METABOLIC AND PHYSIOLOGICAL STUDIES

I N

BILATERALLY ADRENALECTOMIZED RATS

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B Y

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A C K N O W L E D G E M E N T

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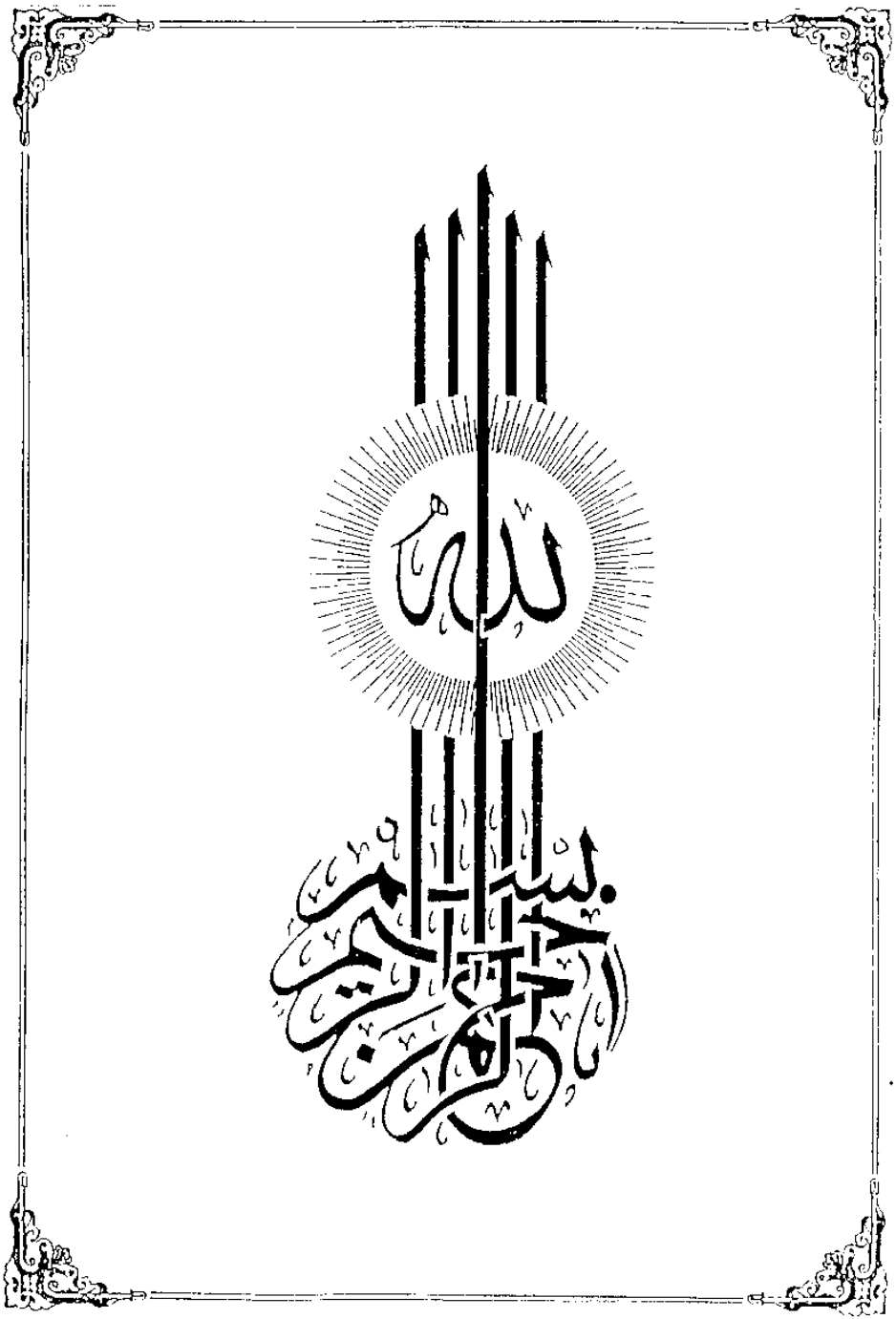

