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I am submitting herewith a dissertation written by Debra Ann Kirby entitled "Manipulating Renal Responses to Noxious Stimuli in the Cynomolgus Monkey: A Renal/Behavioral Model of Essential Hypertension." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

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We have read this dissertation
and recommend its acceptance:

Accepted for the Council:

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Graduate Studies and Research

MANIPULATING RENAL RESPONSES TO NOXIOUS STIMULI IN THE CYNOMOLGUS MONKEY: A RENAL/BEHAVIORAL MODEL OF ESSENTIAL HYPERTENSION

A Dissertation

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Degree

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DEDICATION

This dissertation is dedicated to my mother, Thelma B. Nantz, who taught me to value the learning process.

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ABSTRACT

Behavioral influences on excretion of Na^+ and H_2O and on mean arterial blood pressure (MBP) were studied during saline diuresis in three unanesthetized adult female monkeys. Infusions of isotonic saline (70 ml/kg and 0.5 ml/min, iv) caused excretion of 195 ± 3 µl H_2O/kg/min and 31.8 ± 3.0 µeg Na^+/kg/min. Inulin clearance (C_{In}) was 4.3 ± 0.1 ml/kg/min. Naloxone hydrochloride, an opiate receptor antagonist, had no effect on Na^+ and H_2O excretion or MBP. Electric shock (5 ma, 200 msec, 12/min for 30 min) delivered to the tail reduced excretion of Na^+ and H_2O to 84 ± 6% and 78 ± 6% of baseline values, but values returned to baseline before the end of the 30 min shock exposure. C_{In} decreased initially, then rose above baseline values. MBP increased 3.4% ± 2.5% during shock exposure. The role of opiate receptors in adaptation to electric shock was studied by administering naloxone (10 mg/kg, iv) immediately before electric shock was delivered. After naloxone, electric shock reduced Na^+ and H_2O excretion to 42 ± 10% and 44 ± 10% of baseline values, and delayed return to baseline values. C_{In} was decreased throughout the 30 minutes. MBP increases were slightly greater than increases in response to shock alone. Continuous broadband noise at 96 dB decreased Na^+ and H_2O excretion by 20%, but 108 dB noise had inconsistent effects. After naloxone, however, 108 dB noise decreased excretion of Na^+ and H_2O to 70 ± 17% and 62 ± 15% of baseline values. MBP decreased slightly in response to both levels of noise, but increased by 4% in response to noise after naloxone. Results of these

experiments suggest that unconditional renal and blood pressure responses to noxious sensory stimuli are moderated by endogenous opiates.

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I. INTRODUCTION

This dissertation focuses on three related concerns: the effects of noxious sensory stimuli on renal function; the central integrative processes whereby noxious stimuli may influence renal function; and the implications of these findings for a proposed renal/behavioral model of essential hypertension.

The results of these studies suggest that noxious sensory stimuli elicit neurogenic and hormonal mechanisms which result in reduced sodium (Na^+) and water (H_2O) excretion. The data further suggest that these processes are modulated by central neurochemical mechanisms involving opiate receptors.

The preliminary framework for an integrative, multiple process model of behavioral hypertension is proposed, one which emphasizes the essential role of the renal system in long term blood pressure regulation. The processes are represented diagramatically in Figure 1. In essence, the model proposes that one possible link between behavioral stimuli and chronic elevation of blood pressure is the response of central neural regulators of renal function to such stimuli. The response within the kidney under these circumstances could take the form of alterations in renal blood flow, filtration dynamics, changes in tubular handling of electrolytes, or enhanced renin release. Neuroendocrine responses to such stimuli may include release of adrenocorticotropic hormone (ACTH) from the anterior pituitary and antidiuretic hormone (ADH) from the posterior pituitary. Direct reabsorption of sodium via sympathetic

Figure 1. Renal/behavioral model of essential hypertension.

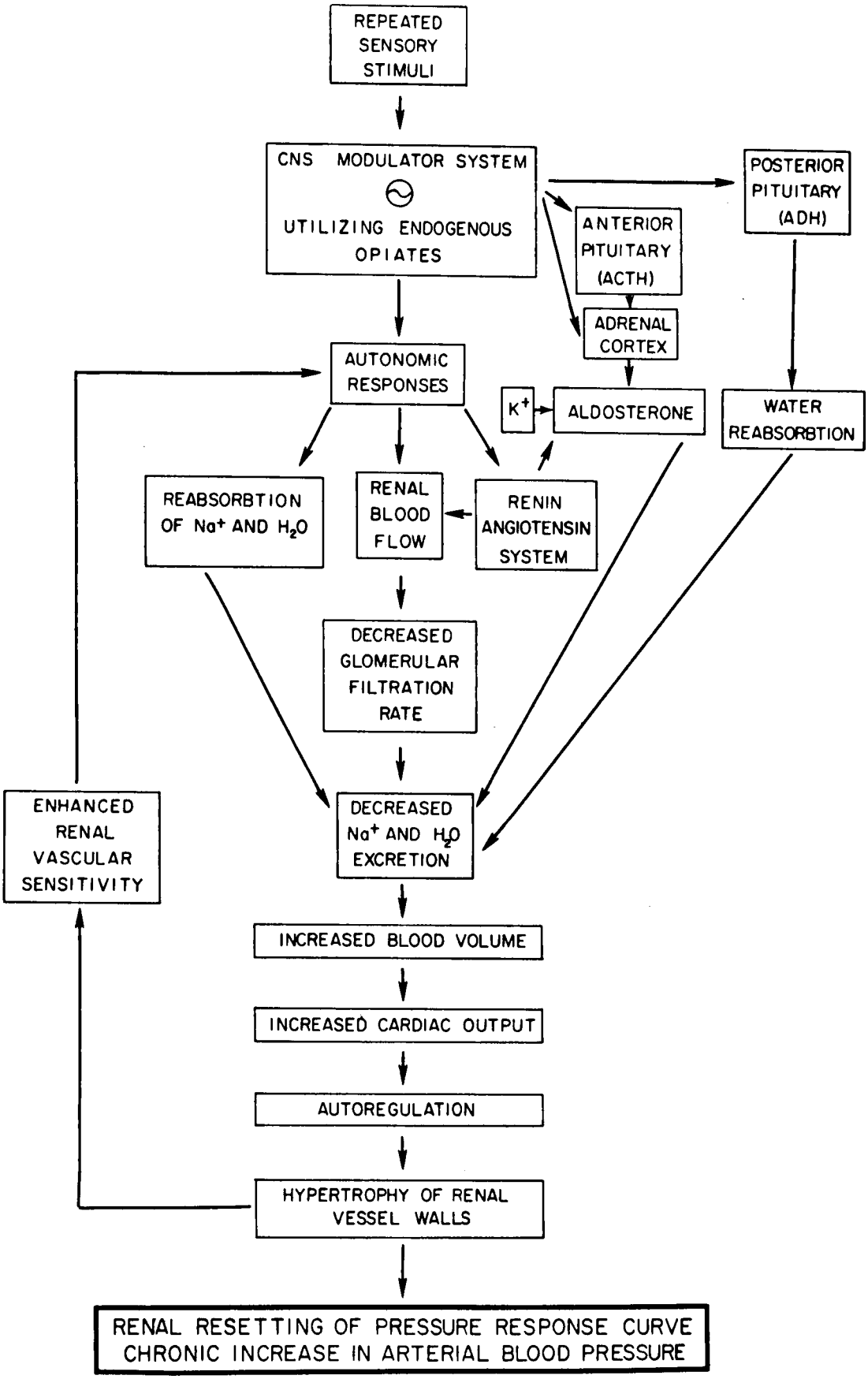

REPEATED SENSORY STIMULI
CNS MODULATOR SYSTEM
UTILIZING ENDOGENOUS OPIATES
POSTERIOR PITUITARY (ADH)
ANTERIOR PITUITARY (ACTH)
ADRENAL CORTEX
AUTONOMIC RESPONSES
K+
ALDOSTERONE
WATER REABSORBTION
REABSORBTION OF Na+ AND H2O
RENAL BLOOD FLOW
RENIN ANGIOTENSIN SYSTEM
DECREASED GLOMERULAR FILTRATION RATE
ENHANCED RENAL VASCULAR SENSITIVITY
DECREASED Na+ AND H2O EXCRETION
INCREASED BLOOD VOLUME
INCREASED CARDIAC OUTPUT
AUTOREGULATION
HYPERTROPHY OF RENAL VESSEL WALLS
RENAL RESETTING OF PRESSURE RESPONSE CURVE
CHRONIC INCREASE IN ARTERIAL BLOOD PRESSURE

Figure 1

innervation of the renal tubules could also result. Repeated elicitation of such responses could alter fluid balance and thus provide the means for permanent changes in the vasculature or function of the kidney. This change could permit permanent elevations in blood pressure caused by the "resetting" of the pressure diuresis curve described by Guyton as characteristic of the essential hypertensive (Guyton, 1977). This process is described in detail in a later section.

These studies are based on the proposition that noxious sensory stimuli can act on the kidney in a manner analogous to the effects of psychologically stressful stimuli. The significance of psychologically stressful events has long been emphasized in the investigation of the pathophysiologic process resulting in essential hypertension. The mechanisms involved in the process remain unknown. This research offers evidence of relationships between centrally integrated renal and blood pressure responses and sensory stimuli, specifically electric shock and loud noise.

All of the experiments described in this work were conducted in unanesthetized, chair-restrained, cynomolgus monkeys (Macaca fascicularis). The data presented indicate that renal excretion of H_2O and Na^+ decrease to approximately 80% of baseline values as an unconditional response to electric shock presented during a constant infusion of saline. Presentation of continuous broadband noise at 96 dB also caused decreases to 80% of baseline levels. However, exposure to 108 dB noise had inconsistent effects on excretion of water and sodium during the saline infusion. These results suggest that unconditional renal responses to noxious stimuli exist in the cynomolgus monkey.

It has become increasingly apparent that the central nervous system plays an essential role in the regulation of blood pressure, regional blood flow and fluid balance. Recent research on the complex system of opiate receptors and endogenous opiate peptides has provided evidence to suggest that this system may be part of a sensitive mechanism designed to evaluate and moderate responses to behavioral stimuli. Evidence also exists of nuclei and tracts within the central nervous system which play a significant role in either cardiovascular or renal regulation and also show evidence of endogenous opiate activity. These issues are discussed in detail in the section concerned with experimental models of hypertension.

The results of studies presented in this dissertation suggest that opiate receptors in the CNS moderate renal responses to noxious stimuli in the manner suggested by Figure 2. The administration of naloxone, an opiate receptor antagonist, immediately before the administration of electric shock, exaggerated the reductions in Na^+ and H_2O excretion to approximately 45% of baseline values. Furthermore, Na^+ and H_2O excretion did not return to baseline values during shock presentation when naloxone was administered prior to the onset of shock. When naloxone preceded the 108 dB noise stimulus a marked reduction in renal excretion was observed, with H_2O and Na^+ excretion reduced to approximately 65% of baseline values.

Mean blood pressure increased in response to electric shock, and shock after opiate receptor blockade resulted in slightly greater increases. MBP decreased in response to noise but increased during noise exposure under naloxone.

Figure 2. Involvement of central endogenous opiates in renal and cardiovascular responses to behavioral stimuli. Dashed lines represent hypothesized relationships between factors.

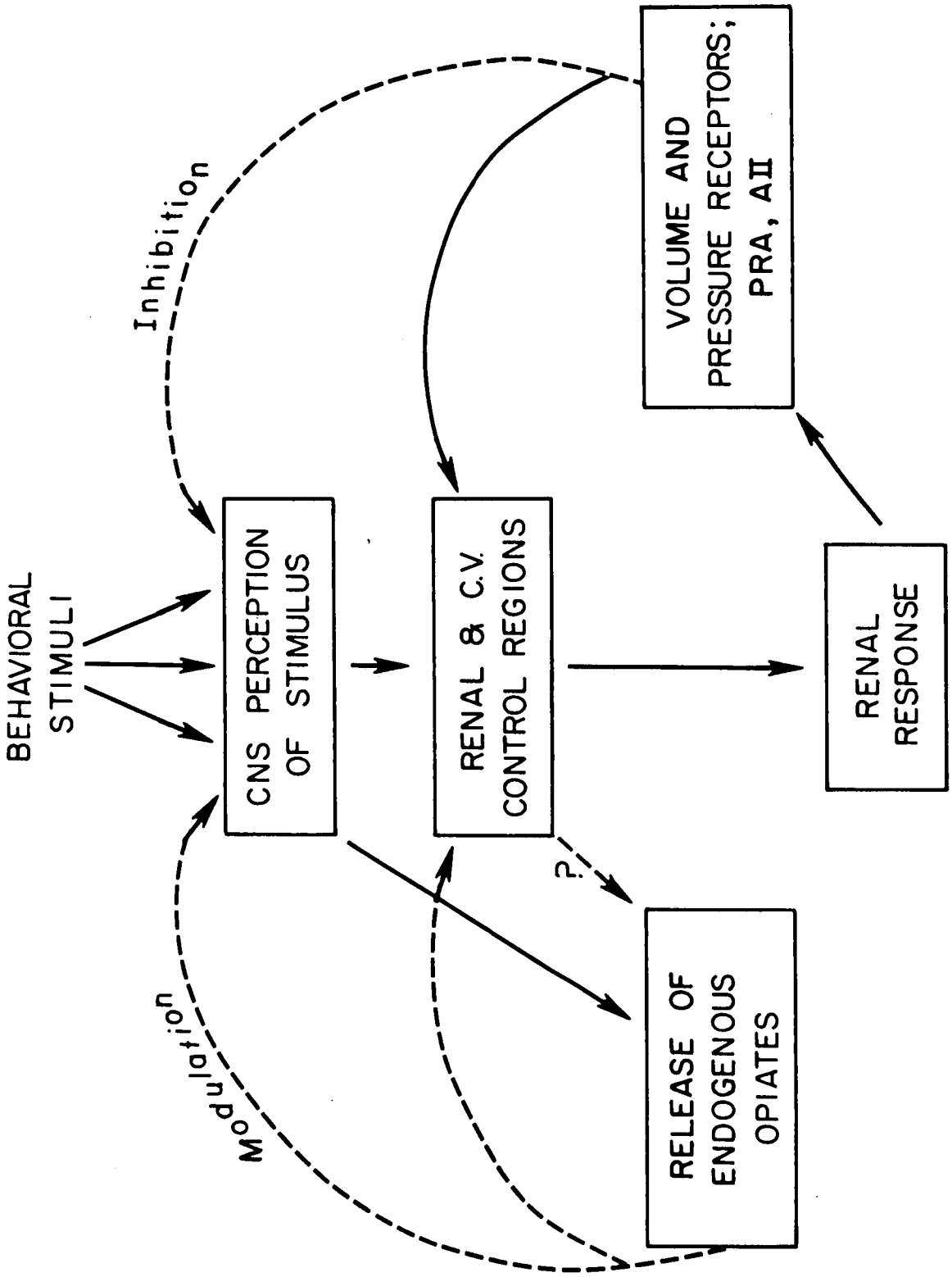

BEHAVIORAL STIMULI
CNS PERCEPTION OF STIMULUS
RENAL & C.V. CONTROL REGIONS
VOLUME AND PRESSURE RECEPTORS; PRA, AII
RENAL RESPONSE
RELEASE OF ENDOGENOUS OPIATES
?
Inhibition
Modulation

Figure 2

The specific nature of these response patterns, as well as the suitability of these data to a renal/behavioral model of hypertension will be discussed. It is possible that these findings may provide a preliminary framework for a useful model of central integration of the effects of sensory stimuli on renal regulation of fluid balance in the nonhuman primate.

II. LITERATURE REVIEW

The complexity and flexibility of cardiovascular responses to physiological needs makes the necessity of central integration of such a process obvious. The precise locations of all control centers and pathways and the mechanisms of action are not yet as apparent. Central aspects of some important regulatory systems are better understood than others. The baroreflex, with pressure receptors in the carotid sinus and aortic arch, is controlled by afferent vagal fibers which synapse in the nucleus of the tractus solitarius and the reticular formation (Doba and Reis, 1974). Other afferent fibers travelling in the vagus nerve carry impulses from atrial and pulmonary stretch receptors. These receptors are elements of a feedback loop which can alter renal function and autonomic sympathetic cardiac activity. Vagal connections have been found in the medulla (Urabe, Tsubokawa, and Hamabe, 1968), which has long been known to be a central pressor and depressor control area.

The complexity of such direct and reflex control mechanisms is well illustrated by the cardiovascular responses to exercise, during which the subsystems controlling cardiac function, arteriolar resistance and venous capacitance are able to alter typical interrelationships in order to specifically serve the body's needs under those conditions. Reflex and direct cardiovascular responses to hemorrhage include reduction in renal excretion of Na^+ and water and release of antidiuretic hormone, both designed to replenish blood volume. Blood flow is redirected to the most essential organs, and cardiac output is reduced (Herd, 1970).

The most complex CNS involvement in cardiovascular regulation probably occurs during responses to behavioral stimuli. Long-term exposure to behavioral shock postponement and other behavioral schedules, exposure to psychosocial stressors, and exposure to loud noise all have been shown to evoke cardiovascular and renal function changes of varying duration in experimental animals. These and other behavioral studies will be reviewed in a later section. It is this relationship between CNS responses to behavioral and sensory stimuli and physiological changes which serves as a basis for the model of central regulation of renal responses to sensory stimuli proposed in this dissertation.

A. Human Essential Hypertension

In essential hypertension, the reflex and control mechanisms described above continue to operate, but the results are somewhat different from the results of such action in normotensive individuals because arterial blood pressure is maintained at hypertensive levels. Although clinical definitions of hypertension vary, 140 mmHg systolic and 90 mmHg diastolic is a commonly accepted guideline. The hemodynamic and physiological factors regulating blood pressure can be represented simply by the diagram in Figure 3, based on Arthur Guyton's model of cardiovascular control (Guyton, Coleman, Cowley, Scheel, Manning, and Norman, 1972). Blood pressure is directly determined by the combined influences of cardiac output and total peripheral resistance. High blood pressure may result from a higher than normal level of either factor. Alterations in renal function could play a dominant role in the pathogenesis or maintenance of essential hypertension, a common form of hypertension in

Figure 3. Factors controlling arterial blood pressure. Dashed arrow indicates a negative effect. Modified from Guyton et al., 1972.

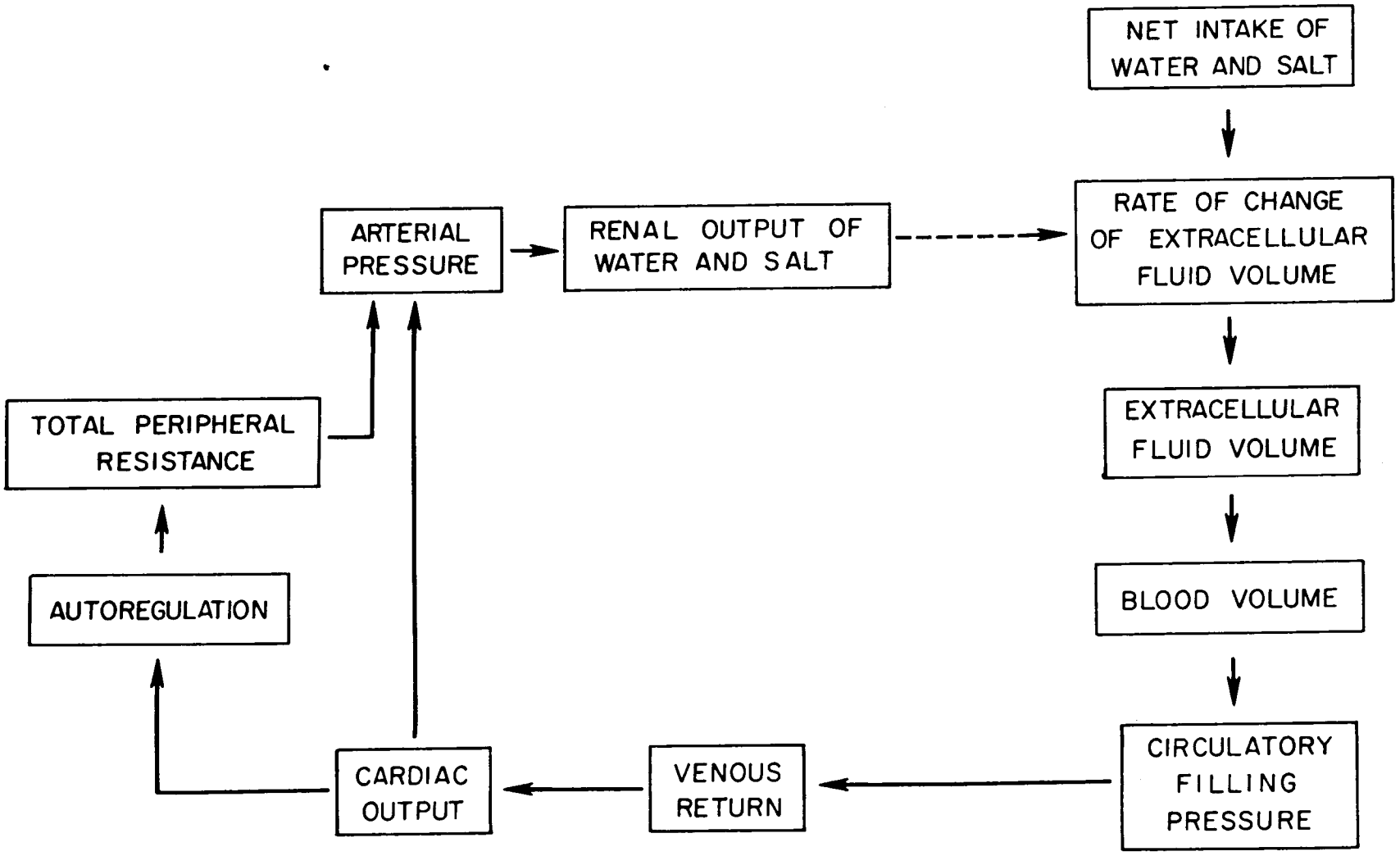

NET INTAKE OF WATER AND SALT
RATE OF CHANGE OF EXTRACELLULAR FLUID VOLUME
EXTRACELLULAR FLUID VOLUME
BLOOD VOLUME
CIRCULATORY FILLING PRESSURE
VENOUS RETURN
CARDIAC OUTPUT
AUTOREGULATION
TOTAL PERIPHERAL RESISTANCE
ARTERIAL PRESSURE
RENAL OUTPUT OF WATER AND SALT

Figure 3

which there are no apparent abnormalities in cardiac, renal, or adrenal function. In the labile or beginning stages of essential hypertension, cardiac output is often increased, but total peripheral resistance is usually not enhanced. In established essential hypertension, cardiac output is usually normal, total peripheral resistance is often elevated (Julius and Esler, 1975), and renal blood flow may be moderately reduced without glomerular filtration being significantly affected (Friedman, Selzer, and Rosenblum, 1941). In general, plasma renin activity and aldosterone levels are generally normal or low (Padfield, Beevers, Brown, Davies, Lever, Robertson, Schalekamp, and Tree, 1975). However, one study reports 20% of 219 essential hypertensives to have high renin levels (Brunner, Laragh, Baer, Newton, Goodwin, Krakoff, Bard, and Bühler, 1972).

Important evidence linking CNS function to control of blood pressure has been provided by studies of centrally-acting anti-hypertensive drugs. Studies of the action of methyldopa (L-α-methyl-3,4-dihydroxyphenylalanine) and clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline HCl) suggest that methyldopa operates by stimulating central noradrenaline receptors, while clonidine is known to exert agonistic action at central α-adrenergic receptors, and can be blocked by central noradrenergic antagonists. Both drugs appear to affect receptors in the brainstem (Henning, 1975).

Another approach to the question of central and autonomic involvement in the manifestations of essential hypertension involves assessment of the baroreceptor reflex. Clinical studies suggest that baroreceptor reflexes in hypertensive individuals are hindered by impaired sensitivity

(Bristow, Honour, Pickering, Sleight, and Smyth, 1969; Takeshita, Tanaka, Kuroiva, and Nakamura, 1975). When patients with uremia and high blood pressure were evaluated with stimuli designed to test both the afferent and efferent limbs of the baroreceptor reflex (amyl nitrite inhalation and cold pressor test, respectively), the afferent limb of the reflex was apparently impaired. No evidence of volume excess or increased plasma renin activity was found, leading the authors to suggest that hypertension in some uremic patients may be related to increased neurogenic activity caused by baroreceptor dysfunction (Levy, Lilley, and Stone, 1978).

The development of a sensitive double isotope derivative assay (Engleman and Portnoy, 1970) has greatly enhanced the accuracy of measurements of circulating catecholamines in hypertensive individuals. Several studies using this method provide evidence of elevated levels of total catecholamines or norepinephrine (NE) in hypertensive populations (DeQuattro and Chan, 1972; Louis, Doyle, and Anaveka, 1973; DeChamplain, Farley, Cousineau, and VanAmeringen, 1976). A microneurographic recording technique was used to evaluate sympathetic activity in skin and muscle nerves of hypertensives, and results indicated "an elevated baroreflex working range in hypertension" (Wallin, Delius, and Hagbarth, 1973, p. 9). A systematic review of the hemodynamic and humoral characteristics of borderline hypertensives outlined at least "adequate" support for a role for the autonomic nervous system in 6 out of the 10 characteristics discussed (Julius and Esler, 1975). Frohlich directly implicated the sympathetic nervous system in his clinical descriptions of

hypertension related to a hyperdynamic beta-adrenergic circulatory state (Frohlich, Dustan, and Page, 1966).

Finally, the responsiveness of the vascular beds themselves contributes to the neurological "portrait" of the hypertensive individual. Sydney Friedman summarized a review of the clinical evidence available concerning vascular reactivity in essential hypertension as follows:

> 1. Hyperactivity to NE is a constant feature of peripheral vascular beds in essential hypertension and can be demonstrated by well-planned clinical experiments.
> 2. An increase in the contractile mass of the vascular tunica media alters the geometry of the vessels sufficiently to produce an "apparent" hyperactivity.
> 3. The increase in the contractile mass of the vascular tunica media results in an increased work output per unit of agonist so as to produce a "real" hyperactivity.
> 4. There appears to be an additional element of real hyperactivity which is myogenic or functional, as distinct from geometric or structural.
>
> These clinical observations do not provide any direct evidence concerning pathogenesis. (Friedman, 1977, p. 470)

Both distortions of centrally controlled cardiovascular reflexes and hyperactive peripheral vasculature are possible factors in the pathogenesis of essential hypertension. Both conditions also serve as models for distortions in reflexes which involve the kidney and stimuli which trigger renal vascular responses that may affect renal handling of Na^+ and water, such as behavioral stimuli described below.

