meneely and others, 1953; Dahl, Heine, and Tassinari, 1962), dogs (Allen and Cope, 1942; Wilhelmj, Waldmann and McGuire, 1951), pigs (Cohen and others, 1980), and humans. Genetic variability of response has been demonstrated in rats, pigs and humans. In the early 1960's Dahl developed two strains of rats from common Sprague-Dawley stock which exhibited opposite responses to high levels of dietary salt (Dahl, Heine, and Tassinari, 1962). Three generations of inbreeding followed by selective outbreeding, based on the blood pressure response to salt, resulted in two strains, a salt sensitive (DS) and a salt resistant (DR) strain. Since that time the two strains have served as useful models in the study of salt-induced hypertension.

When DS male rats have been maintained on low salt diets (0.3 percent NaCl), growth alone resulted in increased systolic blood pressure over a 14-week time period. The rise in systolic pressure, as measured indirectly, was from 115 mm Hg to 145 mm Hg over 14 weeks. The DR strain showed a smaller systolic blood pressure change with growth, from 115 mm Hg to 125 mm Hg on the same diet (Tobian and others, 1979). Data specific to the Dahl rats on the changes in heart rate with age could not be located in the literature.

Several factors have been identified which influence the development of the hypertensive process in the DS rats. Dahl and others (1968), reported that the age at which the DS rats were started on a high salt regimen was a significant feature in the later development of hypertension. It was found that starting high salt at weaning, 3 months, and 6 months post weaning altered the hypertension development. The authors stated that "among rats with a genetic predisposition to hypertension, a high NaCl diet intake started when the animal was mature still led to the development of hypertension and death ... delaying the high NaCl intake resulted in a more slowly developing less fulminant type of hypertension" (Dahl and others, 1968). Increases in the amount of salt in the diet also increased the rate of hypertension development, pressure attained, and mortality of the DS rats (Dahl and others, 1968).

Potassium was found to exert a protective effect when combined with a high sodium diet (Meneely, 1957). The rate of blood pressure rise and the pressure attained were found to be

inversely related to the potassium/sodium ratio in the diet (Dahl, Leitl, and Heine, 1972). Recently, Goto, Tobian, and Iwai (1981) found that the DS rats have a much more pronounced blood pressure pressor response to intracerebroventricular hypertonic saline and angiotensin II than DR rats. Further it was found that increasing the dietary potassium intake (either KCl or K-citrate) of DS male rats reduced the pressor response to intracerebroventricular hypertonic sodium and angiotensin II almost to the level of DR rats. The authors stated that this effect might explain part of the protective action of dietary potassium in DS rats.

Diuretic drugs (chlorothiazide) have been shown to be effective in preventing the development of hypertension in the DS rats on a high salt diet (Tobian and others, 1979).

Even though the development of the Dahl rat strains was based on a single hypothesis the models have shown a multitude of divergent characteristics. Early work demonstrated that the kidney was a prominent factor in the hypertension process. Cross-strain transplantation studies, that is when DS kidneys where transplanted to DR rats or the reverse, demonstrated that the sensitivity or resistance to salt-induced hypertension tended to follow the kidneys. DS kidneys transplanted to a DR rat made the rat sensitive to salt, and DR kidneys transplanted to hypertensive DS rats reduced the hypertension (Dahl, Heine, and Thompson, 1974).

Investigation also suggested a circulating hormonal factor of some kind. Parabiotic experiments, in which a grafted area

joined two animals, demonstrated a transfer of some factor from a DS to a DR rat which caused the blood pressure to rise in the DR rat (Dahl, Knudsen, and Iwai, 1969). It was suggested that a circulating substance from the kidney produced this effect. In more recent work a natriuretic factor (deWardener, 1980), and a anti-natriuretic factor (Tobian and others, 1979), have been postulated as factors in the hypertensive response of the DS rats. The kallikrein-kinin vasodepressor system has been suggested as another factor important in this model. It has been found that the DS rats have a very much lower level of urinary kallikreins than did the DR rats (Carretaro and others, 1978). The absence of this diuretic, natriuretic, vasodepressor has been postulated as a causal factor in the hypertensive process.

Recent work with the isolated DS and DR kidneys have demonstrated some intrinsic differences in sodium excreting capacities. It was found that the pre-hypertensive DS kidney was much less (about 50 percent) able to excrete sodium. This shift to the right of the pressure-natriuresis curve resulted in the isolated DS kidney excreting much less sodium at a given arterial pressure than the DR kidney. The isolated DS kidney must, therefore, have an increased arterial pressure to excrete a similar sodium load compared to the DR kidney (Tobian and others, 1978).

Genetic studies have suggested that the source of the salt sensitivity lay in two to four genetic loci (Knudsen and others, 1970). Marked sex differences were found in the development of hypertension and the blood pressure level attained. The male was

shown to develop hypertension much more rapidly and reach a higher blood pressure level than the female. It has been found that castration of the male did not alter this process, however castration of the female resulted in a similar pressure response to that of the males (Dahl and others, 1975).

The sympathetic nervous system must be intact for the development of hypertension as was demonstrated by the prevention of salt-induced hypertension in the DS rats with 6OH dopamine sympathectomy (Takeshita and Mark, 1978). Gordon, Matsuguchi, and Mark (1981) found that prehypertensive and hypertensive DS female rats exhibited an impaired baroreflex function which augmented responses to pressor stimuli. The authors speculated that this defect might "contribute to the development of salt-induced hypertension in the Dahl strain".

It was also found that stress in the form of: electric shocks, bright lights, loud noise, and crowding failed to alter the course of hypertension compared to controls on the same diet (Dahl and others, 1968a). A behavioral study showed the pre-hypertensive DS rats to be less explorative when exposed to a new environment compared to DR rats (Welner and others, 1968).

Evidence gathered from many types of research and several animal models, most notably the Dahl rats, have helped to clarify the importance of dietary sodium in the course of hypertension. Many important areas remain to be elucidated. Early identification of those people sensitive to the hypertensive effects of salt may increase the effectiveness of diet and lifestyle modification in the prevention or reduction

of hypertension.

Physical Training and Hypertension

The past two decades have witnessed an increasing amount of attention toward the potential benefits of physical training in the reduction or prevention of hypertension. Several factors have made physical training a welcome approach to the management of hypertension. Factors such as the reluctance to use pharmacological products (Morgan, Carney, and Myers, 1980), and the increasing popularity of physical fitness, have made physical training a desirable alternative to drugs (Black, 1979). From the practitioners point of view, however, more definite proof of the efficacy of physical training has been needed (Denolin and Mallion, 1977).

Many methods have been used in the search for relationships between blood pressure and physical activity, training, and fitness. However, problems have arisen in the search. In human studies problems such as insufficient numbers of subjects, variation in the type or intensity of the training, and variability of the subjects' symptoms, have made interpretation difficult. In general, the research has been grouped into several types, including mass survey studies, human training studies, and animal model training studies. Each method has provided valuable information on this problem.

Montoye and others in 1972, reported a large survey of the males of a small North American community. Eighty-two per cent of the population, which consisted of 1696 males between 16 and 64 years of age, participated in the study. The testing methods

used included a questionnaire, an interview, and a medical examination. Daily activity levels were calculated on the basis of daily energy expenditure in order to divide the subjects into three groups: least active, intermediate, and most active. Within the community, the least active men had the highest mean blood pressures, both systolic and diastolic. When grouped according to age, it was found that within each specific age group, the mean blood pressure was highest in the least active and lowest in the most active men. It was concluded that "physical activity and body fatness are each clearly related to blood pressure, the former inversely and the latter directly".

In 1977, Gyntelberg reported a similar survey. This survey involved 5,249 males aged 40 to 59 years of age. All were employees of large enterprises in Copenhagen. The methods included: an interview, a questionnaire, blood pressure measurement, height and weight measurement, and an indirect maximal oxygen consumption measurement. The author reported a highly significant correlation between physical fitness and systolic and diastolic blood pressure. Gyntelberg went on to suggest that, from a preventive medicine point of view, there were benefits from an increase in physical fitness and a decrease in mean body weight. The author also stated that a causal relationship seemed to exist between elevated blood pressure, body weight, and physical fitness.

Several studies have been conducted on the blood pressure response of human subjects, both normotensive and hypertensive, to physical training. The results have shown reduction of blood

pressure in some cases. These results have, however, been somewhat equivocal. In 1967, a study of the responses of four hypertensive male subjects, over a six week progressive training program on a treadmill (3 times per week, work to exhaustion in approximately 35 minutes), were reported by Johnson and Grover. Their findings indicated that blood pressure was not reduced by training. The authors speculated that the results had been affected by the use of sustained hypertensives rather than labile hypertensives. They also suggested that the training program itself might not have been of sufficient intensity to exert an effect. With a sample size of four, little in the way of conclusions were possible.

In 1970, Boyer and Kasch conducted a more extensive study. The subjects (male, 35-61 years) trained for six months at 60 to 70 percent of their age related maximal heart rate. The training sessions were held twice per week. Subjects included 22 normotensive and 23 hypertensive males. Over the training period, diastolic pressures of the hypertensive group decreased 2 to 30 mm Hg (mean decrease 11.8 mm Hg), while the normotensives exhibited a mean decrease of 6 mm Hg. Only the hypertensive subjects recorded a decrease in systolic pressure, a mean decrease of 13.5 mm Hg over the course of the training. The authors suggested the vasodilating effect of endurance exercise might have been the cause of the blood pressure changes.

Hanson and Nedde (1970) published preliminary observations of physical training on six hypertensive male subjects (30-54

years, nonobese, nonsmokers). Downward trends were found in both systolic and diastolic blood pressures as a result of the training (one hour of various activities such as: muscle stretching and flexibility exercises, isometric-isotonic maneuvers, distance running, and competitive sports) three times per week for seven months. The number of subjects was insufficient for the differences recorded to reach statistical significance. The authors suggested the course, severity, and consequences of labile and essential hypertension could be modified through programs of physical fitness, particularly when initiated early.

Kiveloff and Huber (1971) examined another form of training. Using brief maximal isometric exercise three times per day over five to eight weeks, a substantial blood pressure reduction was noted. Eight male subjects aged 57 to 72 recorded blood pressure drops of 2 to 24 mm Hg diastolic, and 16 to 42 mm Hg systolic. Five subjects who had been taking hypotensive drugs also recorded blood pressure drops during the experiment, 4 to 28 mm Hg systolic and 2 to 14 mm Hg diastolic. Two subjects substituted isometric exercise for their hypotensive drug treatment and were able to remain normotensive for eleven months. No changes were noted in the four normotensive subjects. Three possible explanations were given:

1. With less mechanical pressure on the muscle capillaries an increased venous return may stimulate low baroreceptors. This reflexly leads to peripheral vasodilation by reducing vasoconstrictor tonus. The increased venous return produces an increased cardiac output against less peripheral resistance, thereby lowering diastolic and systolic blood

pressures.

2. Stimulation of the high baroreceptors in the carotid and aortic sinuses intermittently during isometric exercise may cause an intermediate reflex slowing of the heart, which in turn may reduce arterial blood pressure.
3. Repeated daily isometric exercise over a long period may cause growth of the capillary bed in muscles and thereby increase the volume of blood in this area, which in turn may decrease arterial blood pressure.

This study by Kiveloff and Huber is quite unique as most studies have utilized aerobic training rather than isometric exercise. Maximal isometric exercise has usually been counterindicated for hypertensives (Storer and Ruhling (1981)).

"Borderline" hypertensives were the subjects of a 1973 study by Choquette and Ferguson. "Borderline" was defined as the presence of either a systolic pressure of 140 to 159 mm Hg, a diastolic pressure of 90 to 95 mm Hg, or both. The six month training program consisted of a weekly two hour session plus daily home calisthenics of approximately 10 to 15 minutes. The subjects included 37 borderline hypertensives and 128 normotensive men. After the training program it was found that both the borderline hypertensives and the normotensives significantly reduced their blood pressures. The reductions of both the systolic and diastolic pressures at rest were significantly greater for the hypertensives. This study suggested that borderline hypertensive subjects derived a great benefit from a program of physical training.

Another 1973 study reported the effects of a six week bicycle ergometer training program on "borderline latent arterial hypertensive men of the hyperkinetic type". Training took place over six weeks, three times per week, five 12 minute

intervals per session, at a workload set to achieve a heart rate of 150 to 160 beats per minute by the end of each 12-minute interval. The sample size was again small (five men), however, some findings were significant. The training resulted in trends of lower resting heart rate, cardiac output, and arterial blood pressure. The decrease in blood pressure was significant between paired observations. It was suggested that physical training with subjects of this kind "contributes to the normalization of their circulation toward a normokinetic one, thereby also normalizing their blood pressure level and achieving a more economic energy expenditure in the cardiovascular system" (Sannerstedt and others, 1973).

Bonnano and Lies (1974) reported on the effects of physical training on coronary risk factors. Of the total 39 male subjects, 20 trained (12 hypertensives and 8 normotensives) for 12 weeks, while 19 acted as controls (15 hypertensives and 4 normotensives). There were three 40 to 55 minute training sessions per week, of which 30 to 35 minutes was intense enough to attain a heart rate of 70 to 85 per cent of maximal. The authors found a significant reduction in diastolic pressure in all the groups, that is, normotensive and hypertensive, trained and untrained. Systolic blood pressure was significantly reduced only in the hypertensive subjects who trained. The mechanism for the blood pressure reduction was obscure, but the authors suggested that training could have resulted in a decrease in sympathetic tone and peripheral resistance, both at rest and during exercise. Regardless of the mechanism, however, without

any other form of hypertensive therapy (drugs, sodium restriction, or weight reduction), a significant reduction of blood pressure was achieved.

In a published panel discussion in 1976 (Hellerstein and others, 1976), a physician stated "if a person has a low pressure before training the value doesn't change. On the other hand, both systolic and diastolic pressure drop significantly after conditioning if the person is elevated initially". Another panel member when asked the treatment he utilized for borderline hypertensives stated, "I'd have him see the dietician for a low sodium diet, and I'd advise him to stay away from processed foods, lose some weight, and start an exercise program". It appeared, based on the responses of the physicians on the panel, that the medical community was starting to recognize the value of nonpharmacological treatment for hypertension. Exercise and sodium restriction have taken an important role in this type of treatment.

Denolin and Mallion in 1977 published a review of the major findings in exercise and hypertension. They were able to state based on their review:

> although the results are debatable, it seems that a controlled physical training program can possibly bring about a moderate reduction of the arterial blood pressure in normotensives but that this reduction becomes much more significant in hypertensives... the mechanism of this hypertension reduction still has to be elucidated: a reduction of sympathetic tone has been considered. On the other hand, training level, type, and frequency of exercises, and selection of cases still remain problems to be solved before defining the place of physical activity in the treatment of hypertension.

A recently translated abstract of a Russian study revealed some interesting information. Khomazink and others (1979) reported the effects of a two year training program on 314 hypertensive patients. Specifics of the methodology were lacking, however, regular physical training was found to decrease blood pressure. The mechanism proposed and tested involved the kallikrein-kinin blood pressure depressor system. It was stated, in translation:

> Regular physical training during the initial stages of development of hypertensive disease aided the functioning of depressor systems: results indicated a possible reversibility of changes in the blood pressure depressor-kinin system of patients in the initial stages of hypertensive disease. Under regular physical training the average levels of kallikrein and kallikrein inhibitor increased (p less than .001, and p less than .05 respectively)

In 1979 Black compiled a review of nonpharmacological therapy for hypertension. The rationale for this type of therapy was stated,

> since nonpharmacological treatment for hypertension is inexpensive and probably safe, the time is right for extensive research to determine the efficacy, applicability, patient compliance, and safety of this approach ... nonpharmacological methods are cheaper than drugs and although only modest reductions in blood pressure have been consistently reported, this degree of success may be enough to safely treat patients with boarderline and mild hypertension, the group in whom pharmacological therapy has yet to be convincingly demonstrated as effective.

Physical Training and Hypertension in Rats

The use of animal models in the study of physical training and hypertension has been a relatively recent occurrance, primarily confined to the past decade. Much like the study of human subjects, research using animal models has encountered

equivocal results. Up to now, most of the studies in this area have used genetically spontaneously hypertensive rats (SHR) as subjects. The SHR model was developed in the early 1960's (Okamoto and others, 1960), but has only recently been used in physical training studies. Other hypertension models: genetic, surgical, and pharmacological which have been developed have also been used to varying degrees.

The earliest study on rats and physical training with an emphasis on blood pressure response was published in 1973 by Tipton and others. The authors found, using normotensive male rats, 10 weeks of physical training (intensity not stated) resulted in a reduction in mean arterial blood pressure. The difference was significant only in the sprint trained animals. Blood pressure was measured directly via the carotid artery at the termination of the training period. This report also contained a pilot study of female SHR which showed a substantial decrease in blood pressure due to the training (10 weeks).

Dunne and others (1974) conducted a small study of three different states of training. In this experiment SHR (3 male, 3 female) were divided into three groups: control (no exercise), ad libitum exercise on activity wheels, and forced exercise (5 days per week, 2 hours per day, 0.42 mph.) for a six-month period. Measurement of systolic blood pressure was made using the tail-cuff technique. Their results suggested that ad libitum exercise enhanced the development of hypertension in the SHR. Systolic blood pressure increased steadily in all three treatments. Heart rates of the trained groups were lower. There

was a temporary decrease in systolic blood pressure in the trained rats which the authors thought might be due to dehydration. Overall this experiment showed no beneficial effect of training and possibly a detrimental effect of ad libitum activity.

Tipton, Callahan, and Matthes (1975) found a positive relationship between physical training and lower systolic blood pressure in male and female SHR. Specifically they found 10 to 12 weeks of training resulted in a tendency toward lower systolic blood pressure compared to weight paired controls. However, this difference was not statistically significant. Twelve to 13 animals were in each trained and control group. It was suggested that the most beneficial role of exercise might have occurred if the exercise had been combined with antihypertensive drugs.

Tharp (1976) used Carworth normotensive and hypertensive rats in a training study (8 weeks, 5 days per week, up to 0.8 mph, 1 hour per day). Tail-cuff systolic blood pressure was recorded. No significant difference in systolic blood pressure between trained and control groups was obtained. These results suggested that chronic exercise did not lower systolic blood pressure in Carworth rats.

Burgess and others (1976), however, reported a large study of 100 male SHR over 68 weeks. The groups were 50 sedentary control SHR and 50 which trained three times per week on a treadmill (40 ft/min, 15 percent slope). Systolic blood pressure was determined by the tail-cuff method. Here it was found that

training significantly lowered systolic blood pressures. The authors suggested beneficial effects of training (1 hour per day, 3 days per week) on the cardiovascular system of the SHR.

Critz and Lipsey (1976) studied the effect of swim training before and after applying a surgical and pharmacological hypertensive treatment (unilateral nephrectomy, deoxycorticosterone acetate (DOCA), and 1 percent NaCl drinking water) to male Sprague-Dawley rats. The indirect tail-cuff method was used to obtain systolic blood pressures. The rats initially subjected to the hypertensive treatment and later to the swim training were not affected by the swimming program; their systolic blood pressures were the same as the non-swimming controls. The results were different, however, in the group which was trained prior to the hypertensive treatment. The group which was trained for six weeks prior to hypertensive treatment demonstrated a delay in the onset of hypertension to eight weeks, whereas in those animals without prior training the onset of hypertension had occurred by four weeks after the hypertensive treatment. One of the control groups in this experiment, exercise without hypertensive treatment, also recorded an increase in systolic pressure. The delay in the onset of hypertension in the pretrained rats subjected to a powerful hypertensive treatment tended to indicate a preventive benefit from the physical training. As for the increased systolic pressure in the control rats the authors suggested this might have been due to the stress associated with the swimming.

The authors (Critz and Lipsey, 1976) also found normotensive controls to have the smallest heart weights with normotensive swim trained rats having significantly greater heart weight/body weight ratios. All the hypertensive rats had significantly greater heart weight/body weight ratios than the normotensive groups. The relative heart weights of the hypertensive swim trained groups were not significantly different from the hypertensive sedentary group, except when the swimming and hypertensive treatment were initiated simultaneously. When initiated at the same time the swimming resulted in a greater heart weight/body weight ratio.

Rock and others (1976) failed to show any blood pressure reducing effect of physical training on the SHR. The methods employed by these authors were similar to those of Dunne and others (1974) (3 male and 3 female SHR in each of 3 groups sedentary controls, ad libitum activity, and forced running 3 hr per day, 1.1 mph, 5 days per week). Systolic blood pressure was measured by the indirect tail-cuff technique. Overall there was a slight tendency for the systolic blood pressure to become higher and the heart rate lower in the trained SHR compared to the sedentary controls. To sum up the authors stated, "strenuous exercise had no apparent beneficial effect on SHR".

Tipton and others reported a very extensive group of experiments in 1977. The experiments included a short term physical training program of gradually increasing treadmill running (10 to 12 weeks), and a long term program on motor driven activity wheels (3 to 21 months). The models for these

experiments included normotensive Spague-Dawley male rats and male and female SHR. Predominantly indirect systolic measurements were reported. Some terminal direct measurements were also made. Another experiment was conducted on borderline hypertensive rats (normotensive rats given intramuscular injections of DOCA without saline supplement). Systolic blood pressures were measured indirectly using the tail cuff method. The authors found all the trained groups (that is short and long term SHR and DOCA treated, male and female) to have lower systolic blood pressures than their nontrained controls, and in most cases the differences were statistically significant.