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Review of Literature

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CARDIOVASCULAR EFFECTS OF ADRENALECTOMY

Effect of Adrenalectomy on Arterial Blood Pressure

Dating back to the nineteenth century Oliver and Schafer in 1895, observed that extracts of the suprarenal gland decreased the size of the radial artery and raised the blood pressure of his own child. Using adrenalectomized cats, Elliott (1914) observed "paralysis" of the vasomotor mechanism. Injection of epinephrine produced a rise in blood pressure in these animals. In a following report by Swingle and his co-workers in 1938, they found that adrenalectomized dogs exhibiting circulatory collapse promptly reacted to intravenous injection of hypertonic saline by restoring their blood pressure and hemoconcentration to normal. The effect was temporary since the fluid was not held in the circulation. Shock developed again and death from circulatory failure occured unless adequate amounts of cortical hormone were administred.

Hypotension in adrenalectomized animals has been reported by many workers in different aniamls (Remington, 1951; Colton and Pincus, 1955; Hofmann and Sobel, 1964; Allan and Sutfin 1964; Harakal et al., 1968 Imms and Jones, 1967 and 1968). This finding was, also, confirmed

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by Carpi and Cartoni (1968) who reported that in adrenalectomized rats the blood pressure levels were 30 mmHg lower than cotnrols. While Drew and Leach (1970) showed in chronic adrenalectomized rats a decrease in resting blood pressure which reached 10-15 mmHg lower than sham-adrenalectomized or intact rats.

The recent work of Friedman et al. in 1984 had confirmed that adrenalectomy in rats for 7 days significantly reduced both systolic and diastolic blood pressures. Plasma sodium levels were depressed while plasma potassium levels were elevated. Depressed tissue sodium without change in tissue potassium were also reported. While prolonging the post adrenalectomy period to 9 days increased the severity of the blood pressure fall it did not affect other measurements. Replacement therapy in these animals with either aldosterone or cortisone partially normalized the blood pressure and plasma electrolyte values without raising cell sodium. They concluded that the restoration of arterial blood pressure in the adrenalectomized rat is independent of sodium concentration, but is associated with enhanced sodium transport activity.

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Effect of Adrenalectomy on Peripheral Resistance

Swingle et al, in 1934, attributed the cause of death in adrenal insufficiency to capillary atony with resulting dilatation, stasis, and peripheral vascular stagnation, and believed that this defect could be corrected by cortical hormone. That adrenal crisis was precipitated by failure of some part of the cardiovascular apparatus was suggested by Remington et al in 1941. They denoted that asthenia of the arterioles may be the primary fault involved. A finding which was later on confirmed by Secker (1949).

In agreement with the previous finding many authors reported that adrenalectomy decreased the total peripheral resistance in dogs and rats (Remington, 1951; Hofmann and Sobel, 1964 and Imms and Neame, 1974). To the contrary , Von Euler (1954) showed increase in the total peripheral resistance after bilateral adrenalectomy in humans. Also increased peripheral resistance in unaneasthetized dogs was reported by Reidenberg et al. (1958), Rosenfeld et al. (1959) and Harakal et al. (1968).

Decreased response of effector organ, namely the blood vessels, despite the compensatory increase

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in sympathetic activity and the high titre of constrictor materials was shown in adrenalectomized animals by Sheehan (1948). This observation was later confirmed by Von Euler (1954) in humans. In a more recent study , Reidenberg et al. in 1963 showed that the compensatory sympathetic nervous system responses were not affected by adrenalectomy in rats. Furthermore,Imms and Jones (1967) reported increased activity of sympathetic nervous system after adrenalectomy in rats. However, this activity was shown to be inhibited by corticosterone.