Responses to Behavioral Stimuli by Essential Hypertensives

The following description of the classic hemodynamic response pattern of the hypertensive individual under emotional stress was developed 20 years ago by Brod. He utilized mental arithmetic as a stressor, and

provided the following summary of the comparison between normotensive and hypertensive subjects:

1. Detailed hemodynamic changes during emotional stress (mental arithmetic), producing a rise of blood pressure were followed in 8 normotensive subjects and 10 hypertensive subjects with no evidence of heart failure.
2. During the blood pressure rise in both the normotensive and hypertensive subjects a renal vasoconstriction and a vasodilation in muscle were found. There was suggestive evidence of splanchic vasoconstriction.
3. Changes of the total peripheral vascular resistance may depend on the balance between simultaneous muscular vasodilation and visceral vasoconstriction.
4. Cardiac output rose in 13 out of 17 observations where it could be followed, and fell in those 4 subjects in whom the increase of total peripheral vascular resistance was the greatest.
5. There was no difference in the quality of response between normotensives and hypertensives. Quantitatively, the hypertensives responded with greater renal vasoconstriction and possibly less vasodilation in the muscles.
6. The hemodynamic response tended to persist longer after the cessation of the emotional stimulus in the hypertensive than the normotensive subjects.
7. The detailed hemodynamic response to emotional stress resembles that occurring on strenuous exercise. It is suggested that it is probably the same reaction, activated by situations which might necessitate strenuous muscular exercise. (Brod, Fencl, Hejl, and Jirka, 1959, p. 277)

These results and the results of a later experiment (Brod, Fencl, Hejl, Jirka, and Ulrych, 1962) fomented the description of the essential hypertensive as a type of "hyper-reactor" in whom emotional stimuli trigger an excessive and prolonged condition of physiological readiness for action. Subsequent research from many other sources support and expand this hypothesis (Baumann, Ziphran, Godicke, Hartrodt, Naumann, and Läuter, 1973; Lawler, 1980; Julius and Esler, 1975).

These impressions are supported by a recent study in which individuals with essential hypertension, normotensives with one hypertensive parent, and a control group of normotensive subjects with

no family history of hypertension were exposed to a mildly stressful psychological stimulus, a nonverbal IQ test. The hypertensive subjects responsed with transient increases in arterial blood pressure (over 7 mmHg) and heart rate, sustained decreases in renal blood flow, and significant increases in plasma renin activity. The normotensive subjects responded with small changes in blood pressure, significant increases in renal blood flow, and decreases in plasma renin activity. Subjects with a family history of hypertension fell between these two groups. The authors conclude that both the subjects with essential hypertension and normotensives with a family history of essential hypertension have an abnormality in control of both renin release and renal blood flow in response to stressful psychological stimuli (Hollenberg, Williams, and Adams, 1981).

Theories of Renal Involvement in Essential Hypertension

One of the most comprehensive theories concerning the significance of renal function in hypertension is Guyton's renal-fluid volume theory (Guyton, Coleman, Cowley, Scheel, Manning, and Norman, 1972; Guyton, 1977). The hypothesis suggests that the mechanisms of major importance in acute regulation of arterial pressure, i.e., total peripheral resistance (TPR), cardiac output, venous tone and compliance, and total blood volume are dominated in the long run by renal-fluid volume mechanisms. Sustained elevations in blood pressure can only come about when the "state" of the kidney is altered in such a way as to reset the threshold level of arterial pressure which governs the renal excretion of Na^+ and water. According to Guyton, the renal-fluid volume mechanism

is the only blood pressure control mechanism which demonstrates an "infinite gain" feedback capacity. Unlike the baroreceptor feedback system, which requires the stimulus of some continued elevation in pressure in order to continue to respond, the normal kidney will always eventually excrete enough salt and water to return the fluid volume and blood pressure to its original balance. Important questions at this point include: (1) if sustained elevations in blood pressure can only exist when the state of the kidney is altered, causing an increase in blood volume, why do most essential hypertensives show normal or reduced levels of blood volume? (2) If elevated peripheral resistance is not a causative factor, why does such a high percentage of essential hypertensives show consistent elevated peripheral resistance? Two concepts are relevant to these questions: the "cascade effect" of extracellular fluid volume on blood pressure, and the autoregulation response of the vasculature. Guyton has demonstrated experimentally that a 2 percent increase in extracellular fluid volume (an increase probably undetectable clinically) can cause a 5 to 10 percent increase in cardiac output. After an adaptation of baroreceptor and central blood volume reflexes, a process which could take days or weeks, autoregulation would begin to affect the TPR. Autoregulation is a process whereby overperfusion of the tissues eventually triggers a vasoconstriction of the tissue vessels, presumably a local response to the smooth muscle. The result of this sequence of events is a chronically elevated arterial pressure, caused by a change in the kidney's ability to regulate fluid volume, and maintained (not caused) by an elevation in TPR. The apparent "normal" renal function

found in many patients with essential hypertension is thus not really normal, because it permits the elevated pressures to persist (see Figure 4).

The question of what mechanism causes the change in the state of the kidney is of obvious importance. Guyton points out three major categories of renal abnormalities that could cause the increased retention of salt and water necessary to elevate blood volume: (1) increased vascular resistance, (2) decreased glomerular filtration, and (3) increased sodium reabsorption in the renal tubules.

The pivotal role of the kidney in hypertension is also favored by Louis Tobian (Tobian, 1977). The initial "resetting" of the kidney, according to Tobian, is triggered by excess sympathetic stimulation, a condition which is "permitted" or perhaps genetically predisposed by CNS activity (the kidney-CNS axis). The hypertension is maintained in part by a stiffening of the walls of resistance vessels as they take in sodium and water during vasoconstriction. Such changes could take place in the renal arteries as well, contributing to the elevations in pressure following removal of Goldblatt clamps or discontinuation of salt or DOCA in these forms of experimental hypertension. Tobian points out, as does Guyton, that the most successful treatment of human hypertension involves the reduction of extracellular fluid, cardiac output, or sympathetic output of renin. All three of these factors implicate the kidney and sympathetic activity.

The most widely studied renal influence on blood pressure today is the renin-angiotensin-aldosterone system. Extensive reviews of the control of renin (Vander, 1967; Pickering, 1968) and of the clinical

Figure 4. Comparison of renal function curve for normotensives and essential hypertensives. Modified from Guyton et al., 1972.

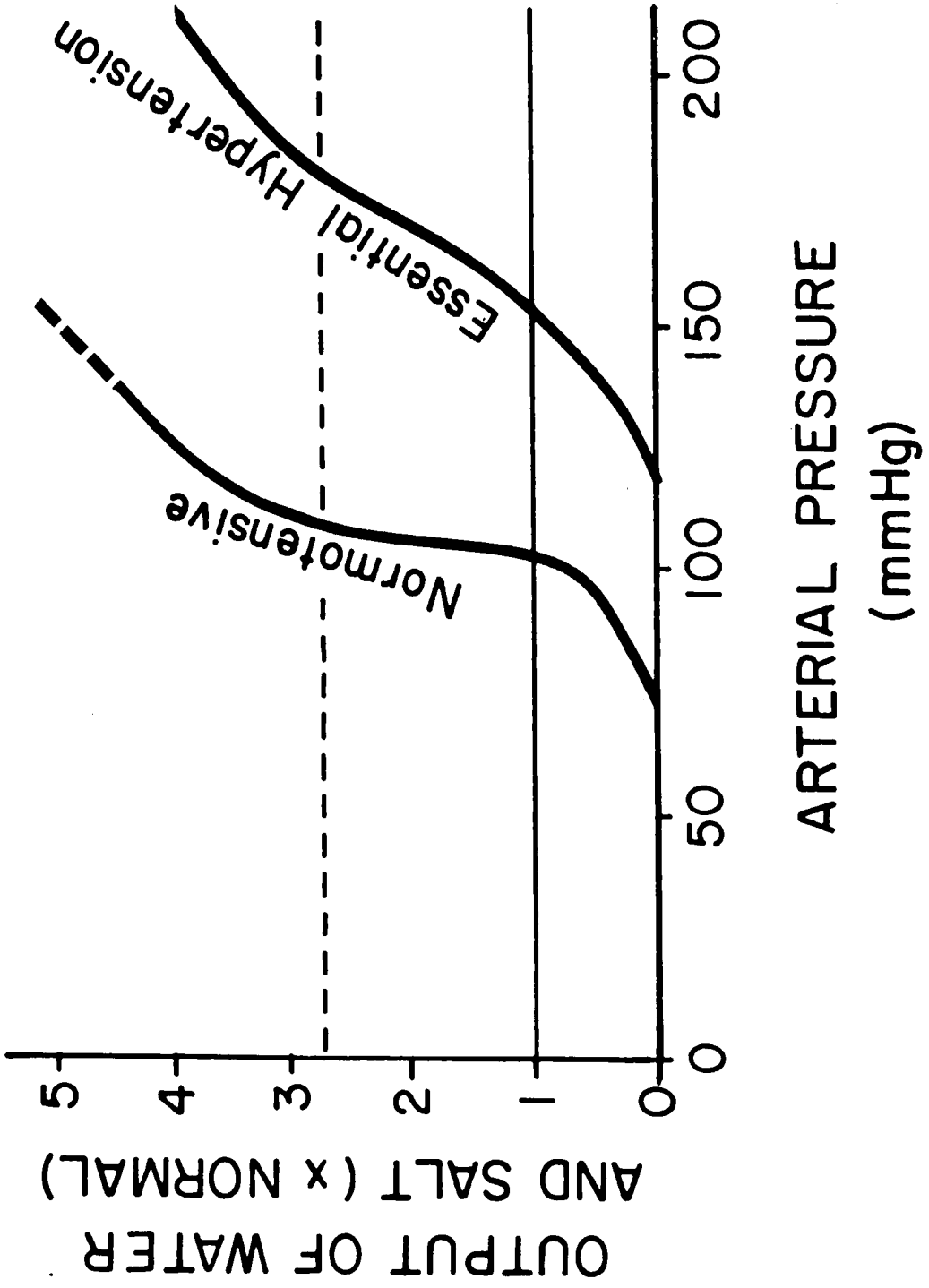

OUTPUT OF WATER
AND SALT (x NORMAL)
5
4
3
2
1
0
0
50
100
150
200
ARTERIAL PRESSURE
(mmHg)
Normotensive
Essential Hypertension

Figure 4

implications of the system in hypertension (Krakoff and Laragh, 1977) are available, thus only a general description will be included here.

Renin is an enzyme produced by the juxtaglomerular cells of the kidney. By acting on a protein substrate present in the plasma, it produces a decapeptide, angiotensin I. Conversion of angiotensin I to to angiotensin II occurs primarily in the pulmonary circulation. Angiotensin II is an extremely potent pressor substance which causes constriction of the smooth muscle of arteries. It also acts upon the adrenal cortex to induce release of aldosterone, a sodium-retaining hormone (Skeggs, Dorer, Kahn, Lentz, and Levine, 1976; Erdös, 1976). Although there is evidence of the existence of renin-like enzymes in other tissues (Ganten, Schelling, Vecsei, and Ganten, 1976), the kidney is the principle source. Control of renin release is complex. Freeman and Davis (1977) suggest three different types of mechanisms: (1) two intrarenal receptors, a vascular receptor which responds to changes in wall tension in the afferent arteriole, and the macula densa, which is probably activated by a decrease in sodium in the renal tubule; (2) the renal sympathetic nerves activated by a β-adrenergic receptor; and (3) various humoral agents (catecholamines, angiotensin II). Because of its significance in hypertension, the relationship between sodium intake and the renin-angiotensin system has been extensively studied. Under conditions of sodium deprivation, renin release is increased (Fray, 1978), increased angiotensin levels contribute to decreased venous compliance (Coleman, Cowley, and Guyton, 1975), aldosterone secretion increases (Spielman and Davis, 1974), and the vascular response to angiotensin decreases (Swales, Tange, and Thurston, 1975).

It is possible that centrally mediated alterations in renal blood flow, renin release, renal sympathetic activity, and renal excretion of Na^+ and water in response to behavioral and sensory stimuli could be a factor in the pathogenesis of hypertension. Evidence exists of aberrations of other CNS controlled reflexes and cardiovascular responses in the hypertensive individual, as well as altered patterns of renal responses to behavioral stimuli. More information is needed about CNS control of renal responses to such stimuli.

B. Experimental Models of Hypertension

1. Renal models. The best known model of experimental hypertension is renovascular hypertension, created in experimental animals by constricting the blood flow in one or both renal arteries. The classic Goldblatt model utilized dogs (Goldblatt, Lynch, Hanzal, and Summerville, 1934; Goldblatt, 1958), and subsequent experiments with rats (Wilson and Byrom, 1939) and rabbits (Pickering and Prinzmetal, 1938) have been similarly successful. Constrictions of one renal artery without interference with the contralateral kidney (two-kidney Goldblatt hypertension techniques) results in an increase in blood pressure which is typically transient. Removal of one kidney following constriction of the contralateral renal artery results in a condition referred to as one-kidney Goldblatt hypertension. This condition is usually permanent, and can proceed in two phases—a benign phase followed by a malignant phase. Both types of hypertension can develop with normal blood urea levels and normal creatinine, inulin and p-aminohippurate clearance (PAH). The development of a malignant phase can, of course, alter these parameters.

Research suggests that renin plays a dominant role in maintaining elevated pressure in the two-kidney model, whereas sodium and water volume appear to be the significant factors in one-kidney hypertension (Carretero and Romero, 1977).

Infusions of either renin or angiotensin II for periods of 10 to 18 days can cause hypertension with patterns of renal vascular pathology similar to that accompanying renovascular experimental hypertension. Hypertension may also be induced in animals by mineralocorticoid administration, salt loading alone, or salt loading in conjunction with reduction of renal mass. Research suggests that hypertension in these models involves sodium and water retention (Folkow and Hallbäck, 1977).

2. Genetic models. At least two of the genetic models, including the Milan strain of spontaneously hypertensive rats (MHS), show evidence of renal involvement (Bianchi, Baer, Fox, Duzzi, Pagetti, and Giovannetti, 1975). Transplantation of MHS kidneys to normotensive controls from the same strain (NCR) results in a transfer of the elevated pressure condition, whereas exchanging MHS kidneys for NCR kidneys will lower pressure in the MHS (Bianchi, Fox, DiFrancesco, Giovannetti, and Pagetti, 1974). During the development of pressure elevations, MHS show signs of increased blood volume resulting from increased sodium retention. Glomerular filtration rate is decreased, and plasma renin levels are reduced. When the moderate increases in blood pressure are established, these parameters return to normal levels (Folkow and Hallbäck, 1977). Although renal and other peripheral vascular resistances have not been measured in this model, the pattern of the development of hypertension is

at least superficially compatible with an autoregulation hypothesis. Also, MHS show an exaggerated natriuretic response to saline infusions.

The Brookhaven strains of salt-sensitive and salt-resistant rats developed by Dahl and co-workers (Dahl, Knudsen, and Iwai, 1970) appear to have genetically determined differences in renal responses to salt. The salt-sensitive strain will readily become hypertensive in response to an 8 percent NaCl diet, while the salt-resistant strain on the same diet will remain normotensive. Cross transplantation of kidneys and parabiosis experiments suggest hypertensinogenic characteristics are present in the salt-sensitive kidney and its secretions (Folkow and Hallbäck, 1977). The hypertension-prone animals also show heightened responsiveness to DOCA-NaCl treatments and unilateral renal artery clipping, both techniques used to induce experimental hypertension (Dahl, Heine, and Tassari, 1962).

Spontaneously hypertensive rats (SHR) show no specific signs of primary renal abnormalities during the development of their hypertension. Plasma volume, blood volume (Sen, Hoffman, Stowe, Smeby, and Bumpus, 1972) and sodium content and balance are generally normal (Folkow and Hallbäck, 1977). Plasma renin activity and aldosterone are normal according to one report (Koletsky, Shook, and Rivera-Velez, 1972) or slightly elevated in young SHRs (Sen, Semby, and Bumpus, 1972). The adrenal cortex and the mineralocorticoids do not seem to be involved in the pathogenesis of hypertension in this model (Baer, Knowlton, and Laragh, 1972). However, spontaneously hypertensive rats do respond to a saline load with an exaggerated natriuresis, and a recent study suggests that this response is related to a lack of aldosterone mediated

distal tubular sodium reabsorption (Willis and Bauer, 1978). Salt loading does not trigger a significant pressor response in the SHR (Barsanti, Pillsbury, and Freis, 1971). The New Zealand strain of genetically hypertensive rats developed by Smirk in the 1950's seems to resemble the SHR in that they show a lack of evidence of obvious renal involvement in the development of hypertension.

3. Neurogenic models. Elevation of blood pressure via electrical stimulation of the hypothalamus was first demonstrated by Karplus and Kreidl (1927). Mapping of behavioral responses to stimulation of such subcortical areas was provided by Hess, using unanesthetized animals (1949). Uvnäs, using anesthetized animals (1960), was able to elicit a complex pattern of sympathetically mediated cardiovascular changes by stimulating the perifornical region of the lateral hypothalamus, parts of the tegmentum, and midbrain central gray. The response pattern included increases in blood pressure, cardiac output, stroke volume and heart rate. Adrenergic vasoconstriction of the skin and the renal and intestinal vascular beds was also noted, as well as activation of the adrenal medulla, increased intestinal motility and cholinergically mediated vasodilation in muscle. It is this set of responses that became known as the Abwehrreaktion, or defense reaction (Hess and Brügger, 1943). Weak, intermittent stimulation of the hypothalamic defense area (10 sec. per minute, 12 hours daily for 4 months) caused a gradual, significant increase in systemic blood pressure in rats. Pressure returned to normal within 2 weeks after stimulation was discontinued (Folkow and Rubinstein, 1966).

The strongest evidence supporting involvement of central noradrenergic neurons in hypertension comes from research involving baroreceptor denervation. Denervation of the carotid sinus and aortic arch results in permanent elevations in blood pressure (Koch and Mies, 1929). The procedure also is associated with a significant increase in turnover of NE in the thoracolumbar region of the spinal cord. This increase suggests increased activity in bulbospinal noradrenergic neurons innervating the lateral horns of the spinal cord. The elevation in blood pressure results from a corresponding increase in peripheral sympathetic activity (Chalmers and Wurtman, 1971). Pretreatment with 6-hydroxydopamine (6-OHDA) causes a reduction in NE in the brain stem and prevents increases in blood pressure (Chalmers and Reid, 1972).

The nucleus solitarius and its surrounding tract (NTS), located dorsolaterally in the medulla, have provided the basis for a relatively new model of experimental hypertension involving the CNS. Bilateral lesions of the NTS can produce acute fulminating hypertension in the rat (Doba and Reis, 1974). Destruction of this link in the central afferent baroreceptor pathway causes increased peripheral resistance, decreased cardiac output and hypertension. NTS hypertension has been shown to be caused by increased sympathetic discharge which can be reversed by α-adrenergic blockade. Systemically administered 6-OHDA prevented the hypertension, but only after adrenalectomy. Injections of 6-OHDA in the hypothalamus did not affect the rise in blood pressure. Intracisternal injection (600 μg) blocked pressure increases and lowered norepinephrine content in the spinal cord but not in the heart. These data suggest, according to Doba and Reis, that the effect of 6-OHDA on NTS hypertension

operates via central noradrenergic bulbospinal mechanisms. The NTS model also carries implications for the role of the baroreceptor reflex in cardiovascular responses to environmental stimuli.

Baroreceptor function can be altered experimentally by volume loading (Vatner, Boettcher, Hendrickx, and McRitchie, 1975) and chronic heart failure (Higgins, Vatner, Eckberg, and Braunwald, 1972). In hypertension induced in dogs by chronic infusion of angiotensin II, baroreceptor resetting accounted for 35 percent of the gradual increase in pressure (Cowley and DeClue, 1976). When comparisons were made between short- and long-term angiotensin infusion and hypertension induced by salt loading, the magnitude of influences of baroreceptor resetting was found to be inversely related to the rapidity of the pressure elevation.

The effect of loss of baroreceptor influence was studied in rabbits and dogs. Increased cardiac output was a major cause of increased pressure in sinoaortic denervated (SAD) rabbits studied acutely (1-40 hours after denervation), but elevated total peripheral resistance was the primary factor in animals studied 3 to 30 days after surgery. In the acute animals, renal blood flow was increased and renal resistance low or normal. In the chronic animals, renal resistance was increased, suggesting increased sympathetic activity (Alexander and DeQuattro, 1975).

In the dog experiments, increases in plasma renin activity were found following sinoaortic denervation and after vagotomy (Yun, Delea, Bartter, and Kelly, 1977). The increase in plasma renin activity (PRA) following vagotomy appeared to be mediated by increased sympathetic discharge to the kidney, while the increases following sinoaortic

denervation were probably a function of increased activity of the renal nerves and response to catecholamines released by the adrenal medulla. Experimental procedures evoking a carotid sinus response to reduced pressure also caused increased release of renin (Jarecki, Thorén, and Donald, 1978). In intact animals, however, activation of vagally innervated cardiopulmonary receptors or increases in renal arterial pressure blocked the release of renin caused by carotid hypotension.

Finally, evidence of baroreceptor resetting secondary to elevated blood pressure was found in spontaneously hypertensive rats. Resetting could be prevented in young SHR's by early treatment with antihypertensive drugs, and could be reversed by treatment in 50 percent of older animals. Correlations were found between aortic hypertrophy and baroreceptor resetting (Sapru and Wang, 1976).

It would appear that baroreceptor resetting in experimental models of hypertension occurs as a function of the hypertension and results in elevated peripheral sympathetic activity. It could be suggested that the diminished sensitivity found in patients with hypertension may be secondary to changes in vessel walls caused by sustained elevations in pressure. The impaired sensitivity could in turn lead to a tonic hyperactivity of the peripheral nerves and resistance vessels, causing the increased peripheral resistance often seen in hypertensives.

Efforts intended to link various experimental models of hypertension with enhanced sympathetic activity have taken many different forms. Prolonged stimulation of the stellate ganglion in dogs produced elevated blood pressure and peripheral resistance. Initially, elevations in pressure were caused by increased cardiac output (CO), but after 24 hours

CO returned to normal and elevated blood pressure was maintained by α-adrenergic mechanisms (Liard, Tarazi, Ferrario, and Manger, 1975). Increases in norepinephrine content and neurogenic contractile response were found in the blood vessels of rabbits made hypertensive by coarctation of the abdominal aorta. These indicators of increased sympathetic activity were only found above the constriction, where arterial pressure was increased (Bevan, Purdy, Su, and Bevan, 1975).

The role of enhanced neurogenic activity in the pathogenesis or maintenance of hypertension appears quite varied in the experimental models involving rats. The SHR shows evidence of increased sympathetic activity at an early age histochemically and pharmacologically. Evidence also exists of CNS mediated hyperreactivity in SHR in response to stress (Folkow and Hallbäck, 1977). The New Zealand strain of genetically hypertensive rat (GHR) developed by Smirk in the 1950's also shows some evidence of elevated sympathetic activity.

According to Folkow and Hallbäck, neither the Milan strain of spontaneously hypertensive rats (MHS) (Bianchi, Fox, DiFrancesco, Bardi, and Radice, 1973) nor the Brookhaven hypertension-sensitive strain developed by Dahl (Dahl, Heine, and Tassinari, 1962) show significant involvement of sympathetic activity in their respective forms of hypertension. However, a recent study using the Brookhaven rats demonstrated that 50 percent of the increase in vascular resistance produced in these animals by high salt diet was maintained by neurogenic mechanisms (Takeshita and Mark, 1978).

Based on both clinical and experimental evidence, it appears that the role of the peripheral sympathetic nervous system in hypertension

includes some degree of elevated activity. Whether this elevated activity is secondary to CNS changes or genetic aberrations, and whether it plays an initiating or merely permissive role in essential hypertension, is yet to be determined.

4. Behavioral models. It is probable that environmental factors will prove to be hypertensinogenic in only a select group of people who develop hypertension. The factors determining this group may be genetic, psychological, dietary, or a combination of these elements. In many cases, stress may aggravate other conditions or cardiovascular disease states. Many hypertension hypotheses involve a two-factor model: one set of stimuli raises the pressure acutely and, in so doing, triggers some process which fixes both the blood pressure and the total peripheral resistance at a consistently high level. The role that environmental stress plays in this model requires further investigation, as the research effort has met with difficulties.

Many of the major problems are methodological, including (1) difficulties in quantifying stressor stimuli, (2) maintaining the general health of animals exposed to stressful conditions over long periods of time, (3) accurate measuring of cardiovascular and renal function in conscious animals, and (4) accounting for the interaction effects which are probably integral to the success of any environmental model of hypertension. There has been a tendency to focus on only one or two dependent variables, thus making necessary integration difficult. When species differences in terms of responses to stressors are added to these factors, along with the very basic question of what constitutes a

stressor, it becomes obvious that the task of assembling a model of experimental hypertension which is significantly related to environmental stress is a difficult one. And yet there exists a vast quantity of data based on research of both borderline and essential hypertension in humans which implicates stress factors, and strongly suggests the need for just such a model. This brief review will outline some of the data provided by nonhuman subjects responding to such variables as psychosocial stress, operant and classical conditioning and variations in ambient temperature, restraint, shock, conflict, pain and noise.

In an attempt to approximate the quality of various stressors that may be present in human environment, mice were exposed to conditions which presented various threats: mature animals from different colonies were mixed, groups were exposed to a predator, and conflicts for territory were created. All methods resulted in significant elevations of systolic blood pressure (ascertained by tail cuff measurement) which were sustained during the 6 to 12 month experimental period. Males presented pressures on the order of 160 mmHg, females averaged 140-150 mmHg. Pressures returned to normal following administration of reserpine, but were not affected by ether anesthesia. There was some evidence of increased renal vasoconstriction, and histological examination revealed interstitial nephritis in the most severely hypertensive group (Henry, Meehan, and Stephens, 1967). Further studies revealed an increase in the catecholamine synthesizing enzymes (Henry, Stephens, Axelrod, and Mueller, 1971), increases in heart weight, permanent myocardial fibrosis (Henry, Stephens, and Santisteban, 1975) and arteriosclerotic degeneration of the

aorta and the coronary vessels (Henry, Ely, Stephens, Ratcliffe, Santisteban, and Shapiro, 1971).

Operant and Classical Conditioning

Squirrel monkey pairs were subjected to environmental stress by exposing one animal of the pair to a Sidman avoidance schedule, a paradigm in which the animal must make an operant response within a specified time interval in order to avoid a painful shock. The "partner" of each animal received a simultaneous shock each time the avoidance monkey received one for failing to respond (Corley, Mauck, and Shiel, 1975). Results of this and a similar previous study (Corley, Shiel, Path, Mauck, and Greenhoot, 1973) demonstrated a difference in cardiovascular response between experimental animals and their yoked partners. Avoidance monkeys from the 1973 experiment showed myofibril degeneration, suggesting sympathetic activation. The yoked animals in the 1975 study showed bradycardia with ventricular arrest. The avoidance monkeys paired with partners in the later experiment showed no ill effects. Differences in the length of time the animals were exposed to the schedule were suggested as an explanation. Blood pressure was not significantly altered by either treatment in the two monkeys monitored in each condition.

An extensive set of experiments (carried out for 4 to 11 months) also using squirrel monkeys and operant conditioning procedures has demonstrated significant sustained elevations in blood pressure. Animals restrained in primate chairs were trained to press a key in order to turn off a light which functioned as a discriminative stimulus for shock. As the animals became adept at the task, they responded more frequently and

received fewer shocks. During this time, mean blood pressure consistently increased. Eventually the pressures remained at hypertensive levels both during and between sessions (Herd, Morse, Kelleher, and Jones, 1969). In another experiment (Herd, Morse, Kelleher, and Grose, 1971), following a similar training regimen, the response key was removed from the apparatus and elevations in blood pressure were used as the operant. Elevated pressures were maintained throughout the experimental sessions. When termination of the light was made contingent on decreases in pressure, pressures fell nearly to control values (Benson, Herd, Morse, and Kelleher, 1969). One animal out of the five which showed elevated pressures died during the experiment and subsequent pathologic examination showed hemorrhages of the renal cortex and changes in the renal arteries (Benson, Herd, Morse, and Kelleher, 1970). Pharmacological manipulations revealed a high level of sympathetic tone throughout the experiment. Blood pressure was reduced and heart rate increased in response to phentolamine. Propranolol and methyl atropine were not effective in reducing blood pressure (Kelleher, Morse, and Herd, 1972).