The DOCA injected groups showed that exercise instituted after the hypertensive treatment delayed the rise in blood pressure. This result was similar to that reported by Critz and Lipsey (1976), but, in this case the hypertensive treatment was far less severe. It seemed the lower severity allowed the training protocol imposed after the treatment to exert a delaying effect. Critz and Lipsey, however, found the delaying effect only when the training was performed prior to the hypertensive treatment.

Another interesting experiment by this group involved combining the effects of hypertensive drug therapy (resperine, chlorothiazide, and hydralazine) and physical training. Tipton, Callahan, and Matthes (1975) had speculated that the combined effect of drug therapy and training would produce the most beneficial result. It was found, however, that training did not modify the effect of the drug therapy. If anything, the training

slightly reduced the anti-hypertensive action of the drugs (Tipton and others, 1977).

The authors (Tipton and others, 1977) found no differences between heart and kidney weights of trained and nontrained groups of rats. A significantly greater heart weight was noted in the nontrained SHR receiving anti-hypertensive drugs than the trained group on the same therapy.

Some possible mechanisms were suggested by Tipton's group to account for the pressure reduction in the trained groups. One possibility suggested that training might alter the responsiveness of volume and/or pressure receptors in the body. A similar suggestion had been made by Kiveloff and Huber (1971). A reduction in cardiac output at rest with training was also suggested as a method by which blood pressure might have been reduced. A decrease in peripheral resistance was considered a less likely possibility.

From their observations Tipton and others (1977) made the following statement:

> Our results from normotensive, borderline hypertensive, or genetic hypertensive rats indicated that chronic exercise will be associated with lower resting blood pressures. However, chronic exercise cannot normalize blood pressure in adult hypertensive animals and it would be unrealistic to advocate exercise for this purpose.

Weiss, in 1978, published a study of eleven male SHR and ten male normotensive rats on a running training program. The training program lasted 16 weeks, 5 days per week, 45 minutes per day, attaining 30 m/min by the 8th week. Systolic blood pressure was indirectly measured using the tail-cuff method. The

overall finding was that physical training did not significantly alter the resting systolic blood pressure compared to untrained controls as measured by the tail-cuff technique. The author went on to postulate a reason for the difference between her results compared to many human studies.

> One great difference between man and rat, however, probably inherent is the fact that a programme of physical training is, if anything experienced as a "stressful event" by the rat since they are forced to run under threat. On the other hand, in most people with sedentary occupations which frequently involve elements of mental stress, exercise is commonly experienced as a fairly pleasant occurrence leading to relieved feelings of mental tension and strain. It therefore seems likely that the beneficial effects of exercise on the blood pressure levels in hypertensive man is essentially due to some psychophysiological mechanisms rather than to structural and functional changes in the heart and vascular bed per se.

Weiss (1978) was able to detect significantly lower hindquarter resistance in the trained SHR. This was taken by the author to indicate that previous encroachment of the vascular walls into the lumen of the blood vessels had been compensated for by the structural widening, or that new vessels had developed, or both.

Edwards and Diana (1978) studied pre- and postcapillary resistance of the male and female SHR and the effect of physical training. The training consisted of running on a treadmill 11 times per week for 10 weeks from the age of 8 to 18 weeks (increasing from 5 min at 5 percent grade and 0.6 mph to longer durations). There were 5 to 11 animals in each group. The diets were manipulated to minimize weight differences between trained and untrained groups. The indirectly measured systolic blood

pressures in the trained male and female SHR were lower by 14.9 and 9.8 per cent respectively, compared to untrained controls. There was a significant difference due to training in normotensive rats only when trained and untrained male siblings were compared. Perfused isolated hindpart preparations were used to determine pre- and postcapillary resistance, filtration coefficients, and capillary hydrostatic pressure. A substantial decrease (20-30 percent) in precapillary resistance was noted in the trained SHR. The postcapillary resistance, however increased very substantially due to training, 70 per cent higher in trained as compared to control. The results suggested that the structural or intrinsic muscle tone (not influenced by neural or hormonal stimuli) of the precapillary resistance was reduced due to training. The increase in the postcapillary resistance was explained by the authors as follows: "conceptually, an enhanced venous tone would shunt blood from peripheral capacitance vessels to the central pool and provide an effective mechanism to augment cardiac output".

Data pertinent to this study was presented by Pfeffer and others (1978) looking predominantly at the ventricular morphology in the trained versus nontrained normotensive and SHR female rat. Twelve to 14 SHR, WKY, and normotensive Wistar rats were allocated to trained and control groups. Systolic blood pressure was measured during the course of the training using the tail-cuff technique. However a terminal direct blood pressure measurement was also made via the carotid artery. The training consisted of a swimming program which started at 3

weeks of age for 30 min. per day and progressed by the 13th week to 2 hours per day until termination at 28-32 weeks. The training failed to significantly alter the progress of hypertension development in the SHR. All the normotensive strains studied showed similar blood pressure levels in trained and controls. An interesting result in this study indicated a strong trend toward diastolic pressure reduction due to training where no similar trend existed for systolic pressure. The reduction of diastolic pressure agreed with several authors from human studies dicussed previously (Boyer and Kasch, 1970; Choquette and Ferguson, 1973; Bonnano and Lies, 1974). Due to the nature of the indirect tail-cuff blood pressure method used by almost all authors, few results of diastolic pressures have been reported.

Pfeffer and others (1978) also reported that training exerted a strain specific effect on resting heart rates of female rats. Although both trained and nontrained rats of each strain showed a decrease in resting heart rate with age, trained normotensive Wistar rats had lower heart rates than their sedentary counterparts. Wistar-Kyoto rats showed no heart rate difference as a result of training. SHR showed a pronounced bradycardia as a result of training. It was also found that the intrinsic heart rates of the trained animals was slower than their nontrained controls. The authors found no difference between kidney weights of trained and nontrained groups. Heart weights, however, differed significantly between swim trained and sedentary controls. The hearts of the SHR and both

normotensive groups were heavier as a result of training compared to sedentary controls.

Evenwel and Struyker-Boudier (1979) compared the development of hypertension in the trained versus nontrained male SHR. The training program, which started when the animals were 4-5 weeks old, continued for 11 weeks. The rats swam 4 days per week beginning with unweighted swimming for 20 min. and progressing to swimming 1 hour per day with an additional 3 percent of the body weight attached to the tail. Indirect tail-cuff measurements were made to determine systolic blood pressure. They found that training significantly reduced or slowed the development of hypertension.

Evenwel and Struyker-Boudier (1979), also found heart rates to decrease as a result of training compared to sedentary controls in Wistar-Kyoto and SHR strains. They found swim training to result in a relatively greater heart weight in male Wistar-Kyoto rats. No difference between the relative heart weights of trained and nontrained SHR were detected. Relative kidney weights were the same in trained and nontrained animals of both strains.

A review recently published by Tipton and others (1979), pointed out that the SHR has demonstrated an impaired temperature regulation ability. As a result of this impairment, in exercise studies the animals were often working at the upper limits of their temperature tolerance. This review went on to suggest mechanisms of the effect of exercise in blood pressure control. The authors postulated that "reduction in sympathetic

tone, decreases in baroreceptor sensitivity, changes in myogenic structures, tone, or relationships, and/or decreases in resting cardiac output are the most important".

Recently, Shepherd and others (1980) reported in an abstract a study on the effect of training on the Dahl strains of rats. Two experiments were reported, one began with eight week old S and R male rats subjected to a high salt (8 percent NaCl) diet and endurance running for an eight week period. The training consisted of treadmill running at 20 m/min for 1 hour per day, 5 days per week. Systolic blood pressure was measured by tail-cuff under light ether anesthesia. In this experiment a significantly lower systolic blood pressure was recorded in the trained S rats compared to untrained S rats. In the R strain a slightly higher systolic blood pressure was reported due to training. In the second experiment S strain rats were simultaneously trained and fed a high salt diet. Although not stated in the abstract results presented at the Lewis K. Dahl symposium, May, 1981, stated this work was performed using female DS rats. It was stated that the training program greatly reduced the effect of the high salt diet, normalizing the systolic blood pressure for the eight week course of the experiment.

Booth and others (1980) investigated the effect of exercise on the longevity of a new strain of obese hypertensive (cp/cp) male and female rats. The training consisted of treadmill running 7 days per week at 20 m/min, for up to 60 min per day. After 6-8 months, the training had to be reduced to 10-20 min.

per day at 7 m/min. This study found a shorter life span as a result of the physical training compared to the sedentary controls. The authors stated that the treadmill running in these obese, blind, hypertensive rats may have contributed to early death in this strain of rat.

Due to the equivocal nature of the published results of training on hypertension, a concise summary has been difficult. The survey research has left little doubt of the correlation between physical activity or fitness and freedom from hypertension (Montoye and others, 1972; Gyntelberg, 1977). This type of research, however, cannot establish any cause-effect relation. The multi-dimensional nature of both physical fitness and hypertension has made this task impossible with survey research.

Research on human hypertension and training has demonstrated several important findings. Early work has found, in most cases, a decrease in the systolic and diastolic blood pressure levels due to training particularly in hypertensives. Several different types of training programs have been shown to result in blood pressure reductions. Variation of the training procedures and results of various experimenters has made clarification of the role of physical training difficult.

Another problem has been the lack of human subjects with similar type and severity of hypertension. As a result, several studies have been performed with sample populations of only four to six men (Johnson and Grover, 1967; Hanson and Nedde, 1970; Sannerstedt and others, 1973). The small sample made attainment

of statistical significance almost impossible. To date, no study of hypertensives has reported significant increases in blood pressure due to the effects of physical training, whereas several significant blood pressure reductions have been reported (Boyer and Kasch, 1970; Kiveloff and Huber, 1971; Choquette and Ferguson, 1973; Sannerstedt and others, 1973; Bonnano and Lies, 1974; Khomanziuk and others, 1978)). Non-significant blood pressure reductions have also been reported (Johnson and Grover, 1967; Hanson and Nedde, 1970). Despite the blood pressure reductions frequently found, difficulty in identifying the mechanisms by which training has modified blood pressure has remained. Mechanisms have been suggested, but experimental verification of any mechanisms has been absent.

The experimental hypertension models which have been utilized in the most recent research have proven to have been a valuable tool. Experiments with the various models have each added a new perspective on the role of physical training. The SHR has been shown to be responsive to the benefical effects of training in only certain conditions. To this date, aerobic conditioning from an early age has seemed the most promising (Tipton and others, 1977; Edwards and Diana, 1978; Evenwel and Struyker-Boudier, 1979). Here again, however, the mechanisms have proven elusive.

Based on the current literature, further research into this problem must attempt to isolate the types of hypertension which respond to physical training. The use of animal models with hypertension of known origin may give more direct clues to the

mechanisms involved. In addition, measurement of associated factors such as hormonal levels or dietary components has been scarce in the literature. Data of this kind could give valuable insights into the possible mechanisms.

Blood Pressure Measurement

The accurate measurement of blood pressure has been a difficult, but essential requirement in the study of blood pressure and blood pressure modification. This requirement has only rarely been met (Idvall, 1978). Research involving indirect methods and small laboratory animals may have been obtaining measurements not necessarily reflecting the intraarterial pressure.

Rev. Stephen Hales made the first attempts at measuring arterial blood pressure in 1733. He obtained direct blood pressure measurements via the carotid artery of a restrained unanesthetized mare. Since these early attempts many direct and indirect systems of measuring blood pressure have been developed, with varying degrees of success (Geddes, 1970).

Indirect measurements of blood pressure were developed and utilized because they were simple and repeatable. Sacks (1979) has pointed out, however that there are problems with indirect measurements of blood pressure. As he stated, "As with all indirect measurements, we must face the fact that we are not really measuring what we want to measure but rather something else that we believe is closely related to it" (Sacks, 1979).

In general the indirect methods involve a pressure cuff to occlude blood flow, and some indicator of blood flow distal to

the cuff. Neither of these instruments measure blood pressure. The requirement of the pressure cuff to collapse the artery to stop the blood flow has made the elastic behavior of the arterial wall very important (Sacks, 1979). Changes in the vessel wall due to hypertension induced thickening or atherosclerosis could substantially alter the behavior of the artery and result in a substantial measurement error.

The indirect blood pressure measurement in the laboratory rat by way of the tail-cuff, in addition to the above described problems, has several other complications. The animal must be confined, heated, and often lightly anesthetized. The confinement is necessary to keep the animal stationary and to keep the tail within the cuff. To do this it is important to have a restraining box of the correct size to permit free breathing, but small enough to keep the tail in place (Palbol and Henningsen, 1979). The heating has been performed to increase the blood flow to the tail thereby increasing the signal to noise ratio for the blood flow detecting instrument and therefore, the accuracy of the measurement. This procedure has been proven effective, increasing the blood flow about one hundred times (Johansen, 1962). However, the overheating and discomfort may induce changes in the blood pressure (Proskauer, 1945).

The results of comparisons between direct and indirect measurement results have shown several inconsistancies. Bunag, McCubbin, and Page (1971) found unanesthetized rat tail-cuff measures to differ considerably from the intraarterial

pressures. Ether anesthesia reduced the difference between measures, however, catecholamines (norepinepherine) greatly increased the disparity between measures, apparently due to the constriction of the tail artery. It was found that systolic pressure in the unanesthetized rat's tail was always lower by about 30 mm Hg than that measured in the aorta. It was stated that,

> The assumption that the tail artery in unanesthetized rats is a passive tube that reflects changes in systemic arterial pressure with complete accuracy, does not appear to be a valid one.

Maistrello and Matscher (1969) also compared the indirect tail-cuff method to direct intraarterial pressure recordings. They found several factors which influenced the value obtained via the tail-cuff method. Cuff size, body weight, and the elasticity of the rubber sleeve were found to affect the measurement. In long term experiments in which growth of the animals was involved considerable systematic error could develop if cuff size was not continually adjusted to suit the animal during growth.

Chiueh and Kopin (1978) found that some strains of rats responded differently to the stress of the tail-cuff method. SHR were found to demonstrate systolic blood pressures approximately 25 mm Hg higher when restrained in a tail-cuff apparatus than resting in their cages. Further SHR demonstrated a greater increase in plasma catecholamines than Wistar-Kyoto rats when placed in the measurement apparatus. Given the results of Bunag, McCubbin, and Page (1971) the increase in catecholamines in

addition to altering the blood pressure, would reduce the blood flow to the tail, decreasing the signal to noise ratio of the measurements.

Borg and Viberg (1980) found an error within tail-cuff measurements of 5 to 10 percent. This error changed with the animal size and sex. The tail-cuff measurement was 5 to 10 percent higher than the direct method in full grown males, but 5 to 10 percent lower in the females.

A major drawback of the indirect methods has been the inability to obtain an accurate measure of diastolic or mean arterial blood pressure (Geddes, 1970). Systolic pressure alone offers limited information, variations in pulse pressure and total peripheral resistance cannot be recorded.

In general direct methods have been shown to require few assumptions and were able to provide more complete pressure information. There are some difficulties, however, in direct measurement in small animals. The higher pulse frequency and small catheters required place considerable demands on the measurement system (Idvall, 1977).

The study of blood pressure depends on accurate and reliable measurement. Therefore it would seem that the method used should, where possible, measure pressure directly. Where changes in size and possibly changes in arterial elasticity are involved inherent errors could counterindicate the use of indirect methods. Direct methods, although not free of difficulties, have demonstrated accuracy (Geddes, 1970) and give more complete information with regard to the hemodynamic changes

(Berne and Levy, 1972).

Growth and Feeding Characteristics of Trained Rats

Excess body weight or obesity has been identified as one of the factors in the pathogenesis of hypertension (WHO, 1978). Several authors have found that physical training can affect body weight and food intake. The laboratory rat has proven a useful model in the study of the effects of training on growth and food intake (Crews and others, 1969; Drori and Folman, 1975; Pitts and Bull, 1977). Studies on the effect of body weight or growth on the blood pressure of rats could not be located.

Investigators have reported varied results when trained and nontrained male rats are compared with respect to growth. Crews and others (1969) trained male Wistar rats for 12 weeks beginning at 7 weeks of age. The training consisted of treadmill running (8 percent incline) 5 days per week beginning with two 10-minute runs at 22 m/min. and progressing to 120 minutes at 31 m/min. with 1 minute sprints (42 m/min.) at 10 min intervals. It was found that the trained groups on either a normal or low protein diet gained less weight and had a lower carcass fat content than the nontrained controls. The differences were attributed to a increased caloric expenditure and a decreased food intake by the trained groups.

Drori and Folman (1976), found two minutes of daily treadmill running to have no effect on growth rates of male random bred Norway male rats.

Pitts and Bull (1977), found exercise training to decrease the rate of growth of male rats compared to nontrained controls

both on normal and high fat diets. The training consisted of treadmill running twice per day, 7 days per week, attaining 18 m/min., at a 14 percent grade, for 30 minutes. The training effect on growth rate was shown to be completely reversible. When the training program was stopped the trained animals gained weight up to that of the control animals which had been sedentary throughout the experiment. The body composition data of this experiment suggested that "exercise decreased masses of both the fat and fat free compartment below values for the sedentary groups" (Pitts and Bull, 1977).

Pfeffer and others (1978), studying the effect of prolonged swim training (previously described, pp. 35-36) on female normotensive (Wistar and Wistar-Kyoto) and hypertensive (SHR) rats, found no significant effect of training on body weight or growth rates of the normotensive rats, however the trained female SHR weighed less than their sedentary controls.

In a recent review Nikoletseas (1979) made several interesting statements about food intake in the exercising rat. The author suggested that food intake of male and female rats differed in response to forced exercise, the female rats increased their food intake, the male rats did not. He went on to state that "this conclusion may apply only to those situations in which a pre-mixed diet (eg chow) is offered".

Dahl and others (1958) reached the conclusion that the reduction of weight in obese people by dietary resriction is frequently accompanied by blood pressure reduction as a result of the concomitant salt intake reduction, not as a result of the

caloric restriction. This finding has recently been disputed by Reisin and others (1978). Heyden and Hames (1980) stated that despite recent findings Dahl's hypothesis has not been disproven. Research of this type has not been performed on the DS rats.

C. METHODS

Experimental Animal Model

The Dahl salt sensitive (DS) male rat was selected as the model for this experiment. This strain was developed at Brookhaven National Laboratories, Upton, New York (Dahl, Heine, and Tassinari, 1962), through three generations of selective inbreeding of standard Sprague-Dawley rats followed by careful outbreeding and selection based on blood pressure response to dietary salt. The rationale underlying the development of this strain arose from the hypothesis that within any population of animals subgroups existed which exhibited differing blood pressure responses to the hypertensive effects of dietary salt. As a result of the investigation of this hypothesis two strains of rats were developed. The DS strain showed a marked elevation of blood pressure when given a high salt diet. The resistant (DR) strain, however, showed no elevation of blood pressure despite high levels of dietary salt.

For this experiment rats of the DS strain were obtained from the Brookhaven National Laboratories. Only male animals were utilized. The rats were maintained at the Brookhaven Laboratories until shortly after weaning whereupon they were shipped by air from New York to Vancouver. Immediately after arrival at Vancouver the rats were transported to the Simon Fraser University Animal Care Facility (SFUACF). Upon arrival at the facility the animals were weighed and placed in individual cages and maintained on a reverse 12-hour day-night cycle. All housing and experimentation throughout the study took place at

the SFUACF. The DS rats were housed in a room separate from all other animals to minimize possible disease transmission.

The housing room was maintained at 24 +/- 1 degree C throughout the experiment. Housing, training, and surgery were each performed in separate rooms. The animals were transported to the treadmill room for training on a rack containing 12 to 30 cages. Transport to the surgery area was done one animal at a time. Only the animal undergoing the measurement was in the surgery room during the surgery and recovery. All procedures including training, weighing, handling, changing of food and water, and surgery were performed during the dark portion of the day-night cycle.

The cages for housing the animals were Hoeltge 24 X 18 X 18 cm mounted on a 6-tiered metal rack. Litter beneath the cages was changed 2 to 3 times per week. Animals in their cages did not have any contact with each other. Cages were changed bi-weekly. The area within the cage was reduced by the food container which was placed in one corner and held in place by a metal spring.

Diet

All animals were given ad libitum diets of both food and tap water. The tap water was provided in 500 ml bottles with ball-bearing spouts. Water intake was measured daily by weighing to the nearest gram; the amount lost due to dripping was not measured. Any time the water level dropped below 200 ml or if the water had not been changed for 3 days, the water bottle was replaced with a fresh bottle after the weight had been

ascertained.

The "normal chow" diet consisted of Purina Laboratory Chow, code 5001. The ingredient list is shown as table 3-1. The diet was fed in meal form in containers which held up to 3 days allotment of food (up to 90 grams).

The high salt diet consisted of additional reagent grade sodium chloride added to the Purina chow (36 grams NaCl per 964 grams of meal). The additional sodium chloride was first powdered by hand with a mortar and pestle then thoroughly mixed with the meal. The food was then distributed in the same manner as the normal chow. Food intake was measured daily by weight. Food spillage did occur but could not be accurately measured.

The Training Program

The training program consisted of treadmill running at constant speed and inclination for increasing lengths of time, five days per week.

In preparation for the training protocol all animals, both those destined to be used as experimental and control, were trained to run on the treadmill for 5 minutes at the criterion speed of 26.4 meters per minute at 5 percent grade. Prior to this treadmill education period, the animals were given one day after arrival at the SFUACF to acclimatize. Thereafter the animals were run daily on the treadmill at increasing speeds until at 10 days they were able to run at the criterion speed for 5 minutes. The duration and speed utilized each day of the treadmill education is shown on table 3-2.