Effect of Adrenalectomy on Cardiac Output

In 1951 Remington showed that adrenalectomized dogs in crisis has increased cardiac output as compared to normal animals. In contrast,it was proved later on that adrenalectomy in dogs reduced the cardiac output secondary to reduced circulating blood volume and venous return as infusion of dextran in amounts estimated to restore plasma volume increased the cardiac output in these animals (Reidenberg et al.,1958; Rosenfeld et al., 1959).Reduced cardiac output following adrenalectomy in dogs was confirmed by Harakal et al (1968), and in rats by Imms and Neame (1974).

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Effect of Adrenalectomy on the Heart

As early as 1855, Addison gave a picture of feebleness of heart's action in his classical description of adrenal insufficiency. Weakness of myocardil contractile force was also blamed as a cause of circulatory failure in adrenal insufficiency (Fowler and Cleghorn , 1942 and Clarke et al .,1947) .In 1950, Hamilton et al; reported that animals dying in adrenal crisis showed a slow heart rate and a small heart size which indicated a slower ventricular relaxation with inadequate filling. That extreme sensitivity of adrenalectomized animals to ether anaesthesia is due to loss of the positive inotropic effect of catecholamines on the heart, which counters the negative effect of ether,was demonstrated by Brewster et al in 1953. Brown and Remington (1955) confirmed that the mean heart rates of chronic adrenalectomized dogs were slower, while that of acute adrenalectomized animals were slightly faster.

Adrenalectomy in open-chest vagotomized dogs resulted in significant decrease in the left ventricular systolic contractile force, diastolic myocardial tension, and heart rate (Cotten and Pincus, 1955). Inability of the adrenalectomized animal's heart to respond

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normally to changes in venous return or to increase the systemic arterial pressure was also reported by Hofmann and Sobel in 1964. In agreement with the previous reports, it was reported that adrenolectomy in dogs reduced the myocardial contractile force (Allan and Sutfin, 1964; and Webb et al., 1965). The same finding in cats was reported by Verrier and Lefer (1967). In addition, Allan and Sutfin 1964, showed that the heart rates of these animals were significantely decreased and that removal of adrenal glands or treatment with mepyrapone did not influence the amplitude of the QRS complex. In experiments on unanaesthetized adrenalectomized dogs, Harakal et al. (1968) showed that there was significant increase in heart rate and reduction in left ventricular pressure without impairment of the ability of the heart to increase these parameters in response to endogenous catecholamines released by tyramine injection.

Adrenalectomy in rats increased the total activity of monoamine oxidase (MAo) in rat hearts (Avakian and Callingham, 1968; Caesar et al., 1970; Corte and Callingham, 1977; and Dailey et al ., 1982).

Kaye et al (1964) showed no significant depletion of total myocordial cotecholamines stores in adrenalectomized dogs treated with desoxycorticosterone trimethy-

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lacetate. In agreement with this finding Avakian and Vogt (1966) reported that in adrenalectomized rats there is little or no change in endogenous content of cardiac noradrenaline stores. However, Harrison and Seaton (1966) reported that adrenal medullectomy in monkeys caused reduction in myocardial epinephrine but an increase in myocardial norepinephrine content.

More recently Hackel et al. (1980) showed in an experiment on dogs that had been previously treated by cardiac denervation and adrenalectomy decreased myocardial L-norepinephrine content.

Adrenalectomy in rats was associated with an increase in myocardial beta-adrenergic receptors, this increase occured after 6 hours. The administration of cortisol (80 mg/Kg/day) prevented the increase in beta-adrenergic receptors (Abrass and Scarpace, 1981). These workers concluded that this finding does not support the hypothesis that glucocorticoids enhance the tropic effect of catecholamines by an increase in beta-adrenergic receptors (Baxter and Forsham, 1972).

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The recent work of Phornchirasilp and Matangxasombat(1982) showed that adrenalectomy has no effect on basal cardiac cyclic AMP level but the cardiac response to isoprenaline was significantly reduced in rats maintained on drinking saline for one week. This could not be restored by acute administration of dexamethasone. This effect disappeared when the animals were maintained for two or four weeks.

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