Studies in rhesus monkeys on Sidman avoidance schedules for 15 days resulted in significant elevations of arterial pressure which appeared to increase in duration as a function of the severity of the stress (Forsyth, 1968). During more extensive studies, which lasted from 2 to 14 months, pressures were elevated in response to similar paradigms, and tended to remain elevated throughout the day of the experimental session. Changes in regional blood flow were determined using radioactive microspheres, and cardiac output was measured using a dye dilution technique. Changes in regional blood flow under stressful conditions

mimicked the acute stress and hypothalamic defense reaction pattern found in humans, i.e., increased cardiac output, decreased peripheral resistance, and increased blood flow to muscles at the expense of the viscera (Forsyth and Harris, 1970).

In an experiment which exposed rhesus monkeys to 72 continuous hours of Sidman avoidance conditioning, cardiac output decreased as the session progressed, until blood pressure elevations were maintained completely by increased total peripheral resistance (Forsyth, 1971). However, evidence of myocardial pathology was found in some animals following the 72-hour period, suggesting that some of the animals may have been in poor health before the stress exposure.

The stressful effects of the pre-avoidance period in addition to the avoidance period were elevated in several experiments with dogs. The pre-avoidance pattern consisted of elevations in blood pressure and decreases in heart rate. These changes were observed to begin as early as 15 hours before the avoidance session. Onset of avoidance resulted in further increases in blood pressure and increases in heart rate (Anderson and Brady, 1973). Further studies indicated that the pre-avoidance increases in blood pressure were a function of increased peripheral resistance, while the increases during avoidance took place despite a decrease of peripheral resistance (Anderson and Tosheff, 1973). Superficially, at least, dogs in pre-avoidance situations facing an unavoidable unpleasant experimental session appear to react in a manner similar to "yoked partner" monkeys enduring unavoidable shock.

Lawler, Obrist and Lawler (1975) found similar pre-avoidance and avoidance patterns in two dogs. Extensive evaluation of myocardial

function revealed an increase in aortic dp/dt (an indicator of sympathetic activation and increased contractile force) and increased stroke volume and heart rate with the onset of avoidance. A positive relationship between the nervous demeanor of the dogs tested and their cardiovascular reactivity suggests support for a model of individual differences in both physiological and psychological vulnerability.

Finally, classical conditioning was used in a recent study to demonstrate the effects on blood pressure of abolition of baroreceptor function via lesions in the nucleus tractus solitarii. Conditioned responses to tones which signalled forthcoming shock were found to be five times greater in lesioned animals compared to animals with sham lesions (Nathan, Tucker, Severini, and Reis, 1978). The role of the central nervous system in stress-induced experimental hypertension is a relatively unexplored area of investigation. It is possible that advances in knowledge and methodology will reveal new research questions.

Restraint, Noise and Cold

Forsyth and Baireuther (1967) measured systemic arterial blood pressure and mean plasma levels of epinephrine and norepinephrine in rhesus monkeys restrained in primate chairs. Intra-arterial catheters were used for blood samples and hourly measurements of blood pressure. They found no difference in any of the variables when comparisons were made with measurements taken in quiet, trained monkeys using an arm cuff and auscultation of the bracheal artery (Smith and Ansevin, 1957). Spontaneously hypertensive rats, however, were shown to respond with significant elevations in systolic pressure (25 mmHg) when placed in restraint during tail-cuff measurements of pressure. Levels of plasma

catecholamines also increased during restraint, although basal levels measured in the home cages did not differ between SHRs and Wistar-Kyoto controls (Chiueh and Kopin, 1978).

In Sweden, a study was done comparing defense reactions to alerting stimuli in 11-week and 7-month-old spontaneously hypertensive rats, 12-week-old rats with hypertension induced by unilateral renal artery clipping (RHR) and normotensive rats matched to each age group (NHR). Both ages of SHR demonstrated greater reactivity to light, noise and vibration stimuli (Hallbäck and Folkow, 1974). The presence of an increased sympathetic tone was suggested when beta-blockade decreased heart rate more in the SHR than in controls. Decreased vagal tone in SHR was indicated by the lesser increase in heart rate under vagal block. The fact that the RHR animals did not show the same hypersensitivity to alerting stimuli suggests that the hypertensive condition alone is not responsible. This point was further supported by the demonstration of hyperreactivity in the 10-11 week old "prehypertensive SHRs."

Hallbäck and Folkow suggest a centrally mediated, exaggerated neurohumoral defense in the SHR which is genetically determined. Not only do the SHRs exhibit increased aggression and overreaction to environmental stimuli—the opportunity to engage in such reactions can aggravate the development of hypertension, and the lack of such environmental stimuli can retard the progression of the state (Hallbäck, 1975).

Both cold and noise stressors have been shown to be related to elevations in blood pressure. Squirrel monkeys exposed to ambient temperatures of 10°C and 28°C responded with increases in blood pressure, heart rate and oxygen consumption when exposed to the lower temperature

(Wasserstrum and Herd, 1977). Exposure to 10 minutes of auditory stimulation 5 days per week from weaning until up to 890 days of age produced hypertension in the older of two groups of rats (Medoff and Bongiovanni, 1945). Sixty-one percent of the 18 rats 400 to 900 days old developed systolic pressures over 160 mmHg. However, 10 percent of the control animals also developed hypertension, and all blood pressure measurements were determined only with regard to placement within one of four 20 mmHg pressure ranges. Increases in blood pressure in rats in response to auditory stimulation have also been reported by Yeakel, Shenkin, Rothballer and McCann (1948). In a subsequent study by McCann, Rothballer, Yeakel and Shenkin (1948), adrenalectomy lowered blood pressure to subnormal levels, and treatment of adrenalectomized animals with cortical extract and salt returned blood pressure to pre-stress levels. Combinations of auditory, visual and motion stimuli (Buckley, Koto, Kinnard, Aceto, and Estevez, 1964) caused hypertension, and a similar paradigm elevated blood pressure, urinary catecholamines and adrenal and plasma corticosterone. Catecholamines reached a maximal level within four hours and returned to control levels at the end of four weeks. Corticosterone levels returned to normal by the eighth week (Rosecrans Watzman, and Buckley, 1966). This stressful paradigm produced elevations in blood pressure in an additional study (Buckley and Smookler, 1970). The inhibition of catecholamine synthesis via alpha-methyltyrosine prevented the elevations in pressure.

The most successful experimental animal studies to date on noise-induced hypertension have been carried out on rats (see above). Progress has been made on the investigation of mechanisms involved in the blood

pressure changes with catecholamine, adrenal, renal and neurogenic components implicated. Primary difficulties in this work stem from the interaction effects of other types of stimuli frequently combined with noise, such as vibration and light, and the high susceptibility of the rat to autogenic seizure, which suggests an enhanced species specific vulnerability to autogenic stress.

Recent research using nonhuman primates has found significant disturbances in diurnal patterns of heart rate and blood pressure as well as systolic blood pressure increases of 43 percent by the twenty-first day of noise exposure. The subject, a female rhesus monkey, was exposed to a recorded noise sequence intended to approximate a noisy urban industrial environment (Peterson, Augenstein, Hosek, Klose, Manas, Bloom, Lovett, and Greenburg, 1975).

Shock and Conflict

In a study evaluating the effects of shock alone and signaled shock on rats of the hypertension-prone strain developed by Dahl, no effect of stress on blood pressure was found in any of the three groups (over a 4-6 month period) fed different salt diets. One experiment did suggest that stress impaired the decline in blood pressure expected when hypertensive rats were placed on low salt diets (Dahl, Knudsen, Heine, and Leitl, 1968). Elevations in pressure were found when rats of the same strain were exposed to a paradigm involving a conflict between food and shock. Food was response-produced on a variable interval schedule; shock was produced by the same response on a variable ratio schedule. Pressures rose to hypertensive levels during the 13-week experiment and most pressures returned to normal during a 13-week recovery period,

although some animals did show pressure elevations which extended beyond the stress-free period (Friedman and Dahl, 1975). When rats from a genetically resistant strain were exposed to this paradigm, no elevations were noted (Friedman and Iwai, 1976). During these experiments, all animals were maintained on a low salt diet.

C. Basis for Renal/Behavioral Model of Hypertension

The preceding literature review has provided a description of characteristics of neural and renal function typical of persons with essential hypertension, emphasizing evidence of kidneys which tolerate, via as yet unknown mechanisms, arterial blood pressure at hypertensive levels without overt clinical signs of renal abnormalities. Theories reviewed include local autoregulation of the renal vasculature in response to frequent over-perfusion of tissue, and alterations in the tunica media of the renal vessels resulting from and further enhancing vascular reactivity. In addition, essential hypertensives demonstrate chronically elevated peripheral vascular resistance and impaired baroreceptor reflexes.

Additional research depicts the essential hypertensive as a hyper-responder to psychological stimuli as well, particularly stimuli of a stressful or noxious nature. Very recent work assists in integrating neural and renal facets of essential hypertension by demonstrating that some patients with essential hypertension respond to a mildly stressful psychological stimulus with a constellation of renal responses, including increases in PRA and decreases in renal blood flow.

The hyper-responsive pattern, the abnormalities in neurogenic control of circulation and reflex patterns, the evidence of heritability and the success of centrally acting antihypertensive drugs all implicate the central nervous system in the pathogenesis and/or maintenance of at least some forms of essential hypertension. The hypothesis is supported by experimental models of hypertension based on genetic susceptibility, surgical or pharmacological manipulation of the central or peripheral nervous system, and repeated exposure to behavioral stimuli.

The literature review also offers substantial evidence in support of the contention that subtle changes in the structure or function of the kidney can result in permanent hypertension. Alterations in pressure diuresis with and without saline challenge in the hypertensive individual, the emphasis on renal involvement in experimental models of hypertension, and the emphasis placed on PRA and fluid balance in the diagnosis and treatment of essential hypertension are widely documented.

The focal point of this dissertation is the contention that these two perspectives, the neurogenic/behavioral approach and the renal/fluid dynamics approach, are more useful as two aspects of one integrated model than as alternative hypotheses. The impetus for such a perspective comes from the integration of the three areas of research:

1. Relatively new knowledge about opiate receptor involvement in central nervous system responses to behavioral stimuli, and anatomical locations of potentially responsive areas;

2. Detailed information about specific nuclei and localized regions in the central nervous system which affect blood pressure, renal blood flow, renin release, and regulation of fluid balance;

3. Information about the responsiveness of the kidney to behavioral stimuli.

The endogenous opiate peptides which have been identified include leucine^5-enkephalin, methionine^5-enkephalin, and B-endorphin. These substances are considered to be endogenous opiate receptor ligands because they can exert pharmacologic actions indistinguishable from those of morphine and other opiates, and their action can be blocked at the receptor site by naloxone, a specific opiate receptor antagonist (Beaumont and Hughes, 1979). Both enkephalins and endorphins are found in many areas of the central and autonomic nervous system and the endocrine system. Evidence suggests that endorphins are activated in the brain and released from the pituitary gland (along with adrenocorticotropin) in response to certain types of stress, and that they act as neurotransmitters and modulators of physiological and behavioral responses to aversive stimuli (Amir, Brown, and Amit, 1980).

Endorphins are known to be mobilized in brain and pituitary in response to such varied stressors as electric shock, restraint and insulin-induced hypoglycemia (Amir, Brown, and Amit, 1980). Noise stimuli have been shown to mask the hypothermic effect of naloxone in rats (Stewart and Eikelbloom, 1979). In addition, endorphins and enkephalins are thought to be related to some types of stress-induced analgesia but not others (Bodnar, Kelly, Brutus, and Glusman, 1980). Stress-induced analgesia adapts upon repeated exposure to the stressor (Amir and Amit, 1978) and may lead to hyper-responsiveness to pain and decreased endorphin activity in brain (Madden, Akil, Patrick, and Barchas, 1977). There is strong evidence that analgesia produced in humans by electrostimulation

of sites in brain adjacent to the third ventricle is mediated by endorphins (Terenius, 1978). Levels of endorphin in cerebral spinal fluid rise following stimulation, and the effects are antagonized by naloxone in some patients.

The role of endorphins in stress responses may be very complex. The release of ACTH in response to such stimuli is triggered by corticotropin releasing factor (CRF), which is located in neurosecretory cells in the supraoptic and periventricular nuclei of the hypothalamus. These areas show high levels of opiate receptors (Bugnon, Block, Lenys, and Fellman, 1979) as do the posterior lobe of the pituitary and the pancreas (Ipp, Dobbs, and Unger, 1978). Opiate peptides may play a role in the coordination of release of such hormones as vasopressin, glucagon and insulin in response to stress (Amir, Brown, and Amit, 1980).

The essence of the renal/behavioral model of hypertension is that localized brain centers intimately involved in regulation of blood pressure and renal function may be highly sensitive to the direct effects of environmental and behavioral stimuli. Research described below shows that these centers are appropriately rich in endogenous opiate receptors which could be utilized to moderate the responses of the nuclei controlling such essential physiological systems.

It is interesting that many areas rich in endogenous opiates are closely associated with dopaminergic, noradrenergic and serotonergic neuronal systems (Beaumont and Hughes, 1979). These are primary central cardiovascular control neurotransmitters, and it is known that the cardiovascular system is very sensitive to both exogenous (Evans, Nasmyth, and Stewart, 1952) and endogenous opiates (Floréz and Mediavilla, 1977).

Endogenous opiates may act on or with central inhibitory noradrenergic neurons to influence peripheral sympathetic nervous system activity. Naloxone has been shown to reverse endotoxin hypotension (Holaday and Faden, 1978) and to prevent the fall in blood pressure that normally accompanies the early states of sleep (Rubin, Blaschke, and Guilleminault, 1981). In addition, synthetic opiate pentapeptides produced hypotension when introduced into the cisterna magna of anesthetized dogs (Laubie, Schmitt, Vincent, and Remond, 1977), and the effect was reversed by naloxone. Finally, the potential role of endogenous opiates in blood pressure regulation is supported by the fact that the nucleus of the tractus solitarius is rich in opiate receptors detected by the autoradiographic localization of stereospecific [^{3}H] diprenorphine binding sites (Atweh and Kuhar, 1977b), as is the anterior hypothalamus (Simantov, Kuhar, Pasternak, and Snyder, 1976). The NTS plays an essential role in the cardiovascular baroreceptor reflex, and from this position, could be acted upon by, or interact with, endogenous opiates to modify reflex responses to sensory stimuli. Assessment of the effects of opiate receptor blockade under various conditions on the baroreceptor reflex would offer important insights into these interactions.

The questions of central control of autonomic responses in the kidney is essential to the renal/behavioral model. Under normal resting conditions in conscious animals, including primates, the sympathetic vasomotor nerves of the kidney are supposedly inactive (Pappenheimer, 1960). Hemodynamic changes occur, however, in response to renal nerve stimulation related to exercise, changes in posture, and changes in the system circulation. Pain (Wolf, 1943) and psychogenic stimuli (Wolff,

Pfeiffer, Ripley, and Winter, 1948) can cause renal vasoconstriction. Barger and co-workers have noted that the renal nerves are involved in the retention of sodium and edema fluid during experimental congestive heart failure (Barger, Leibowitz, and Muldowney, 1959; Barger, Muldowney, and Leibowitz, 1959). It is interesting to note that sympathetic vasoconstriction can take place in the vascular bed of the intestines, which are innervated by the same abdominal sympathetic ganglia (Mitchell, 1956), without vasoconstriction occurring in the kidney. The reverse condition is also possible (Hoff, Kell, Hastings, Sholes, and Gray, 1951). Pappenheimer and others (Korner, 1976; Ferrario, McCubbin, and Berti, 1976) postulated the existence of specific neurons or nuclei, probably in the brain stem, responsible for renal sympathetic stimulation.

Efforts were made to map such areas in the diencephalon and rostral mesencephalon in cats which were responsive to electrical stimulation (Feigl, 1964). Some direct and specific effects on renal blood flow were found in the central gray and in the nucleus interpeduncularis of the lateral hypothalamus in addition to other areas. Stimulation of these areas resulted in renal vasoconstriction, modest increases in blood pressure and a passive increase in muscle blood flow.

Recent research using autoradiographic localization techniques indicated that the periventricular central gray and the lateral hypothalamus in the rat are rich in opiate receptors (Atweh and Kuhar, 1977b). A study of the regional distribution of enkephalin activity in the rhesus monkey brain also indicated high levels of activity in these specific brain regions (Simantov, Kuhar, Pasternak, and Snyder, 1976).

Central nervous system centers for renal control of Na^+ and H_2O may be associated with angiotensin-sensitive receptors in the brain which are currently the subject of considerable controversy (Reid, 1977). The original demonstration provided evidence for a direct CNS pressor effect of angiotensin II (Bickerton and Buckley, 1961). Other effects have since been documented, including increased secretion of adrenocorticotropic hormone, antidiuretic hormone and stimulation of drinking behavior. Preliminary research indicated the failure of circulating angiotensin to cross the blood-brain barrier (Ganten, Hutchinson, and Schelling, 1975). It appeared unlikely, therefore, that angiotensin II injected into the brain provided a viable model of physiological responses to angiotensin formed and released systemically. It was later established that some receptors capable of the same responses were located outside of the blood-brain barrier: in the area postrema (Ferrario, Gildenberg, and McCubbin, 1972), the subfornical organ (Simpson and Routtenberg, 1973), the median eminence (Gann, 1969), and the pituitary (Maran and Yates, 1974). Thus far, there is additional evidence of angiotensin-sensitive areas within the blood-brain barrier which are responsive to intraventricular injections of angiotensin but not affected by angiotensin injected into cerebral vessels. Two of the areas studied are the subnucleus medialis, which shows a pressor effect (Gildenberg, Ferrario, and McCubbin, 1973) and the supraoptic nucleus, which can trigger ADH secretion (Nicoll and Barker, 1971). Despite the obvious potential of this research, it has been plagued by methodological problems, most frequently involving assays designed to establish the presence of angiotensin synthesized in the brain. The substances necessary for

synthesis are present, however, and an active form of angiotensin can be formed by injecting exogenous renin into the cerebral ventricles (Reid, 1977).

Hypothalamic stimulation decreases peripheral plasma renin activity (PRA) by 50 percent, apparently without changing renal blood flow, and regardless of low salt diet (Zehr and Fiegl, 1973). Electrical stimulation of the dorsolateral pons in anesthetized cats caused an increase in rate of renin release (renal plasma flow × venoarterial difference in plasma renin activity) of more than 100 percent. Denervation, β-block via propranolol, and prevention of vasoconstriction via phenoxybenzamine indicate the effect was dependent on intact renal nerves rather than renal blood flow changes (Richardson, Stella, Leonetti, Bartorelli, and Zanchetti, 1974).

A succinct summary of what is generally known about the relationship between the CNS and renin secretion is provided by Ganong and Reid (1976):

> It is apparent that the central nervous system can affect renin secretion in a number of ways. These include not only the direct effects mediated via the renal nerves and circulating catecholamines on β-adrenergic receptors that are probably located in the membranes of the juxtaglomerular cells, but changes secondary to alterations in blood pressure, renal vasoconstriction and vasopressin secretion. Stimulation of α-adrenergic receptors in the brain decreases sympathetic outflow to the juxtaglomerular cells, but the exact location of these α-adrenergic receptors and their role in day-to-day regulation of renin secretion are still unknown. (p. 272)

It is possible that sensory stimulation could cause release of renin from the kidney or in the brain. The role of the resultant angiotensin II could be in part to act as a feedback-moderator at the CNS level, perhaps interacting with endogenous opiates to modify renal responses (including Na^+ and H_2O excretion) to noxious sensory stimuli.

Recent investigation into the nature of the relationship between brain regions rostral to the brainstem and fluid balance have exposed the significance of the region anteroventral to the third ventricle (AV3V) in several experimental models of hypertension. The studies reviewed here were stimulated by the discovery that this area was of significance in drinking behavior (Johnson and Buggy, 1978) and was a site of action for the stimulation of drinking behavior by angiotensin II (Johnson and Buggy, 1977). Angiotensin II and sodium concentration are both known to activate thirst and antidiuretic mechanisms (Anderson, 1971), and manipulation of both of these humoral factors can affect arterial blood pressure (Morris, Campbell, and Pettinger, 1976). It was hypothesized by Brody and his colleagues that "the same stimuli that activate control systems for water balance may also be monitored by central mechanisms that regulate the circulatory control of body fluid distribution" (Brody, Fink, Buggy, Haywood, Gordon, and Johnson, 1978, pp. I 1-I 2).

Lesions of the AV3V region prevented one-kidney and two-kidney Goldblatt experimental hypertension (Buggy, Fink, Johnson, and Brody, 1977; Haywood, Fink, Buggy, Boutelle, and Brody, 1978) as well as low renin, steroid-salt hypertension in rats (Fink, Buggy, Johnson, and Brody, 1977). The fact that a low renin model of experimental hypertension can be prevented by AV3V lesions, and the knowledge that angiotensin II has not been shown to cross the blood-brain barrier, led the investigators to some speculation about the nature of the receptors present in the AV3V. It is possible that these receptors are sensitive to changes in osmolarity. Preliminary data show an early elevation in

the level of osmolarity in cerebral spinal fluid over that of plasma in one-kidney hypertension. A role for vasopressin (released via stimulation of the median eminence) was also suggested, as destruction of the median eminence prevents increases in blood pressure typically caused by electrical stimulation of the AV3V (Brody, Fink, Buggy, Haywood, Gordon, and Johnson, 1978).

Commonalities exist between each of these four aspects of central control of renal function and areas of opiate receptor density or other indicators of endogenous opiate activity. Brain regions apparently linked to renal vasoconstriction have already been discussed. Areas of angiotensin II sensitivity in the brain, such as the AV3V, which are intimately involved in regulation of drinking behavior and fluid balance as well as implicated in several experimental models of hypertension, are densely populated with opiate receptors in the monkey. The periaqueductal gray is, in fact, one of the areas most enriched in opiate receptor binding. The hypothalamus, both anterior and posterior regions, and the dorsolateral pons, both implicated in central control of renin release, are among opiate receptor sites of moderate density (Simantov, Kuhar, Pasternak, and Snyder, 1976; Atweh and Kuhar, 1977a).

It is not unreasonable to hypothesize interactions between brain regions intimately involved in regulation of renal function and renal responses to environmental stimuli and brain systems which are apparently involved in the modulation of brain responses to such stimuli. Evidence of renal sensitivity to behavioral and environmental stimuli is essential to such a hypothesis, however.

Aside from classic descriptions of the renal vasoconstriction response to emotional stress found in both normotensives and hypertensives (Brod, Fencl, Hejl, and Jirka, 1959) and some early studies demonstrating renal vasoconstriction in response to pain (Wolf, 1943) and psychogenic stimuli (Wolf, Wolff, Pfeiffer, Ripley, and Winter, 1948), there is very little information available about the full range of renal responses to environmental stressors. The possible significance of alterations in renal function as a mediating force in the development of hypertension in response to stress may have been overlooked during attempts to demonstrate permanent hypertension in experimental animals. A small collection of recent studies provides evidence of the sensitivity of the renin-angiotensin system to stressors of various types. The question of the effect of stress on the kidney's control of sodium and water retention has seldom been addressed.

Research has shown that plasma renin activity in mice isolated since birth was elevated when they were placed together in an interconnecting cage system. PRA rose for the first two days, decreased for three weeks, then rose again and continued to rise for the duration of the experiment (six months). Blood pressure rose after one week, then continued to rise, also (Vander, Henry, Stephens, Kay, and Mouw, 1978). In another study, rats were exposed to a novel environment (an open field) and later to a cat. PRA increased significantly under both conditions. In the open field experiment, plasma renin substrate was not altered, differences in salt levels in the diet did not affect results, and propranolol reduced the renin response by 50 percent (Clamage, Sanford, Vander, and Mouw, 1976). An interesting set of

experiments using human subjects indicated that two short-term stressors, a puzzle-solving session and a disturbing film, elevated blood pressure but did not elevate PRA significantly. However, individuals who were anxious about the experimental procedures, and who had not been told in advance what to expect during the experiments, did show significantly elevated levels of PRA when compared to informed, relaxed subjects (Clamage, Vander, and Mouw, 1977).

Intermittent electric shock was found to elevate PRA by 500 percent in rats exposed for 24 hours to the stimulus. The response decreased after 1-2 hours, and was apparently mediated by β-adrenergic receptors (Leenen and Shapiro, 1974). Exposure to three hours of a Sidman avoidance operant conditioning schedule raised PRA levels in six baboons trained to avoid shock. PRA levels were compared during and after conditioning to levels obtained at the same time on a control day. There was no correlation between PRA and the number of shocks received or the number of responses. Plasma renin substrate did not change (Blair, Feigl, and Smith, 1976). Baboons exposed to temperatures of 42.5-49.0°C also showed elevations in PRA over control levels. Renal blood flow decreased, renal vascular resistance increased, and blood pressure fell only slightly. Both propranolol and saralasin (1-sar-8-ala = angiotensin II) prevented the reduction in renal blood flow, but only propranolol prevented the increase in PRA (Eisman and Rowell, 1977). The authors concluded that the renal vasoconstriction caused by hyperthermia was mediated by a β-adrenergic release of renin.

Although autogenic stress had been widely used as a stressor in research dealing with other physiological responses (Welch and Welch,

1970), very few studies are available which evaluate changes in renal function under these conditions. One study using adrenalectomized rats found an antidiuretic response resulting from exposure to two seconds of 20 KHz noise stimulation. The antidiuresis response was shown to be related to release of vasopressin (Ogle and Lockett, 1968). In normal and neurohypophysectomized rats, the high frequency sound stimulation triggered diuresis and natriuresis. The diuretic response in the normal animals was attributed to an epinephrine-induced inhibition of vasopressin secretion.

Another study involving rats found that 115 dB (broad-band) noise increased plasma renin activity in rats on a normal diet, while only 90-100 dB levels were required to increase PRA in salt-deprived animals (Vander, Kay, Dugan, and Mouw, 1977).

Research already described suggests that a major element in the response of the kidney to behavioral stimuli is sympathetic activation. Investigation of the relationship between sympathetic activation and changes in renal function have focused on renin release, renal circulation and renal retention of sodium and water. There exists some controversy about the nature of the renal renin response to sympathetic stimulation. It has been suggested that renin release is controlled by the macula densa, which could detect a decrease in filtered sodium caused by renal nerve stimulation or infused catecholamines (Vander, 1965). In support of this contention it has been demonstrated that intact renal innervation was not an absolute requirement for renin release (Osborn, Hook, and Bailie, 1977). On the other hand, neural stimuli triggered release of renin in response to hemorrhage when renal perfusion pressure and flow

were held constant. NE infused into the renal artery caused renin release but isoproterenol, angiotensin and vasopressin did not (Bunag, Page, and McCubbin, 1966). The fact that low sodium diets enhanced hemorrhage-induced renin release in the animals led the authors to suggest that perhaps the state of sodium balance may alter the responsiveness of the renin releasing mechanism. Renin release studied in vitro showed that kidney slices would release renin in response to physiological doses of E, NE, and isoproterenol (Weinberger, Aoi, and Henry, 1975). These results contrast with the in vivo responses to isoproterenol in the Bunag et al. study. Serial section electron microscopy provides evidence for direct neural inter-connection between granular cells and arteriolar and tubular systems (Barajas and Müller, 1973), suggesting that the renin release response can be mediated by several factors simultaneously. It would appear that renin release is directly controlled by a β-adrenergic system, related to sodium balance, and indirectly affected by hemodynamic changes.