TABLE 3-1 PURINA 5001 CONTENT

Approximate Chemical Composition

Protein	23.4 percent
Fat	4.5 percent
Fiber	5.0 percent
Ash	7.3 percent
Potassium	1.10 percent
Sodium	0.48 "
Chlorine	0.58 "
Calcium	1.20 "
Phosphorous	0.86 "
Magnesium	0.21 "
Fluorine	35.0 ppm.
Iron	198.0 "
Zinc	58.0 "
Manganese	51.0 "
Copper	18.0 "
Cobalt	0.4 "
Iodine	1.7 "

Reprinted from Purina Laboratory Chow, Code: 5001, Revised 10/8/75.

TABLE 3-2 TREADMILL EDUCATION SCHEDULE

Day	Duration	Speed	
1	2.5 minutes	9.2 m/min	
2	5.0 "	9.2 "	
3	5.0 "	13.0 "	
4	5.0 "	16.5 "	
5	5.0 "	16.5 "	**
6	5.0 "	19.6 "	
7	5.0 "	20.7 "	
8	5.0 "	22.9 "	
9	5.0 "	24.6 "	
10	5.0 "	26.4 "	

** electric shock motivation started

The running was performed on a Quinton rodent treadmill (Quinton Instrument Co., Seattle, model 20-40). The treadmill consisted of a large moving belt over which was suspended 10 compartments 10 cm X 47.5 cm. At the rear of each compartment was an electrified grid. The grid was used to motivate the animals to run since if the animals stopped or ran more slowly than the moving belt it would come into contact with the grid and receive a shock. This conditioned the animals to run at the front portion of the compartment. Electrical contact was enhanced by wetting the hind area of the rats with warm tap water prior to each treadmill session. The electric shock procedure was first used on the fourth day of treadmill education and continued each running session thereafter throughout the experiment. Control animals did not receive electrical shocks after the treadmill education period.

At the conclusion of the treadmill education, the animals were randomly divided into four groups: normal chow nontrained (NCN), normal chow trained (NCT), high salt nontrained (HSN), and high salt trained (HST). All the groups were handled identically with the exception of the diet and the running on the treadmill, which were allocated to the specific experimental groups. The trained and nontrained groups were placed on treadmills for the same time period each day at the same time. The nontrained animals were, however, placed on a nonmoving treadmill of identical dimensions. In this way the trained and nontrained animals received identical handling, exposure to other animals, and access to food and water during the

experimental program.

Each treadmill could hold up to 10 animals. During the treadmill education period only 2 to 4 animals were running at once. During the experimental period the animals were run in groups of up to 8 at one time. The stationary treadmill was occupied by a similar number of control animals.

The speed and inclination of the treadmill were kept constant throughout the experiment, while the duration increased each week. The schedule is shown on table 3-3. After the second measurement the training sessions were divided into two sessions daily with a 3 to 6 hour rest between runs. This procedure allowed the animals to complete time requirement of the run more easily. As the training was always performed in the dark portion of their 24-hour cycle the lighting in the treadmill area was reduced as much as possible. The measurement of food and water intake as well as the weights of the animals were performed immediately after training.

Occasionally animals received minor injuries, such as injured feet or tails. These injuries were treated immediately upon discovery with a disinfectant spray. If at any time an animal was experiencing difficulty in continuing to run, the animal was removed from the treadmill temporaily and returned to the training session the same day after a short rest. This happened infrequently.

The Blood Pressure Measurement Apparatus

The blood pressure measurement system consisted of a non-bevelled 1 cm segment of PE 50 tubing inserted into a 13-cm

TABLE 3-3 TRAINING SCHEDULE

Day	Duration of Run	Day	Duration of Run
1	7.5 minutes	43	62.5 minutes
2	12.5 "	44	67.5 "
3	15.0 "	45	70.0 "
4	15.0 "	46	70.0 "
5	15.0 "	47	70.0 "
6	rest	48	rest
7	rest	49	rest
8	17.5 minutes	50	72.5 minutes
9	22.5 "	51	77.5 "
10	25.0 "	52	80.0 "
11	25.0 "	53	80.0 "
12	25.0 "	54	80.0 "
13	rest	55	measurement
14	rest	56	rest
15	27.5 minutes	57	30.0 minutes
16	32.5 "	58	42.5 "
17	35.0 "	59	35.0 "
18	35.0 "	60 *	45.0 + 12.0 minutes
19	35.0 "	61 *	35.0 + 35.0 "
20	rest	62	rest
21	rest	63	rest
22	37.5 minutes	64 *	40.0 + 35.0 minutes
23	42.5 "	65 *	40.0 + 40.0 "
24	45.0 "	66 *	50.0 + 45.0 "
25	45.0 "	67 *	50.0 + 45.0 "
26	45.0 "	68 *	50.0 + 45.0 "
27	measurement	69	rest
28	rest	70	rest
29	15.0 minutes	71 *	52.5 + 45.0 minutes
30	25.0 "	72 *	57.5 + 45.0 "
31	35.0 "	73 *	60.0 + 45.0 "
32	45.0 "	74 *	60.0 + 45.0 "
33	50.0 "	75 *	60.0 + 45.0 "
34	rest	76	rest
35	rest	77	rest
36	52.5 minutes	78 *	72.5 + 35.0 minutes
37	57.5 "	79 *	82.5 + 30.0 "
38	60.0 "	80 *	95.0 + 20.0 "
39	60.0 "	81 *	105.0 + 10.0 "
40	60.0 "	82	115.0 minutes
41	rest	83	terminal measurement
42	rest		

* two seperate sessions per day

segment of PE 90 tubing. A 19 gauge needle shortened to 1-cm without bevel was inserted into the other end of the PE 90 tubing. The needle was in turn attached to a 3 way valve in line to a Statham P23BB strain gauge pressure transducer (Hato Rey, Puerto Rico). The strain gauge transducer was kept at the level of the heart. The third outlet of the 3 way valve was attached to a 10-ml syringe containing heparinized saline. This syringe was used to push saline through the catheter when necessary.

The transducer chamber contained boiled isotonic saline. In all cases the system was fully cleared of air bubbles.

The signal from the transducer was passed to a carrier preamplifier (Physiograph Mk II, E & M Instruments Co. Inc., Houston Tx.), to a transducer coupler (Narco Biosystems type 7173), then to a chart recorder (Hewlett Packard, 7404A recorder, medium gain preamplifier type 17401A with zero suppression).

Calibration of the system before and after each measurement was performed using a mercury column.

Mean arterial blood pressures were calculated mathematically using the following formula:

P mean = P diastolic + 1/3 (P systolic - P diastolic)

(Berne and Levy, 1972, p. 89; Spence, Sibbald, and Cape, 1980).

Direct Blood Pressure Measurement

All blood pressure measurements were made by direct catheterization of either a femoral or carotid artery and the measurement of pressure pulses in the artery with a strain gauge pressure transducer.

In every case the blood pressure of each animal was measured after the fourth, eighth, and twelth week of the experimental period. The first measurement was made from the right femoral, the second from the left femoral, and the final measurement from the right carotid artery.

Twenty four hours rest followed the previous training session before the measurement was performed. The 24-hour time period was chosen to allow time for recovery from the previous training. A further 40 to 48 hours after the measurement allowed the animals sufficient time to return to the next training session.

On the surgery day the rats were taken individually in their cages to the surgery where they were then handled to calm them.

The surgical area was kept clean but not sterile. Postoperative wound infection was not a problem during the study.

During the surgery and the measurement of the blood pressure the animals were anesthetized with a halothane-nitrous oxide-oxygen mixture. The gas was administered via a Boyle Apparatus (Medical Section of British Oxygen Engineering Ltd., London). The machine was calibrated prior to the experiment. The closed system was used, recirculating the gas after carbon dioxide removal in a Boyle Absorber Mark III (British Oxygen Co. Ltd.). Oxygen and Nitrous Oxide (Linde) were obtained from Union Carbide Canada. The inhalant anesthetic was halothane (Fluothane, Ayerst Laboratories, Montreal Canada).

The choice of anesthetic for this experiment was based on several considerations: rapid induction and recovery, safety to the experimenter and the animal, availability of the anesthetic and the means to administer it, and the results of pilot work. The Halothane-Nitrous Oxide proved most advantageous on each of these considerations. The less favourable features of the Halothane-Nitrous Oxide anesthetic include: a general blood pressure depressor effect, and the absence of literature available on the effects of Halothane-Nitrous Oxide on the rat.

Throughout the procedure the oxygen and nitrous oxide flow rates were kept constant at 1 liter per minute and 2 liters per minute respectivly. The halothane level changed as follows during the surgery: 2.5 percent during induction, 1.7 percent during artery exposure and cannulation, 1.0 percent during the data collection, and 1.7 percent to the termination of the procedure. The time at each stage of anesthesia for each animal varied. These times were recorded and appear in Appendix C and D.

During induction each animal was placed in a large glass jar with a loosely fitting metal plate covering the opening. The inlet and outlet tubes from the anesthetic machine were connected to two holes in the metal plate. The animal was observed closely during this induction phase. When the animal lost consciousness it was transferred to the surgical table. The inlet and outlet hoses were moved and attached to a fixed nose cone into which the animal's snout was placed. During the transfer the halothane level was decreased from 2.5 to 1.7

percent.

After transfer from the induction container the animal was placed on its back and immediately secured in place on a surgical table. Adhesive tape was placed loosely over all four limbs to help stabilize the animal and expose the surgical sites. The surgical site was then shaved with an electric clipper. This was followed by a rinse of the site with 70 percent alcohol. In the case of the femoral artery surgery, the site was further shaved with a safety razor to remove most of the remaining fur. The site was then wiped dry.

The femoral artery site measurements on the right and left sides were procedurally identical and will be described first. Following the site preparation, an incision approximately 1 to 1.5 cm in length was made on the upper inner thigh close to the abdomen. The tissue was separated to expose the femoral artery. The artery was then isolated with special care to separate all accompanying nerves and connective tissue. Following isolation three silk ligatures were drawn under the artery and loosely tied. The most proximal was no. 1 silk (Ethicon code A57) This proximal ligature served as a blood flow control; by tightening this ligature blood flow was occluded, when loosened blood could flow through the vessel. The two distal ligatures were no. 4-0 silk (Ethicon code A53).

Once the artery was isolated and loosely ligated, the most distal ligature was tightened securely with a square knot, permanently ligating the artery. The artery was then stretched between the proximal and distal ligatures stopping blood flow in

the area between the ligatures.

A very small incision was made in the artery between the ligatures. The resulting small hole in the artery was then explored with fine tipped forceps. When the forceps were partially opened the tip of the catheter (PE 50 tubing) was inserted into the artery. The catheter was then held in the artery while the forceps were removed. Once in the artery the catheter was secured in place by tightening the center ligature around the catheter within the artery. The proximal ligature was then released allowing blood flow onto the catheter tip and transmitting the pressure pulses to the pressure transducer. At this point the halothane level was decreased to 1.0 percent.

Once in place the patency of the catheter was ensured by the injection of a very small amount of heparinized saline (9 parts sterile isotonic saline to 1 part heparin sodium (1000 USP units, source swine intestinal mucosa, pres. benzyl alcohol 0.9 percent v/v, Allen and Hanburys). Further injection of small quantities were made when necessary to maintain patency. The 1.0 percent halothane level was maintained during the blood pressure recording until a stable measurement was obtained. Once the recording was completed the halothane level was returned to 1.7 percent for catheter removal and wound closing.

In order to remove the catheter the following procedure was used. The proximal ligature was again tightened to stretch the artery and stop the blood flow to the segment of the artery between the outer ligatures. The catheter was then removed. The center ligature, which formerly held the catheter in place was

moved proximally and tightened and permanently tied with a square knot preventing any further blood flow to the segment formerly catheterized. The most proximal ligature was loosened and removed. The excess ligature from the two distal ligatures was cut off. The wound was closed with 4 or 5 sutures (non-absorbable surgical suture, 00 silk, Ethicon Sutures Ltd.). Each suture was closed with a square knot and the excess thread removed. As soon as the wound was closed the halothane level was dropped to 0.0 percent and the nitrous oxide flow was stopped. Oxygen was continued at 1.0 liters per minute while the area surrounding the wound was cleaned and the wound dusted with antibiotic powder (Eye and Wound powder, Ayerst Laboratories, Montreal, Canada). The animal was then removed from the operating tray and recovery was encouraged by warming and gentle stimulation by patting and stroking. Once the animal regained consciousness and locomotor ability it was returned to its cage and observed until complete consciousness returned. The animal was then returned to the housing room and replaced in the cage rack.

In the days following the surgery the animals were carefully observed for cleanliness of the wound and general health. In any case where the sutures remained one week post surgery they were removed. Removal of the sutures was accomplished without the need for anesthetic. In most cases the animals removed the sutures themselves by the sixth day, making removal by the experimenter unnecessary and leaving a very clean wound. In all cases the animals were given greater than 40 hours

recovery time following the surgery before the next training period on the treadmill. The trained animals were closely watched on the treadmill to ensure that they were able to complete the training in the week following the surgery.

The right carotid artery catheterization and blood pressure measurement was performed only as a terminal measurement after the twelth week of the experiment. The anesthetic induction procedure was identical to that described previously for the femoral artery measurements. The site was prepared by shaving, as closely as possible, a large area on the ventral side of the neck using electric clippers. The area was then rinsed with 70 percent alcohol and dried. A midline incision was made along the length of the neck. The underlying tissue was separated to expose the trachea and tissue retractors were applied to keep the trachea exposed. Further separation exposed the sheath containing the carotid artery. The artery was carefully isolated from all the other tissues. Once isolated three loosely tied ligatures were placed around the artery, and catheterization was performed in the same manner as described in the femoral artery procedure.

Once the catheter was in place the halothane level was reduced immediately to 1.0 percent and the patency of the catheter confirmed by a very small injection of heparinized saline. The pressure was allowed to stabilize and the measurement was recorded.

After a stable record was obtained the halothane level was again raised to 1.7 percent, the catheter removed, and the

artery securely ligated above the catheterization site. The retractors were then removed. The animal was then partially exsaguinated by cardiac puncture and the withdrawal of 4 to 6 ml of blood. The extracted blood was immediately cooled in an ice water bath and spun at 600 G for 15 minutes. The plasma was then drawn off and frozen. Following the cardiac puncture the animal was removed from the nose cone. The heart and both kidneys were then removed for further study. Wet weight measurements of the heart and left kidney were made. The soleus muscle from each leg was removed and immediately quick frozen in liquid nitrogen and subsequently stored over dry ice. Kidney and aorta samples were prepared for histological examination at a later time.

Analysis of the Data

Body weight, food intake, duration of measurement procedures, heart rate, and blood pressure data were analyzed by analysis of variance for repeated measures models with unequal cell size. The computation was performed with the use of Biomedical Computer Programs Series-P (BMDP) developed at The University of California, Los Angeles (BMDP2V, pp. 549-52)

Organ weight data were analyzed by analysis of variance with unequal cell sizes. The computation was carried out with the use of BMDP (BMDP1V, pp. 523-31)

Analysis of covariance in the case of food intake-body weight covariance and blood pressure-body weight covariance was performed for one grouping variable, one trial factor, and one covariate changing over trials. The computation was carried out with the use of BMDP (BMDP2V, pp. 560-62)

Differences between groups were considered statistically significant where the probability of the event was less than 0.05.

D. RESULTS AND DISCUSSION

This chapter represents a presentation and discussion of data collected from August 1980 to April 1981. The methods employed in collecting the data were described in the previous chapter.

Age of the Experimental Animals

The age at division into experimental groups and initiation of the diet and training regimens is recorded in Appendix A. The mean age of the groups at the initiation of the experimental protocol were: NCN - 40.9 days, NCT - 41.9 days, HSN - 41.7 days, HST - 41.4 days, all within a range of one day.

It was found that the animals tolerated the diet and exercise programs without major difficulties (that is weight gain and general health of the animals seemed normal). The number of animals sucessfully measured at each 4-week interval was recorded in Appendix B. Data is missing where the catheterization was unsuccessful or when animals died prematurely. The incidence of premature mortality was distributed across groups. Four deaths occurred in the HSN group, two in the HST group, and one in the NCT group.

Body Weights

The data recorded on table 4-1 represent weekly mean weights of the animals. Analysis of the data revealed statistically significant differences ($p < 0.0001$) in body weight changes between trained and nontrained groups on the two diet regimens. Figures 4-1 and 4-2 represent the weight changes for the NC and HS groups respectively.

TABLE 4-1 BODY WEIGHT

Mean Post-Training Body Weight (grams) +/- SEM (n)

Normal Chow *

Week	Group NCN	NCT
1	178.4 +/- 3.8 (20)	186.8 +/- 3.1 (21)
2	225.7 +/- 4.0 (20)	225.6 +/- 3.2 (21)
3	269.4 +/- 3.9 (20)	256.7 +/- 3.1 (21)
4	301.3 +/- 3.8 (20)	282.4 +/- 2.9 (20)
5	322.8 +/- 4.4 (20)	299.4 +/- 3.0 (20)
6	342.5 +/- 4.8 (20)	311.8 +/- 3.1 (20)
7	362.1 +/- 5.3 (20)	323.8 +/- 3.0 (21)
8	375.6 +/- 5.4 (20)	331.9 +/- 3.2 (21)
9	383.0 +/- 5.5 (20)	336.4 +/- 3.1 (20)
10	394.1 +/- 5.8 (20)	339.8 +/- 3.1 (20)
11	405.9 +/- 5.9 (20)	341.2 +/- 3.1 (20)
12	412.5 +/- 6.8 (20)	338.7 +/- 3.3 (20)

High Salt *

Week	HSN	HST
1	187.7 +/- 4.1 (23)	177.2 +/- 3.8 (19)
2	230.9 +/- 4.4 (23)	212.8 +/- 3.9 (19)
3	266.1 +/- 4.2 (23)	242.6 +/- 4.0 (19)
4	294.3 +/- 4.9 (23)	264.3 +/- 4.6 (19)
5	315.1 +/- 6.7 (23)	278.9 +/- 5.0 (19)
6	331.8 +/- 7.4 (23)	292.3 +/- 5.1 (19)
7	344.4 +/- 8.4 (22)	302.8 +/- 4.9 (19)
8	350.1 +/- 7.5 (21)	313.4 +/- 4.5 (19)
9	358.1 +/- 8.0 (21)	314.0 +/- 4.8 (19)
10	366.8 +/- 9.1 (20)	319.4 +/- 5.5 (18)
11	373.8 +/- 7.5 (19)	321.7 +/- 4.7 (18)
12	374.9 +/- 7.3 (19)	315.9 +/- 4.4 (18)

* p less than 0.0001

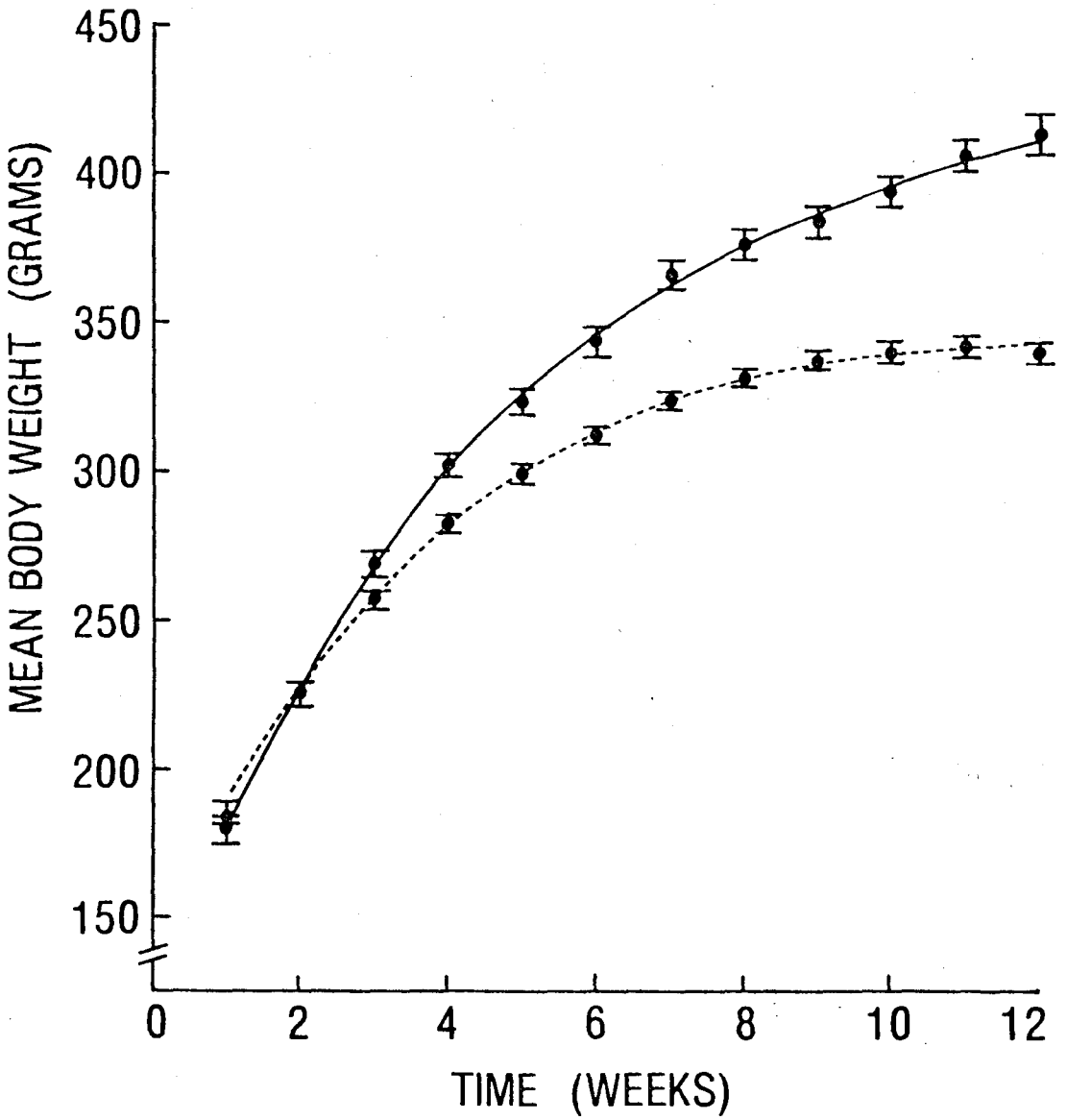

FIGURE 4 - 1

MEAN BODY WEIGHTS (± STANDARD ERROR) OF DS RATS ON NORMAL CHOW DIET.