The intrarenal blood flow response to neural stimulation has been studied in depth by Barger, Herd, and associates (Pomeranz, Birtch, and Barger, 1968; Barger and Herd, 1971). Renal clearance of ^{85}Kr (krypton) and silicone rubber casts were used to evaluate changes in renal blood flow in response to renal nerve activation. Results indicated that mild stimulation may not change total renal blood flow, but a significant redistribution of flow within the kidney does occur. Perfusion of the cortical peritubular capillaries is decreased while blood flow is redirected to the outer medulla. This redirection of renal blood flow correlated well with increased sodium reabsorption found under conditions

causing similar flow changes (Barger, Muldowney, and Liebowitz, 1959; Sparks, Kopald, Carriere, Chimoskey, and Barger, 1965).

The kidney is designed to maintain filtration in the face of reduced blood flow in response to stress. However, doses of E and NE can reduce renal blood flow and filtration rate (Pitts, 1974). The effect of sympathetic stimulation on renal reabsorption of sodium and water is a somewhat controversial issue. Diuresis and natriuresis following renal denervation were observed in the early part of the century, but were considered to take place only as a response to increased renal blood flow (Marshall and Kolls, 1919). Subsequent research has demonstrated the effect while controlling renal blood flow (Bello-Reuss, Colindres, Pastoriza-Muñoz, Mueller, and Gottschalk, 1975), and while controlling or even reducing glomerular filtration rate (Bonjour, Churchill, and Malvin, 1969). Speculation about the mechanism responsible for denervation diuresis included possible effects of sympathetic innervation on sodium reabsorption in the proximal tubules (Kriss, Futcher, and Goldman, 1948; Bello-Reuss, Colindres, Pastoriza-Muñoz, Müeller, and Gottschalk, 1975; Colindres and Gottschalk, 1978), and redistribution of filtration to nephrons within the kidney which have less absorptive capacity (Blake and Jurf, 1968). Recent investigation of the renal cortex in the monkey using electron microscopic and histochemical techniques has provided direct evidence of both adrenergic and cholinergic innervation of the proximal and distal tubules (Muller and Barajas, 1972). Further, renal blockade of angiotensin II (Zambraski and DiBona, 1976) and prostaglandin synthesis (DiBona, Zambraski, Aguilera, and

Kaloyanides, 1977) do not alter the antinatriuretic effect of low level renal nerve stimulation.

The renal/behavioral model focuses on the potential interactions between brain regions which control renal responses to behavioral stimuli and the endogenous opiate mechanisms which appear to play an important role in the modulation of central responses to such stimuli. The literature review has summarized evidence of the presence of opiate receptors and/or endogenous opiate activity in brain regions which are related to control of renal blood flow, renal renin release, sensitivity to centrally injected angiotensin II, regulation of fluid balance and blood pressure, and ADH release. The renal response to behavioral stimuli is complex and multifaceted, and includes changes in blood flow, renin release, and alterations in excretion of electrolytes and water. A model is needed which can integrate such patterns of responding with the etiology of essential hypertension.

III. GENERAL METHODOLOGY

A. Experimental Animals

Three female cynomolgus monkeys (Macaca fascicularis) weighing 2.5-3.7 kg were used. All were mature adults purchased from Primate Imports of New York, N.Y. Upon arrival at the New England Regional Primate Research Center, the animals were quarantined for a four- to six-week period.

B. Laboratory Animal Care

The animals were housed individually in 61 cm by 61 cm by 79 cm stainless steel wire cages in a room containing about 28 other monkeys. The room lighting was controlled by an automatic timing device which provided light from 08.00-20.00 hr each day. The cages were cleaned three times per week and food (Purina High Protein Monkey Chow, Ralston Purina Co., St. Louis, MO) and water were provided ad lib.

C. Experimental Apparatus

1. The primate chair. The design of the primate chair was similar to restraining chairs already in use for a blood pressure screening project in progress in the laboratory (Herd, Hartley, and Low, 1979). The monkey sat on a small plexiglas seat which was divided in the middle to allow feces to drop through into a waste pan. Three adjustable plexiglas plates restrained the monkey at the waist, chest and neck. The waist and neck plates kept the animal in the chair, and the chest plate prevented the animal from damaging the catheter tubing protruding from the back of

the animal's protective nylon jacket. The monkeys were able to feed themselves from a food cup mounted to the chest plate. During the 24-hour period needed to prepare for and carry out each experiment, the intravenous saline infusions and fruit were substituted for ad lib water to allow control of fluid intake. A large funnel was mounted under the seat and a piece of latex tubing was attached to the funnel spout. This tubing exited the chamber through a small hole drilled in the lower portion of the chamber wall, such that any urine which leaked from an improperly functioning urethral catheter could be detected immediately without disturbing the animal by opening the chamber door.

2. The experimental chamber. The monkey and the chair were placed in a temperature-controlled isolation chamber (Model 20, Forma Scientific, Marietta, Ohio). This chamber was able to maintain a constant temperature of 27°C, which was maintained during all of the experiments. The chamber temperature was monitored by two thermometers, one built into the chamber and one independent temperature probe (YSI Telethermometer, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio) mounted inside the chamber at the monkey's chest level. Ventilation by a constant flow of room air was maintained by the fan on the heating-cooling unit of the chamber.

The chamber was illuminated during all experiments by a 7.5 watt incandescent light bulb mounted on the side wall. The chamber was sound attenuating, and any laboratory sounds which may have been audible inside the chamber were masked by the sound of the ventilation fan motor. Blood pressure and heart rate recordings showed no evidence that the monkeys responded to activity outside the chamber.

D. Delivery of Unconditional Stimuli

1. Shock administration. A 5 ma A.C. shock, 200 ms in duration, was administered to the tail via a pair of brass electrodes (2 cm by 8 cm) coated with electrode paste, which rested on the dorsal surface of a shaved portion of the tail. The shock was generated by a 650 volt transformer and controlled by an electromagnetic relay built by the engineering staff of the Psychobiology Department. The tail was secured to the chair leg by bandage tape, and it rested on a plexiglas electrode platform also attached to the chair leg. The tail was secured comfortably in a natural position. On two of the animals, the electrodes were located 10-25 cm from the tail tip. On one animal, the electrodes were attached to the base of the tail because of previous injury to the tail tip.

Schedule of shock delivery was controlled by two timers: one which triggered the shock relay, and the other which timed the 5-sec. inter-shock interval. Onset and termination of stimulus delivery sessions were controlled manually.

The intensity level of the shock was selected on the basis of previous success in maintaining bar press responding on a shock postponement schedule. All three of the experimental animals responded well at this shock level on the postponement schedule.

2. Noise. The noise stimulus consisted of continuous broadband "white" noise, generated by a BRS Audio Generator (Model #AU-902/112-05, BRS/LVE, Tech Serve Co., Beltsville, MD). The noise was delivered through two small 8 ohm speakers (Archer #40-245, Lafayette Electronics)

mounted on the sides of the rectangular plexiglas helmet. The helmet was attached to the neckplate of the primate chair by two metal screws, and was easily attached when needed. The open face of the helmet allowed the monkey to eat or drink if necessary. Sound pressure levels, which were measured in decibels (dB), were altered by adjusting the resistance within the audiogenerator via a potentiometer.

The sound pressure levels chosen for experimentation, 96 dB and 108 dB, fall below levels known to cause auditory damage (Hunter-Duvar and Elliott, 1972). Sound pressure levels were measured by a Sound-Level Meter (Model #1551-C, General Radio Co., Concord, MA) with the noise helmet in position attached to the primate chair. The microphone was placed at the approximate location of the center of the monkey's head. The onset and termination of the noise stimulus were controlled manually.

Broadband, or "white noise," was used because of its frequent use in both acoustic and cardiovascular research. Also, preliminary experiments indicated that the monkeys were more responsive to white noise than to pure tones.

E. Indwelling Vascular Catheter Techniques

1. Catheter placement. Venous vascular catheters were constructed in the laboratory from polyvinyl chloride tubing (.025"ID, .053"OD; Norton Co., Akron, Ohio). Arterial catheters were assembled from a thin wall tubing (.025"ID, .040"OD) bonded to the thicker wall tubing with cyclohexanone. All catheters were fitted with 3 mm wide sections of a slightly larger diameter tubing encircling and bonded to the catheter 4.5 centimeters and 11 centimeters from the end inserted into the vessel.

These cuffs were used to secure the catheter to the exterior of the vessel and to muscle tissue proximal to the vessel. The original catheters for each animal were placed in the right internal iliac artery and external iliac vein. Iliac catheters which became unusable were replaced by either a similar pair of catheters placed in the iliac vessels on the monkey's left side, or a venous catheter placed in the right internal jugular. In one case (animal 209-79), a replacement arterial catheter was placed in the left common carotid artery, and patency of the vessel was maintained by closing the arterial wall with a purse string suture of 5-0 silk.

Monkeys were food- and water-deprived for 12 hours before surgery, and blood samples were drawn for determination of complete blood count. Prior to surgery, animals were sedated with ketamine HCl (10 mg/kg) (Vetelar, Parke-Davis, Detroit, MI) and anesthetized with Halothane (Halocarbon Laboratories, Hackensack, N.J.) in oxygen. The operative site, shaved previously, was sterilized with Betadine (providone-iodine, Purdol Fredrick Co., Norwalk, CT). Full sterile procedures were used for the surgery, and catheters were sterilized in Detergicide (USCI, Billerica, MA). A right paramedian abdominal skin incision was made by electrocautery, then an incision was made in the abdominal wall and was expanded by blunt dissection. The iliac fossa was carefully exposed without damaging the peritoneum. The internal iliac artery and external vein were identified and exposed. A small cut was made in each vessel, and the catheters were guided upstream to the level of the mid-abdominal aorta or vena cava. The distal end of the vessel, immediately behind the point of catheter entry, was tied off. The distal

ends of the catheters were guided subcutaneously to the middle of the back, using a sharpened stainless steel trocar and then guided out through the skin on the back. The catheters were filled with dilute heparin (50 USP units sodium heparin per ml saline) and closed with a stainless steel obturator. The abdominal incision was closed and the monkey was given a 1 ml intramuscular injection of Flo-Cillin (Bristol-Myers, Syracuse, N.Y.). The monkey was dressed in an infant shirt and a nylon mesh jacket to protect the catheters.

Similar procedures were used to implant jugular or carotid catheters, beginning with a 4 centimeter incision in the skin at the base of the neck.

2. Catheter maintenance. Three times per week, catheter contents were withdrawn into a syringe and replaced with sterile saline solution. Each week, the sterility of the catheters was checked by placing samples of catheter contents on bacteriological Petri dishes which were then incubated. Any colonies of bacteria that grew were identified and sensitivities were determined by the Bacteriology Department. Catheters found to be contaminated were filled with the prescribed antibiotic after each of two consecutive flushing sessions.

3. Intravenous and intraarterial infusions. Approximately 24 hours and 1.5 hours prior to each experiment, the animals were given intravenous infusions of normal saline to stimulate urine flow. In order to accomplish this, extension tubing was connected to the animal's venous catheter and passed under the jacket and through an opening in the wall of the chamber. The tubing was connected outside the chamber to a 50 ml

infusion-withdrawal syringe which was attached to a Harvard Infusion Pump (Harvard Apparatus Co., Dover, MA). During blood pressure recording, patency of the arterial catheter and the extension tubing connecting it to the pressure transducer was maintained by infusing heparinized saline (50 units/ml) at the rate of 0.01 ml per minute using a second Harvard Infusion Pump. This rate had been previously determined not to interfere with the accuracy of the blood pressure measurement (Herd, Hartley, and Low, 1979).

4. Blood sampling. Blood was withdrawn periodically during experiments for use in determination of renal clearance of inulin and PAH. To withdraw these blood samples, the arterial infusion line was disconnected from the pump, and the infusion line contents plus .5 ml of blood was drawn into a 1 ml syringe through a 21 gauge adapter. This syringe was set aside and 3 heparinized capillary tubes were filled with the blood dripping slowly from the infusion tubing. After the sample was taken, the contents of the syringe were reinfused followed by a 1 ml flush of saline to clear the tubing and catheter. The tubing was then reconnected to the infusion pump.

Blood samples were also drawn from the arterial catheters once per week for determination of complete blood counts to assess the general health of the animals.

F. Blood Pressure and Heart Rate Measurements

For determination of mean arterial blood pressure and heart rate (HR), the arterial catheter was connected, via extension tubing, to a strain gauge pressure transducer (Model #P23 Ia, Statham Laboratories,

Inc., Hato Rey, Puerto Rico) filled with heparinized saline (50 units/ml). The transducer was located on the outside wall of the chamber at approximate heart level and was connected to a low level D.C. preamplifier (Model #7P1B, Grass Instrument Co., Quincy, MA), a driver amplifier (Model #7DAE, Grass Instrument Co.) and a polygraph recorder (Model #7WC12PA, Grass Instrument Co.). Proper functioning of the arterial catheter was verified at the beginning and ending of each experiment by observing the amplitude and pattern of pressure oscillations. Blood pressure values for each 10-minute segment of the experimental session were determined manually using a horizontal line of best fit measure of the integrated mean value from the instantaneous recordings. Mean and standard error for the three phases of each experiment (baseline, intervention and postintervention) were then determined.

Heart rate was determined by passing the amplified, unfiltered signal from the arterial pressure transducer to a cardiotachometer (Model #7P4b, Grass Instrument Co.). Heart rate values for each 10-minute segment of the experimental session were determined by the horizontal line of best fit method.

G. Renal Function Measurements

1. Urethral catheters. Animals were lightly sedated with ketamine (10 mg/kg), the urethral orifice was swabbed with Betadine, and coated with an antibiotic ointment (Terramycin, Pfizer, Inc., New York, N.Y.). A sterile, pediatric size foley catheter (Bardex, C. R. Bard, Inc., Murray Hill, N.J.) was fitted with a sterile stainless steel spring guide (diameter, .025", USCI, C. R. Bard, Inc., Billerica, MA), and

coated with the ointment. The foley catheter with the spring guide inside was clamped with a hemostat to keep the wire in place. The catheter, stiffened by the guide, was gently inserted into the urethral opening and passed into the bladder, a distance of approximately 4 centimeters. The spring guide was then removed, and the balloon at the tip of the catheter was filled with 3 ml of sterile water to hold the catheter in place. When the monkey was positioned in the chair, the balloon end of the catheter was seated lightly at the bladder sphincter by means of a small hollow lead fishing weight which had been slipped into the catheter before it was inserted. This weight provided just enough pressure on the catheter to keep the balloon in place and prevent leakage of urine. Any leakage could be detected from outside of the chamber by observing urine flow from the tubing attached to the funnel mounted under the chair. The foley catheter was attached to latex tubing which also passed through an opening in the chamber wall. Urine was caught in 15 ml plastic collection tubes which were changed at the end of each 10-minute collection period throughout the experiment.

Following the removal of the catheter, the animals were given an oral dose of amoxicillin (200 mg/kg) (Amoxi-drop, Beecham, Inc., Bristol, TN) to prevent bladder infection.

2. Urinary Na^+ determinations. The volume of each 10-minute sample was determined, and samples were diluted 1:200 with a lithium solution (.89 g/l $LiNO_3$). Sodium concentrations were analyzed by flame photometry (Technicon Auto Analyzer III, Technicon Instruments Corp., Ardsley, N.Y.). Urine excretion rates (ml/kg/min) and sodium excretion rates (μeq/kg/min)

were computed for each sample from the sample volume, the length of time of the urine collection, and the concentration of sodium.

3. Inulin clearance. Clearance of inulin is used to measure glomerular filtration rate (GFR) in the kidney. The use of radioactively labeled inulin for such clearance measurements is a relatively new but reliable method (Levinsky and Levy, 1972). In these studies, inulin clearance was determined by sampling plasma and urine during a continuous infusion of inulin labeled with either tritium (Inulin, [^{3}H (G)]-357.4 mCi/g, New England Nuclear, Boston, MA) or carbon 14 (inulin-Carboxy 1 (carboxyl-^{14}C)-2.5 mCi/g, New England Nuclear). A bolus injection of ^{3}H inulin in normal saline was administered via the venous infusion tubing 40 minutes before the first clearance samples were taken. Initially, a 20-minute interval was used, but this time period was not sufficient for stabilization of plasma and urine values. The bolus injection contained between 10 to 12 μCi of ^{3}H inulin, and was immediately followed by a constant infusion of 0.9 to 1.0 μCi/min, which was delivered in the ongoing saline infusion. To determine inulin clearance, an arterial blood sample was drawn midway through a 10-minute urine collection. Blood collected in hematocrit tubes was centrifuged at 11,500 rpm for 5 minutes. Hematocrit values were recorded, and 50 μl each of urine and plasma were placed in glass scintillation vials with 10 ml of scintillation fluid (Biofluor, New England Nuclear, Boston, MA). The activity of each sample was counted for either 1 or 10 minutes in a scintillation counter (Delta 300, 6890 Liquid Scintillation System, Searle Co., Des Plaines, IL), with previously set energy range windows at

the appropriate levels for counting ^{3}H or ^{14}C activity, or both. Background samples of both urine and plasma, drawn 10 minutes prior to the injection of the isotope, were also counted and subtracted from the sample CPM. Clearance of inulin was determined by multiplying the corrected CPM in the urine sample by the urine flow in ml/min, and then dividing the result by the corrected CPM of the plasma sample. More simply stated, the standard equation for inulin clearance is $UV/P = C_{In}$, where U = inulin concentration in urine, V = urine flow in ml/min and P = inulin concentration in plasma (Reubi, 1963).

4. PAH clearance. Renal clearance of tritiated sodium para-aminohippurate (Aminohippuric Acid, p-[glycyl-2-^{3}H]-4.0 Ci/m mol, New England Nuclear) was used to approximate renal plasma flow in the kidney. True indicators of total renal plasma flow require catheterization of the renal vein, but samples drawn from the abdominal aorta can be used to determine 91 percent of total renal plasma flow, and the technique is referred to as a measurement of effective renal plasma flow. The clearance formula used in this case is the same as the inulin clearance formula: $UV/P = C_{PAH}$ (Reubi, 1963).

When clearances of ^{14}C inulin and ^{3}H PAH were determined simultaneously, differential counting techniques were used. Bolus injections for these double clearance experiments consisted of 8 mCi of ^{14}C and 15 mCi of ^{3}H in normal saline. Isotopes were infused following the bolus at rates of 0.8 μCi/min of ^{14}C inulin and 1.6 μCi/min of ^{3}H PAH. The clearance of PAH and inulin was calculated with the clearance formula previously described.

H. Data Collection and Analysis

A Data General Micro NOVA computer (Data General Co., Westboro, MA) was used to calculate urine and sodium excretion rates, inulin and PAH clearances, and to collapse these and other data. Programs were written in Dartmouth Extended Basic language.

To facilitate comparisons between control and experimental data, the 120-minute observation period was divided into three phases; a 40-50-minute baseline period referred to in all reports of the data as phase 1, a 30-minute phase 2 period during which experimental interventions could be instituted, and a postintervention period, referred to as phase 3. For measurements of Na^+ and urine water excretion, phase 1 of each experiment consisted of either 4 or 5 10-minute collection samples, depending on the precise timing of the onset of the intervention. Phase 2 consistently contained 3 10-minute collection samples. Measures of heart rate and mean blood pressure also were divided into 10-minute segments during each phase. Two-way analysis of variance with interaction (ANOVA) was used to analyze the group data for phase differences (treatment) and interactions (Freund, 1973). The last 30 minutes of phase 1 was compared to the entire 30 minutes of phase 2 in order to have equal numbers of measures for ANOVA calculations.

In the interest of clarity and simplification, emphasis in reports of the results of these experiments is placed on the differences between phase 1, the baseline measures, and phase 2, the intervention period. Information about the third phase is included primarily for descriptive purposes.

Measurements of inulin and PAH clearance are included in the data reports with the other parameters, but changes in these measures are discussed only in descriptive terms. The inherent variability of these measures and the small number of samples in each phase (often only one) preclude meaningful statistical analysis in many cases. The data are useful for discussion of physiological mechanisms involved in the responses observed.

IV. EXPERIMENTAL OBSERVATIONS

A. Control Studies of Renal and Cardiovascular Function

1. Introduction. This series of experiments was designed to assess the characteristics of renal function in the conscious chair-restrained cynomolgus monkey. Chamber temperature (27°C), level of illumination (provided by 7.5 watt incandescent bulb) and other environmental stimuli were constant in these and all subsequent experiments, except when altered by experimental design. Monkeys were adjusted to chairing procedures, restraint, urethral catheterizations and infusions before these control experiments.

2. Methods. Three trained monkeys were tested in isolation chambers. The animals were fitted with a urethral catheter and chaired 24 hours prior to the experimental session. Mean arterial blood pressure and heart rate recordings were begun shortly after chairing, using procedures described in Section III (General Methodology). An intravenous infusion of isotonic saline (50 ml/kg) was administered during the first two hours following the chairing procedure. The preliminary infusion facilitated urine flow during the experiment 24 hours later. Monkeys were hand-fed Monkey Chow and fruit both the evening before and the morning of the experiment. The chamber light was extinguished at approximately 6 p.m. the evening before and reilluminated at 8:30 a.m. the morning of the experiment.

Following the 24-hour adaptation period, an intravenous infusion of 70 ml/kg of isotonic saline was administered within 30 minutes to stimulate excretion of urine water and sodium. The bolus infusion was followed immediately by a constant infusion of saline at the rate of .5 ml/min, which was continued for 180 minutes. Radioactively labeled inulin and PAH were added to the infusate either 60 or 90 minutes after the beginning of the saline infusion. Isotope sampling accuracy was improved when the 60-minute interval was used. The control observation period began 90 minutes after the bolus infusion was started (when urine output had stabilized) and continued for 120 minutes. Urine collections were taken outside of the chamber at 10-minute intervals. Mean arterial blood pressure and heart rate measurements continued throughout the observation period, but were periodically interrupted momentarily to allow blood to be withdrawn through the catheter tubing connected to the blood pressure transducers mounted to the outside wall of the chamber. Plasma samples used for determination of inulin and PAH clearance were taken about every 20 minutes, always at the midpoint of the ongoing 10-minute urine collection period. A description of the techniques used to determine inulin and PAH clearances is included in Section III (General Methodology).

3. Results. Sodium excretion for 3 monkeys (mean ± SEM) for the entire 120-minute control observation period was 31.8 ± 3.0 ueq/kg/min in response to the saline infusion. There were no apparent differences between phase 1 and phase 2 in any animal, and only one animal (191-79) showed any differences between phase 1 and phase 3. Graphic

representation of raw data patterns for each variable for a typical animal (29-80) are represented in Figure 5.

Two-way analysis of variance between phases 1 and 2 for the group of three monkeys showed no significant differences between phase 1 and phase 2 Na^+ excretion rates. Tabular summary of each phase of each variable for individual animals is presented in the Appendix. Normalized group data for each variable are presented graphically in Figure 6 and summarized in tabular form in Table 1. Analysis of variance data for Na^+ excretion are presented in Table 2.

Excretion of urine water for the 120-minute period was 195 ± 3 µl/kg/min during the saline infusion. Analysis of variance results for the group data indicated no significant differences between phase 1 and phase 2 (see Table 3).

Clearance of inulin and PAH were relatively stable over the 120-minute period. Inulin clearance for the group during the 120-minute control period was 4.3 ± 0.1 ml/kg/min, and PAH clearance rate was 13.9 ± 1.9 ml/kg/min. Because only one sample was available from each animal's baseline phase, no analyses of variance were used to compare the phases. Clearance data in subsequent experiments were evaluated and used descriptively.

Mean heart rate for the entire control period was 181.7 ± 4.7 bpm for the three monkeys. Two-way analysis of variance of group heart rate data indicated a significant ($p < .05$) difference between phase 1 and phase 2 (see Table 4). Because the baseline rates were not stable during

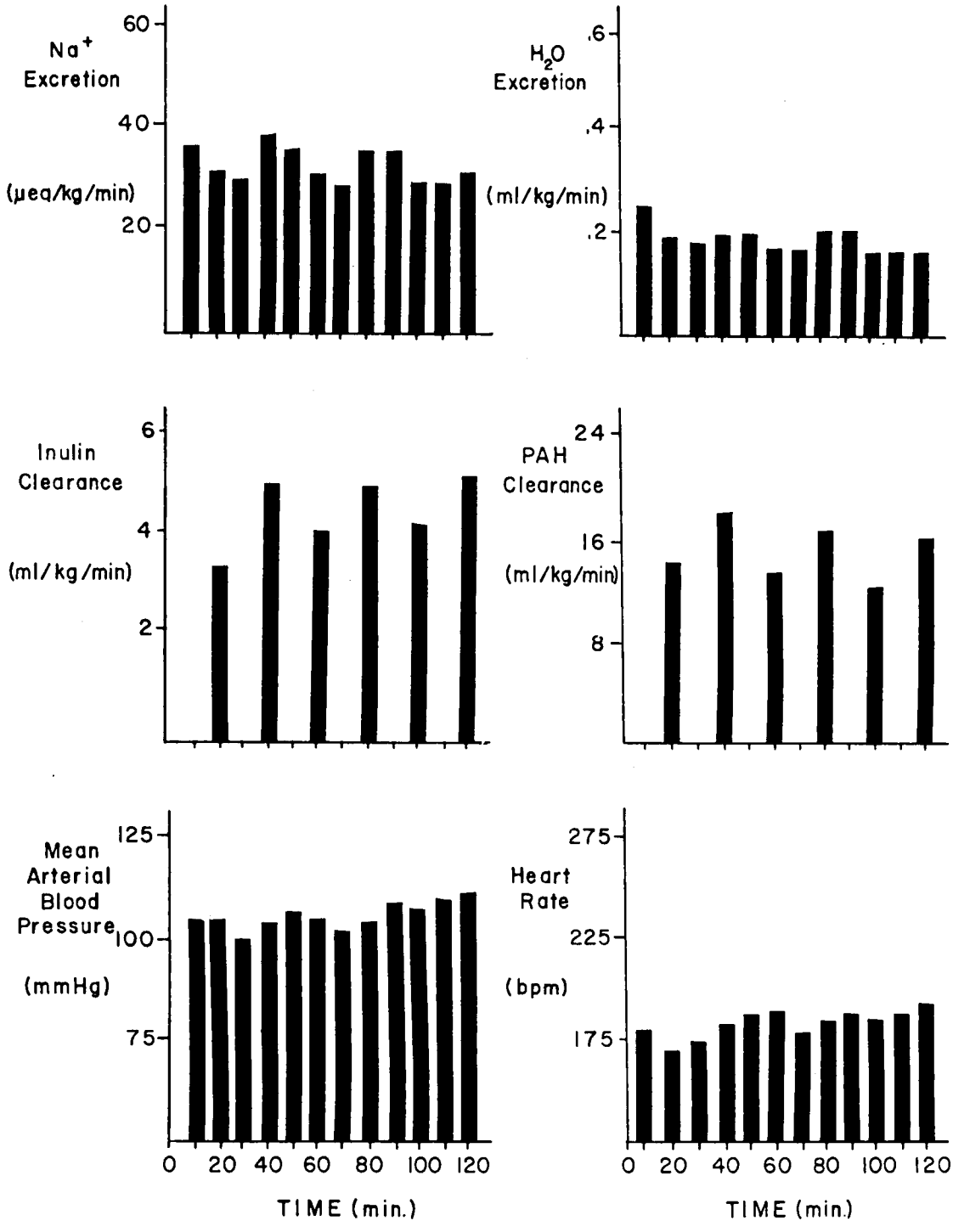


Figure 5. Renal and cardiovascular function under control conditions, #29-80.

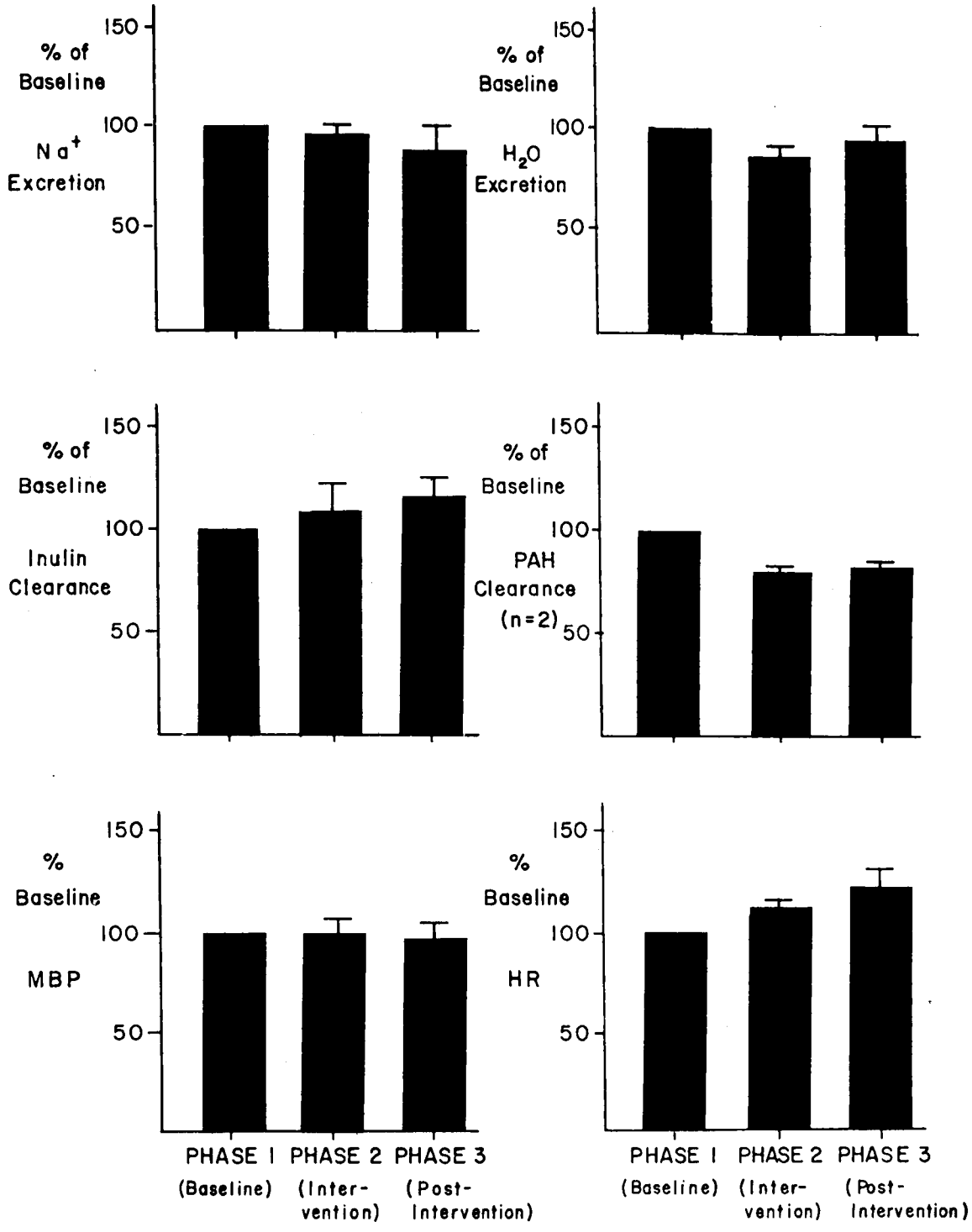


Figure 6. Renal and cardiovascular function under control conditions, three monkeys (Mean ± SEM).

TABLE 1

GROUP DATA: CONTROL VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	91.0 +/- 2.3	98.4 +/- 6.5
NA+ EXCRETION	(3)	93.6 +/- 4.1	89.1 +/- 11.3
INULIN CLEARANCE	(3)	105.5 +/- 14.2	116.9 +/- 9.6
PAH CLEARANCE	(2)	79.3 +/- 1.0	86.0 +/- 0.6
HEART RATE	(3)	112.3 +/- 3.7	120.8 +/- 7.5
BLOOD PRESSURE	(3)	100.9 +/- 3.0	98.5 +/- 5.0

* Mean +/- Standard Error

TABLE 2

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION UNDER CONTROL CONDITIONS

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	7.34375	7.34375	.1485
Animals	2	601.84	300.92	
Interactions	2	48.5859	24.293	.491235
Error	12	593.434	49.4528	
Total	17	1251.2		

*Significant at .05

**Significant at .01

TABLE 3

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION UNDER CONTROL CONDITIONS

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	4.49955E-04	4.49955E-04	.195158
Animals	2	1.64443E-03	8.22216E-04	
Interactions	2	5.32806E-04	2.66403E-04	.115546
Error	12	2.76671E-02	2.30559E-03	
Total	17	3.02943E-02		

*Significant at .05

**Significant at .01

TABLE 4

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR HEART RATE UNDER CONTROL CONDITIONS

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	1422.19	1422.19	10.5563**
Animals	2	1744.5	872.25	
Interactions	2	144.375	72.1875	.535818
Error	12	1616.69	134.724	
Total	17	4927.75		

*Significant at .05

**Significant at .01

control observations, group HR data were not subjected to statistical testing in subsequent experiments, but were included in graphs and summary tables.

Mean arterial blood pressure for the entire control period was 105.2 ± 2.3 mmHg for three monkeys. Two-way analysis of variance of group data indicated no significant differences between phase 1 and phase 2 of the control period (see Table 5).

4. Discussion. Consistent output of sodium and water during the 120-minute control period was achieved by manipulating the saline content of the infusate, the volume of the bolus infusion, and the rate of the constant infusion during preliminary studies. The 24-hour pre-experimental saline infusion was also found to be a useful and necessary stimulus for brisk and continuous urine flow during the experiment.

All clearance measures of renal function determined in these control experiments were comparable to values recorded for humans during saline infusion (Altman and Dittmer, 1974). The M.fascicularis values were slightly higher because of the priming infusion.

	M. fascicularis female (3.4 kg ± .3)	Human male (approx. 70 kg)
Inulin clearance:	4.3 ml/kg $.min^{-1}$	1.64 ml/kg $.min^{-1}$
PAH clearance:	13.9 ml/kg $.min^{-1}$	8.45 ml/kg $.min^{-1}$

Mean blood pressure and heart rate values were within the normal range for adult M. fascicularis restrained in primate chairs (Herd, Hartley, and Low, 1979).

TABLE 5

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR MEAN ATERIAL BLOOD PRESSURE UNDER CONTROL CONDITIONS

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	4.5	4.5	.669249
Animals	2	425.5	212.75	
Interactions	2	108.937	54.4587	8.1007*
Error	12	80.6875	6.73296	
Total	17	619.625		

*Significant at .05

**Significant at .01

It is important to note that, although analysis of variance of group data for Na^+ and urine H_2O excretion and MBP indicated no statistically significant differences between phases 1 and 2 (treatment effects), there were significant variations between animals in all but the H_2O data, which were reflected in the interaction components of the ANOVAs. These factors were probably the inevitable result of the small number of animals utilized in the studies, as well as the inherent individual differences in physiological responses and their measurement.

B. Renal and Cardiovascular Responses to Shock as an Unconditional Stimulus

1. Introduction. This series of experiments was designed to assess the cardiovascular and renal responses of the cynomolgus monkey to exposure to a noxious stimulus.

2. Methods. Urethral catheterization, chair restraint, and 24-hour adaptation period were identical to the control study procedures. For these studies, however, the animal's tail was secured in an electrode apparatus attached to the leg of the primate chair. During the intervention phase of the experiment, a 5 ma 200 msec electric shock was delivered to the tail every 5 seconds for 30 minutes, using procedures described in Section III, General Methodology.

3. Results. In all three animals, Na^+ and water excretion decreased during shock administration, but returned to baseline values during the 30-minute shock exposure period. Inulin clearance rates during shock showed an initial decrease followed by an increase in rate

which rose above baseline values. PAH clearance was not measured in these studies. Graphic display of the data for all variables for animal 29-80 are presented in Figure 7. Raw data for this animal best illustrates the response patterns generally followed by all three subjects. Tables summarizing means and standard errors for each phase for each individual animal are presented in the Appendix.

Heart rate and mean arterial blood pressure were measured in two monkeys, 191-79 and 29-80. During shock exposure, HR decreased slightly in 191-79 and increased in 29-80. Mean BP increased in both monkeys.

Graphic representation of normalized group data is presented in Figure 8, and tabular summary of those data is presented in Table 6. Excretion of Na^+ in the group during phase 2 (shock administration) fell to 84 ± 6% of baseline values, excretion of urine H_2O fell to 78 ± 6%, HR was 110 ± 13%, and MBP rose to 103 ± 3% of baseline measures. Inulin clearance in phase 2 was 166 ± 42%. This value represents the initial decrease followed by a substantial increase in phase 2.

Two-way analysis of variance for the group for Na^+ excretion (Table 7) and urine H_2O excretion (Table 8) showed no significant differences between phase 1 and phase 2. Mean arterial blood pressure increased significantly ($p < .05$) in response to shock according to F values (see Table 9).

4. Discussion. All three subjects showed moderate decreases in Na^+ and urine water excretion in response to electric shock, and an apparent adaptation to that stimulus during the 30 minutes of shock presentation. All animals showed a return to baseline values before the termination of

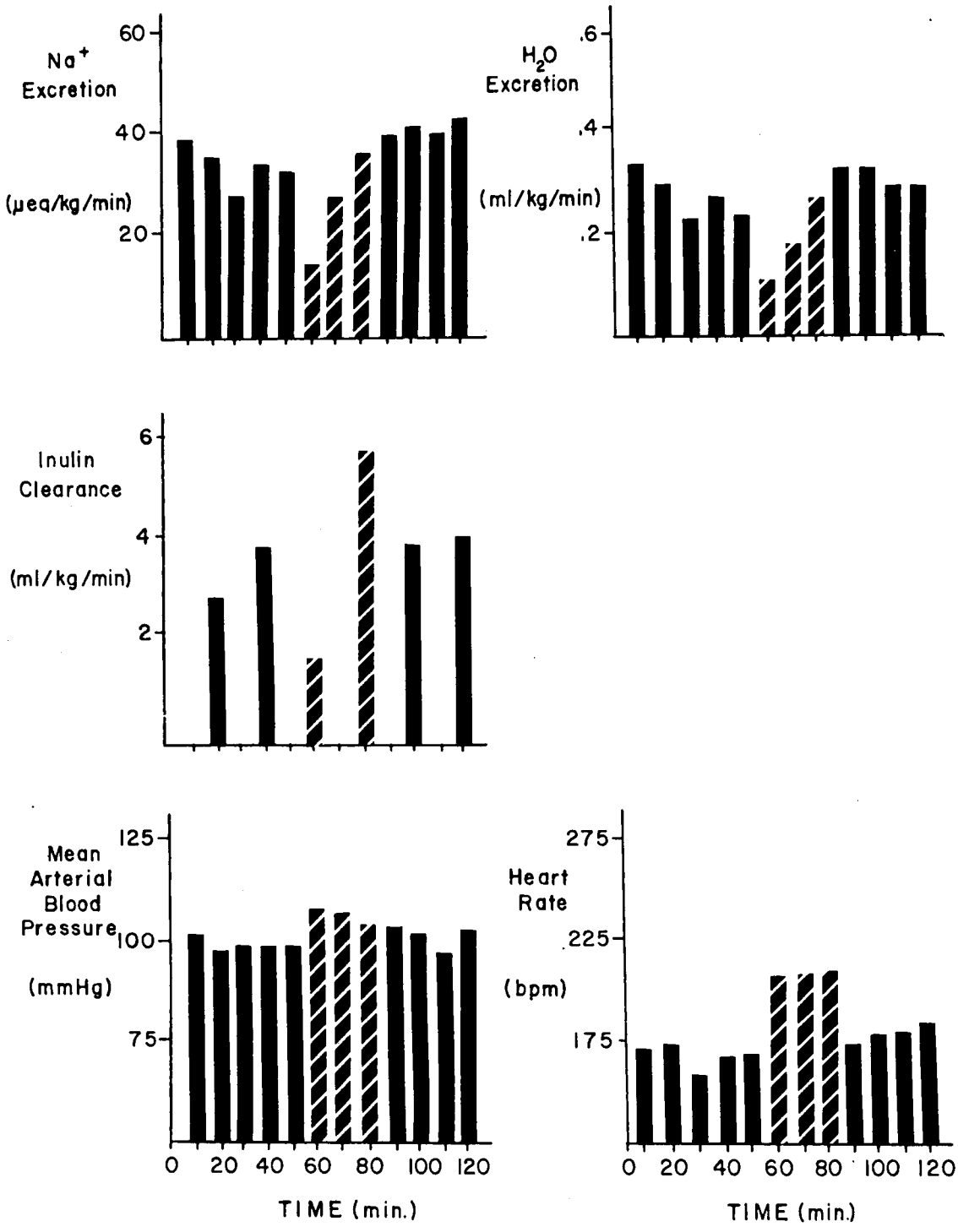


Figure 7. Renal and cardiovascular function during electric shock used as an unconditional stimulus, #29-80. Patterned bars indicate administration of shock.

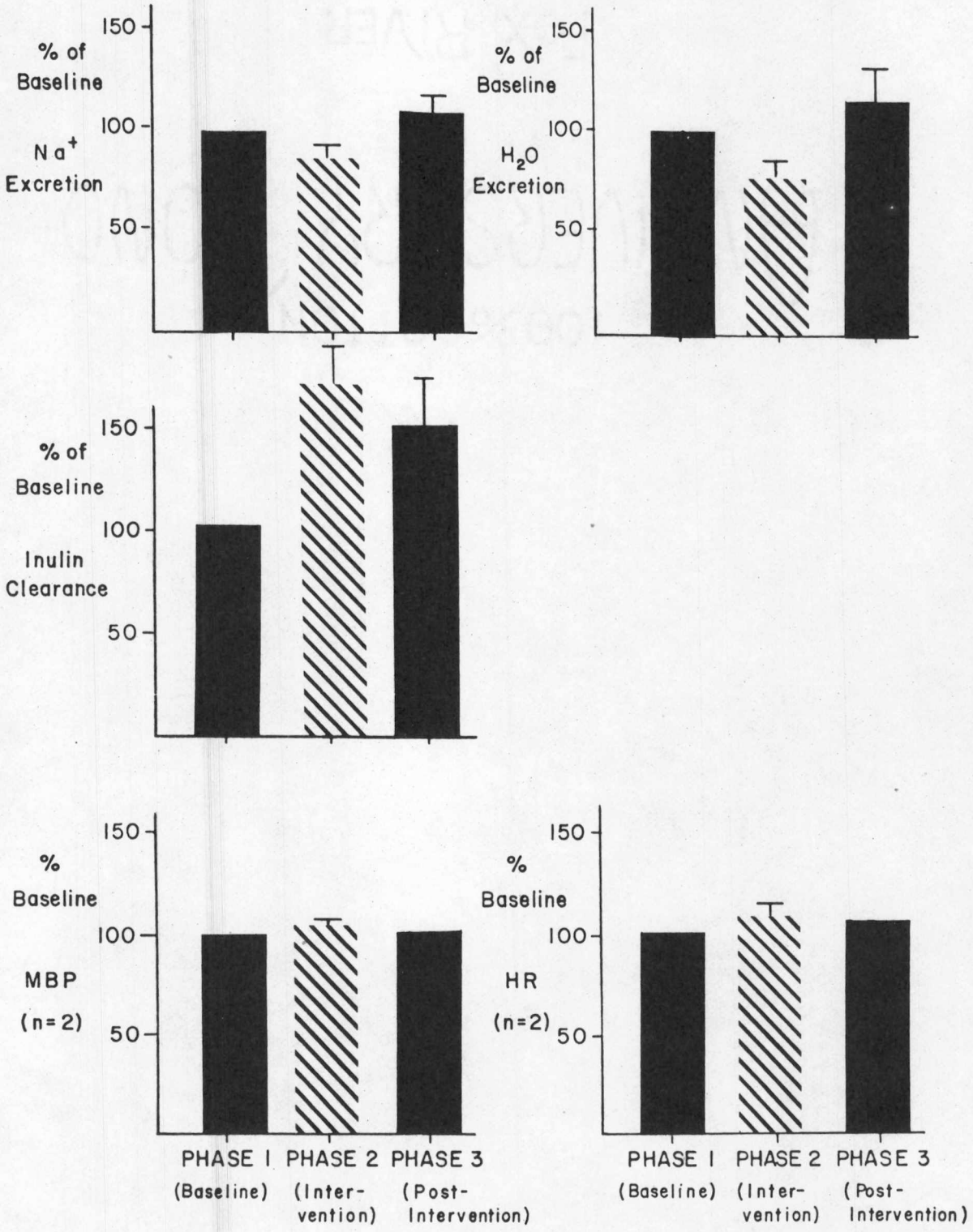


Figure 8. Renal and cardiovascular function during electric shock as an unconditional stimulus, three monkeys (Mean ± SEM).

TABLE 6

GROUP DATA: SHOCK VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	77.8 +/- 5.8	116.5 +/- 15.5
NA+ EXCRETION	(3)	83.6 +/- 6.2	106.1 +/- 6.2
INULIN CLEARANCE	(3)	166.3 +/- 42.3	150.8 +/- 27.5
PAH CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
HEART RATE	(2)	109.9 +/- 12.9	105.1 +/- 0.2
BLOOD PRESSURE	(2)	103.4 +/- 2.5	101.0 +/- 0.0

* Mean +/- Standard Error

TABLE 7

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR EXCRETION OF Na^+ DURING SHOCK

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	129.074	129.074	1.93209
Animals	2	4240.96	2120.48	
Interactions	2	54.7773	27.3887	.409977
Error	12	801.664	66.8053	
Total	17	5226.47		

*Significant at .05

**Significant at .01

TABLE 8

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR EXCRETION OF URINE H_2O DURING SHOCK

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	1.3889E-02	1.3889E-02	3.90627
Animals	2	.206034	.103017	
Interactions	2	3.81052E-03	1.90526E-03	.535858
Error	12	4.26664E-02	3.55554E-03	
Total	17	.2446		

*Significant at .05

**Significant at .01

TABLE 9

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA
FOR MEAN ARTERIAL BLOOD PRESSURE DURING SHOCK
(N = 2)

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	56.4375	56.4375	21.1848**
Animals	1	96.4375	96.4375	
Interactions	1	26.875	26.875	10.088*
Error	8	21.3125	2.66406	
Total	11	201.062		

*Significant at .05

**Significant at .01

shock. Decreases in glomerular filtration rate coincided with the decreases in Na^+ and H_2O excretion, and increases in GFR well above baseline rates coincided with the return to baseline values in Na^+ and H_2O measures.

One of the two animals in which HR and MBP were measured showed substantial increases in HR and increases in MBP in phase 2. This monkey, 29-80, also demonstrated the greatest decreases in Na^+ and H_2O excretion.

C. Renal and Cardiovascular Responses to 96 dB Noise as an Unconditional Stimulus

1. Introduction. This series of experiments was designed to assess the cardiovascular and renal responses of the cynomolgus monkey to a noxious unconditional stimulus differing from shock. A moderate level of continuous broadband (white) noise was selected.

2. Method. All experimental procedures were identical to those used in the control experiments. A plexiglas helmet in which two small audio speakers were mounted was lowered over the monkey's head and secured to the primate chair before the experiment began. The noise stimulus was presented continuously for 30 minutes during phase 2 of the experiment.

3. Results. All three animals displayed decreases in Na^+ and urine excretion rates in response to 96 dB white noise during phase 2. The data indicated that Na^+ excretion decreased in 191-79 and 29-80, and urine excretion decreased in 191-79. Excretion rates in phase 3 remained below baseline levels.

Inulin and PAH clearance were measured in animal 29-80 only. These measurements indicated slight increases during the noise exposure. For 29-80, the largest decrease in Na^+ excretion occurred in the last 10 minutes. During this period, filtration fraction (inulin clearance divided by PAH clearance) decreased.

Raw data for all variables for 191-79, who typified the response pattern to the 96 dB noise stimulus, are presented graphically in Figure 9. Phase means for each individual animal are presented in the Appendix.

Normalized group data are presented graphically in Figure 10, and summarized in Table 10. Excretion of Na^+ was 79.4 ± 5.4% of baseline rates in phase 2, and 79.1 ± 10.1% in phase 3. Excretion of urine H_2O was 83.0 ± 5.4% in phase 2 and 87.9 ± 5.6% in phase 3. Two-way analysis of variance indicated that decreases in both Na^+ and urine H_2O excretion rates in response to 96 dB noise were statistically significant ($p < .05$) (see Tables 11 and 12).

Heart rate was measured in animals 191-79 and 29-80. Heart rate increased in both monkeys, and the combination of results from these two animals in phase 2 was 106 ± 0% of baseline values. Mean arterial blood pressure was measured in three animals. Two animals showed decreases in MBP, while 209-79 showed a slight increase. Two-way analysis of variance indicated a statistically significant decrease in MBP between phase 1 and phase 2 (see Table 13). Interaction effects were highly significant, however, indicating that the majority of the treatment effect was attributable to 29-80.

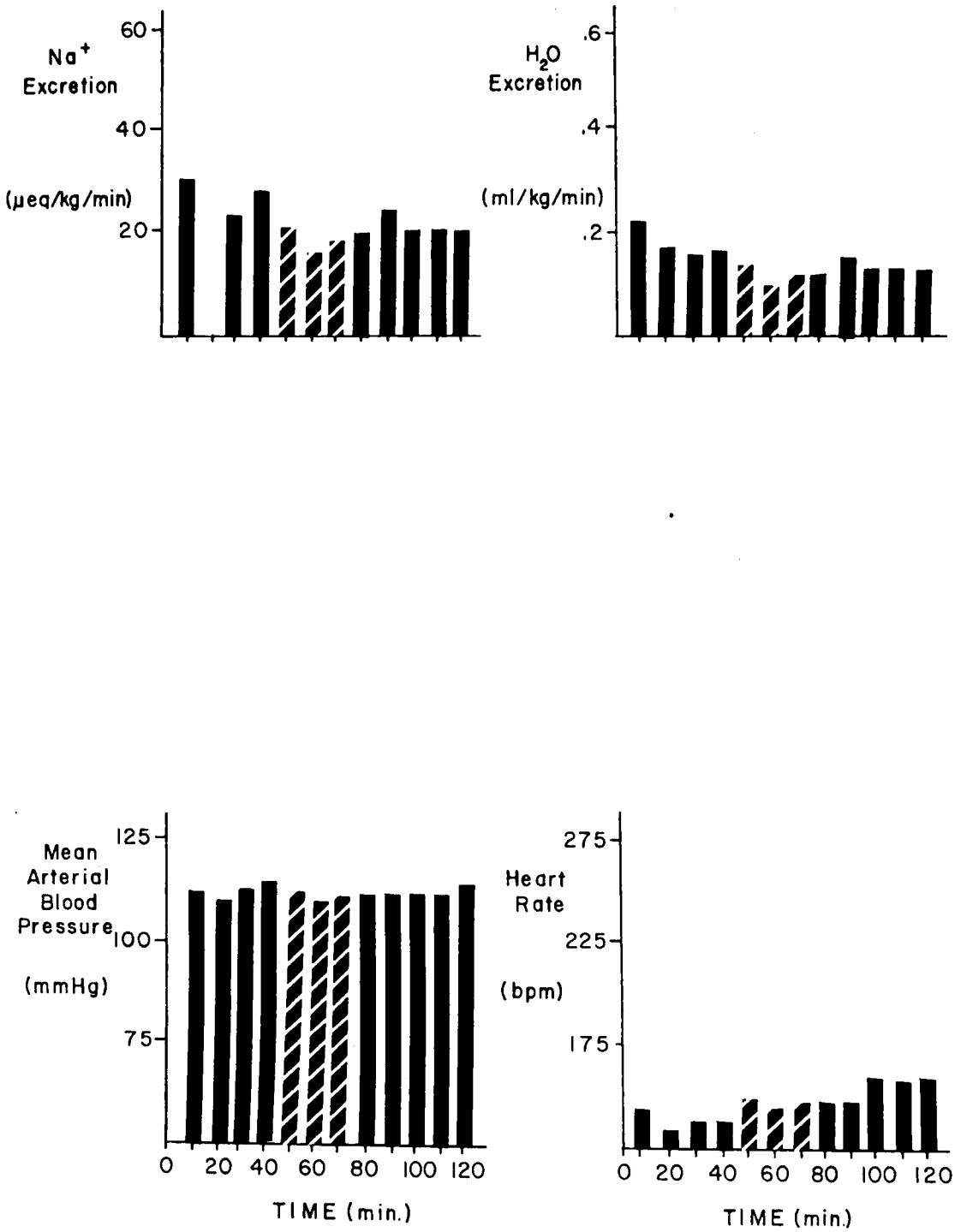


Figure 9. Renal and cardiovascular function during 96 dB noise used as an unconditional stimulus, #191-79. Patterned bars indicate noise stimulus.

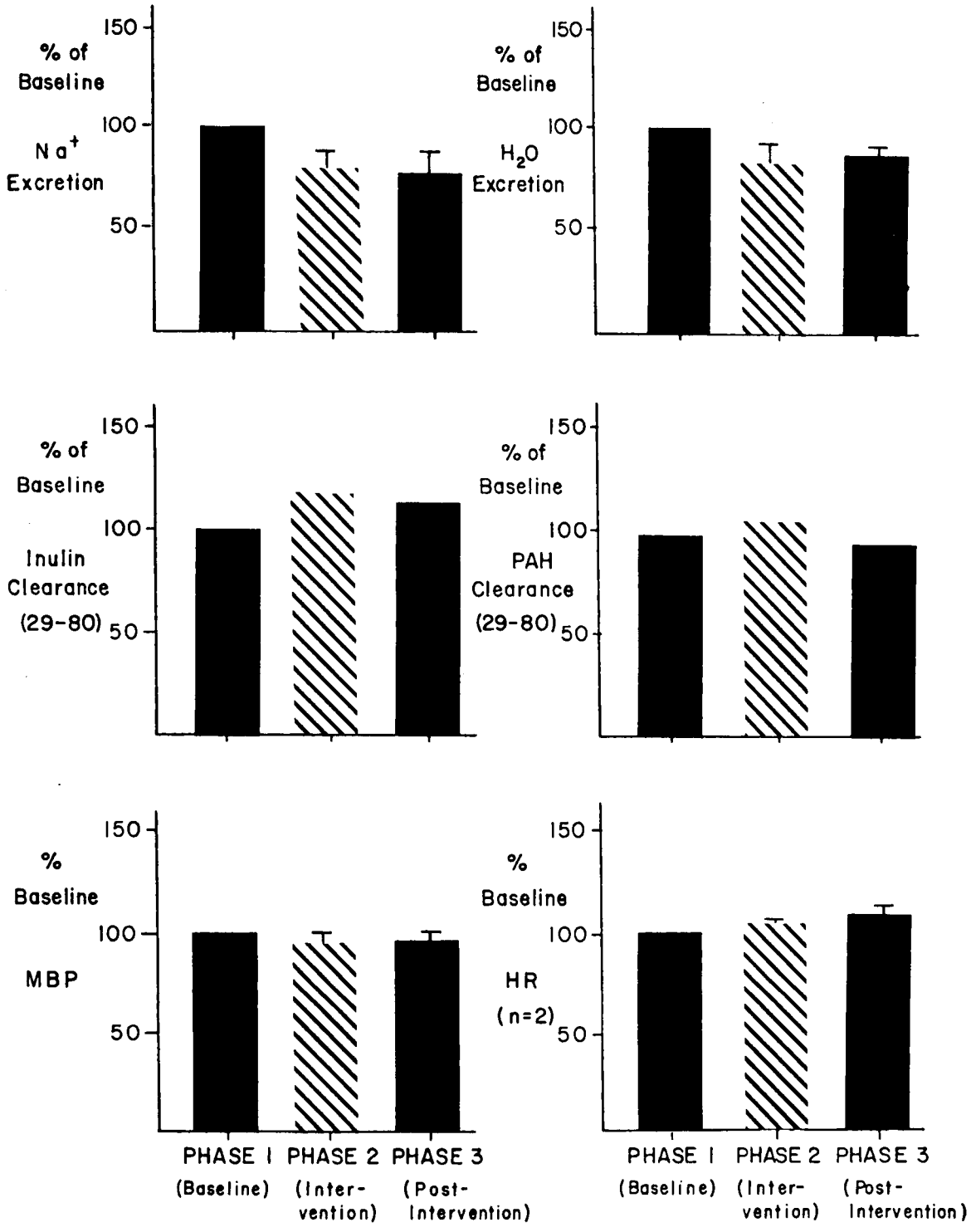


Figure 10. Renal and cardiovascular function during 96 dB noise used as an unconditional stimulus, three monkeys (Mean ± SEM).