NCN = NORMAL CHOW NONTRAINED (SOLID LINE)
NCT = NORMAL CHOW TRAINED (DASHED LINE)

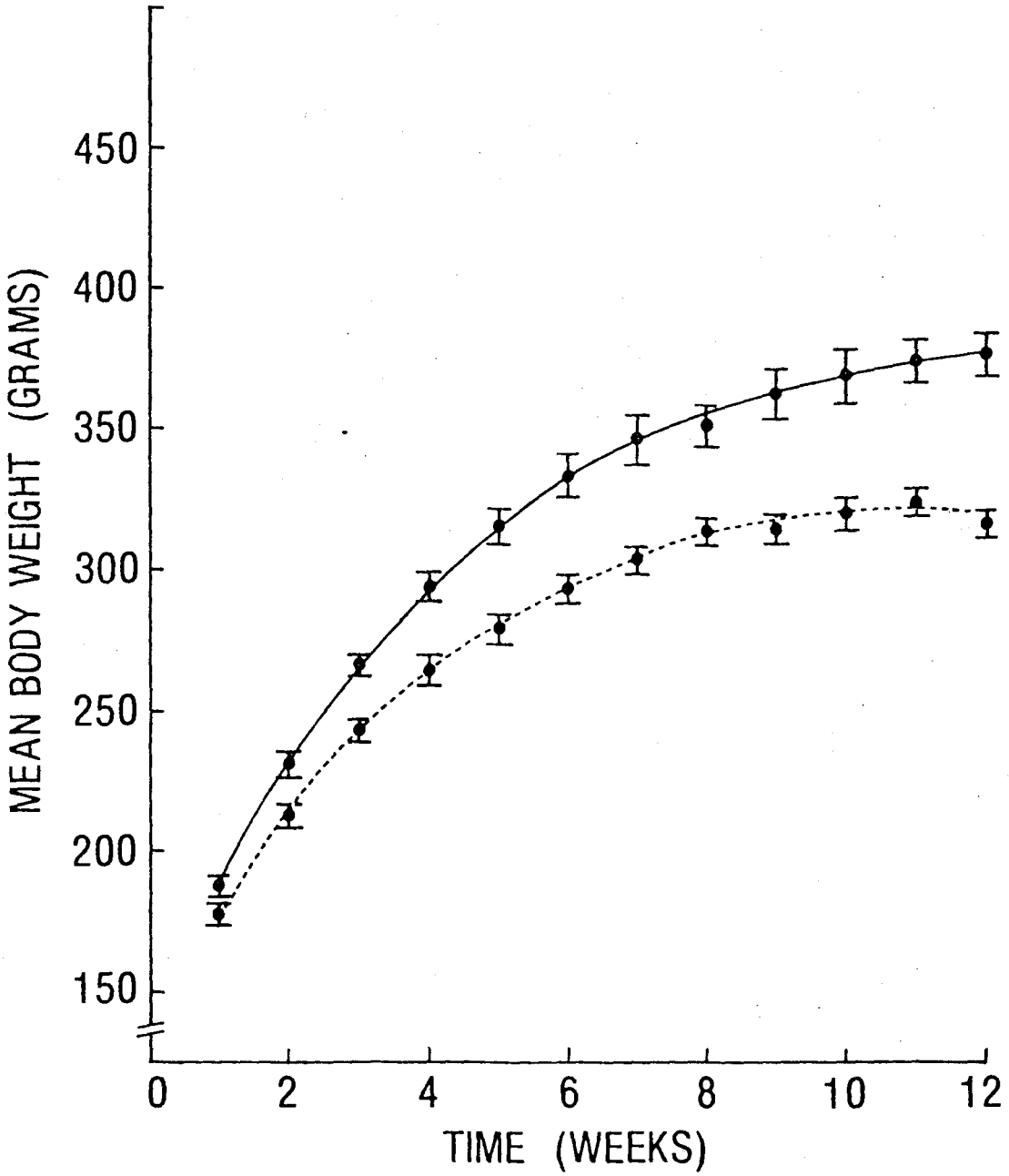

FIGURE 4 - 2

MEAN BODY WEIGHT (± STANDARD ERROR) OF DS RATS ON HIGH SALT DIET.

HSN = HIGH SALT NONTRAINED (SOLID LINE)
HST = HIGH SALT TRAINED (DASHED LINE)

Previous authors have reported alterations of growth similar to those reported in the present study (Crews and others, 1969; Pitts and Bull, 1977). Previous investigation has also revealed that very light training did not result in growth alterations (Driori and Folman, 1976). The training employed in the present study was similar in type and intensity to those previous studies reporting alterations in growth due to training (Crews and others, 1969; Pitts and Bull, 1977) and much more intense than the investigator reporting no effect of training (Driori and Folman, 1976).

Pfeffer and others (1978), studying the effect of prolonged swim training (previously described) on female normotensive (Wistar and Wistar-Kyoto) and hypertensive (SHR) rats, found no significant effect of training on body weight or growth rates of the normotensive rats. However the trained female SHR weighed less than their sedentary controls. This significant weight difference did not however, accompany blood pressure differences between trained and nontrained groups of female SHR.

Food Intake

Food intake was recorded daily. The data presented on Table 4-2 (Figure 4-3 and 4-4) represent the food intakes over one week time periods (the group mean of the total food consumed by each animal in 7 days divided by 7). Spilled food was not measured. On occasions when the amount of food consumed appeared excessive, suggesting excessive food spillage, the measurement was discarded. Water intake was measured daily but due to the type of water container used, reliable measures of actual water

consumption were not obtained. This data has not been included.

The absolute amount of food consumed by the NCN group was significantly greater (p less than 0.01) than the NCT group. When the animal weight was used as a covariate this difference was no longer significant (p greater than 0.05). There was no significant difference between absolute food intakes of the HSN and HST groups (p greater than 0.1). When body weight was used as a covariate the HST group consumed a greater amount of food than the HSN (p less than 0.01) (Table 4-3).

The results of the present experiment are similar to previous studies. On the normal chow diet, the food intake did not increase to make up for the increased caloric expenditure of the trained group. As a result, the trained group gained weight more slowly reaching a lower maximum weight at the end of the 12-week training period. The high salt trained group did tend to eat proportionally more than the nontrained group. The reason for this difference was not known: similar results could not be found in the literature. As the differences in food intake between HSN and HST groups was most pronounced in the later weeks of the protocol the differences might be associated with the prolonged high salt consumption.

Blood Pressure

The results are shown in Tables 4-4 and 4-5 and Figures 4-5, 4-6, and 4-7. Analysis of covariance was also performed with growth as a covariate and appears in Table 4-6.

The comparisons between trained and nontrained groups of each regimen detected significant differences (p less than

TABLE 4-2 FOOD INTAKE

Mean Daily Food Intake (grams) +/- SEM (n)

Normal Chow *

Week	Group NCN	NCT
1	23.8 +/- 0.5 (20)	23.7 +/- 0.5 (21)
2	24.9 +/- 0.5 (20)	23.8 +/- 0.4 (21)
3	25.5 +/- 0.7 (20)	24.1 +/- 0.3 (21)
4	26.7 +/- 0.6 (20)	24.9 +/- 0.4 (20)
5	26.1 +/- 0.5 (20)	24.4 +/- 0.3 (20)
6	25.7 +/- 0.4 (20)	23.7 +/- 0.3 (20)
7	25.8 +/- 0.6 (20)	24.9 +/- 0.3 (20)
8	24.5 +/- 0.6 (20)	22.7 +/- 0.3 (20)
9	23.5 +/- 0.4 (20)	21.4 +/- 0.4 (20)
10	23.7 +/- 0.4 (20)	22.3 +/- 0.4 (20)
11	24.4 +/- 0.4 (20)	23.4 +/- 0.5 (20)
12	22.6 +/- 0.4 (20)	23.1 +/- 0.5 (20)

High Salt **

Week	HSN	HST
1	24.7 +/- 0.5 (23)	23.4 +/- 0.6 (19)
2	24.9 +/- 0.4 (23)	23.6 +/- 0.5 (19)
3	26.2 +/- 0.3 (23)	25.1 +/- 0.4 (19)
4	26.5 +/- 0.7 (22)	26.0 +/- 0.5 (19)
5	26.1 +/- 0.9 (23)	26.3 +/- 0.6 (19)
6	27.0 +/- 0.7 (22)	26.4 +/- 0.6 (18)
7	24.3 +/- 1.1 (20)	26.8 +/- 0.5 (19)
8	24.0 +/- 1.0 (21)	25.1 +/- 0.6 (18)
9	24.1 +/- 0.9 (20)	24.7 +/- 0.9 (17)
10	23.8 +/- 0.8 (19)	24.9 +/- 0.6 (17)
11	24.0 +/- 0.7 (18)	24.5 +/- 0.6 (18)
12	23.3 +/- 0.9 (18)	24.3 +/- 0.7 (18)

* p less than 0.01, ** p greater than 0.1

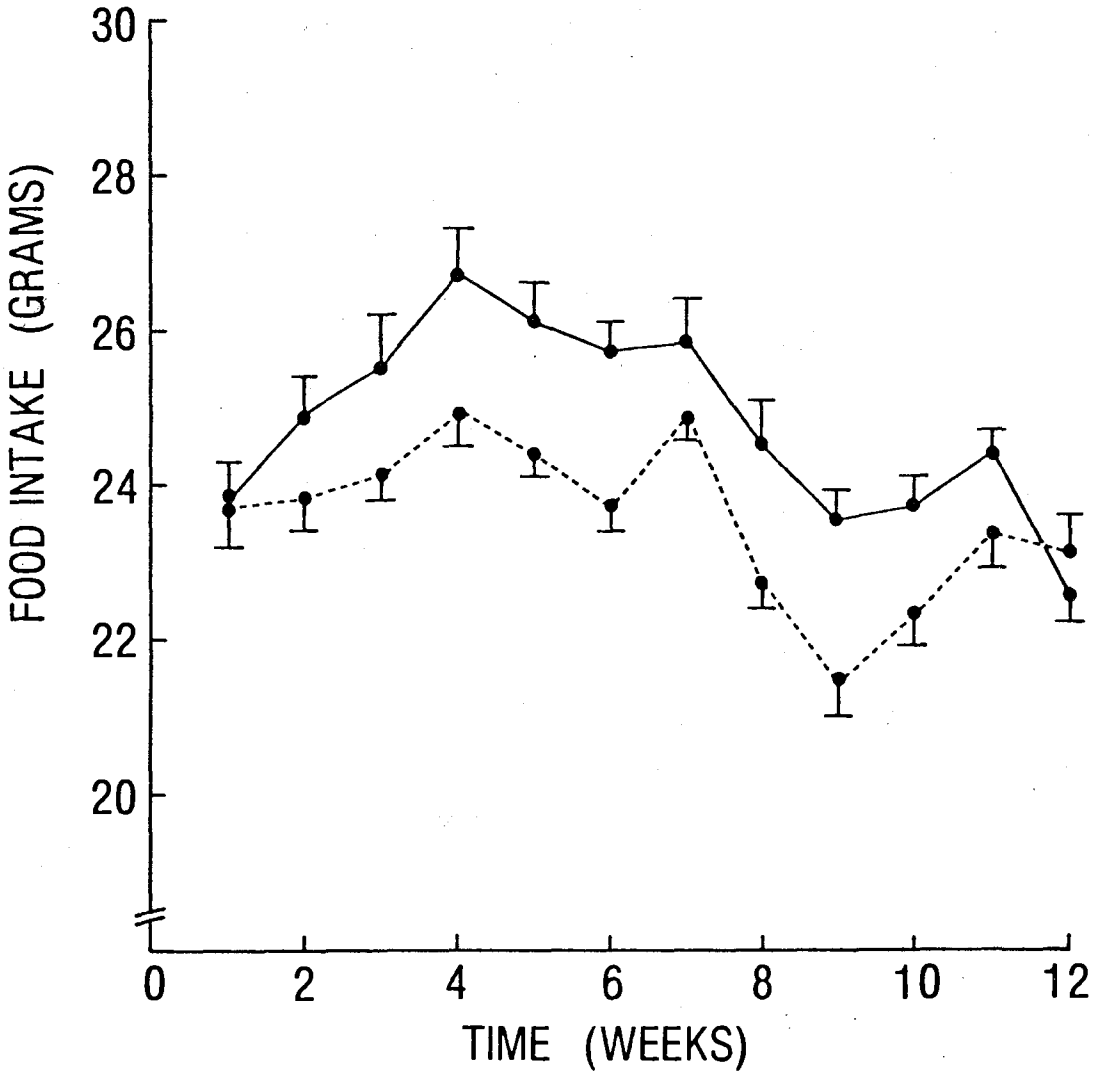

FIGURE 4-3

MEAN DAILY FOOD INTAKE (±STANDARD ERROR) OF DS RATS ON NORMAL CHOW DIET.

NCN = NORMAL CHOW NONTRAINED (SOLID LINE)
NCT = NORMAL CHOW TRAINED (DASHED LINE)

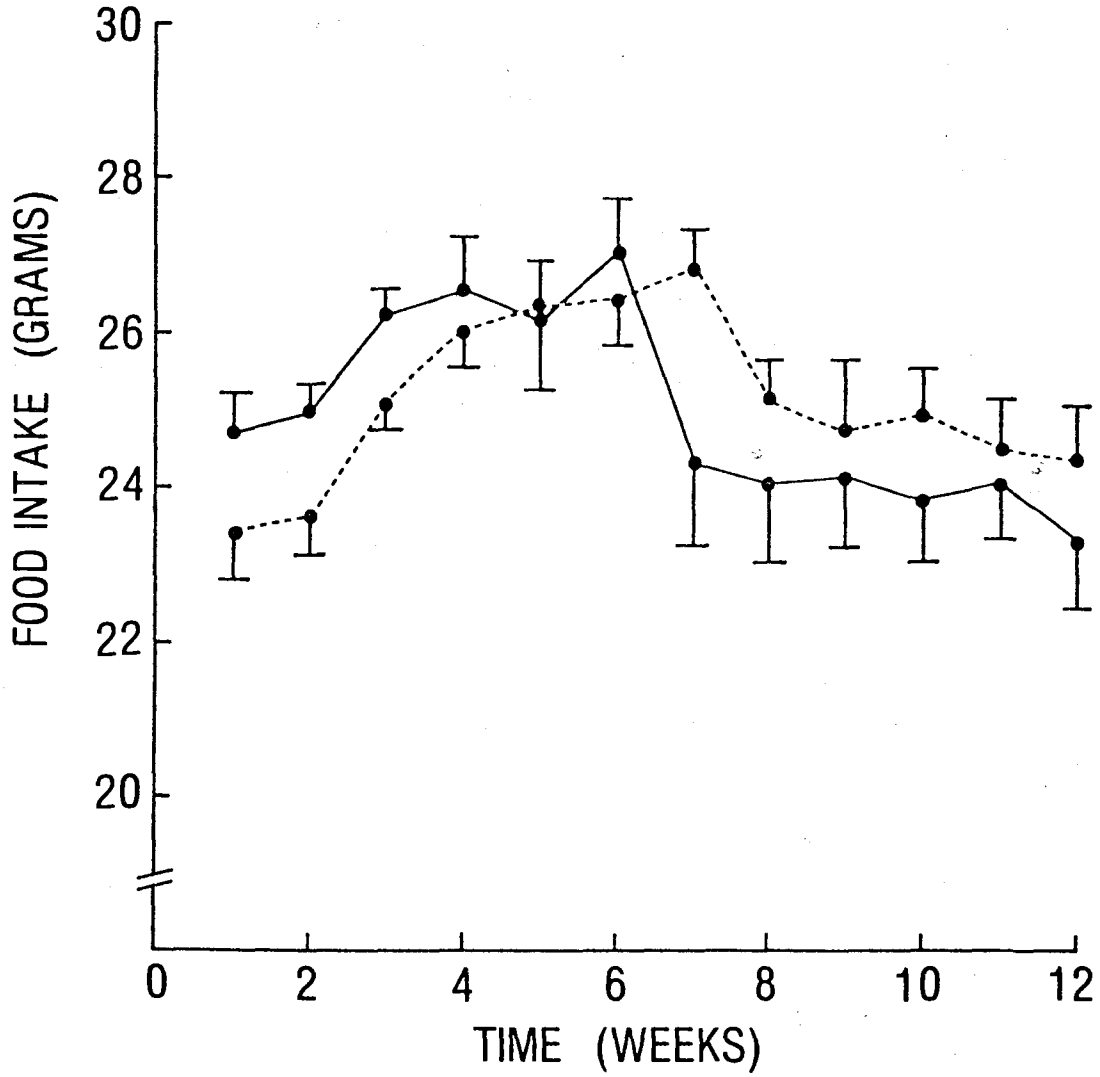

FIGURE 4-4

MEAN DAILY FOOD INTAKE (± STANDARD ERROR) OF DS RATS ON HIGH SALT DIET.

HSN = HIGH SALT NONTRAINED (SOLID LINE)
HST = HIGH SALT TRAINED (DASHED LINE)

TABLE 4-3 FOOD INTAKE ADJUSTED FOR GROWTH

Mean Food Intakes (grams) Adjusted for Growth Rate

Week	Group NCN	NCT	HSN	HST
1	30.70	30.18	31.19	29.95
2	29.29	28.22	28.91	28.42
3	27.51	26.92	28.60	28.73
4	27.07	26.19	26.34	28.30
5	25.22	24.80	26.84	27.76
6	23.81	23.47	26.41	27.39
7	22.85	23.97	22.11	27.26
8	20.87	21.39	22.39	25.02
9	19.40	19.82	21.50	24.17
10	19.03	20.57	20.93	24.23
11	19.06	21.54	20.45	23.49
12	16.98	21.44	19.65	23.40

TABLE 4-4 BLOOD PRESSURE

Mean Systolic and Diastolic Blood Pressure (mm Hg) +/- SEM (n)

Normal Chow *		Group NCN	NCT
Week			
4	Systolic	122.71 +/- 3.6 (14)	111.92 +/- 2.5 (19)
	Diastolic	89.32 +/- 2.4	79.34 +/- 1.1
8	Systolic	133.63 +/- 1.9 (20)	120.35 +/- 2.3 (20)
	Diastolic	95.13 +/- 1.3	82.95 +/- 1.8
12	Systolic	147.58 +/- 2.9 (20)	117.95 +/- 2.1 (19)
	Diastolic	108.00 +/- 2.2	86.08 +/- 1.6

High Salt *		HSN	HST
Week			
4	Systolic	145.5 +/- 3.0 (22)	131.9 +/- 3.1 (18)
	Diastolic	103.9 +/- 2.4	91.2 +/- 2.7
8	Systolic	165.0 +/- 3.3 (21)	145.3 +/- 3.9 (19)
	Diastolic	118.3 +/- 3.0	100.6 +/- 3.8
12	Systolic	166.1 +/- 4.9 (19)	133.8 +/- 3.9 (18)
	Diastolic	123.1 +/- 3.9	98.3 +/- 3.2

* p less than 0.0001

TABLE 4-5 CALCULATED MEAN ARTERIAL BLOOD PRESSURE

Group Mean Arterial Pressure (mm Hg) +/- SEM (n)

Normal Chow *	Group	
Week	NCN	NCT
4	100.46 +/- 2.6 (14)	89.54 +/- 1.5 (19)
8	107.74 +/- 1.4 (20)	96.03 +/- 1.8 (20)
12	120.68 +/- 2.3 (20)	97.03 +/- 1.7 (19)

High Salt *		
Week	HSN	HST
4	117.87 +/- 2.5 (22)	104.97 +/- 2.7 (18)
8	133.90 +/- 3.0 (21)	114.08 +/- 4.0 (19)
12	137.40 +/- 4.2 (19)	111.58 +/- 3.4 (18)

* p less than 0.0001

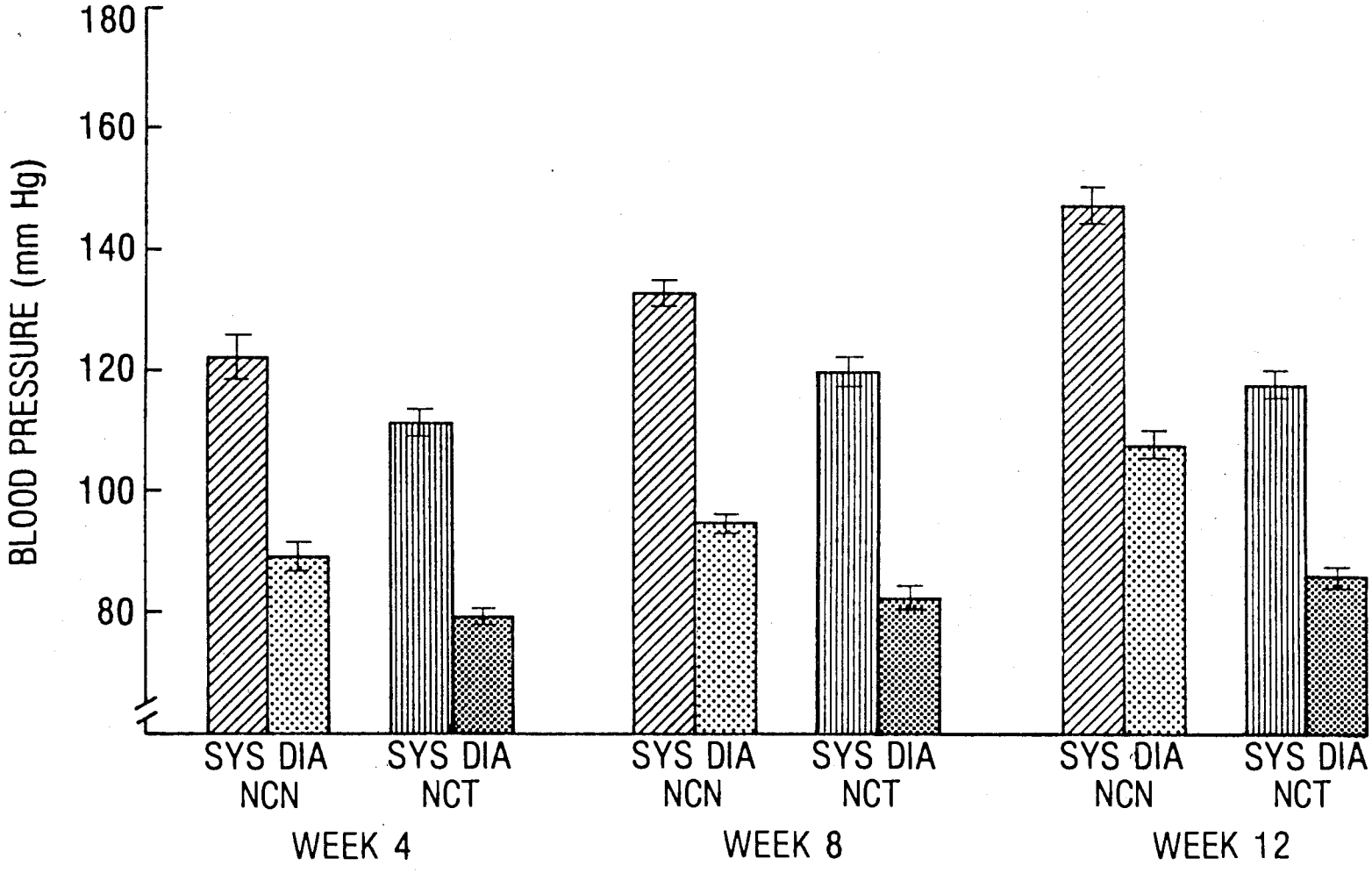

FIGURE 4 - 5

SYSTOLIC AND DIASTOLIC BLOOD PRESSURE (±STANDARD ERROR) OF DS RATS ON NORMAL CHOW DIET.