TABLE 10

GROUP DATA: NOISE (96dB) VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	83.0 +/- 5.4	87.9 +/- 5.6
NA+ EXCRETION	(3)	79.4 +/- 9.2	79.1 +/- 10.1
INULIN CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
PAH CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
HEART RATE	(2)	105.7 +/- 0.0	109.6 +/- 1.9
BLOOD PRESSURE	(3)	97.2 +/- 2.9	96.4 +/- 1.4

* Mean +/- Standard Error

TABLE 11

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION DURING 96 dB NOISE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	199.336	199.336	12.7339**
Animals	2	1138.23	569.117	
Interactions	2	90.8125	45.4062	2.90062
Error	12	187.848	15.654	
Total	17	1616.23		

*Significant at .05

**Significant at .01

TABLE 12

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION DURING 96 dB NOISE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	4.0502E-03	4.0502E-03	9.72024**
Animals	2	6.60787E-02	3.30394E-02	
Interactions	2	8.32617E-04	4.16309E-04	.999118
Error	12	5.00011E-03	4.16676E-04	
Total	17	7.59616E-02		

*Significant at .05

**Significant at .01

TABLE 13

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR MEAN ARTERIAL BLOOD PRESSURE DURING 96 dB NOISE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	34.6875	34.6875	14.1702**
Animals	2	1024.37	512.187	
Interactions	2	90.0625	45.0312	18.3957**
Error	12	29.375	2.44792	
Total	17	1178.5		

*Significant at .05

**Significant at .01

4. Discussion. All three animals showed slight to moderate decreases in Na^+ and urine water excretion when exposed to 96 dB white noise. In contrast to the pattern of responses to the shock stimulus, however, only one animal demonstrated a return to baseline values either during the noise exposure or during the 40-50 minutes of postintervention measurement (phase 3). Animal 29-80 showed a return to baseline values for urine water excretion, and this recovery took place fully 40 minutes after the termination of the noise stimulus. Heart rate increased in both of the animals measured, and these elevations were sustained throughout phase 3. Blood pressure decreases were greatest in animal 29-80, whose pressure fell 9 mmHg during noise exposure and recovered partially during phase 3. These results indicate that the adaptation process suggested by the patterns of response to the shock stimulus may be less effective and slower to respond to an auditory stimulus.

D. Renal and Cardiovascular Responses to 108 dB Noise as an Unconditional Stimulus

1. Introduction. This series of experiments was designed to assess the cardiovascular and renal responses of the cynomolgus monkey to a loud noise stimulus which was different from the 96 dB noise stimulus used in the previous studies. Continuous broadband noise at a sound pressure level of 108 dB was used.

2. Method. All experimental procedures were identical to those used in the 96 dB noise experiments.

3. Results. Two of the three animals measured showed increases in both Na^+ and H_2O excretion rates during noise exposure. Animal 209-79 showed increases in both Na^+ and urine water. Na^+ and H_2O excretion continued to rise or remained at phase 2 levels after the termination of the noise. Clearance of PAH and inulin increased during the noise exposure in both monkeys.

Heart rate increased in both animals but mean blood pressure decreased slightly in 191-79 and increased in 209-79. Data for all variables for 209-79, who responded most dramatically to this noise stimulus, are presented in Figure 11. Data for each phase for all three animals are presented in tables in the Appendix.

Animal 29-80, in contrast to the other animals, showed slight but sustained decreases in Na^+ and H_2O excretion and in both clearance measures. Decreases during the noise exposure were slight, but output of Na^+ and H_2O continued to decline after the termination of the noise.

Heart rates increased in 29-80 during noise exposure in both phases 2 and 3, from 168 bpm during baseline measures, to 216 bpm in phase 3. Mean blood pressure decreased in response to 108 dB noise as it had done in response to the 96 dB noise in this animal.

Graphic representation of normalized group data (Figure 12) shows group means and standard errors for each phase calculated from the percentage of baseline values for each phase for each animal. The variables that showed appreciable changes during the intervention were Na^+ and H_2O excretion. Other variables showed little change. Summaries of these data are presented in Table 14.

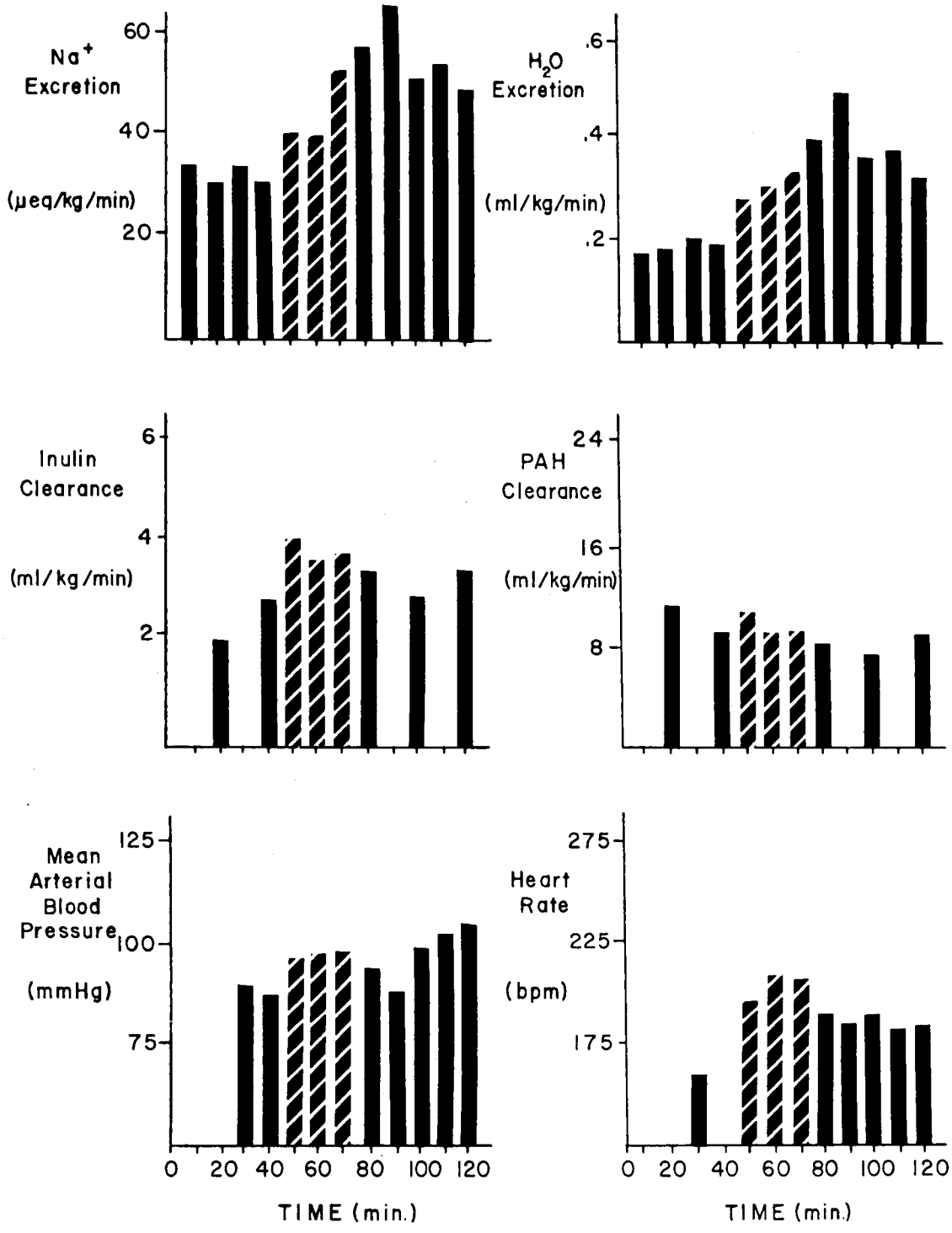


Figure 11. Renal and cardiovascular function during 108 dB noise used as an unconditional stimulus, #209-79. Patterned bars indicate noise stimulus.

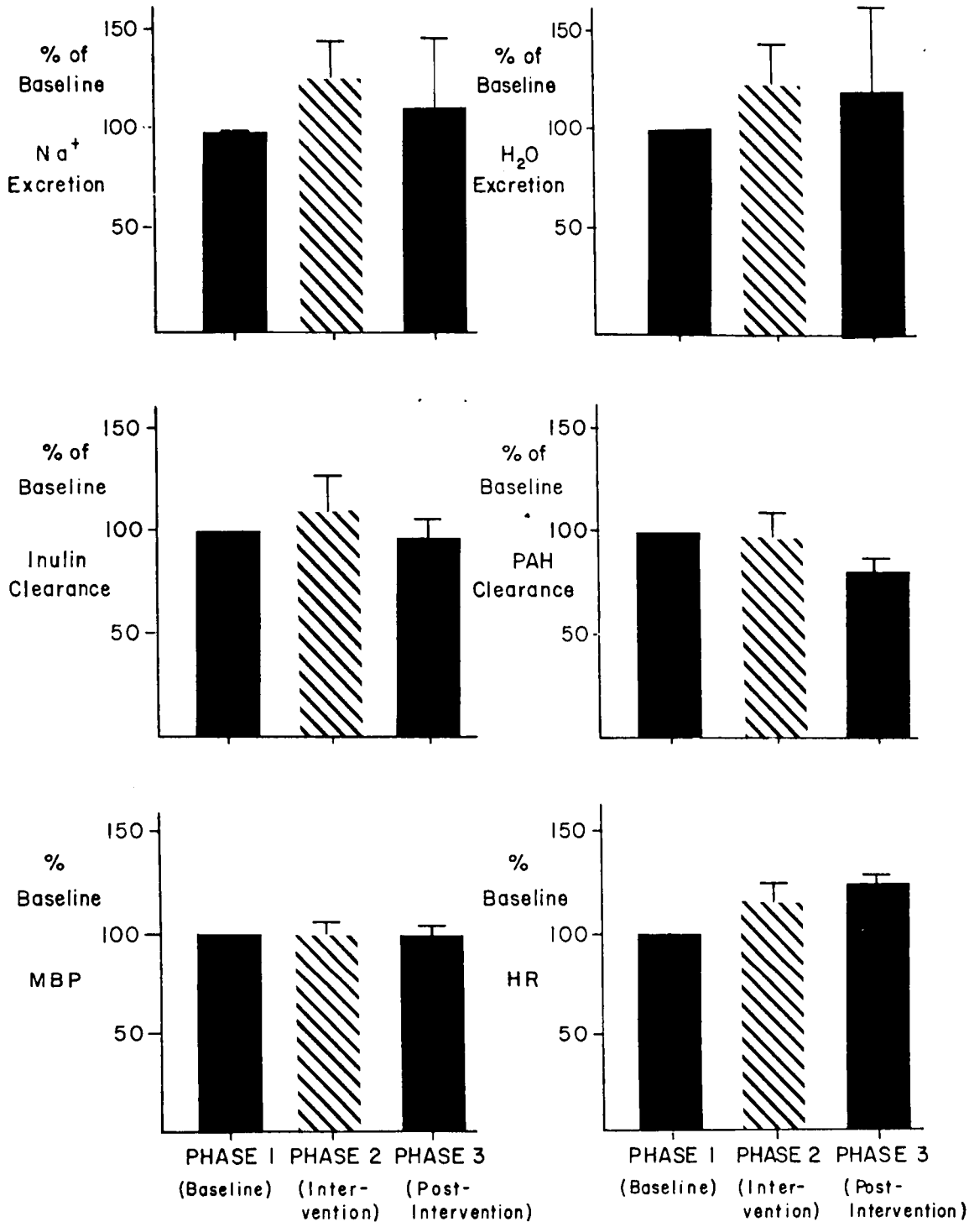


Figure 12. Renal and cardiovascular function during 108 dB noise used as an unconditional stimulus, three monkeys (Mean ± SEM).

TABLE 14

GROUP DATA: NOISE (108 dB) VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	124.2 +/- 22.8	121.0 +/- 42.0
NA+ EXCRETION	(3)	123.4 +/- 22.1	110.1 +/- 34.1
INULIN CLEARANCE	(3)	111.2 +/- 16.8	97.2 +/- 9.0
PAH CLEARANCE	(3)	98.1 +/- 12.1	82.8 +/- 3.1
HEART RATE	(3)	116.2 +/- 7.0	118.0 +/- 6.8
BLOOD PRESSURE	(3)	99.5 +/- 5.4	97.7 +/- 6.2

* Mean +/- Standard Error

Two-way analysis of variance was used to compare group data for phases 1 and 2. No significant treatment effects were found in Na^+ excretion (Table 15) or urine H_2O excretion (Table 16). Interaction effects were highly significant, however ($p < .01$), indicating the fundamental differences in response patterns between 191-79 and 209-79, whose excretion rates increased substantially, and 29-80, whose rates dropped in response to 108 dB noise. ANOVA values for MBP were computed using the MBP values from 29-80 and 191-80 (Table 17) because the number of data points in phase 1 for 209-79 was inadequate for ANOVA calculations. As a result, the ANOVA indicates a statistically significant ($p < .01$) decrease in MBP for the group. Animal 209-79 had shown an increase in pressure of 9 mmHg in response to the 108 dB noise.

4. Discussion. The combination of two different patterns of response to this noise stimulus detracts from the value of the group data, and results in the large standard errors. Examined individually, two of the three animals responded to 108 dB noise with increased excretion of both Na^+ and H_2O, which coincided with increases in both glomerular filtration rate and effective renal plasma flow. In both animals, rate of H_2O excretion continued to increase after the noise stimulus had been terminated, and in 209-79, rate of Na^+ excretion continued to increase also for 20 minutes. Excretion of Na^+ and H_2O and HR all remained above baseline values for all or part of phase 3. This lack of adaptation effect and failure to return to baseline values was similar to the pattern of phase 3 responses found for 96 dB noise, except the direction of the renal changes was reversed.

TABLE 15

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION DURING 108 dB NOISE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	19.8359	19.8359	.248548
Animals	2	847.477	423.738	
Interactions	2	1554.98	777.49	9.74209**
Error	12	957.687	79.8073	
Total	17	3379.98		

*Significant at .05

**Significant at .01

TABLE 16

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION DURING 108 dB NOISE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	4.99964E-03	4.99964E-03	4.12822
Animals	2	1.22108E-02	6.10542E-03	
Interactions	2	.026434	.013217	10.9133**
Error	12	.014533	1.21109E-03	
Total	17	5.81775E-02		

*Significant at .05

**Significant at .01

TABLE 17

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR MEAN ARTERIAL BLOOD PRESSURE DURING 108 dB NOISE (N = 2)

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	120.375	120.375	11.3712**
Animals	1	8.375	8.375	
Interactions	1	5.25	5.25	
Error	8	84.6875	10.5859	
Total	11	218.687		

*Significant at .05

**Significant at .01

Animal 29-80 responded to the 108 dB noise stimulus with responses similar to those made to the lower volume noise. The adaptation and/or recovery effects were less obvious than those seen during and after exposure to electric shock.

E. Naloxone Control Studies

1. Introduction. This series of experiments was designed to assess the effects of 10 mg/kg of naloxone, an opiate receptor antagonist, on cardiovascular and renal function in the cynomolgus monkey.

2. Method. All experimental procedures were identical to those used in control experiments. Following baseline measurements of MBP, HR, excretion of Na^+ and urine H_2O and clearance of inulin and PAH, naloxone was administered. Naloxone hydrochloride (Endo Laboratories, Inc., Garden City, N.J.), a rapid acting specific opiate receptor antagonist, was administered intravenously at 10 mg/kg. One mg/kg is sufficient to block morphine, but higher dosages apparently are needed to block endogenous opiates such as enkephalin and endorphin (Bodnar, Kelly, Brutus, and Glusman, 1980). Naloxone blocks opiate receptors for periods of 1 to 2 hours (Pace, Parrish, Lieberman, Wong, and Blatnick, 1979). The naloxone (in approximately 1 ml of saline) was injected into the venous catheter via the extension tubing connected to the infusion pump outside of the chamber. The tubing was reconnected to the pump and the infusion of saline (.5 ml/min) that had been in progress was resumed. The injection time was noted on the polygraph record.

3. Results. There were no consistent or significant effects of naloxone during phase 2 on any of the renal function measurements in any of the three animals tested. Two animals (191-79 and 209-79) showed increases in urine H_2O excretion in phase 3. Raw data for all variables for 209-79, who typified the responses of the group, are presented in Figure 13. Tabular presentations of phase means for each animal are provided by Tables in the Appendix.

Normalized group data are presented graphically in Figure 14, and in tabular form in Table 18. Excretion of Na^+ following intravenous administration of 10 mg/kg of naloxone was 98 ± 12% of baseline values during phase 2, and 103 ± 12% in phase 3. Excretion of urine H_2O was 102 ± 16% of baseline in phase 2 and 120 ± 18% in phase 3. Inulin clearance in phase 2 was 98 ± 14% of baseline, and in phase 3 was 101 ± 13%. PAH clearance was 96.5 ± 22% in phase 2 and 99 ± 9% of baseline in phase 3.

Heart rate and MBP values remained quite close to baseline levels. In phase 2, HR was 107 ± 2%, and in phase 3, 114 ± 3% of baseline. Mean arterial blood pressure for the group was 102 ± 5% in phase 2 and 98 ± 5% of baseline values in phase 3.

Two-way analysis of variance indicated no statistically significant differences in group values for Na^+ excretion (Table 19) or urine H_2O excretion (Table 20). MBP did not change significantly (Table 21).

4. Discussion. Naloxone had no significant effects on either Na^+ or urine H_2O excretion rates in phase 2. Urine H_2O excretion did increase in 191-79 and 209-79 during phase 3, and these two animals had stable

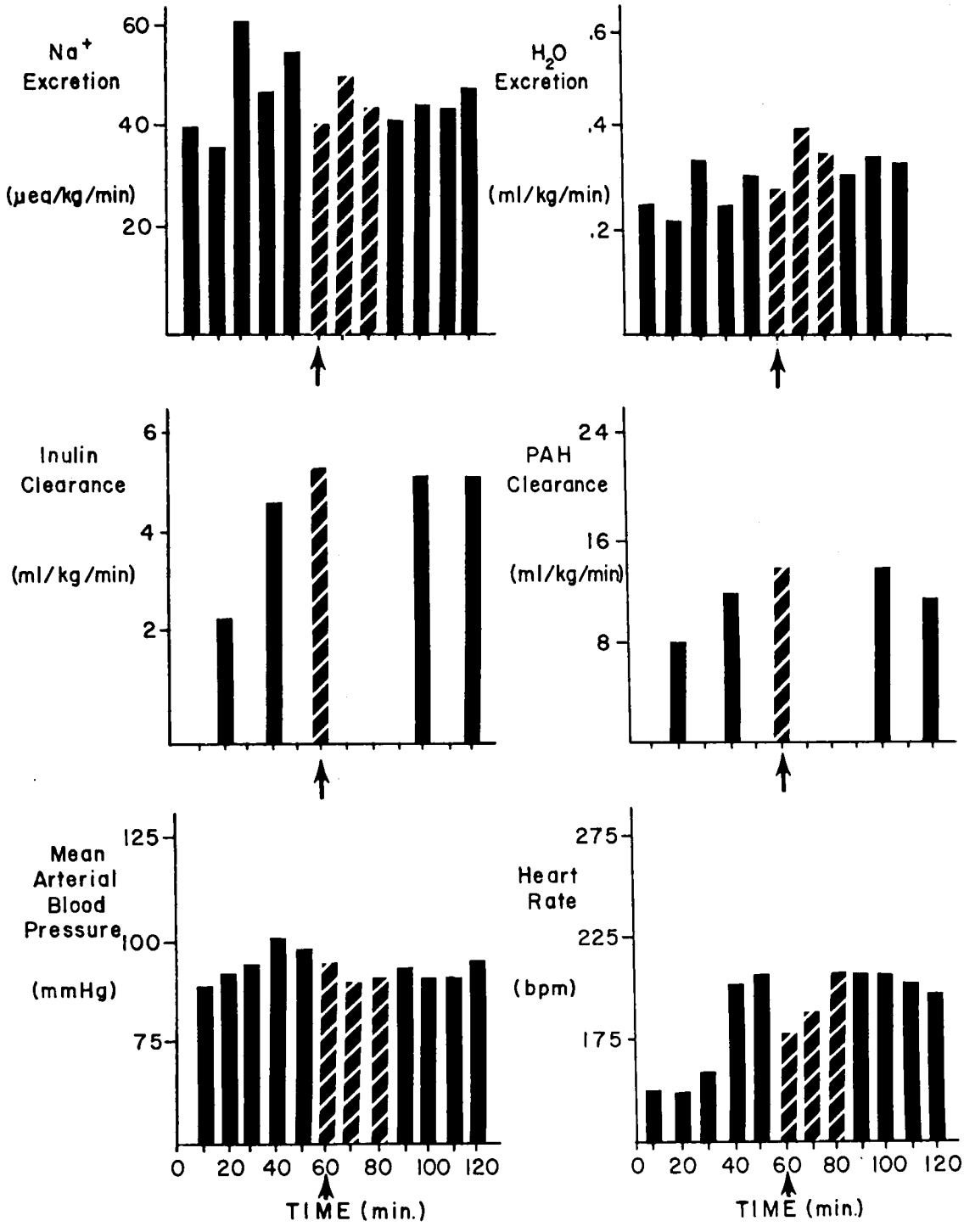


Figure 13. Renal and cardiovascular function under naloxone (10 mg/kg), #209-79. Arrows indicate naloxone injection. Patterned bars indicate phase 2 period, during which stimuli are presented in subsequent experiments.

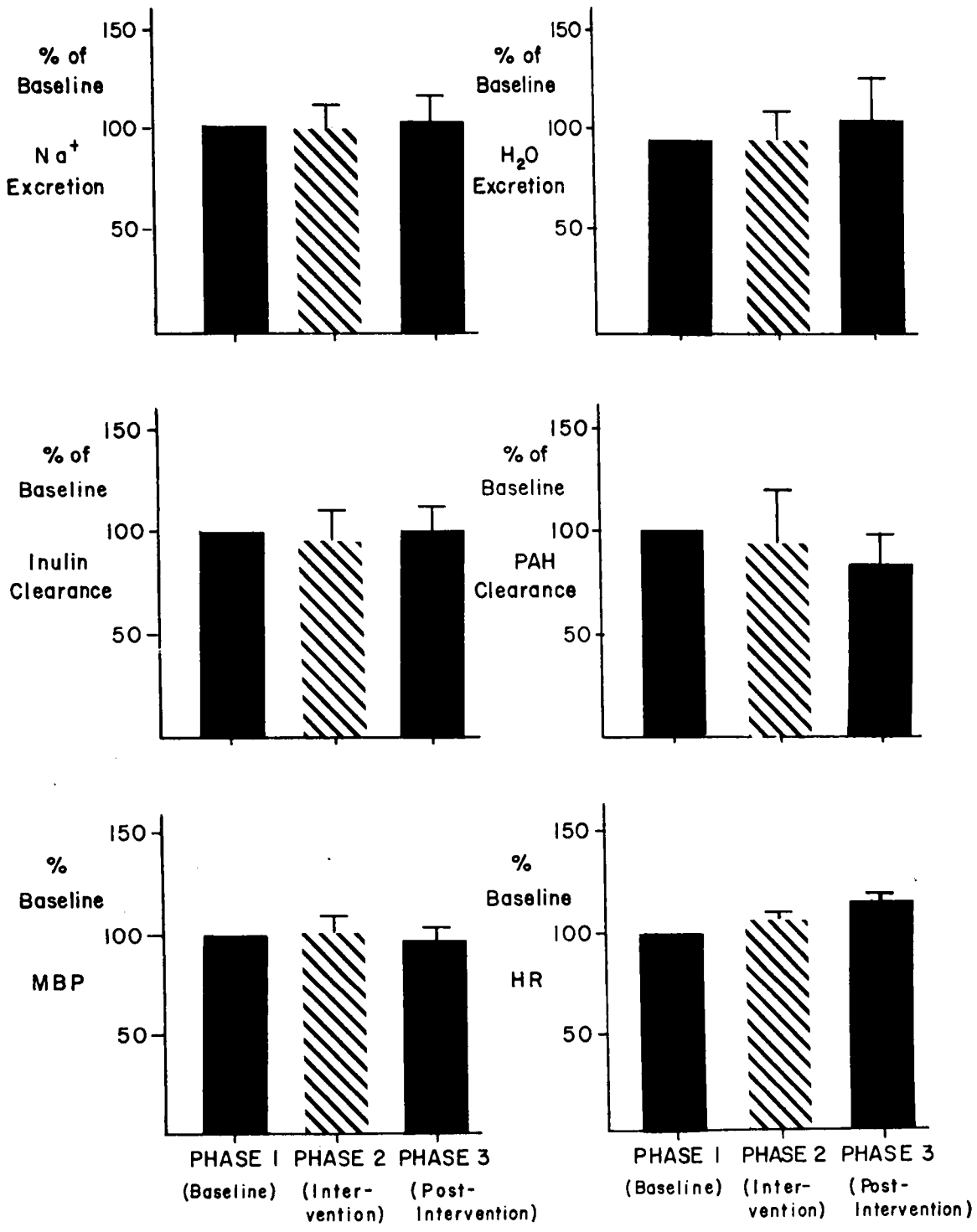


Figure 14. Renal and cardiovascular function under naloxone (10 mg/kg), three monkeys (Mean ± SEM).

TABLE 18

GROUP DATA: NALOXONE CONTROL VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	102.4 +/- 15.5	119.7 +/- 17.9
NA+ EXCRETION	(3)	98.2 +/- 12.0	103.0 +/- 11.7
INULIN CLEARANCE	(3)	97.7 +/- 14.4	100.6 +/- 13.4
PAH CLEARANCE	(2)	96.5 +/- 22.3	99.1 +/- 8.6
HEART RATE	(3)	106.9 +/- 1.8	114.4 +/- 3.1
BLOOD PRESSURE	(3)	101.6 +/- 5.0	98.3 +/- 5.3

* Mean +/- Standard Error

TABLE 19

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	30.9453	30.9543	.896441
Animals	2	3133.62	1566.81	
Interactions	2	189.285	94.6426	2.76166
Error	12	414.242	34.5205	
Total	17	3768.09		

*Significant at .05

**Significant at .01

TABLE 20

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	2.71797E-04	2.71797E-04	.108716
Animals	2	7.05442E-02	3.52721E-02	
Interactions	2	1.04103E-02	5.20515E-03	2.08201
Error	12	3.00007E-02	2.50006E-03	
Total	17	.111227		

*Significant at .05

**Significant at .01

TABLE 21

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA
FOR MEAN ARTERIAL BLOOD PRESSURE UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	2	2	.333333
Animals	2	741	370.5	
Interactions	2	273	136.5	22.75**
Error	12	72	6	
Total	17	1088		

*Significant at .05

**Significant at .01

urine H_2O excretion rates in all 3 phases of control observations. Naloxone could have delayed effects on urine H_2O excretion. Inulin and PAH clearances were relatively stable in all animals tested. In general, it appeared that naloxone alone had no significant effects on heart rate or mean arterial blood pressure under these conditions.

F. Renal and Cardiovascular Responses to Shock under Naloxone

1. Introduction. These studies were designed to assess the effects of an unconditional stimulus, electric shock, presented immediately following the administration of 10 mg/kg of naloxone. Both cardiovascular and renal responses were measured.

2. Method. All experimental procedures were identical to those used in the unconditional shock experiments, with the addition of intravenous administration of 10 mg/kg of naloxone hydrochloride 1 minute before the onset of the shock stimulus.

3. Results. Excretion of Na^+ and urine H_2O in phase 2 decreased from baseline levels in all three animals. Both variables remained below baseline values during phase 3 in all three monkeys. Figure 15 illustrates the response pattern in all parameters for 29-80, whose responses typified the trends seen in the group. Summaries of phase means for individual animals are presented in tables in the Appendix. Group data indicate that phase 2 Na^+ excretion rates were 44 ± 10% of baseline values, and phase 3 rates were 76 ± 2%. Excretion of urine H_2O in the group fell to 42 ± 10% in phase 2 and remained below baseline in

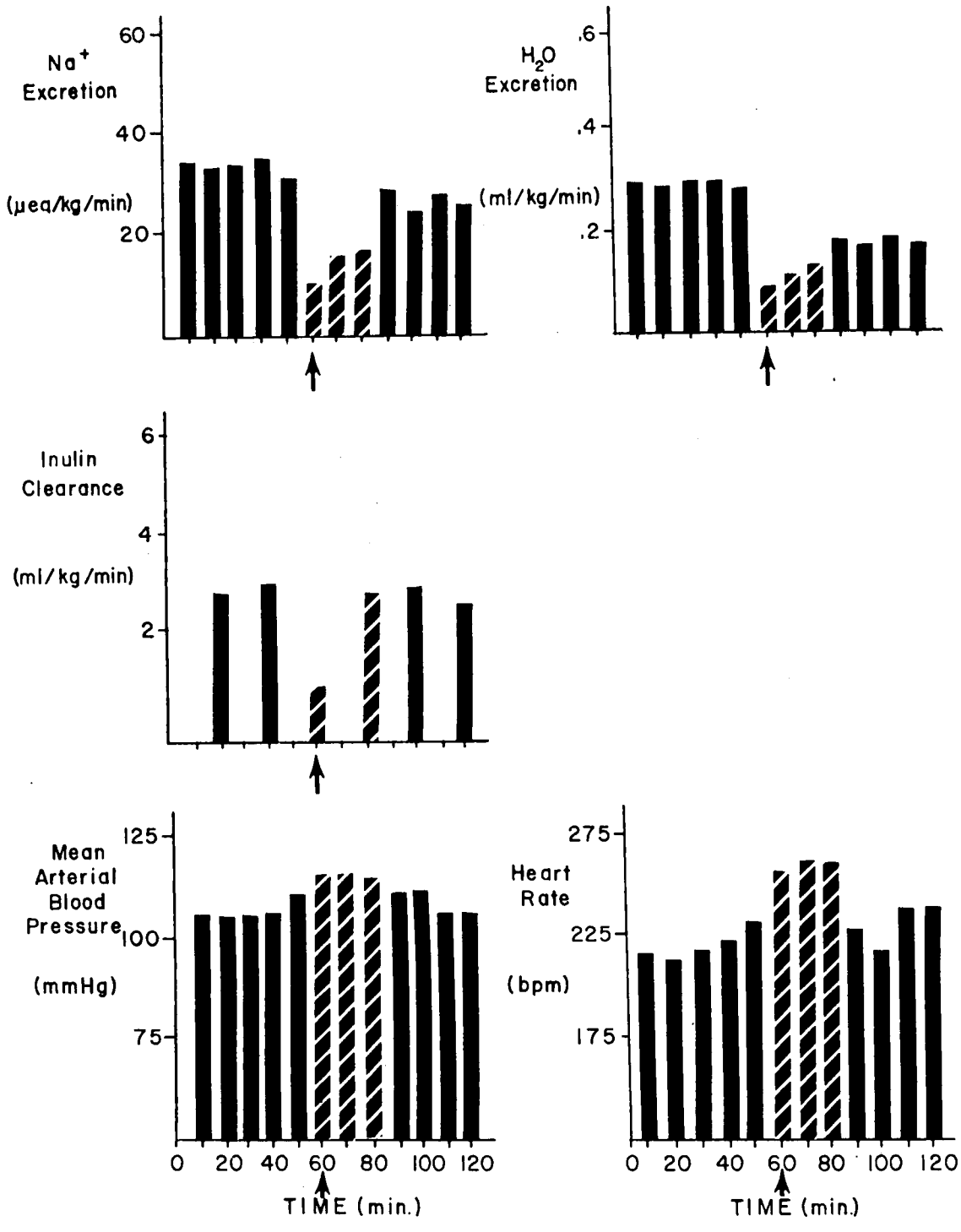


Figure 15. Renal and cardiovascular function during electric shock under naloxone, #29-80. Arrows indicate naloxone injection. Patterned bars indicate electric shock stimulus.

phase 3 at 72 ± 10%. Graphic representation of normalized group data is presented in Figure 16. Group data are presented in tabular form in Table 22.

Two-way analysis of variance indicated that both Na^+ (Table 23) and urine H_2O (Table 24) excretion decreased significantly ($p < .01$) in response to electric shock under naloxone. There were also significant differences between animals and significant interaction effects in the Na^+ excretion analysis.

Inulin clearance decreased substantially in all three monkeys during phase 2. Group mean values for that phase were 57 ± 14% of baseline excretion rates. Phase 3 values were 101 ± 4% of baseline. PAH clearance was not measured in these experiments.

Heart rate increased during phase 2 (as it did in control studies) but returned almost to baseline levels during phase 3 in two out of the three monkeys. Group values for heart rate were 117 ± 1% of baseline in phase 2 and 119 ± 16% of baseline in phase 3. Mean arterial blood pressure increased in response to shock under naloxone in two out of three animals. Two-way analysis of variance (Table 25) indicated this effect was statistically significant ($p < .05$), as were interaction effects. Mean BP for the group in phase 2 was 104 ± 4% of baseline, and 101 ± 2% of baseline during phase 3.

4. Discussion. The administration of shock during opiate receptor blockade resulted in significant retention of both urine Na^+ and H_2O, accompanied and probably mediated by a 43% decrease in glomerular filtration rate. During phase 2, Na^+ excretion rate fell to 44% of

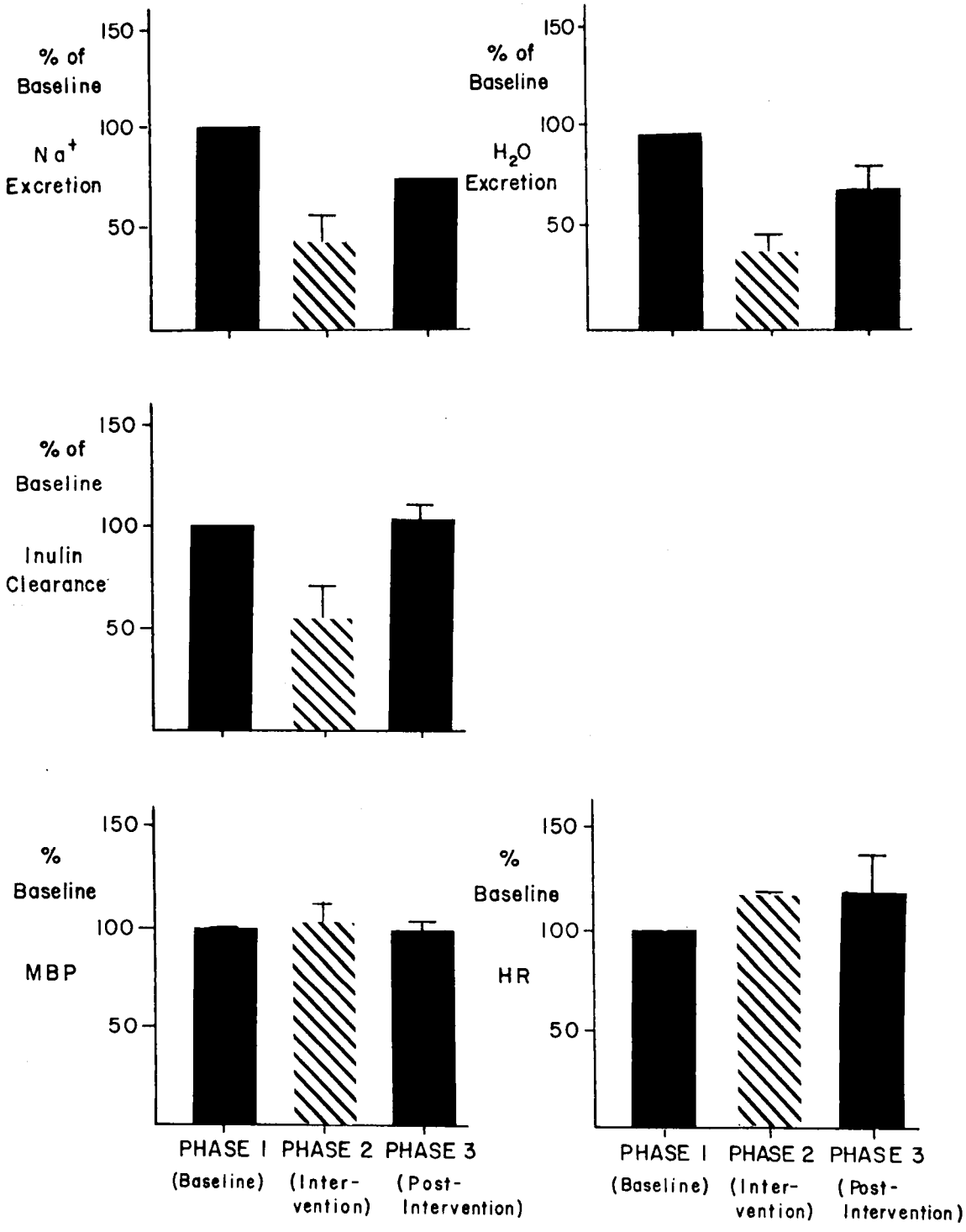


Figure 16. Renal and cardiovascular function during electric shock under naloxone, three monkeys (Mean ± SEM).

TABLE 22

GROUP DATA: SHOCK/NALOXONE VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	42.3 +/- 9.7	72.4 +/- 10.4
NA+ EXCRETION	(3)	44.0 +/- 9.6	75.6 +/- 2.3
INULIN CLEARANCE	(3)	57.4 +/- 13.7	100.8 +/- 4.3
PAH CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
HEART RATE	(3)	117.0 +/- 0.5	119.1 +/- 15.5
BLOOD PRESSURE	(3)	103.9 +/- 3.5	100.8 +/- 2.0

* Mean +/- Standard Error

TABLE 23

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION DURING SHOCK UNDER NALOXONE

Source of of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	2307.47	2307.48	99.4967**
Animals	2	284.055	142.027	
Interactions	2	478.758	239.379	10.3219**
Error	12	278.297	23.1914	
Total	17	3348.58		

*Significant at .05

**Significant at .01

TABLE 24

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION DURING SHOCK UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	.126672	.126672	108.061**
Animals	2	1.29962E-03	6.4981E-04	
Interactions	2	9.81152E-03	4.90576E-03	4.185
Error	12	1.40667E-02	1.17222E-03	
Total	17	.15185		

*Significant at .05

**Significant at .01

TABLE 25

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR MEAN ARTERIAL BLOOD PRESSURE DURING SHOCK UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	56.875	56.875	25.5738**
Animals	2	578.125	289.063	
Interactions	2	146.75	73.375	32.993**
Error	12	26.6875	2.22396	
Total	17	808.437		

*Significant at .05

**Significant at .01

baseline, and urine H_2O excretion fell to 42% of baseline. These effects persisted in part after the termination of the shock stimulus, as indicated by the mean percent of baseline values during phase 3 (72% for urine H_2O, 76% for Na^+ excretion). This partial return toward baseline values contrasts with the very rapid adaptation process which occurred in the experiments in which shock was administered. In those studies, Na^+ and urine H_2O excretion rates fell initially during phase 2, but both parameters returned to baseline levels during shock administration. Inulin clearance rates also fell sharply during the first half of phase 2, rose well above baseline values for the duration of phase 2, then fell to baseline levels during phase 3. In addition, both Na^+ and urine H_2O retention were enhanced by opiate receptor blockade. Urine H_2O excretion rate in phase 2 of the shock experiment was 78% of baseline, while during phase 3 of this shock under naloxone study, urine H_2O excretion was 42% of baseline. Similarly, Na^+ excretion during phase 2 was 84% of baseline during exposure to shock alone, and 44% of baseline during shock exposure with naloxone.

Increase in MBP for the group in response to shock under naloxone was small but statistically significant. These results suggest that unconditional renal and cardiovascular responses to electric shock may be moderated by endogenous opiates.

G. Renal and Cardiovascular Responses to 108 dB Noise Under Naloxone

1. Introduction. These studies were designed to assess the effects of loud (108 dB) noise presented immediately following the administration

of 10 mg/kg of naloxone. Both cardiovascular and renal responses were measured.

2. Method. All experimental procedures were identical to those used in the previous noise experiments, with the addition of intravenous administration of 10 mg/kg of naloxone hydrochloride 1 minute before the onset of the noise stimulus.

3. Results. Excretion of Na^+ in phase 2 decreased from baseline measures in all three monkeys. Na^+ excretion remained below baseline levels during phase 3 in 209-79 and 29-80. Urine H_2O excretion rates also decreased in response to 108 dB noise under naloxone. Urine H_2O excretion remained well below baseline values during phase 3 in all three animals. Figure 17 illustrates the response pattern in all variables for 209-79, whose responses typified the group. Summaries of all phase means for individual animals are presented in tables in the Appendix. Group data indicate that phase 2 Na^+ excretion rates were 70 ± 17% of baseline values, and phase 3 rates were 82 ± 11%. Excretion of urine H_2O for the group fell to 62 ± 15% in phase 2 and remained below baseline in phase 3 at 66 ± 6%. Graphic representation of normalized group data is presented in Figure 18. Group data are presented in tabular form in Table 26.

Two-way analysis of variance indicated that both Na^+ (Table 27) and urine H_2O (Table 28) excretion decreased significantly (Na^+, $p < .05$; H_2O, $p < .001$) in response to 108 dB noise under naloxone. There were significant interaction effects in the urine H_2O analysis.

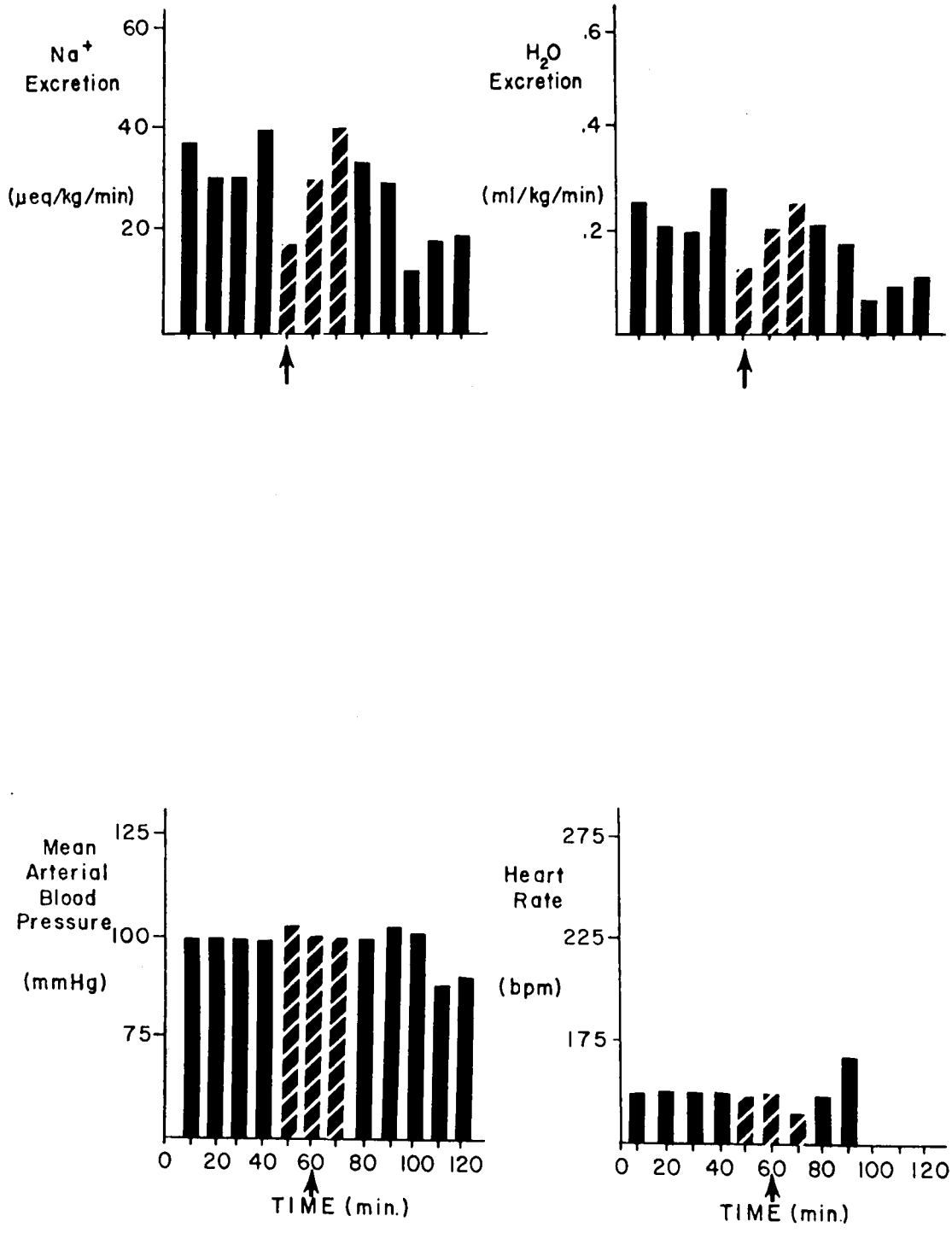


Figure 17. Renal and cardiovascular function during noise (108 dB) under naloxone, #209-79. Arrows indicate naloxone injection. Patterned bars indicate noise stimulus.

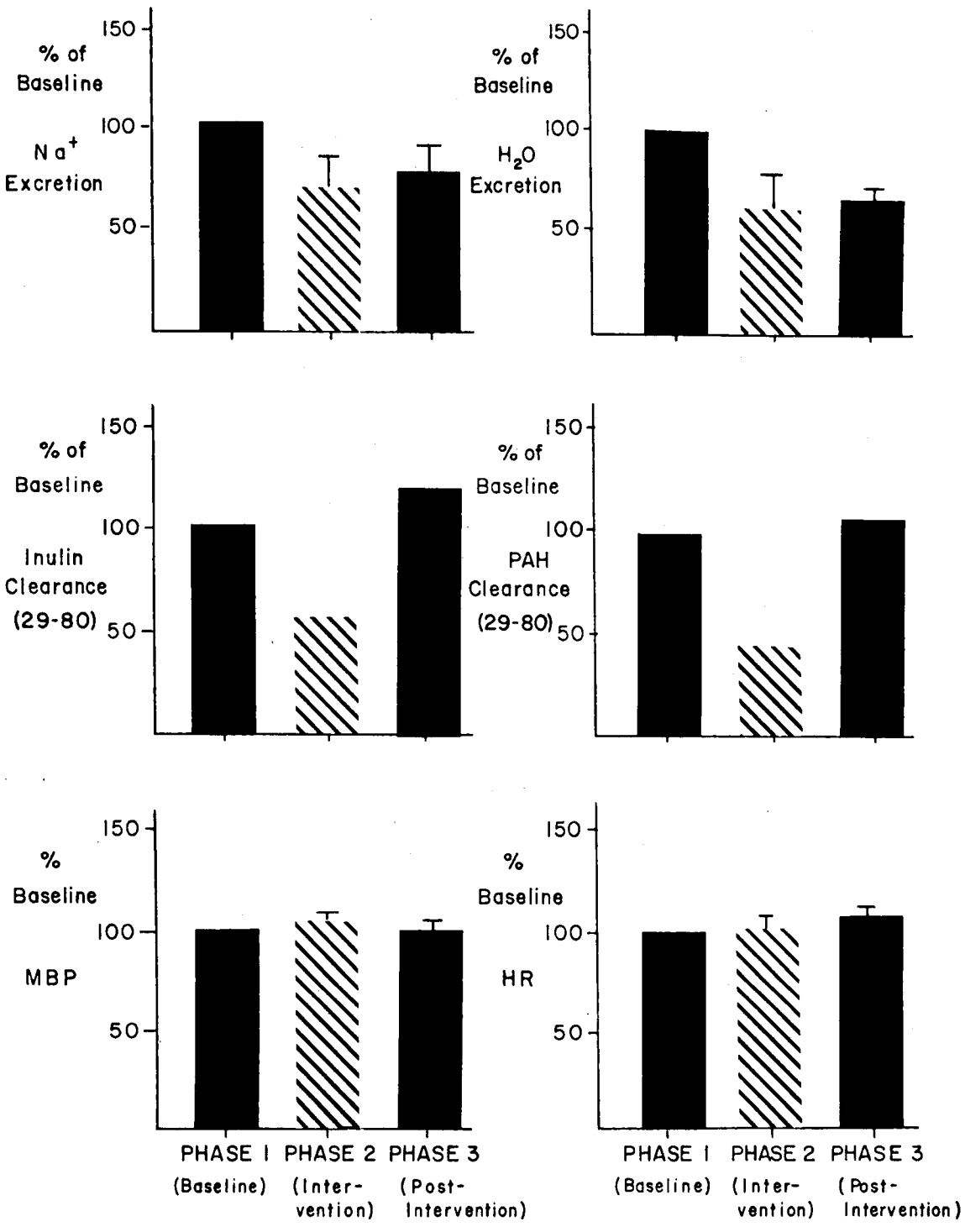


Figure 18. Renal and cardiovascular function during noise (108 dB) under naloxone, three monkeys (Mean ± SEM).

TABLE 26

GROUP DATA: NOISE (108 dB)/NALOXONE VALUES

PARAMETER MEASURED	(n)	PHASE 2 (INTERVENTION) % OF BASELINE*	PHASE 3 (POST-INTERVENTION) % OF BASELINE*
WATER EXCRETION	(3)	61.9 +/- 14.5	66.2 +/- 5.7
NA+ EXCRETION	(3)	70.4 +/- 16.5	81.8 +/- 11.3
INULIN CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
PAH CLEARANCE	(0)	0.0 +/- 0.0	0.0 +/- 0.0
HEART RATE	(3)	100.0 +/- 5.6	104.8 +/- 3.7
BLOOD PRESSURE	(3)	103.7 +/- 1.8	100.8 +/- 2.0

* Mean +/- Standard Error

TABLE 27

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR Na^+ EXCRETION DURING 108 dB NOISE UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	456.02	456.02	9.32982*
Animals	2	83.3633	41.6816	
Interactions	2	426.719	213.359	4.36518
Error	12	586.531	48.8776	
Total	17	1552.63		

*Significant at .05

**Significant at .01

TABLE 28

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR URINE H_2O EXCRETION DURING 108 dB NOISE UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	3.91999E-02	3.91999E-02	29.0369**
Animals	2	1.51005E-02	7.55024E-03	
Interactions	2	1.38998E-02	7.9499E-03	5.14806*
Error	12	1.62001E-02	1.35001E-03	
Total	17	8.44003E-02		

*Significant at .05

**Significant at .01

Inulin and PAH clearance were measured in 29-80 only. Both measures decreased sharply during phase 2; inulin clearance was 58% of baseline and PAH clearance was 45% of baseline. Both variables increased during phase 3 to slightly above baseline rates.

Heart rate in phase 2 fell in 191-79 and 209-79, but increased in 29-80. Maximum change was 21 bpm. Mean arterial blood pressure increased in all three monkeys during noise exposure. Two-way analysis of variance (Table 29) indicated this effect was statistically significant ($p < .01$). However, interaction effects were highly significant. Mean BP for the group was 104 ± 2% of baseline in phase 2, and 101 ± 2% of baseline during phase 3.

4. Discussion. The administration of unconditional 108 dB noise during opiate receptor blockade resulted in significant retention of both urine Na^+ and urine H_2O. Large decreases in effective renal plasma flow and glomerular filtration were seen in 29-80, suggesting that these two factors may be responsible for the Na^+ and urine excretion changes. During phase 2, Na^+ excretion rates fell to 70% of baseline, and urine H_2O fell to 62% of baseline rates. These effects persisted following the termination of the noise stimulus, as indicated by the mean percent of baseline values during phase 3 (82% for Na^+ excretion; 66% for urine H_2O excretion).

The adaptation process which was suggested by the shock exposure studies, and possibly mediated by utilization of opiate receptors, was not as evident in the noise exposure studies. The carryover of stimulus effects into phase 3 was seen in the subjects' responses to both the

TABLE 29

SUMMARY TABLE FOR ANALYSIS OF VARIANCE OF GROUP DATA FOR MEAN ARTERIAL BLOOD PRESSURE DURING 108 dB NOISE UNDER NALOXONE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Value
Treatments	1	72	72	160.744**
Animals	2	569.375	284.687	
Interactions	2	25.25	12.625	28.1861**
Error	12	5.375	.447917	
Total	17	672		

*Significant at .05

**Significant at .01

96 dB and the 108 dB noise levels. A similar carryover pattern existed in these studies.

V. GENERAL DISCUSSION AND SUMMARY

These studies establish the feasibility of assessing changes in renal and cardiovascular function in response to selected sensory stimuli in unanesthetized, chair-restrained, nonhuman primates. Using a priming injection of normal saline followed by a constant low volume infusion, it was possible to evoke a stable flow of urine for a 120-minute period. Urine volume was sufficient to permit measurements of Na^+ and urine H_2O excretion rates and clearances of inulin and PAH every 10 minutes. The sound attenuated, temperature-controlled isolation chamber provided a stable environment for the monkeys, and the measurements of mean arterial blood pressure and renal function were correspondingly stable during the control observation period. Heart rate, however, increased slowly over the entire control period in all three animals, resulting in statistically significant differences over time.

The 120-minute observation period was divided into 12 10-minute collection and measurement periods. These 12 periods were further subdivided into three phases: a baseline phase 1, lasting 40-50 minutes; a 30-minute phase 2, during which interventions were carried out in subsequent experiments; and a 40-50-minute postintervention phase 3.

The results of these experiments indicate that renal function in the cynomolgus monkey is sensitive to two different types of noxious stimuli: electric shock and noise.