SYS = SYSTOLIC BLOOD PRESSURE; DIA = DIASTOLIC BLOOD PRESSURE
NCN = NORMAL CHOW NONTRAINED; NCT = NORMAL CHOW TRAINED

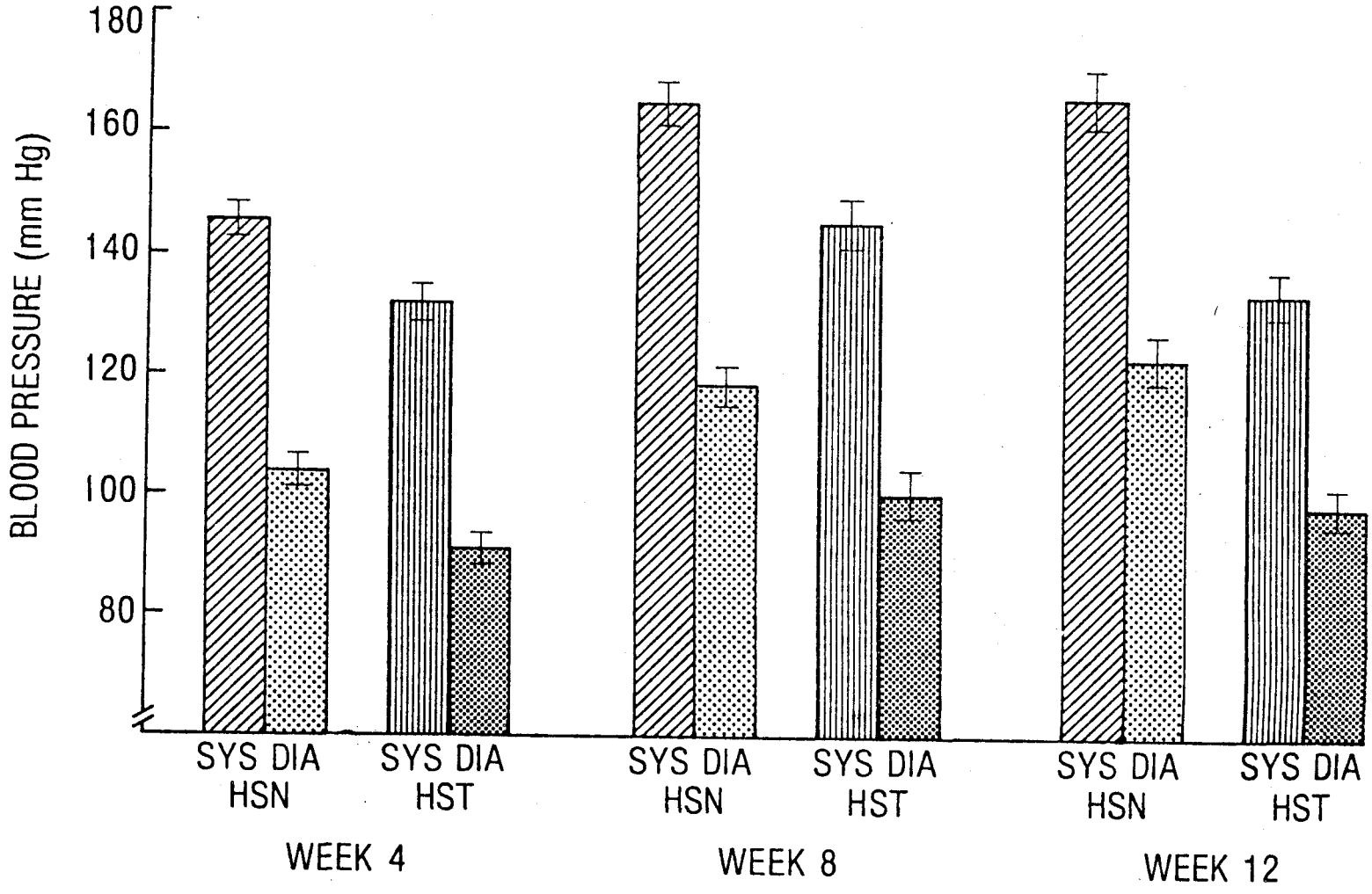

FIGURE 4 - 6

SYSTOLIC AND DIASTOLIC BLOOD PRESSURE (±STANDARD ERROR) OF DS RATS ON HIGH SALT DIET.

SYS = SYSTOLIC BLOOD PRESSURE; DIA = DIASTOLIC BLOOD PRESSURE
HSN = HIGH SALT NONTRAINED; HST = HIGH SALT TRAINED

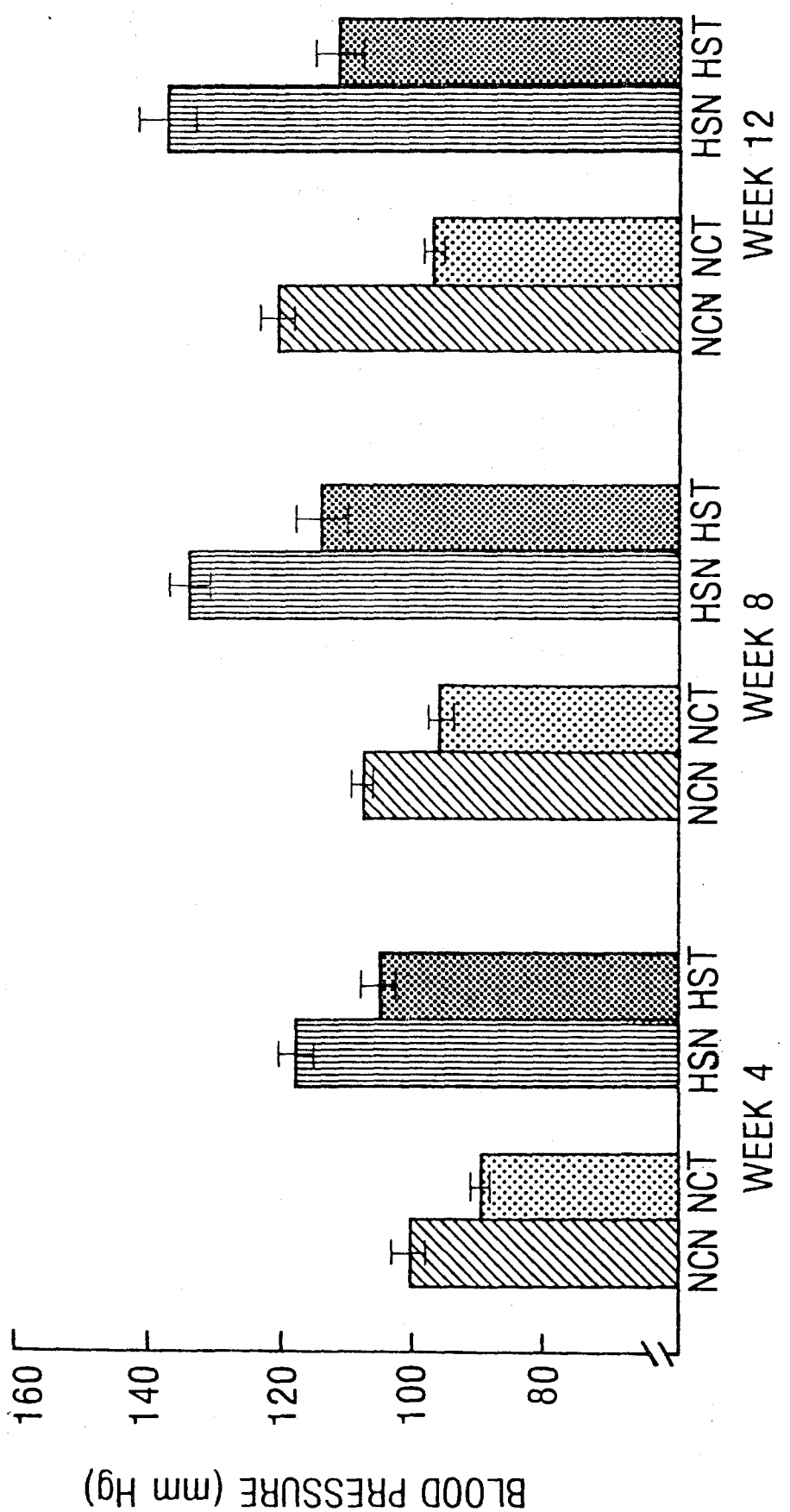

FIGURE 4 - 7

CALCULATED MEAN ARTERIAL BLOOD PRESSURE(± STANDARD ERROR) OF DS RATS ON NORMAL CHOW AND HIGH SALT.

NCN = NORMAL CHOW NONTRAINED; NCT = NORMAL CHOW TRAINED
HSN = HIGH SALT NONTRAINED; HST = HIGH SALT TRAINED

TABLE 4-6 BLOOD PRESSURE ADJUSTED FOR BODY WEIGHT

Group Mean Blood Pressure (mm Hg) Adjusted for Body Weight

Normal Chow

		Group	
		NCN	NCT
Week			
4	systolic	123.65	112.23
	diastolic	90.70	81.03
8	systolic	132.62	120.65
	diastolic	93.47	83.91
12	systolic	144.65	118.15
	diastolic	105.00	86.31

High Salt

		HSN	HST
Week			
4	systolic	148.20	138.03
	diastolic	105.33	94.16
8	systolic	164.75	145.17
	diastolic	120.09	100.21
12	systolic	160.96	135.56
	diastolic	121.04	99.92

0.0001). The systolic and diastolic blood pressure of the trained groups were, under both diet regimens, lower than the nontrained groups. This significant difference remained (p less than 0.01) when the weight factor was partially accounted for mathematically by analysis of covariance.

Several features made the present experiment different from previous experiments on training hypertensive rats. The most notable difference was the experimental model. Previous training studies have utilized normotensive rat strains (Tipton and others, 1973; Critz and Lipsey, 1976; Tharp, 1976; Tipton and others, 1977; Weiss, 1978; Pfeffer and others, 1978; Edwards and Diana, 1978; Evenwel and Struyker-Boudier, 1979), pharmacologically induced hypertensive rats (Critz and Lipsey, 1976; Tipton and others, 1977), the Okamoto SHR strain (Tipton and others, 1973; Dunne and others, 1974; Tipton and others, 1975; Burgess and others, 1976; Tipton and others, 1977; Weiss, 1978; Edwards and Diana, 1978; Evenwel and Struyker-Boudier 1979), as well as other hypertensive strains (Tharp, 1976; Booth and others, 1980). To date only one experiment using Dahl rats in a training study has been reported (Shepherd and others, 1980).

Many previous studies reported in the literature have used female rats (Tipton and others, 1973; Dunne and others, 1974; Tipton and others, 1975; Rock and others, 1976; Tipton and others, 1977; Edwards and Diana, 1978; Pfeffer and others, 1978; Shepherd and others, 1980). Dahl and others (1975) found sex differences in the DS rat to have a significant effect on the

development of hypertension on a high salt diet. Comparisons between the present study and the results of Shepherd (1981) must allow for the significant sex differences between male and female DS rats.

In addition to the animal model utilized considerable differences in the training methods have been reported. After treadmill running, swimming has been the next most commonly used training method (Critz and Lipsey, 1976; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979). Ad libitum activity wheel running has also been reported (Dunne and others, 1974; Rock and others, 1976). Swimming exercise has been criticized as being a foreign means of locomotion for the rat therefore a stress that may lead to a sustained increase in blood pressure (Critz and Lipsey, 1976). Weiss (1978) suggested that treadmill training is also a stress. The results of the present study suggested that even if training was a stressful event blood pressure reductions may still result.

Separating the effect of growth on blood pressure in the absence of any salt or exercise effects is not possible with the results of the present experiment. Previously reported results (Tobian and others, 1979), would suggest that the systolic blood pressure of male DS rats on a low salt diet gradually increased with age. In the present experiment systolic and diastolic blood pressures of the NCN group increased qualitatively similar to the results of Tobian and others (1979). The blood pressure response of the NCT group was however qualitatively more similar to DR rats on a low salt diet.

The blood pressure measurement methods have also differed. The most commonly used method reported in the literature has been the indirect tail-cuff method (Dunne and others, 1974; Tharp, 1976; Burgess and others, 1976; Critz and Lipsey, 1976; Rock and others, 1976; Tipton and others, 1977; Weiss 1978; Edwards and Diana, 1978; Evenwel and Struyker-Boudier, 1979; Shepherd and others, 1980). Direct carotid measurement has been used in some studies as a terminal measurement only (Tipton and others, 1973; Tipton and others, 1975; Tipton and others, 1977; Pfeffer and others, 1978). Anesthetics utilized during the direct procedure have included ether (Pfeffer and others, 1978), pentobarbitol sodium (Tipton and others, 1977), and in some cases the anesthetic agent was not stated (Tipton and others, 1973; Tipton and others, 1975).

As a result of the differences between measurement methods, comparison of the results of different experimenters has been difficult. Comparison of the absolute blood pressure measurements between the present study and previous studies was not performed as the differences in technique or anesthetic would strongly influence the absolute pressure obtained. Only the differences between trained and nontrained groups and the statistical significance of these differences were compared across experimenters.

The present study demonstrated statistically significant differences in systolic and diastolic blood pressure as a result of physical training. This contradicts several previous researchers (Dunne and others, 1974; Tipton and others, 1975;

Tharp, 1976; Rock and others, 1976; Critz and Lipsey, 1976; Weiss, 1978; Pfeffer and others, 1978), who found no significant effect of training on blood pressure of various rat models. This present experiment confirms findings of reductions of blood pressure due to training reported in several previous studies (Tipton and others, 1973; Burgess and others, 1976; Tipton and others, 1977; Edwards and Diana, 1978; Evenwel and Struyker-Boudier, 1979; Shepherd and others 1980).

In this study, the normal chow regimen nontrained group demonstrated a marked increase in systolic and diastolic blood pressure during the 12-week course of the experiment. Similar results were reported by Dahl and others (1968) on a one to two percent NaCl diet. The trained NC group did not experience a similar rise in blood pressure.

The high salt nontrained group experienced a rise in blood pressure similar to that previously reported for the DS rats (Dahl and others, 1968). On the HS regimen also there were marked differences between nontrained and trained groups that persisted throughout the experiment.

The present study has been for the most part phenomenological in nature. That is, the objective was to determine the effect of physical training on the blood pressure of DS rats. Further investigation into the possible mechanisms involved in the differences was not performed. As such the possible mechanism or mechanisms involved remain obscure. The DS rats do, however, have several documented features that may have been involved.

Tobian (1978), found that the isolated DS rat kidneys have significantly different pressure natriuresis curves than those of the DR rats. A transient increase in blood pressure would tend to enhance natriuresis (Tobian, 1981). Normally during intense exercise the kidney receives a reduced blood flow and would, therefore, not be able to excrete excess sodium during that time period. The reduced blood flow to the kidneys in exercise might, however, be altered by salt loading, the intensity of the exercise, or the specific characteristics of DS rats.

Another feature of the DS rat possibly involved in the present study could be their strikingly low urinary kallikrein levels as compared to DR rats (Carretaro and Scicli, 1978). It has been suggested from research on human subjects (Khomaziuk and others, 1979), that urinary kallikrein levels rise in hypertensives as a result of physical training accompanying a reduction in blood pressure levels.

Other hormonal changes as a result of training may have also played important roles in the training effect on blood pressure. Possibilities among these are prostaglandins (Zambraski and Dunn, 1980), renin, angiotensin, and aldosterone.

Rats (Meneely and others, 1957) and particularly DS rats (Dahl and others, 1972), exposed to a high salt diet were partially protected from the hypertension inducing effect of sodium when potassium was also increased in the diet. Recently, Goto, Tobian, and Iwai (1981) found that increasing the potassium intake (either KCl or K-citrate) of DS male rats

reduced the pressor response to intracerebroventricular hypertonic sodium and angiotensin II. Potassium has also been found to "leak" from muscle cells into the extracellular fluid as a result of prolonged aerobic activity in man (McKechnie and others, 1967). Another possibility would be that the increase in extracellular potassium as a result of exercise also acts in some way similar to dietary potassium to aid in the maintainance of lower blood pressure.

Many other factors could play major or minor roles in the effect of physical training. Shepherd (1981), stated that the intensity of the exercise was a very important factor in female DS rats. Based on preliminary data, he postulated that an optimum training intensity existed beyond which training was no longer as effective at modifying blood pressure.

Based on the results of this experiment, the development of salt-induced hypertension was decreased or slowed by the physical training program imposed. Whether the effect on the blood pressure would be prolonged beyond the 12 week period was not investigated. The effect on longevity of the animals was also not determined.

The first four weeks prior to the first measurement would seem to be of particular importance. The separation between the blood pressures of the trained and nontrained groups was already apparent by the 4th week measurement. The events of this time period might yield clues as to the factors initiating the development of the salt-induced hypertension and what part physical training played in ameliorating that development.

Organ Weight

Wet weights appear on Table 4-7. The organ weights also appear as a percent of body weight. Analysis of these results indicated no statistically significant differences (p greater than 0.1) between the heart weights of the trained and nontrained groups on the two diet regimens. (Figure 4-8; 4-9; 4-10; 4-11). When expressed as a percent of body weight, however, in both regimens the trained heart weights were significantly greater than the nontrained (p less than 0.01 HS, p less than 0.0001 NC).

The wet weights of the kidneys were significantly greater (p less than 0.0001) in both the nontrained groups as compared to their trained counterparts. When expressed as a percent of body weight, however, this difference disappeared (p greater than 0.1).

Other investigators have shown heart weights to increase both as a result of training and hypertension (Critz and Lipsey, 1976; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979). Changes in heart weights have not always been detected as a result of training (Tipton and others, 1977). Kidney weights have been unaffected by previous reported training studies (Tipton and others, 1977; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979).

The findings of the present experiment support previously reported results of similar experiments. The heart weight of the trained groups were relatively larger 20.8 percent on the normal chow regimen, and 15.4 percent larger on the high salt regimen.

TABLE 4-7 ORGAN WEIGHT

Mean Organ Weights (grams) and
Relative Organ Weights (percent) +/- SEM (n)

Normal Chow		Group NCN	NCT
Heart Weight	**	1.46 +/- 0.03 g(20)	1.46 +/- 0.02 g(19)
Relative Heart Weight	*	0.355 +/- 0.006 %	0.429 +/- 0.005 %
Kidney Weight	*	1.64 +/- 0.05 g(20)	1.39 +/- 0.02 g(19)
Relative Kidney Weight	**	0.398 +/- 0.007 %	0.409 +/- 0.005 %

High Salt		HSN	HST
Heart Weight	**	1.69 +/- 0.03 g(19)	1.65 +/- 0.05 g(18)
Relative Heart Weight	*	0.455 +/- 0.012 %	0.525 +/- 0.018 %
Kidney Weight	*	1.88 +/- 0.05 g(19)	1.54 +/- 0.03 g(18)
Relative Kidney Weight	**	0.504 +/- 0.012 %	0.489 +/- 0.010 %

* p less than 0.01, ** p greater than 0.1

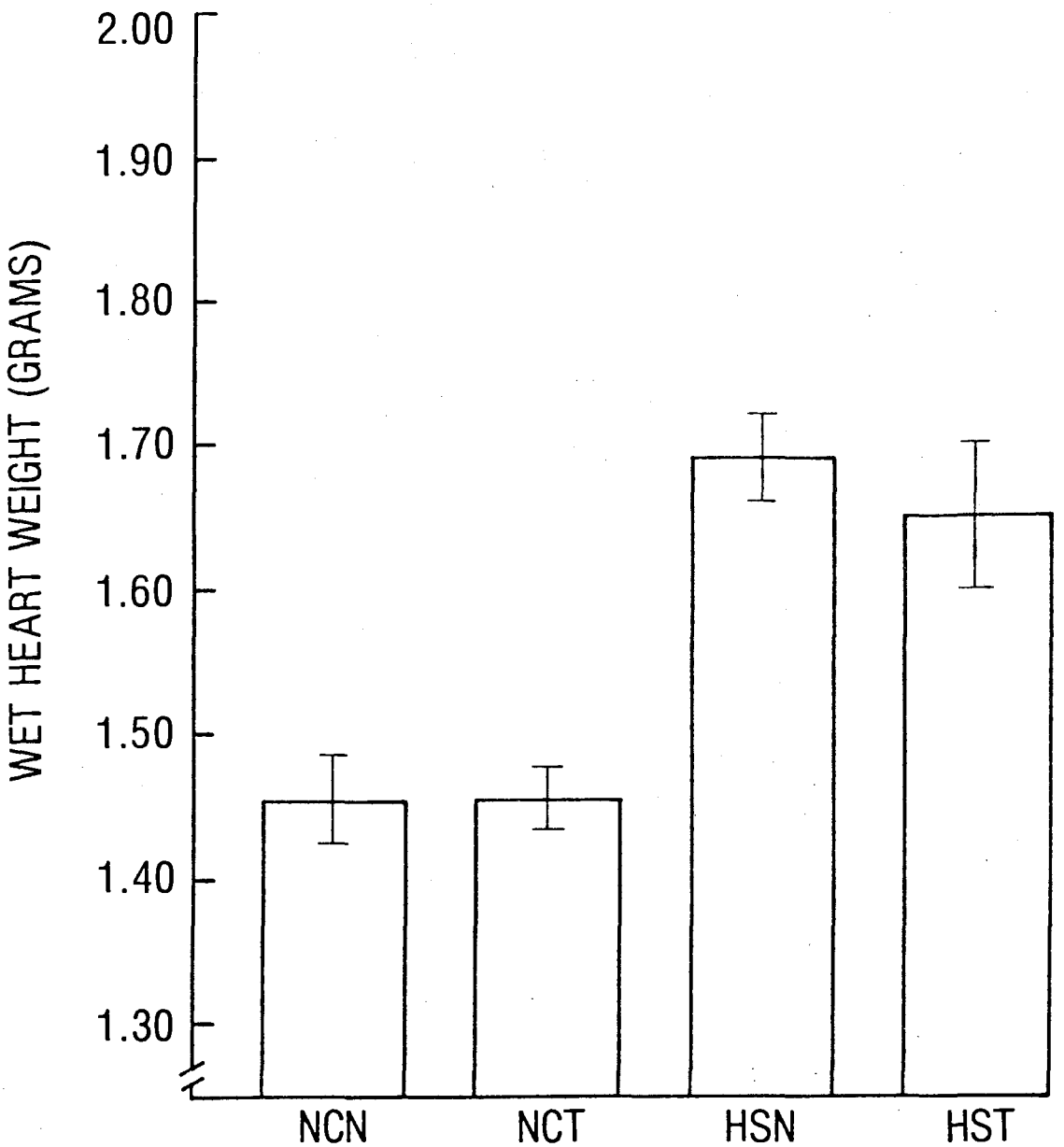

FIGURE 4-8

HEART WEIGHTS (WET)(± STANDARD ERROR) OF DS RATS

NCN = NORMAL CHOW NONTRAINED
NCT = NORMAL CHOW TRAINED
HSN = HIGH SALT NONTRAINED
HST = HIGH SALT TRAINED

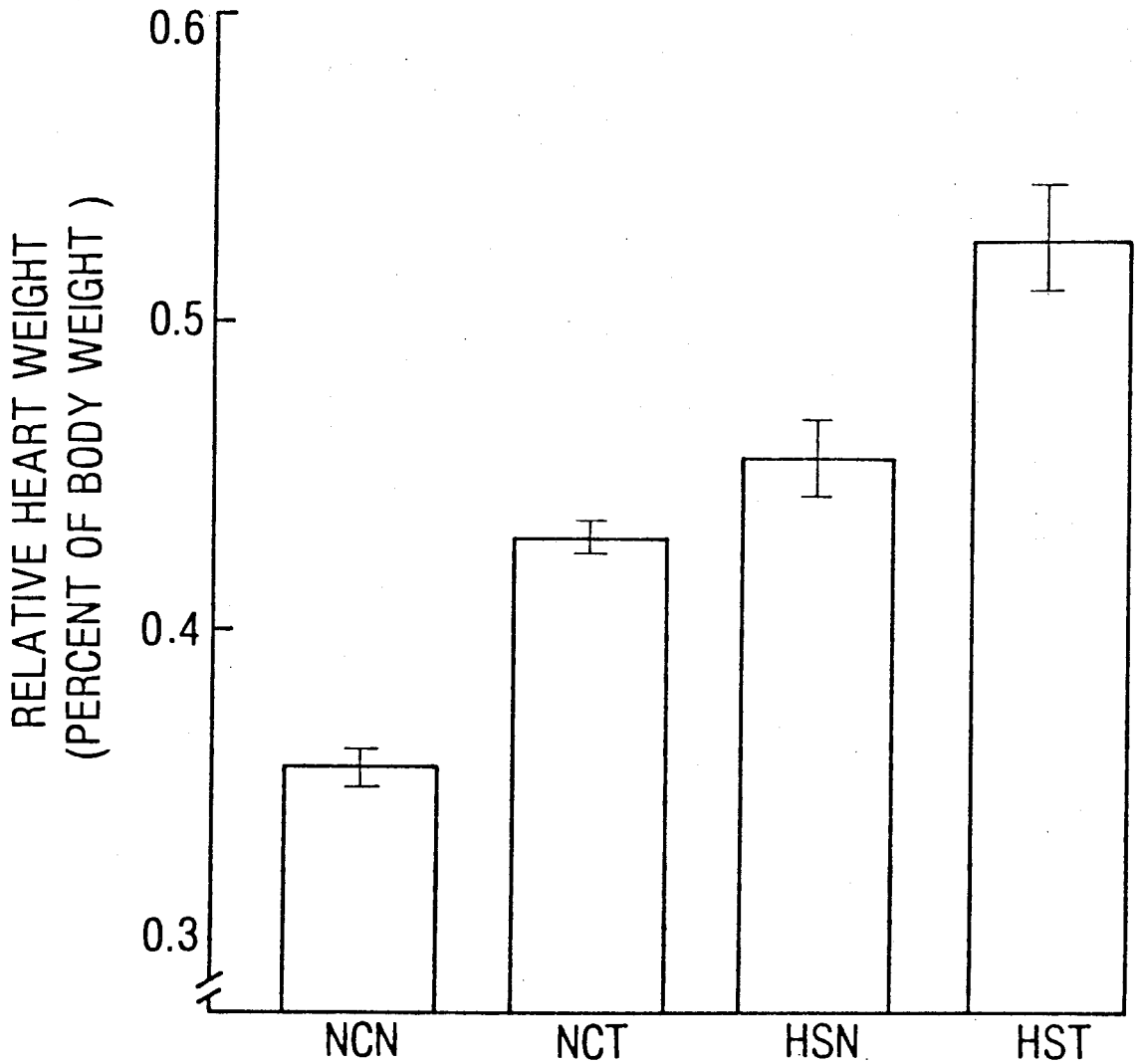

FIGURE 4 - 9

RELATIVE HEART WEIGHT (± STANDARD ERROR) OF DS RATS EXPRESSED AS PERCENT OF BODY WEIGHT.

NCN = NORMAL CHOW NONTRAINED
NCT = NORMAL CHOW TRAINED
HSN = HIGH SALT NONTRAINED
HST = HIGH SALT TRAINED

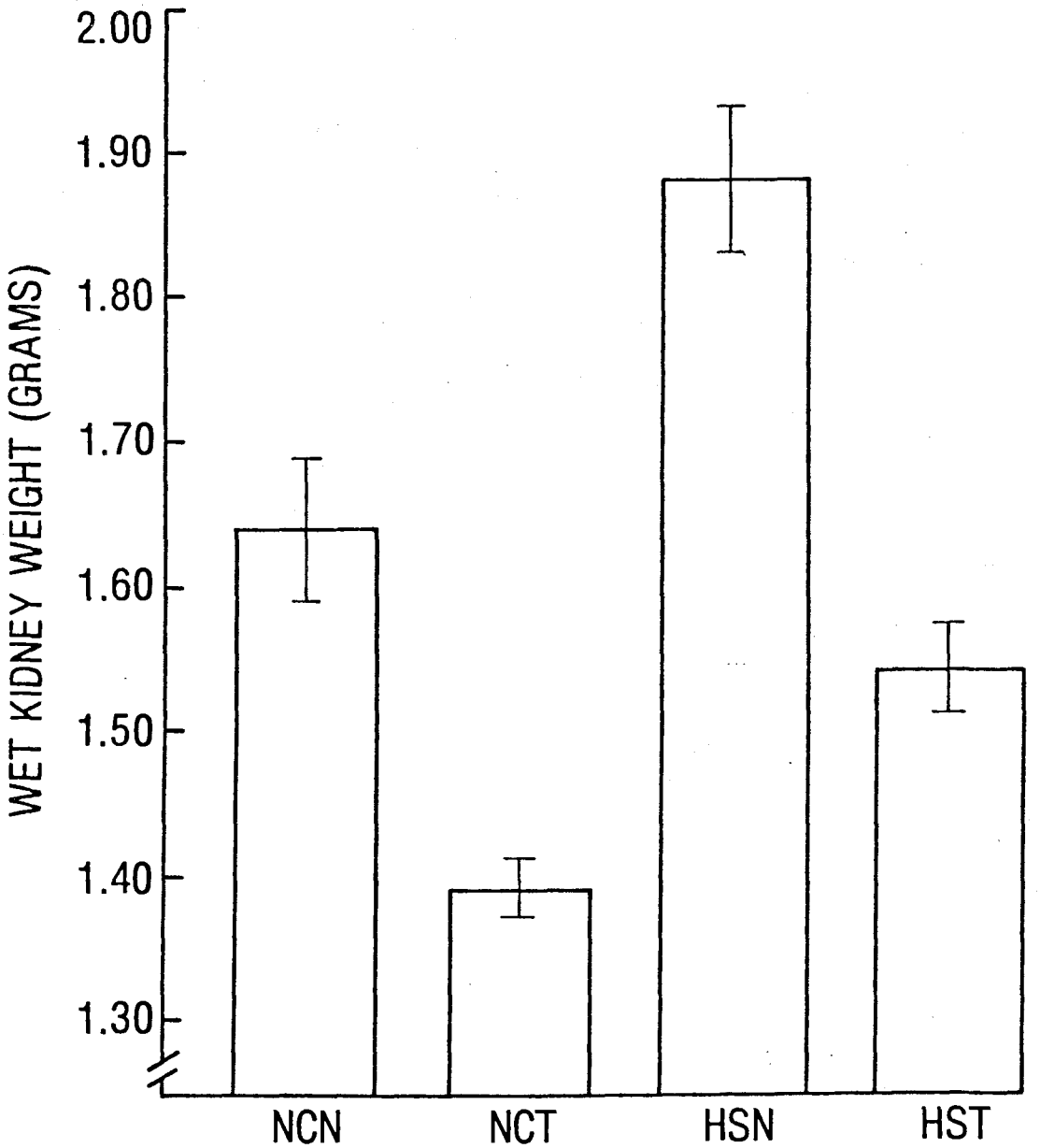

FIGURE 4 - 10

WEIGHTS OF LEFT KIDNEY (WET)(± STANDARD ERROR) OF DS RATS

NCN = NORMAL CHOW NONTRAINED
NCT = NORMAL CHOW TRAINED
HSN = HIGH SALT NONTRAINED
HST = HIGH SALT TRAINED

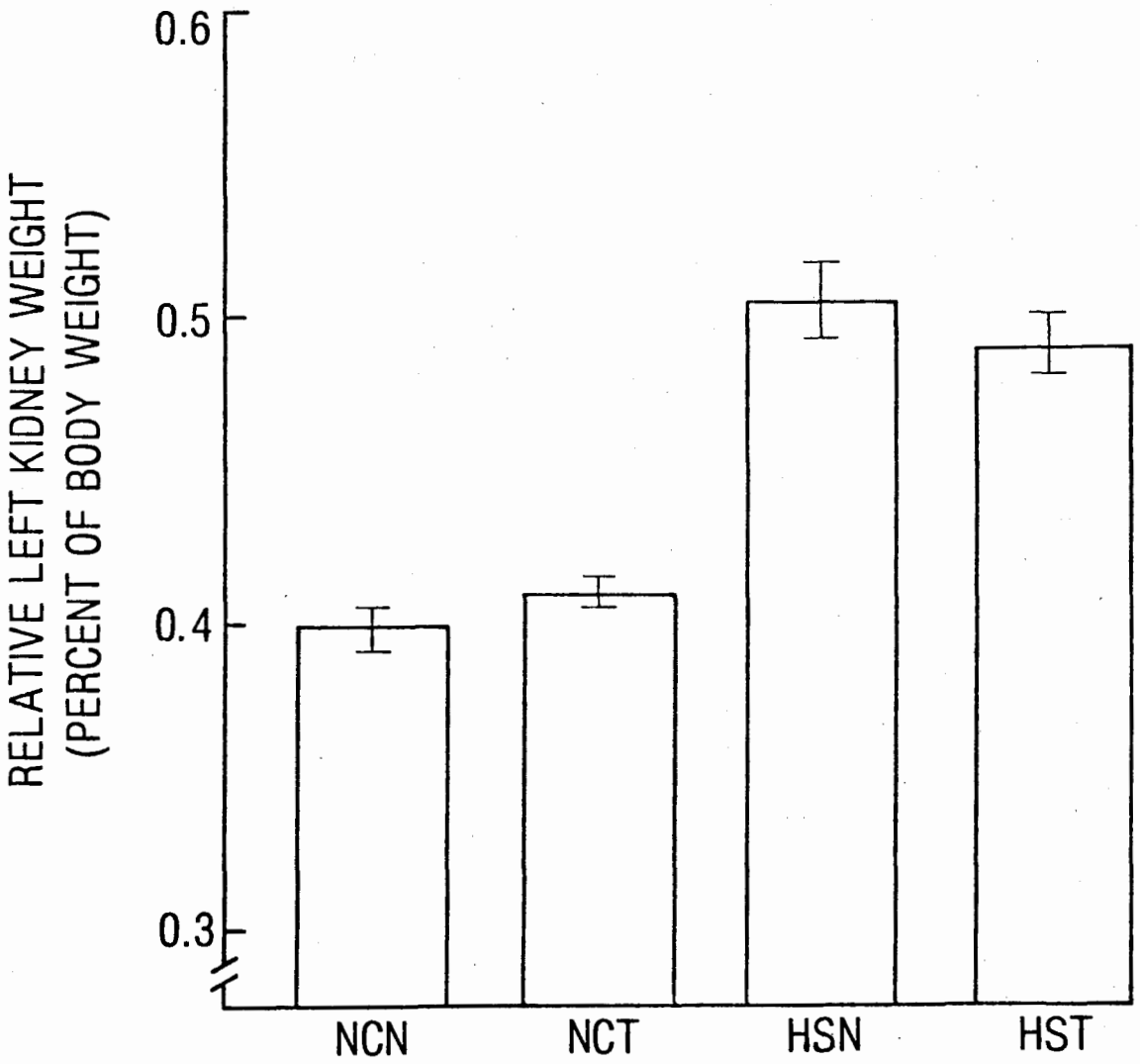

FIGURE 4-11

RELATIVE LEFT KIDNEY WEIGHT (± STANDARD ERROR) OF DS RATS EXPRESSED AS PERCENT OF BODY WEIGHT
NCN = NORMAL CHOW NONTRAINED
NCT = NORMAL CHOW TRAINED
HSN = HIGH SALT NONTRAINED
HST = HIGH SALT TRAINED

In agreement with previous studies, the relative kidney weights were very similar between trained and nontrained groups on both diet regimens.

Heart Rate

The heart and blood pressure measurements were obtained simultaneously by direct arterial catheterization while under anesthesia (Table 4-8). Differences between the heart rates of trained and nontrained groups were statistically significant (p less than 0.0001 for NC, and p less than 0.05 for HS) (Figure 4-12 and 4-13).

The effect of training on the heart rate has been reported frequently in hypertensive and normotensive rats. Several authors (Dunne and others, 1974; Rock and others, 1976; Tipton and others, 1977; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979) have found slower heart rates as a result of training. Dunne and others (1974) and Rock and others (1976) found the decrease in resting heart rate to accompany an increase in systolic blood pressure as measured by the tail-cuff technique. The finding that the heart rates also decreased in the nontrained animals, although to a lesser extent, was also reported by Pfeffer and others (1978) in normotensive and hypertensive rats over the course of a 24-week study.

The result of the present study supports the finding of a decrease in resting or in this case anesthetized heart rate as a result of training. In this experiment the reduction in heart rate accompanied lower blood pressures.

TABLE 4-8 HEART RATE

Mean Heart Rates (beats per minute) +/- SEM (n)

Normal Chow *

Week	Group NCN	NCT
4	421.4 +/- 11.0 (14)	374.1 +/- 6.5 (19)
8	422.7 +/- 7.7 (20)	368.7 +/- 5.0 (20)
12	366.7 +/- 8.1 (20)	310.7 +/- 5.7 (19)

High Salt **

Week	HSN	HST
4	409.0 +/- 8.2 (22)	384.0 +/- 5.3 (18)
8	371.9 +/- 7.0 (21)	361.9 +/- 4.7 (19)
12	319.4 +/- 6.0 (19)	299.5 +/- 6.7 (18)

* p less than 0.0001, ** p less than 0.05

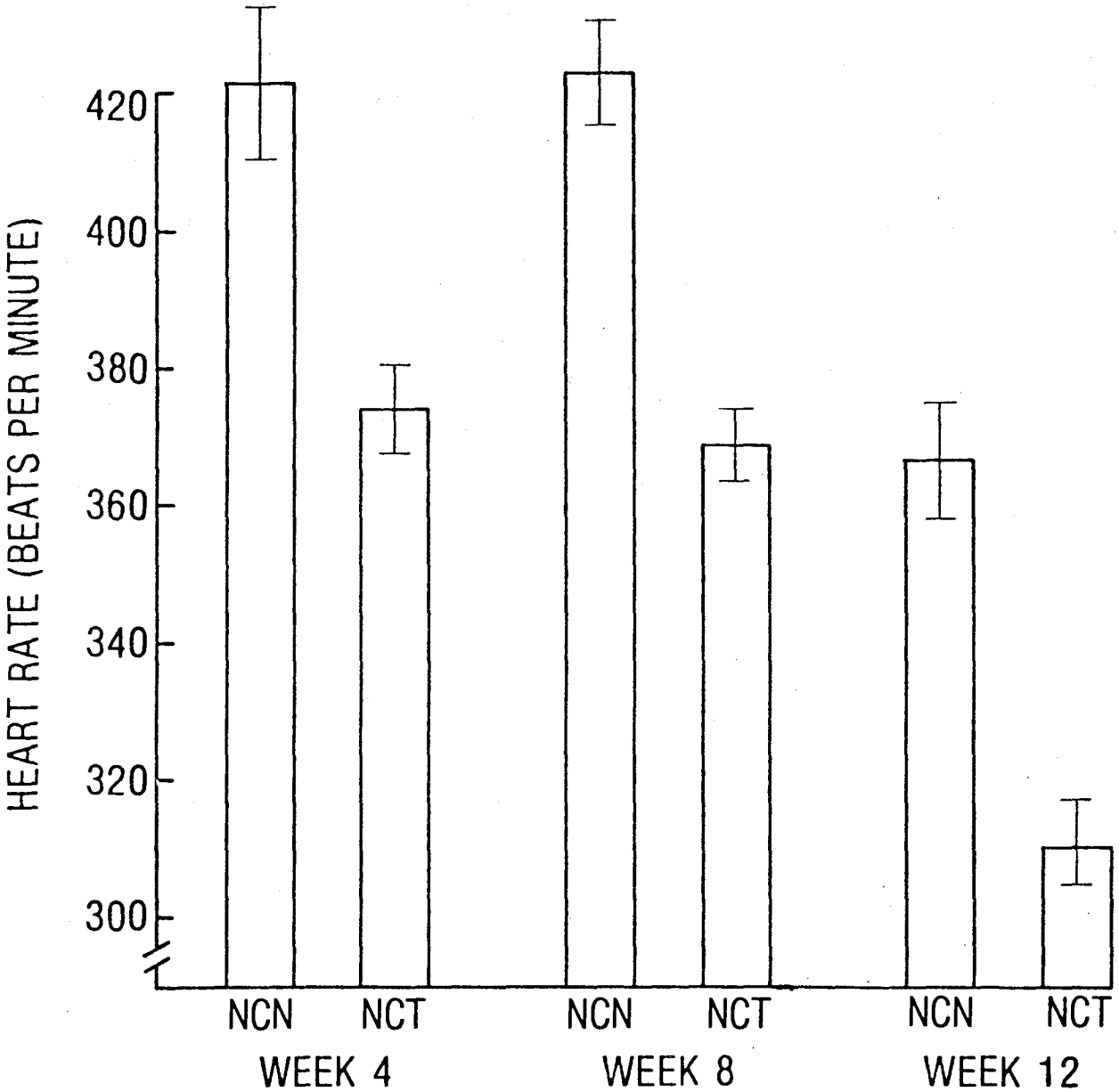

FIGURE 4 - 12

HEART RATES(±STANDARD ERROR) OF DS RATS ON NORMAL CHOW DIET.