A. Renal Responses to Unconditional Noxious Stimuli

The antinatriuretic and antidiuretic effects which corresponded to exposure to electric shock in these experiments were rapid and, in fact, most pronounced during the first 10 minutes of shock exposure in all three animals. Both Na^+ and urine H_2O excretion rates approached and equaled baseline levels during shock exposure, usually within 20-30 minutes. This response pattern suggests some type of adaptation effect operating on the renal response to the stimulus. The antinatriuretic and antidiuretic effects were mediated at least in part by decreases in glomerular filtration rate. Changes in renal blood flow may have been responsible for the GFR decrease, but renal blood flow was not measured in the shock studies. Reabsorption of Na^+ directly mediated by sympathetic nerves and changes in ADH may also have been involved. The decreases in inulin clearance found in these experiments were greatest during the first 10 minutes of shock exposure, and the decreases were followed by increases substantially above baseline levels which occurred during the last 10 minutes of shock exposure. The overshoot of baseline correlated in time with the apparent adaptation to the shock stimulus that was seen in the Na^+ and urine H_2O excretion rates. The 20% overall decrease in Na^+ and H_2O excretion during phase 2 was not statistically significant, probably because of the adaptation effects and the resulting variability in the measurements. The adaptation pattern seen in Na^+ and H_2O excretion and in inulin clearance strongly suggests that some mechanisms were effectively modifying the effects of the stimulus on renal responses.

The renal response to noise was different in several respects from the response to shock. Two different sound pressure levels of broadband noise were tested, 96 dB and 108 dB. In response to the 96 dB noise stimulus, the antinatriuretic and antidiuretic effects were less pronounced during the first 10 minutes of phase 2 than they were during shock exposure. However, the 20% decrease in both Na^+ and urine H_2O excretion that occurred during the first 10 minutes of the 96 dB noise exposure persisted throughout phase 2 and into phase 3, and the return to baseline seen in phase 2 in the shock exposure studies was seen either late in phase 3 or not at all in response to noise.

Inulin and PAH clearances were only measured in one animal, and slight increases were found in both variables. There was, however, a decrease in filtration fraction toward the end of phase 2. This decrease in percent of available plasma filtered may have been instrumental in the decrease in urine and H_2O excretion in this animal, but direct sympathetically mediated Na^+ retention changes in ADH levels must also be considered. In addition, it is possible that increases in PRA and release of aldosterone may have been involved in the response after a sufficient length of time had passed for these peptides to be activated. Noise stimuli have been shown to increase PRA in rats (Clamage, Sanford, Vander, and Mouw, 1976).

The renal responses to the 108 dB noise were inconsistent. One animal showed a decrease in Na^+ and urine H_2O output similar to that seen in the shock and 96 dB noise experiments, and the other two animals showed increases in excretion rates. In all three animals, GFR and

effective renal plasma flow changes were consistent with the changes in Na^+ and H_2O excretion.

B. Opiate Receptor Involvement in Renal Responses to Unconditional Noxious Stimuli

The possibility that endogenous opiates acting on opiate receptors could be responsible for adaptation to the electric shock stimulus was assessed by administering naloxone hydrochloride (10 mg/kg, iv) immediately prior to the onset of the shock stimulus in an additional series of experiments. Electric shock has been shown to increase endogenous opiate levels and to cause temporary analgesia in rats which could be reversed by naloxone. Localized brain regions known to influence renal blood flow, fluid balance and renin release also have high levels of endogenous opiates and/or opiate receptors (see Section II, Literature Review). The adaptation to the shock stimulus may have been mediated by endogenous opiates located in these regions.

The renal response to electric shock under naloxone consisted of an antinatriuresis and antidiuresis roughly three times greater than the renal response to shock without opiate receptor blockade. The decreases under these conditions coincided with a 30% decrease in inulin clearance. The response pattern was also altered by opiate receptor blockade. Under these conditions, the adaptation effect was not in evidence, and the rates of Na^+ and urine H_2O excretion remained below baseline levels during phase 3. Inulin clearance rates did return to baseline levels, but only after the termination of the shock stimulus. The substantial overshoot of baseline apparent in the second half of phase 2 in the previous shock study did not occur.

The effects of opiate receptor blockade on renal responses to unconditional 108 dB noise was also studied. Under naloxone, excretion rates for Na^+ and urine H_2O fell in all three monkeys in response to the noise stimulus, reversing the previous 50% increases seen in two of the monkeys tested with noise alone and enhancing the antinatriuretic and antidiuretic responses previously seen in the third monkey. The decreases persisted throughout the noise exposure and into phase 3. These results suggest that opiate receptors are involved in unconditional renal responses to loud noise. It was not possible to determine the effect of opiate receptor blockade on poststimulus recovery in the renal function variables because recovery apparently occurred some time after phase 3 ended in most studies of either 96 or 108 dB noise. If pre-treatment with naloxone blocked an endorphin-mediated poststimulus recovery and delayed a return to baseline excretion levels, then the processes mediating these responses to shock and noise are similar in nature but follow a different time course.

Endogenous opiates within certain brain regions may function as neurotransmitters, which are released when the organism is exposed to stressful stimuli. As central neurotransmitters, they may inhibit renal vascular and other autonomic responses within the kidney in order to moderate those stress-related changes. This protective mechanism could intervene to prevent extreme or prolonged renal responses rather than to completely block these responses. It has been suggested that the enkephalins and endorphins show only low levels of tonic activity, and activity increases in response to certain stimuli (Terenius, 1978).

Control studies in these animals in which naloxone alone was presented without electric shock or noise support this view.

C. Cardiovascular Responses to Unconditional Noxious Stimuli

The sensitivity of the cardiovascular system to behavioral stimuli has been repeatedly demonstrated. Acute increases in blood pressure have been demonstrated in response to electric shock, noise and vibration and other types of stimuli (see Section II, Literature Review). Chronic exposure to noise has resulted in long-term increases in blood pressure in nonhuman primates, mice and rats.

The results of the present studies suggest that mean arterial blood pressure in the cynomolgus monkey is sensitive to both unconditional electric shock and noise. Heart rate responses during the control observations were not stable over the 120-minute period and, as a result, heart rate was measured but not evaluated statistically during subsequent experiments. Mean blood pressure increased slightly in response to electric shock and decreased in response to both levels of noise. All changes were less than 5 percent. Because there was little variability in the measurements, the changes were statistically significant. In general, only suggestions of effects may be seen in these data.

D. Opiate Receptor Involvement in Cardiovascular Responses to Unconditional Noxious Stimuli

Although it is widely known that the cardiovascular system is sensitive to both endogenous and exogenous opiates (see Section II, Literature Review), the possibility that endogenous opiates might be involved in blood pressure regulation is a relatively new idea. Central

administration of endorphin caused increases in blood pressure and heart rate in dogs, but enkephalin had no effect (Laubie, Schmitt, Vincent, and Remond, 1977). Control studies carried out on these monkeys indicated that naloxone alone had no significant blood pressure effects. Endogenous opiates have been shown to play a role in sleep-induced changes in blood pressure, and brain regions which are important centers of blood pressure control and fluid balance (nucleus and tractus solitarius, the region anteroventral to the third ventricle, and the central gray) also have high levels of opiate receptors.

When the animals were exposed to the electric shock stimulus following the administration of naloxone (10 mg/kg), blood pressure levels increased significantly. Relative increases were slightly greater in response to shock under naloxone than to shock alone. There was no obvious change in the length of time necessary for poststimulus recovery. In response to the 108 dB noise stimulus, the animals given naloxone immediately prior to the onset of the stimulus responded to the noise with small but significant increases in MBP. These results suggest that opiate receptors may play a role in blood pressure responses to sensory stimuli in the cynomolgus monkey. The changes are too modest, however, for any definitive conclusions to be drawn.

E. Renal/Behavioral Model of Hypertension

In these studies, noxious sensory stimuli, consisting of either 96 dB noise or electric shock, caused 20 percent reductions in renal output of Na^+ and H_2O, as indicated in Figure 12 (p. 99) and Figure 8 (p. 83). In the electric shock experiments, an apparent adaptation to the shock

stimulus was evident during the 30 minutes of shock administration, allowing the Na^+ and H_2O excretion rates to return to baseline as illustrated by Figure 7 (p. 82). Figure 2 (p. 7) illustrates a proposed model of the moderating effect of endogenous opiates acting on central control centers of renal function in response to noxious sensory stimuli. The literature review has presented evidence of specific brain regions and nuclei which have been shown to exert influence on renal and endocrine function. Electrical stimulation of the mesencephalic central gray and the nucleus interpeduncularis causes vasoconstriction specific to the kidney. The supraoptic nucleus of the hypothalamus has been shown to respond to intraventricular injections of angiotensin II by causing ADH release. Electrical stimulation of the dorsolateral pons causes increased renin release from the kidney. In addition, the anteroventral region of the third ventricle, which is also sensitive to angiotensin II, has been found to play an important role in regulation of fluid balance, thirst mechanisms, and the development of Goldblatt experimental hypertension.

Each of these specific brain regions has been shown to contain either large numbers of opiate receptors in rat brain, established via autoradiographic techniques, or high levels of endogenous opiate activity in rhesus monkey brain. The significance of the presence of these receptors and substances in these particular areas is not yet known, nor has research specifically been directed toward the corroboration of common sites of central control of renal function and opiate receptor sensitivity. The proposed model suggests that endogenous opiate activity in these areas could serve to moderate renal responses to sensory stimuli. The results of the studies of opiate receptor

blockade via naloxone on renal excretion of Na^+ and H_2O presented in this dissertation support such a contention. As indicated by Table 22 (p.117), renal excretion of Na^+ and H_2O in response to electric shock is reduced by 60 percent when the stimulus is presented during opiate receptor blockade. These results contrast with the 20 percent reduction in excretion caused by the shock stimulus alone. In addition, the adaptation effect seen in the shock study was greatly attenuated under opiate receptor blockade, as illustrated in Figure 15 (p. 114). Results of the studies of 108 dB noise also indicate enhanced renal retention of Na^+ and H_2O under naloxone, demonstrated by a comparison of Tables 14 (p. 100) and 26 (p. 125). These results suggest that endogenous opiates play an important role in modifying centrally controlled renal responses to noxious sensory stimuli.

The mechanisms responsible for such changes in Na^+ and H_2O excretion are not defined by these studies. Data on clearance of inulin and PAH suggest that decreases in renal plasma flow and glomerular filtration parallel the decreases in Na^+ and H_2O excretion, but the data are not complete. Alteration of direct, sympathetically mediated reabsorption of Na^+ in the kidney is a possible mechanism, as well as changes in renin, aldosterone, and ADH levels. The precise mechanisms responsible for these effects remain to be determined.

Arthur Guyton, a major circulatory and fluid dynamics theorist, proposes that repeated episodes of increased renal vascular resistance, decreased glomerular filtration, or increased Na^+ reabsorption by the renal tubules could, via resulting temporary increases in blood volume and cardiac output, trigger an autoregulatory vasoconstriction in the

vasculature, including that of the kidney. Other theorists, including Friedman, suggest that repeated vascular episodes of this kind, stimulated by smooth muscle autoregulation or sympathetic activation originating from higher control centers, could cause permanent changes in the vessel walls which in themselves would accentuate vascular responses. This chain of events provides a hypothetical link between sensory stimuli and acute changes which could evolve into permanent changes in renal function, as illustrated in Figure 1 (p. 2). Evidence of renal function changes and corresponding alterations in pressure diuresis is present in many essential hypertensives and in animal models of experimental hypertension.

The question of which factors determine the individual susceptibility to such a chain of physiological responses is of utmost importance. Not every individual exposed repeatedly to stressful behavioral stimuli develops hypertension. It is reasonable to assume that some individuals could be more susceptible than others, and that the sources of such susceptibility vary. The renal/behavioral model of hypertension focuses on a central "moderator" system or systems which act as an interface between central nervous system processing of behavioral stimuli and renal responses to such stimuli. The "moderator" system within the model suggests that behavioral stimuli may cause the release of endogenous opiates within those particular brain regions which contribute to control of renal functions. The endogenous opiates may act as neurotransmitters capable of moderating both the impact of the noxious stimulus on conscious perception and on physiological responses. This moderation process does not serve to completely obliterate the responses to an

awareness of such stimuli, because to do so would be maladaptive for the organism. Rather, it prevents extreme changes. Data provided in these experiments support the existence of such a system by demonstrating enhanced renal responses to noxious stimuli under opiate receptor blockade. As the right side of the model diagram suggests, other "moderator" processes may exist as well to serve this essential purpose. Evidence exists that triggering baroreceptor reflexes via pharmacologically induced increases in blood pressure reduces the operant strength of responses made to avoid electric shock (Dworkin, Filewich, Miller, Craigmyle, and Pickering, 1979). Also, the nucleus and tractus solitarius, a mesencephalic brain region essential to blood pressure regulation including the baroreceptor reflex, has been shown to play an important role in moderating blood pressure responses to noxious behavioral stimuli. Lesions of the NTS greatly enhance increases in blood pressure responses to such stimuli. The NTS is heavily endowed with opiate receptors although the specific function of these receptors in this region is not known. Finally, renin released in response to sensory or behavioral stimuli is converted to angiotensin II in the body and possibly in brain tissue, as well. Angiotensin-sensitive brain regions, such as the AV3V, may be sites of "moderator" activity. This hypothesized feedback loop may or may not involve the opiate receptors which are prevalent in that region. Release of ADH under such circumstances could also be regulated by a CNS opiate-sensitive system. Although renin, aldosterone and ADH levels were not measured in these studies, they could have been involved in the Na^+ and H_2O changes, and further investigation of humoral and endocrine factors is of importance. The results of measurements of GFR

and PAH changes do suggest, however, that alterations in these parameters paralleled changes in Na^+ and H_2O excretion.

Individuals who become hypertensive as a function of renal responses to repeated exposure to behavioral stimuli may be individuals whose central modulator systems function inadequately as a result of genetic differences or through eventual adaptation of the system via too frequent demands made upon it. The same process which could create permanent changes in the renal vasculature could operate on the peripheral vasculature as well, contributing to the elevated total peripheral resistance so commonly seen in individuals with essential hypertension.

Such conjecture reaches beyond the scope of these studies. This research does present, however, some important new insights into the relationship between noxious sensory stimuli and renal function, and a useful model of the role endogenous opiates may play in CNS influences on renal responses to such stimuli.

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APPENDIX

TABLE 30

CONTROL VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.20 +/- 0.02	0.19 +/- 0.06	0.20 +/- 0.01
SODIUM EXCRETION (μeq/kg/min)	26.0 +/- 2.6	25.9 +/- 8.1	17.5 +/- 2.0
INULIN CLEARANCE (ml/kg/min)	4.3	4.3	5.3 +/- 0.47
PAH CLEARANCE (ml/kg/min)	13.7	11.0	11.7 +/- 1.2
HEART RATE (BPM)	164 +/- 9.4	192 +/- 1.7	205 +/- 3.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	115 +/- 1.1	110 +/- 2.0	102 +/- 0.8

* Mean +/- Standard Error or Single Measurement

TABLE 31

CONTROL VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.23 +/- 0.01	0.20 +/- 0.02	0.25 +/- 0.01
SODIUM EXCRETION (μeq/kg/min)	41.6 +/- 1.9	35.7 +/- 4.0	43.8 +/- 2.4
INULIN CLEARANCE (ml/kg/min)	3.4	4.5	4.4 +/- 0.17
HEART RATE (BPM)	148 +/- 2.5	170 +/- 10.0	194 +/- 1.9
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	99 +/- 0.3	105 +/- 1.7	101 +/- 2.4

* Mean +/- Standard Error or Single Measurement

TABLE 32

CONTROL VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.22 +/- 0.01	0.20 +/- 0.01	0.19 +/- 0.01
SODIUM EXCRETION (μeq/kg/min)	35.5 +/- 1.9	33.9 +/- 1.9	33.6 +/- 1.0
INULIN CLEARANCE (ml/kg/min)	5.0	4.2	4.9 +/- 0.31
PAH CLEARANCE (ml/kg/min)	17.9	14.0	15.5 +/- 1.5
HEART RATE (BPM)	178 +/- 3.2	187 +/- 3.3	189 +/- 1.9
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	104 +/- 1.2	105 +/- 1.2	109 +/- 1.2

* Mean +/- Standard Error or Single Measurement

TABLE 33

SHOCK VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.33 +/- 0.04	0.29 +/- 0.05	0.30 +/- 0.03
SODIUM EXCRETION (μeq/kg/min)	43.4 +/- 5.7	41.5 +/- 8.0	42.9 +/- 4.3
INULIN CLEARANCE (ml/kg/min)	2.3	5.6 +/- 1.15	4.6 +/- 0.70
HEART RATE (BPM)	204 +/- 2.4	198 +/- 1.7	214 +/- 1.3
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	109 +/- 0.8	110 +/- 1.2	110 +/- 1.0

* Mean +/- Standard Error or Single Measurement

TABLE 34

SHOCK VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.09 +/- 0.01	0.07 +/- 0.03	0.13 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	10.2 +/- 1.0	8.2 +/- 3.5	10.3 +/- 1.1
INULIN CLEARANCE (ml/kg/min)	1.9	3.0	2.8 +/- 0.35

* Mean +/- Standard Error or Single Measurement

TABLE 35

SHOCK VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.28 +/- 0.02	0.19 +/- 0.05	0.32 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	34.9 +/- 2.0	26.1 +/- 6.3	41.3 +/- 0.9
INULIN CLEARANCE (ml/kg/min)	4.0	3.9 +/- 2.05	4.2 +/- 0.05
HEART RATE (BPM)	171 +/- 1.9	210 +/- 0.0	180 +/- 2.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	101 +/- 0.6	107 +/- 0.7	102 +/- 1.4

* Mean +/- Standard Error or Single Measurement

TABLE 36

NOISE (96dB) VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.18 +/- 0.01	0.13 +/- 0.01	0.14 +/- 0.01
SODIUM EXCRETION (μeq/kg/min)	27.7 +/- 2.1	19.0 +/- 1.4	21.9 +/- 0.7
HEART RATE (BPM)	140 +/- 2.0	148 +/- 1.7	156 +/- 2.4
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	113 +/- 0.6	112 +/- 0.6	112 +/- 0.4

* Mean +/- Standard Error or Single Measurement

TABLE 37

NOISE (96 dB) VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.27 +/- 0.01	0.24 +/- 0.01	0.24 +/- 0.02
SODIUM EXCRETION (μeq/kg/min)	41.2 +/- 1.7	40.3 +/- 1.8	39.8 +/- 3.3
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	94 +/- 1.4	95 +/- 0.3	89 +/- 1.0

* Mean +/- Standard Error or Single Measurement

TABLE 38

NOISE (96dB) VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.33 +/- 0.03	0.29 +/- 0.01	0.32 +/- 0.02
SODIUM EXCRETION (μeq/kg/min)	33.8 +/- 2.8	24.3 +/- 1.7	20.8 +/- 0.9
INULIN CLEARANCE (ml/kg/min)	4.0	4.7 +/- 0.17	4.6 +/- 0.12
PAH CLEARANCE (ml/kg/min)	11.8	12.9 +/- 0.4	11.3 +/- 0.9
HEART RATE (BPM)	208 +/- 4.4	220 +/- 5.0	224 +/- 1.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	106 +/- 0.8	97 +/- 0.7	101 +/- 1.3

* Mean +/- Standard Error or Single Measurement

TABLE 39

NOISE (108dB) VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.17 +/- 0.01	0.24 +/- 0.04	0.20 +/- 0.03
SODIUM EXCRETION (μeq/kg/min)	19.2 +/- 1.2	29.1 +/- 5.1	20.1 +/- 2.9
INULIN CLEARANCE (ml/kg/min)	3.9	4.7 +/- 0.52	3.7 +/- 0.25
PAH CLEARANCE (ml/kg/min)	12.5	14.2 +/- 1.6	10.3 +/- 0.8
HEART RATE (BPM)	168 +/- 6.0	196 +/- 5.9	219 +/- 3.3
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	109 +/- 1.0	104 +/- 1.3	100 +/- 0.2

* Mean +/- Standard Error or Single Measurement

TABLE 40

NOISE (108dB) VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.21 +/- 0.01	0.32 +/- 0.02	0.41 +/- 0.03
SODIUM EXCRETION (μeq/kg/min)	32.5 +/- 1.0	45.1 +/- 3.9	55.8 +/- 3.0
INULIN CLEARANCE (ml/kg/min)	2.9	3.9 +/- 0.12	3.3 +/- 0.17
PAH CLEARANCE (ml/kg/min)	9.5	10.1 +/- 0.6	8.4 +/- 0.5
HEART RATE (BPM)	160	205 +/- 4.0	187 +/- 1.2
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	89 +/- 1.0	98 +/- 0.3	98 +/- 3.0

* Mean +/- Standard Error or Single Measurement

TABLE 41

NOISE (108dB) VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.24 +/- 0.02	0.19 +/- 0.02	0.12 +/- 0.01
SODIUM EXCRETION (μeq/kg/min)	37.0 +/- 2.3	29.5 +/- 2.1	20.0 +/- 2.1
INULIN CLEARANCE (ml/kg/min)	4.7	3.7 +/- 0.20	3.9 +/- 0.35
PAH CLEARANCE (ml/kg/min)	14.8	11.0 +/- 0.2	11.5 +/- 1.7
HEART RATE (BPM)	178 +/- 7.5	185 +/- 5.0	190 +/- 3.2
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	113 +/- 1.6	105 +/- 2.4	103 +/- 0.8

* Mean +/- Standard Error or Single Measurement

TABLE 42

NALOXONE CONTROL VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.21 +/- 0.04	0.23 +/- 0.04	0.31 +/- 0.02
SODIUM EXCRETION (µeq/kg/min)	16.7 +/- 3.5	20.2 +/- 3.8	21.1 +/- 1.9
INULIN CLEARANCE (ml/kg/min)	6.5	4.6	4.8 +/- 0.33
HEART RATE (BPM)	190 +/- 4.1	198 +/- 4.4	223 +/- 3.5
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	111 +/- 1.8	106 +/- 0.3	99 +/- 1.8

* Mean +/- Standard Error or Single Measurement

TABLE 43

NALOXONE CONTROL VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.28 +/- 0.02	0.35 +/- 0.03	0.35 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	47.0 +/- 4.7	43.9 +/- 2.8	43.2 +/- 1.1
INULIN CLEARANCE (ml/kg/min)	4.5	5.4	5.1 +/- 0.05
PAH CLEARANCE (ml/kg/min)	11.7	13.9	12.6 +/- 1.3
HEART RATE (BPM)	175 +/- 13.2	193 +/- 8.8	206 +/- 2.4
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	95 +/- 1.9	93 +/- 1.2	93 +/- 0.9

* Mean +/- Standard Error or Single Measurement

TABLE 44

NALOXONE CONTROL VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.22 +/- 0.09	0.16 +/- 0.02	0.19 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	30.2 +/- 2.2	24.2 +/- 2.2	27.4 +/- 1.2
INULIN CLEARANCE (ml/kg/min)	4.1	4.2	4.7 +/- 0.52
PAH CLEARANCE (ml/kg/min)	13.6	10.1	12.3 +/- 1.5
HEART RATE (BPM)	195 +/- 2.9	207 +/- 8.8	211 +/- 3.3
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	104 +/- 0.7	116 +/- 0.3	112 +/- 1.0

* Mean +/- Standard Error or Single Measurement

TABLE 45

SHOCK/NALOXONE VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.28 +/- 0.01	0.17 +/- 0.04	0.26 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	29.9 +/- 1.1	18.3 +/- 4.3	21.6 +/- 1.8
INULIN CLEARANCE (ml/kg/min)	3.2	2.5 +/- 0.58	3.2 +/- 0.10
HEART RATE (BPM)	164 +/- 9.8	191 +/- 1.9	246 +/- 13.8
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	102 +/- 1.0	99 +/- 0.7	99 +/- 0.5

* Mean +/- Standard Error or Single Measurement

TABLE 46

SHOCK/NALOXONE VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.32 +/- 0.02	0.09 +/- 0.02	0.21 +/- 0.02
SODIUM EXCRETION (µeq/kg/min)	51.7 +/- 3.4	14.5 +/- 3.7	38.5 +/- 3.5
INULIN CLEARANCE (ml/kg/min)	3.5 +/- 0.05	1.1 +/- 0.39	3.8 +/- 0.35
HEART RATE (BPM)	180 +/- 1.6	210 +/- 8.7	185 +/- 0.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	110 +/- 2.4	117 +/- 0.7	114 +/- 0.9

* Mean +/- Standard Error or Single Measurement

TABLE 47

SHOCK/NALOXONE VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.29 +/- 0.01	0.11 +/- 0.01	0.17 +/- 0.01
SODIUM EXCRETION (µeq/kg/min)	34.2 +/- 0.7	14.6 +/- 2.1	27.4 +/- 1.0
INULIN CLEARANCE (ml/kg/min)	3.2	2.0 +/- 0.90	3.0 +/- 0.15
HEART RATE (BPM)	223 +/- 3.4	263 +/- 1.7	233 +/- 4.8
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	108 +/- 0.6	117 +/- 0.6	110 +/- 1.2

* Mean +/- Standard Error or Single Measurement

TABLE 48

NOISE (108 dB)/NALOXONE VALUES: MONKEY 191-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.29 +/- 0.01	0.21 +/- 0.00	0.22 +/- 0.02
SODIUM EXCRETION (μeq/kg/min)	31.7 +/- 4.6	28.8 +/- 1.8	32.7 +/- 3.5
HEART RATE (BPM)	175 +/- 2.9	160 +/- 0.0	171 +/- 1.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	110 +/- 0.5	112 +/- 0.0	112 +/- 1.4

* Mean +/- Standard Error or Single Measurement

TABLE 49

NOISE (108 dB)/NALOXONE VALUES: MONKEY 209-79

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.25 +/- 0.02	0.20 +/- 0.04	0.14 +/- 0.03
SODIUM EXCRETION (μeq/kg/min)	35.1 +/- 2.6	29.0 +/- 6.3	22.7 +/- 4.0
HEART RATE (BPM)	150 +/- 0.0	147 +/- 3.3	160 +/- 10.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	100 +/- 0.0	102 +/- 0.6	97 +/- 3.2

* Mean +/- Standard Error or Single Measurement

TABLE 50

NOISE (108 dB)/NALOXONE VALUES: MONKEY 29-80

VARIABLE MEASURED	PHASE VALUES* PHASE 1	PHASE 2	PHASE 3
WATER EXCRETION (ml/kg/min)	0.27 +/- 0.02	0.09 +/- 0.00	0.18 +/- 0.02
SODIUM EXCRETION (μeq/kg/min)	38.6 +/- 1.7	14.6 +/- 0.7	30.0 +/- 3.4
INULIN CLEARANCE (ml/kg/min)	3.8	2.2 +/- 0.52	4.6 +/- 0.01
PAH CLEARANCE (ml/kg/min)	11.9	5.3 +/- 1.2	12.6 +/- 0.3
HEART RATE (BPM)	201 +/- 4.3	222 +/- 1.7	221 +/- 1.0
MEAN ARTERIAL BLOOD PRESSURE (mmHg)	110 +/- 1.2	116 +/- 0.0	114 +/- 0.5

* Mean +/- Standard Error or Single Measurement

VITA

Debra Kirby was born in DeWitt, Iowa, on September 11, 1950. She attended elementary schools in the area, and graduated from Central High School in May 1968. The following September she entered Augustana College in Rock Island, Illinois, and in June 1972 received a Bachelor of Arts degree in Psychology. In the fall of 1973 she accepted a graduate research assistantship at the University of Bridgeport in Bridgeport, Connecticut, and was awarded a Master of Science degree in Psychology from that institution in 1975. From January of 1975 until September, Ms. Kirby was employed as an instructor in psychology by the University of Maryland European Division in Heidelberg, Germany.

In September of 1975, she entered the Graduate School of The University of Tennessee in Knoxville. Her dissertation research was carried out at the New England Regional Primate Research Center, Harvard Medical School, in Southborough, Massachusetts. She received her Doctor of Philosophy degree in Psychology in June 1981.