NCN = NORMAL CHOW NONTRAINED
NCT = NORMAL CHOW TRAINED

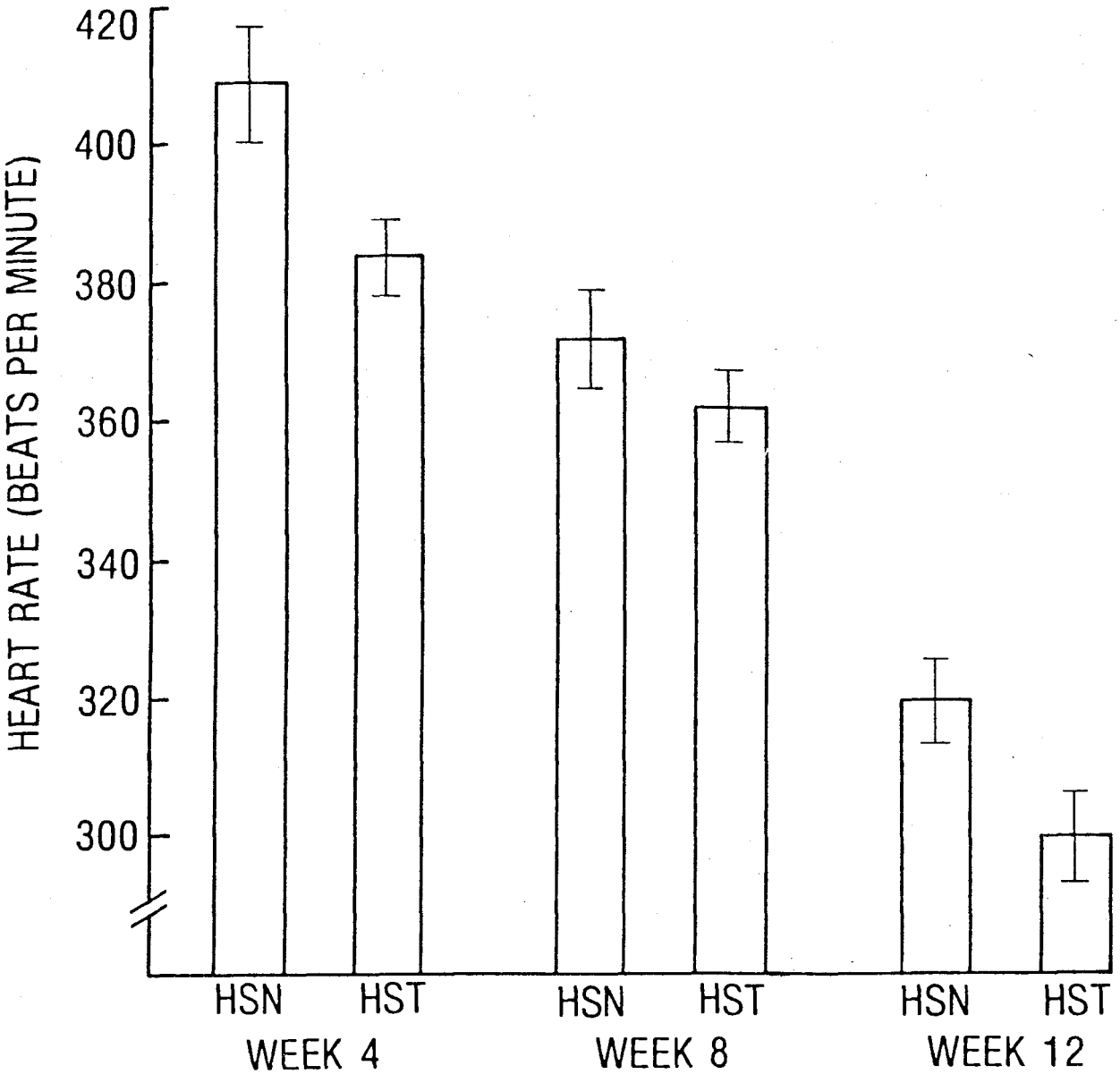

FIGURE 4 - 13

HEART RATE (± STANDARD ERROR) OF DS RATS ON HIGH SALT DIET
HSN = HIGH SALT NONTRAINED
HST = HIGH SALT TRAINED

Duration of Surgical Procedure

The time required to perform the surgical procedures was recorded and analyzed to determine if there had been any systematic difference between groups (Appendix C and D). There were no differences (p greater than 0.1) between the groups in the duration of any of the measurement procedures performed.

E. CONCLUSIONS AND RECOMMENDATIONS

Summary and Conclusions

Male DS rats were placed on a "normal chow" or a sodium chloride supplemented "high salt" diet and divided into trained and nontrained groups. The trained groups ran on a treadmill for increasing time periods over 12 weeks. Direct blood pressure and heart rate measurements were made on the 4th, 8th, and 12th weeks of the training protocol. Additional data were collected after the 12th week measurement.

All experimental procedures in all groups were standardized as far as possible. Empirical checks on the methodology included: the age of the animals at the initiation of the protocol, growth rate, food intake, and the duration of the measurement procedures.

At the initiation of the specific diet and training programs, the range of the mean age of all groups were between 40.9 and 41.9 days of age. The magnitude of the age differences in this study were very small in relation to those of Dahl and others (1968).

The duration of the measurement procedures were also examined to ensure that no significant differences in the durations of induction, catheterization, or measurement times existed. Analysis found no differences in procedure times between groups (p greater than 0.1), therefore, differences in blood pressure and heart rate between groups could not be attributed to differences in the measurement procedures.

The direct blood pressure measurement technique employed in this study proved effective as a means of obtaining anesthetized systolic and diastolic blood pressures as well as heart rates at three intervals during the training schedule. The animals responded well to both the measurement procedure and the return to treadmill running 40 to 48 hours following the first two measurements.

In examining the body weights of the animals it was found that statistically significant differences occurred between trained and nontrained groups on both dietary regimens. The possibility that this difference alone might affect blood pressure has not been tested in the DS rat. Body weight differences due to physical training programs have been reported previously in other rat strains (Pitts and Bull, 1977; Pfeffer and others, 1978). Pfeffer and others (1978), found swim training to significantly reduce the body weights of female free eating SHR without significant effects on blood pressure levels.

When body weight was used as a covariate in the analysis of blood pressure, the differences between trained and nontrained groups, although slightly reduced, remained highly significant ($p < .01$).

The absolute food intake of the NCN group was significantly greater than the NCT group. When the growth rate was used as a covariate, however, the significant differences disappeared ($p > 0.1$). The absolute food intake of the HS groups did not differ significantly ($p > 0.1$). When analysis of covariance was performed the HST group consumed relatively more

food than did the nontrained animals (p less than 0.05).

The salt, as well as the caloric intake paralleled the food intake. Therefore, in the NC groups the absolute salt and caloric intakes of the trained group were different, whereas the relative intake was not different. Absolute salt and caloric intake on the HS regimens was not different, whereas the relative intakes of the trained group was greater.

The hypothesis of Dahl and others (1958), suggested that blood pressure changes as a result of weight loss were due to reductions in salt consumption. Reisen and others (1978), however, suggested that reduction of caloric intake not salt intake, was the critical factor. In the present study, the trained groups, with similar (normal chow) or greater (high salt) relative intakes of salt and calories, maintained lower blood pressures than did their nontrained counterparts.

The relative kidney weights were the same between trained and nontrained animals within each dietary regimen. The wet weights of the left kidney seemed unaffected by the training procedure.

Relative heart weights were affected by the training procedure. Training resulted in significantly greater heart weights than the nontrained groups of both regimens (NC p less than 0.001, HS p less than 0.01). Larger heart weights as a result of physical training have been previously reported in hypertensive animals (Critz and Lipsey, 1976; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979), although this has not always been found (Tipton and others, 1977).

The heart rates were significantly slower in the trained than the nontrained groups on each diet regimen (NC p less than 0.001, HS p less than 0.01). Several studies have reported similar results due to training in hypertensive and normotensive animals (Dunne and others, 1974; Rock and others, 1976; Tipton and others, 1977; Pfeffer and others, 1978; Evenwel and Struyker-Boudier, 1979).

The systolic, diastolic and mean arterial blood pressure levels of both trained groups were significantly lower as compared to their nontrained counterparts, with the differences being highly significant. The differences reported in the present study were greater than several previously reported studies (Dunne and others, 1974; Tipton, Callahan, and Matthes, 1975; Tharp, 1976; Rock and others, 1976; Critz and Lipsey, 1976; Weiss, 1978; Pfeffer and others, 1978) and similar to the preliminary report of Shepherd (1981) on female DS rats.

The normal chow diet in the male DS rats resulted in consistent differences in blood pressure through measurements at the 4th, 8th, and 12th week, with the mean arterial pressure of the nontrained group being 11.4 percent, 13.2 percent, and 25.3 percent higher than the trained group on the 4th, 8th and 12th week respectively.

The high salt diet caused a rapid increase in systolic, diastolic, and mean blood pressure in both trained and nontrained groups up to the first (4th week) measurement. The mean blood pressures of nontrained group were higher on each measurement by 12.0 percent, 16.5 percent, and 24.7 percent on

the 4th, 8th, and 12th weeks respectively.

Overall the aerobic training program had the effect of assuaging the increase in blood pressure on both the normal chow and high salt diets in the trained male DS rats. The blood pressure differences could not be attributed to differences in salt consumption or measurement procedures. Significantly greater body weights of the nontrained groups were noted. However, when body weight was used as a covariate in the analysis of blood pressure data, significant differences between trained and nontrained groups remained. The training also resulted in larger relative heart weights and slower heart rates in animals on both diet regimens.

Recommendations

Further research is needed to determine the mechanisms involved in the observed effect. The following are studies recommended to gain insight into the training effect on DS rats.

1. Further study to determine the effect of body weight on the blood pressure of DS rats.
2. Further investigation into the functioning of the kidney of the DS male rat during aerobic exercise at several intensities.
3. Measurement of the urinary kallikrein levels during the course of a physical training study.
4. The measurement of serum potassium levels in the DS rat during and after exercise to determine if the potassium levels are significantly altered and the duration of any alteration.

5. Further study of methods and intensities of training and the effect of training at various intensities on the blood pressure.
6. Further study to determine the effects of physical training beyond the 12-week period studied in the present experiment and to also determine the effects of training on of the longevity of the DS rat.

F. APPENDICES

APPENDIX A SAMPLE SIZES AT MEASUREMENTS

Number of Successful Measurements

Group	NCN	NCT	HSN	HST
Week 4	14	19	22	18
Week 8	20	20	21	19
Week 12	20	19	19	18

APPENDIX B AGE OF THE ANIMALS

Group	Mean Age at Initiation +/- SD
NCN	40.9 Days +/- 1.86
NCT	41.9 Days +/- 2.35
HSN	41.7 Days +/- 2.34
HST	41.4 Days +/- 1.76

APPENDIX C DURATIONS OF MEASUREMENT PROCEDURES- NORMAL CHOW

Mean Time Required (minutes) for Procedures +/- SEM (n)

Normal Chow		Group	
		NCN	NCT
Procedure	Week		
Induction	4	2.64 +/- 0.06 (12)	2.56 +/- 0.09 (14)
	8	2.73 +/- 0.06 (20)	2.90 +/- 0.05 (20)
	12	2.81 +/- 0.12 (20)	2.67 +/- 0.12 (20)
Catheterization	4	19.28 +/- 1.26 (12)	19.69 +/- 1.75 (14)
	8	17.61 +/- 0.89 (20)	19.16 +/- 1.86 (20)
	12	14.72 +/- 0.73 (20)	13.60 +/- 0.57 (20)
Measurement	4	2.85 +/- 0.55 (12)	1.59 +/- 0.10 (14)
	8	1.82 +/- 0.16 (20)	2.36 +/- 0.52 (20)
	12	2.59 +/- 0.18 (17)	2.60 +/- 0.12 (19)
Total Time	4	31.65 +/- 1.91 (12)	29.90 +/- 1.62 (14)
	8	28.03 +/- 0.99 (20)	29.33 +/- 1.72 (20)
	12	22.89 +/- 0.83 (14)	22.20 +/- 0.47 (15)

APPENDIX D DURATIONS OF MEASUREMENT PROCEDURES- HIGH SALT

Mean Time Required (minutes) for Procedures +/- SEM (n)

High Salt		Group	
		HSN	HST
Procedure	Week		
Induction	4	2.72 +/- 0.14 (20)	3.57 +/- 0.08 (17)
	8	2.79 +/- 0.04 (20)	2.55 +/- 0.07 (18)
	12	2.42 +/- 0.42 (18)	2.42 +/- 0.08 (18)
Catheterization	4	17.81 +/- 0.87 (20)	17.63 +/- 0.90 (17)
	8	17.31 +/- 0.68 (20)	18.22 +/- 1.31 (18)
	12	13.23 +/- 0.37 (18)	13.15 +/- 0.38 (18)
Measurement	4	2.31 +/- 0.65 (20)	2.32 +/- 1.09 (17)
	8	1.70 +/- 0.17 (20)	2.01 +/- 0.57 (18)
	12	3.16 +/- 0.28 (18)	2.64 +/- 0.28 (18)
Total Time	4	28.19 +/- 1.17 (20)	27.44 +/- 0.95 (17)
	8	26.89 +/- 0.76 (20)	27.82 +/- 1.29 (18)
	12	21.75 +/- 0.47 (17)	21.67 +/- 0.54 (16)

REFERENCES

References

Allen, F.M. and O.M. Cope, "Influence of Diet on Blood Pressure and Kidney Size in Dogs" Journal of Urology, 47: 751-768, 1942.

Altschul, A.M. and J.K. Grommet, "Sodium Intake and Sodium Sensitivity", Nutrition Reviews, 38: 393-402, 1980.

Bedford, T.G., C.M. Tipton, N.C. Wilson, R.A. Oppliger, and C.V. Gisolfi, "Maximum Oxygen Consumption of Rats with Various Experimental Procedures", Journal of Applied Physiology, 47: 1278-1283, 1979.

Berne, R.M. and M.N. Levy, Cardiovascular Physiology , 2nd edition, C.V. Mosby, Saint Louis, Missouri, 1972.

Biomedical Computer Programs, P-series, Health Sciences Computing Facility, Departmentof Biomathematics, School of Medicine, University of California, Los Angeles, University of California Press, Berkeley, California, 1979.

Black, H.J., "Nonpharmacologic Therapy for Hypertension", The American Journal of Medicine, 66: 837-842, 1979.

Bonanno, J.A. and J.E. Lies, "Effects of Physical Training on Coronary Risk Factors", American Journal of Cardiology, 33: 760-764, 1974.

Booth, F.W., W.F. MacKenzie, M.J. Seider, and E.W. Gould, "Longevity of Exercising Obese Hypertensive Rats", Journal of Applied Physiology, 49: 634-637, 1980.

Borg, E. and A. Viberg, "Role of Heating in Non-Invasive Blood Pressure Measurements in Rats", Acta Physiologica Scandinavica, 108: 73-75, 1980.

Boyer, J.L. and F.W. Kasch, "Exercise Therapy in Hypertensive Men", Journal of the American Medical Association, 211: 1668-1671, 1970.

Bunag,R.D., J.W. McCubbin, and I.H. Page, "Lack of Correlation Between Direct and Indirect Measurements of Arterial Pressure in Unanesthetized Rats", Cardiovascular Research, 5: 24-31, 1971.

Burgess, L.E., R. Cropper, H.O. Gates, J. Thomas, C. Russ, and M.T. Scott, "Influence of Exercise on the Resting Systolic Blood Pressure and Cardiac Dysfunction of the Spontaneously Hypertensive Rats", Federation Proceedings, 35: 796, 1976.

Carretero, O.A., A.G. Scicli, A. Piwonska, and J. Koch, "Urinary

Kallikrein in Rats Bred for Susceptibility and Resistance to the Hypertensive Effect of Salt and in New Zealand Genetically Hypertensive Rats", Mayo Clinic Proceedings, 52: 465-467, 1977.

Carretero, O.A., V.M. Amin, T. Ocholik, A.G. Scicli, and J. Koch, "Urinary Kallikrein in Rats Bred for Their Susceptibility and Resistance to the Hypertensive Effect of Salt", Circulation Research, 42: 727-731, 1978.

Carretero, O.A. and A.G. Scicli, "The Renal Kallikrein-Kinin System in Human and in Experimental Hypertension", Klinische Wochenschrift, 56(suppl 1): 113-125, 1978.

Carretero, O.A. and A.G. Scicli, "The Renal Kallikrein-Kinin System", American Journal of Physiology, 238: F247-F255, 1980.

Chiueh, C.C. and I.J. Kopin, "Hyperresponsivity of Spontaneously Hypertensive Rats to Indirect Measurement of Blood Pressure", American Journal of Physiology, 234: H690-H695, 1978.

Choquette, G. and R.J. Ferguson, "Blood Pressure Reduction in "Borderline" Hypertensives Following Physical Training", Canadian Medical Association Journal, 108: 699-703, 1973.

Cohen, D.M., R.J. Grekin, J. Mitchell, W.H. Rice, and D.F. Bohr, "Hemodynamic, Endocrine, and Elecrolyte Changes during Sodium Restriction in DOCA Hypertensive Pigs, Hypertension, 2: 490-496, 1980.

Coleman T.G., R.E. Samar, and W.R. Murphy, "Autoregulation Versus Other Vasoconstrictors in Hypertension", Hypertension, 1: 324-330, 1979.

Cooper, R., I. Soltero, K. Liu, D. Berkson, S. Levinson, and J. Stamler, "The Association Between Urinary Sodium Excretion and Blood Pressure in Children", Circulation, 62: 97-104, 1980.

Crews, E.L., K.W. Fuge, L.B. Oscai, J.O.Holloszy, and R.E. Shank, "Weight, Food Intake, and Body Composition: Effects of Exercise and of Protein Deficiency", American Journal of Physiology, 216: 359-363, 1969.

Critz,J.B. and P. Lipsey, "Relationships Between Physical Training and DOCA Hypertension in Rats", Proceedings of the Society for Experimental Biology and Medicine, 151: 552-555, 1976.

Dahl, L.K. and R.A. Love, "Evidence For the Relationship Between Sodium (Chloride) Intake and Human Essential Hypertension", Archives of Internal Medicine, 94: 525-531, 1954.

Dahl, L.K., L. Silver, and R.W. Christie, "The Role of Salt in the Fall of Blood Pressure Accompanying Reduction in Obesity", The New England Journal of Medicine, 258: 1186-1192, 1958.

Dahl, L.K., "Possible Role of Chronic Excess Salt Consumption in the Pathogenesis of Essential Hypertension", American Journal of Cardiology, 8: 571-575, 1961.

Dahl, L.K., M. Heine, and L. Tassinari, "Effects of Chronic Excess Salt Ingestion", Journal of Experimental Medicine, 115: 1173-1190, 1962.

Dahl, L.K., M. Heine, and L. Tassinari, "Role of Genetic Factors in Susceptibility to Chronic Excess Salt Ingestion", Nature, 194: 480-482, 1962a.

Dahl, L.K., M. Heine, and L. Tassinari, "Effects of Chronic Salt Ingestion", Journal of Experimental Medicine, 118: 605-617, 1963.

Dahl, L.K., K.D. Knudsen, M.H. Heine, and G.J. Leitl, "Effects of Chronic Excess Salt Ingestion," Circulation Research, 22: 11-18, 1968.

Dahl, L.K., K.D. Knudsen, M. Heine, and G. Leitl, "Hypertension and Stress", Nature, 219: 735-736, 1968a.

Dahl, L.K., K.D. Knudsen, and J. Iwai, "Humoral Transmission of Hypertension: Evidence from Parabiosis", Circulation Research, 25 & 25(suppl. 1): I21-I33, 1969.

Dahl, L.K., G. Leitl, and M. Heine, "Influence of Dietary Potassium and Sodium/Potassium Molar Ratios on the Development of Salt Hypertension", Journal of Experimental Medicine, 136: 318-329, 1972.

Dahl, L.K., M. Heine, and K. Thompson, "Genetic Influence of the Kidneys on Blood Pressure. Evidence from Chronic Renal Hemografts in Rats with Opposite Predispositions to Hypertension", Circulation Research, 40: 94-101, 1974.

Dahl, L.K., K.D. Knudsen, E.V. Ohanian, M. Muirhead, and R. Tuthill, "Role of the Gonads in Hypertension Prone Rats", Journal of Experimental Medicine, 142: 748-759, 1975.

Denolin, H. and J. Mallion, "Hypertension and Exercise", Medicine Sport, 10: 97-117, 1977.

de Wardener, H.E. and G.A. MacGregor, "Dahl's Hypothesis that a Saluretic Substance May Be Responsible for a Sustained Rise in Arterial Pressure: Its Possible Role in Essential Hypertension", Kidney International, 18: 1-9, 1980.

Drori, D. and Y. Folman, "Environmental Effects on Longevity in the Male Rat: Exercise, Mating, Castration, and Restricted Feeding", Experimental Gerontology, 11: 25-32, 1976.

Dunne, A.P., M.W. Untermeyer, W.M. Manger, M. Wolff, H. Wolinsky, I. von Estorff, J. Birkner, and S. Dufton, "Effect of Exercise on Spontaneously Hypertensive Rats", The Physiologist, 17: 214, 1974.

Edwards, M.T. and J.N. Diana, "Effect of Exercise on Pre- and Postcapillary Resistance in the Spontaneously Hypertensive Rat", American Journal of Physiology, 234: H439-H446, 1978.

Eiser, R.A. and C. Swartz, "Renal and Elecrolyte Alterations During Exercise", in Lowenthal, D.T., K. Bharadwaja, and W.W. Oaks (eds), Therapeutics Through Exercise, Grune & Stratton, New York, N.Y., pp 145-153, 1979.

Evenwel, R. and H. Stuyker-Boudier, "Effect of Physical Training on the Development of Hypertension in the Spontaneously Hypertensive Rat", Pflugers Archives, 381: 19-24, 1979.

Fodor, J.G., E.C. Abbott, and J.E. Rusted, "An Epidemiological Study of Hypertension in Newfoundland", Canadian Medical Association Journal, 108: 1365-1368, 1973.

Folkow, B.U.G., and M.I.L. Hallback, "Physiopathology of Spontaeous Hypertension in Rats", in Genest, J., E. Koiw, and O. Kuchel (eds), Hypertension, Physiopathology and Treatment, McGraw Hill Co., New York, N.Y., pp 507-529, 1977.

Fries, E.D., D. Ragan, H. Pillsbury, and M. Mathews, "Alteration of the Course of Hypertension in the Spontaneously Hypertensive Rat", Circulation Research, 31:1-7, 1972.

Fries, E.D., "Salt Volume and the Prevention of Hypertension", Circulation, 53: 589-595, 1976.

Fries, E.D., "How Effective is the Medical Treatment of Hypertension", in E.D. Fries (ed), The Current Status of Modern Therapy: Treatment of Hypertension, volume 1, University Park Press, Baltimore, Maryland, pp. 1-12, 1978.

Fries, E.D., "Salt in Hypertension and the Effects of Diuretics", Annual Reviews in Pharmacologic Toxicology, 19: 13-23, 1979.

Fujita, T., F.C. Bartter, C.R. Lake, and C.S. Delea, "Factors Influencing Blood Pressure in Salt-Sensitive Patients with Hypertension", The American Journal of Medicine, 69: 334-344, 1980.

Geddes L.A., The Direct and Indirect Measurement of Blood

Presure, Year Book Medical Publishers, Chicago, Illinois, 1970.

Gordon, F.J., H. Matsuguchi, and A.L. Mark, "Abnormal Baroreflex Control of Heart Rate in Prehypertensive Dahl Genetically Salt-Sensitive Rats", Hypertension, 3(suppl 1): I135-I141, 1981.

Goto, A., L. Tobian, and J. Iwai, "Potassium Feeding Reduces Hyperactive Central Nervous System Pressor Responses in Dahl Salt-Sensitive Rats", Hypertension, 3(suppl 1): I128-I134, 1981.

Guyton, A.C., "Arterial Pressure Control During Exercise", in Guyton, A.C. (ed), Arterial Pressure and Hypertension: Ciculatory Physiology III, W.B. Saunders Co., Phil., Penn., pp. 279-281, 1980.

Guyton, A.C., T.G. Coleman, D.B. Young, T.E. Lohmeier,and J.W. DeClue, "Salt Balance and Long-Term Blood Pressure Control", Annual Reviews of Medicine, 31: 15-27, 1980.

Gyntelberg F.,"Body Weight, Physical Fitness and Blood Pressure", Medicine Sport, 10: 118-123, 1977.

Haddy, F.J., "Mechanism, Prevention, and Therapy of Sodium-Dependent Hypertension", The American Journal of Medicine, 69: 746-758, 1980.

Hallback, M., "Consequence of Social Isolation on Blood Pressure, Cardiovascular Reactivity and Design in Spontaneously Hypertensive Rats", Acta Physiologica Scandinavica, 93: 455-465, 1975.

Hanson, J.S. and W.H. Nedde, "Preliminary Observations on Physical Training for Hypertensive Males", Circulation Research, 26 and 27(suppl. 1): I49-I53, 1970.

Hellerstein, H.K., "Exploring the Effects of Exercise on Hypertension", The Physician and Sportsmedicine, 4: 36-49, 1976.

Heyden, S. and C.G. Hames, "Dietary Effects on Blood Pressure", Nutrition and Metabolism, 24(suppl 1): 50-64, 1980.

Idvall, J., K.F. Aronsen, K. Lindstrom, and U. Ulmsten, "Evaluation of Catheter-Manometer Systems for Adequate Intravascular Blood Pressure Measurements in Small Animals", Research in Experimental Medicine, 171: 101-110, 1977.

Jaffe, D., L.E. Sutherland, D.M. Barker, and L.K. Dahl, "Effects of Chronic Excess Salt Ingestion: Morphologic Findings in Kidneys of Rats with Differing Genetic Susceptibilities to Hypertension", Archives of Pathology, 90: 1-16, 1970.

Johansen, K., "Heat Exchange Through the Musk-Rat Tail. Evidence for Vasodilator Nerves to the Skin", Acta Physiologica Scandinavica, 55: 160-169, 1962.

Johnson, W.P. and J.A. Grover, "Hemodynamic and Metabolic Effects of Physical Training in Four Patients with Essential Hypertension", Canadian Medical Assocition Journal, 96: 842-847, 1967.

Kawasaki, T., C.S. Delea, F.C. Bartter, and H. Smith, "The Effect of High-Sodium and Low-Sodium Intakes on Blood Pressure and other Related Variables in Human Subjects with Idiopathic Hypertension", The American Journal of Medicine, 64: 193-198, 1978.

Kannel, W.B. and T.R. Dawber, "Hypertensive Cardiovascular Diease: The Framingham Study", in G. Onesti, K.E. Kim, and J.H. Moyer (ed), Hypertension: Mechanisms and Management, Grune and Stratton, New York, N.Y., pp. 93-110, 1973.

Kempner, W., "Treatment of Hypertensive Vascular Disease with Rice Diet", American Journal of Medicine, 4: 545-577, 1948.

Khomaziuk, I.N., L.I. Goncharenko, L. Zvedeniuk, I.G. Rushkevich, V.N. Khaltagarova, V.M. Khomenko, and L.A. Chernetskava, "Present State and Actual Problems of Using Physical Training in the Treatment and Prevention of Hypertensive Disease", International Sport Sciences, 1: 509-510, 1979.

Kiveloff, B. and O. Huber, "Brief Maximal Isometric Exercise in Hypertension", Journal of the American Geriatric Society, 19: 1006-1012, 1971.

Knudsen, K.D., L.K. Dahl, K. Thompson, J. Iwai, M. Heine, and G. Leitl, "Effects of Chronic Excess Salt Ingestion. Inheritance of Hypertension in the Rat", Journal of Experimental Medicine, 132: 976-1000, 1970.

Kronig, B., F. Knappen, K. Dufey, and H.P. Wolff, "Blood Pressure Response to Physical Activity in Hypertensive Subjects at Different Times of the Day", Clinical Science and Molecular Medicine, 51: 677s-680s, 1976.

Lenel, R., L.N. Katz and S. Robard, "Arterial Hypertension in the Chicken", American Journal of Physiology, 152: 557-562, 1948.

Loggie, J.M.H., "Prevalence of Hypertension and Distribution of Causes", Juvenile Hypertension, M.I. New and L.S. Levine (ed), Raven Press, New York, N.Y., pp. 1-12, 1977.

Lowenthal, D.T. and M.S. Whiteman, "Hypertension and Exercise", in Therapeutics Through Exercise, Lowenthal, D.T., K.

Bharadwaja, W.W. Oaks (ed), Grune & Stratton, New York, N.Y., pp 133-144., 1979.

Maistrello, I. and R. Matscher, "Measurement of Systolic Blood Pressure of Rats: Comparison of Intraarterial and Cuff Values", Journal of Applied Physiology, 26: 188-193, 1969.

McKechnie, J.K., W.P. Leary, and S.M. Joubert, "Some Electrocardiographic and Biochemical Changes Recorded in Marathon Runners", South African Medical Journal, 44: 722-725, 1967.

Meneely, G.R., R.G. Tucker, W.J. Darby, and S.H. Auerbach, "Chronic Sodium Chloride Toxicity in the Albino Rat II", Journal of Experimental Medicine, 98: 71-80, 1953.

Meneely, G.R., C.O.T. Ball, and J.B. Youmans, "Chronic Sodium Chloride Toxicity: the Protective Effect of Added Potassium Chloride", Annals of Internal Medicine, 47: 263-273, 1957.

Meneely, G.R. and H.D. Battarbee, "High Sodium-Low Potassium Environment and Hypertension", The American Journal of Cardiology, 38: 768-785, 1976.

Montoye, H.J., H.L. Metzner, J.B. Keller, B.C. Johnson, and F.H Epstein, "Habitual Physical Activity and Blood Pressure", Medicine and Science in Sports, 4: 175-181, 1972.

Morgan, T., S. Carney, and J. Meyers, "Sodium and Hypertension. A Review of the Role of Sodium in Pathogenesis and the Action of Diuretic Drugs", Pharmacologic Therapy, 9: 395-418, 1980.

Murray, R.H., F.C. Luft, R. Bloch, and A.E. Weyman, "Blood Pressure Responses to Extremes of Na Intake in Normal Man", Proceedings of the Society for Experimental Biology and Medicine, 159: 432-436, 1978.

Nikoletseas, M.M., "Food Intake in the Exercising Rat: A Brief Review", Neuroscience and Behavioral Reviews, 4: 265-267, 1979.

Okamoto, K. and K. Aoki, "Development of a Strain of Spontaneously Hypertensive Rats", Japanese Circulation Journal, 27: 282-293, 1963.

Onesti, G.K., K.E. Kim, J.A. Greco, E.T. del Guercio, M. Fernandes, and C. Swartz, "Blood Pressure Regulation in End Stage Renal Disease and Anephric Man", Circulation Research, 36-37(suppl. 1): I145-I152, 1975.

Page, I.H., "Arterial Hypertension in Retrospect", Circulation Research, 34: 133-142, 1974.

Page, L.B., A. Danion, and R.D. Moellering, "Antecedents of Cardiovascular Disease in Six Solomon Islands Societies", Circulation, 49: 1132, 1974.

Palbol, J. and J. Henningsen, "Blood Pressure Measurements in the Conscious Rat", Scandinavican Journal of Urology and Nephrology, 13: 319-321, 1979.

Pfeffer, J.M., M.A. Pfeffer and E.D. Frohlich, "Validity of an Tail-cuff Method for Determining Systolic Arterial Pressure in Unanesthetized Normotensive and Spontaneously Hypertensive Rats", Journal of Laboratory and Clinical Medicine, 78: 957-962, 1971.

Pfeffer, M.A., B.A. Ferrell, J.M. Pfeffer, A.K. Weiss, M.C. Fishbein, and E.D. Frohlich, "Ventricular Morphology and Pumping Ability of Exercised Spontaneously Hypertensive Rats", American Journal of Physiology, 235: H193-H195, 1978.

Pitts, G.C. and L.S. Bull, "Exercise, Dietary Obesity, and Growth in the Rat", American Journal of Physiology, 232: R38-R44, 1977.

Proskauer, G.G., C. Neumann, and I. Graef, "The Measurement of Blood Pressure in Rats with Special Reference to the Effect of Changes in Temperature", American Journal of Physiology, 143: 290-296, 1945.

Rand. R.P., A.C. Burton, and I. Ing, "The Tail of the Rat in Temperature Regulation and Acclimatization", Canadian Journal of Physiology and Pharmacology, 43: 257-267, 1965.

Rapp, J.P. and J. Iwai, "Characteristics of Rats Selectively Bred for Susceptibility or Resistance to the Hypertensive Effect of High Salt Diet", Clinical and Experimental Pharmacology and Physiology, suppl. 3: 11-14, 1976.

Reisin, E., R. Abel, M. Modan, D.S. Silverberg, H.E. Eliahou, and B. Modan, "Effect of Weight Loss Without Salt Restriction on the Blood Pressure in Overweight Hypertensive Patients", The New England Journal of Medicine, 298: 1-6, 1978.

Rezek, M. and V. Havilicek, "Chronic Multipurpose Cannulas and a Technique for Cannulation of Small Arteries and Veins", Physiology and Behavior, 15: 623-626, 1975.

Rock, T.W., W.M. Manger, H. Wolinsky, M. Wolff, M. Hulse, D. Van Praag, and J. Pearson, "Effect of Strenuous Exercise on Spontaneously Hypertensive Rats", Clinical Research, 24: 619A, 1976.

Rose, L.I. and R.L. Lavine, "Endocrine Aspects of Strenuous Exercise", in Therapeutics Through Exercise, Lowenthal,

D.T., K.Bharadwaja, W.W. Oaks (ed), Grune & Stratton, New York, N.Y., pp 41-46, 1979.

Sacks, A.H., "Indirect Blood Pressure Measurements: A Matter of Interpretation", Angiology, 30: 683-695, 1979.

Sannerstedt, R., H. Wasir, R. Henning, and L. Werko, "Systemic Haemodynamics in Mild Arterial Hypertension Before and After Physical Training", Clinical Science and Molecular Medicine, 45: 145s-149s, 1973.

Sapirstein, L.A., W.L. Brandt, and D.R. Drury, "Production of Hypertension in the Rat by Substituting Hypertonic Sodium Chloride Solutions for Drinking Water", Proceedings of the Society for Experimental Biology and Medicine, 73: 82-85, 1950.

Sasaki N., "The Relationship of Salt Intake to Hypertension in the Japanese", Geriatrics, 19: 735-744, 1961.

Selkurt, E.E., "Effect of Pulse Pressure and Mean Arterial Pressure Modification on Renal Hemodynamics and Electrolyte and Water Excretion", Circulation, 4: 541-551, 1951.

Shepherd, R.E., M.L. Kuehne, K.A. Kenno, J.L. Durstine, and J.P. Rapp, "Normalization of Resting Blood Pressure in Physically Active Dahl Salt-Sensitive Hypertensive Rats", Medicine and Science in Sports and Exercise, 12: 133, 1980.

Shepherd, R.E., "Prevention of Hypertension by Exercise in Dahl Salt-Sensitive Rats", (paper presented at the Lewis K. Dahl Symposium: The Interrelation of Salt and Hypertension, Upton, N.Y., May 1981).

Simpson, F.O., "Salt and Hypertension: A Sceptical Review of the Evidence", Clinical Science, 57: 463s-480s, 1979.

Sobin, S.S., "Accuracy of Indirect Determinations of Blood Pressure in the Rat; Relation to Temperature of Plethysmograph and Width of Cuff", American Journal of Physiology, 146: 179-186, 1946.

Sonne, B. and H. Galbo, "Simultaneous Determinations of Metabolic and Hormonal Responses, Heart Rate, Temperature, and Oxygen Uptake in Running Rats", Acta Physiologica Scandinavica, 109: 201-209, 1980.

Spence, J.D., W.J. Sibbald, and R.D. Cape, "Direct, Indirect, and Mean Blood Pressures in Hypertensive Patients: The Problem of Cuff Artefact Due to Arterial Wall Stiffness and a Partial Solution", Clinical and Investigative Medicine, 2: 165-173, 1980.

Storer, T.W. and R.O. Ruhling, "Essential Hypertension and

Exercise", The Physician and Sportsmedicine, 9: 59-69, 1981.

Strong, W.B., "Hypertension and Sports", Pediatrics, 64: 693-695, 1979.

Taguchi, J., and E.D. Fries, "Partial Reduction of Blood Pressure and Prevention of Complications in Hypertension", The New England Journal of Medicine, 291: 329-331, 1974.

Takehashi, E., N. Sasake, J. Takeda, and H. Ho, "The Geographic Distribution of Cerebral Hemorrhage and Hypertension in Japan", Human Biology, 29: 139, 1957.

Takeshita, A. and A.L. Mark, "Neurogenic Contribution to Hindquarters Vasoconstriction during High Sodium Intake in Dahl Strain of Genetically Hypertensive Rat", Circulation Research, 43(1)suppl. 1: I86-I91, 1978.

Takeshita, A., A.L. Mark, and M.J. Brody, "Prevention of Salt-induced Hypertension in the Dahl Strain by 6-Hydroxydopamine", American Journal of Physiology, 236: H48-H52, 1979.

Tipton, C.M., R.D. Matthes, D.E. Paynter, L.T. Lais, and A K. Callahan, "The Influence of Chronic Exercise on the Blood Pressure of Rats", Medicine Science and Sports, 5: 62, 1973.

Tipton, C.M., A.K. Callahan, and R.D. Matthes, "Influence of Training on the Resting Systolic Blood Pressures of Genetic Hypertensive Rats", Federation Proceedings, 34: 433, 1975.

Tipton, C.M., R.D. Matthes, A. Callahan, Tse-Kia Tcheng, and L.T. Lais, "The Role of Chronic Exercise on Resting Blood Pressures of Normotensive and Hypertensive Rats", Medicine and Science in Sports, 9: 168-177, 1977.

Tipton, C.M., R.D. Matthes, T.B. Bedford, J.R. Leininger, R.P. Oppliger, and L.J. Miller, "Exercise, Hypertension, and Animal Models", in Lowenthal, D.T., K. Bharadwaja, and W.W. Oaks (ed), Therapeutics Through Exercise, Grune & Stratton, New York, N.Y., pp. 115-132, 1979.

Tharp, G., "The Effect of Exercise Training on Blood Pressure and Aortic Strip Tension of Normal and Spontaneously Hypertensive Rats", Federation Proceedings, 35: 796, 1976.

Tobian, L., "Salt and Hypertension", Annals of the New York Academy of Sciences, 304: 178-202, 1978.

Tobian, L., J. Lange, S. Azar, J. Iwai, D. Koop, K. Coffee, and M.A. Johnson, "Reduction of Natriuretic Capacity and Renin Release in Isolated, Blood Perfused Kidneys of Dahl Hypertension-Prone Rats", Circulation Research, 43(1) suppl. 1: I92-I97, 1978a.

Tobian, L., J. Lange, J. Iwai, K. Hiller, M.A. Johnson, and P. Goossens, "Prevention with Thiazide of NaCl-Induced Hypertension in Dahl "S" Rats", Hypertension, 1: 316-323, 1979.

Tobian, L., "The Relation of Salt to Hypertension", The American Journal of Clinical Nutrition, 32: 2739-2748, 1979.

Tobian, L., M. Pumper, S. Johnson, and J. Iwai, "A Circulating Humoral Pressor Agent in Dahl S Rats with Salt Hypertension", Clinical Science, 57: 345s-347s, 1979.

Tobian, L., "Salt and Hypertension", Journal of Medical Association of Georgia, 69: 827-834, 1980.

Tobian, L., "Sodium, Volume, and Hypertension", (paper presented at Symposium: The Role of Sodium in Hypertension, The University of British Columbia, Department of Anatomy, May, 1981).

Tuthill, R.W. and E.J. Calabrese, "Age as a Function in the Development of Sodium-Related Hypertension", Environmental Health Perspectives, 29: 35-43, 1979.

Weinsier, R.L., "Overview: Salt and the Development of Essential Hypertension", Preventive Medicine, 5: 7-14, 1976.

Weiss,L., "Adaptive Cardiovascular Changes to Physical Training in Spontaneously Hypertensive and Normotensive Rats", Cardiovascular Research,12: 329-333, 1976.

Welner, A., D. Ben-Ishay, J.J. Groen, and L.K. Dahl, "Behavior Patterns and Sensitivity to Experimental Hypertension in Rats", Proceedings of the Society of Experimental Biology and Medicine, 129: 886-890, 1968.

Wilhelmj, C.M., E.B. Waldmann, and T.F. McGuire, "Effect of Prolonged High Sodium Chloride Ingestion and Withdrawal upon Blood Pressure of Dogs", Proceedings of the Society of Experimental Biology and Medicine, 77: 379-382, 1951.

Winer, B.H., "The Antihypertensive Actions of Benzothiadiazines", Circulation, 23: 211-218, 1961.

World Health Organization, "Arterial Hypertension-Report of a WHO Expert Committee, Technical Report Series, No. 628, 1978.

Yamori, Y., "Experimental Models of Hypertension as a Tool for the Control and Prevention of Clinical Hypertension", in F. Gross and J.I.S. Robertson (ed), Arterial Hypertension, Pitman Medical Publishing Co. Ltd., Kent, England, pp. 209-226, 1979.

Zambraski, E.J. and M.J. Dunn, "Renal Prostaglandin E2 and F2 alpha Secretion and Excretion in Exercising Concious Dogs", Prostaglandins and Medicine, 4: 311-324, 1980.