CHAPTER II

BACKGROUND INFORMATION

Changes in renal function in hyperthyroidism

It is well known that in hyperthyroidism, an increase in cardiac output with little or no change in mean systolic arterial pressure, implies a general reduction in blood vessel resistance. Bradley (1978) has pointed out that the generalized vasodilation would have effect on renal hemodynamics. The changes of renal hemodynamics in both men and animals were consistent with an increase in intrarenal vasodilation. This might contribute to increase in glomerular filtration pressure and to the afferent arteriole was preponderantly affected. However, the mechanisms involved in local vasodilation are still not completely known.

Measurements of both maximal tubular reabsorptive-glucose Tm and secretory-PAH and Diodrast Tm-capacities have been reported to an increase in hyperthyroidism patients (Hlad and Bricker, 1954, Ford *et al*, 1961), dogs and men receiving thyroid hormone (Hare, *et al*, 1944, Ford *et al*, 1961). It has been suggested that maximal transfer rates may be increased initially by acceleration of the metabolic process of transport (Bradley, 1978). Thyroid-treated dogs appeared to excrete water via urine more quickly and rapidly (Pronina, 1971). Under normal circumstances, animals and men appear to regulate body electrolyte composition within normal limits

despite thyroid hyperactivity. Plasma sodium, potassium, calcium, and phosphorus levels are normal. (Bradley, 1978, Williams, 1981).

It has been reported that the urinary excretion of sodium is increased both in man (Resnick and Laragh, 1982) and dog (Pronina, 1971, Chaiyabutr, 1981). The urinary excretion of calcium and phosphorus are increased in hyperthyroid patients (Williams, 1981). In several studies showed that plasma renin activity increased in hyperthyroidism (Bouhnik, 1981, Resnick and Laragh, 1982) and also plasma angiotensinogen (Dzau and Herrman, 1982). Bradley (1978) concluded that the alteration of resting renal hemodynamic pattern should affect additional adjustments required by new stresses of various kinds.

Changes in renal functions in hypothyroidism

Ablation of the hypothyroidism in experimental animals has been followed in due course by altered renal cellular metabolism (Weil, 1941, Rapport, Canzanelli and Guild, 1946) and by a depression in glomerular filtration rate, renal blood flow and maximal rates of tubular transport (White, Heinbecker and Rolf, 1947, Bradley, 1978 and Chaiyabutr, 1981). This has suggested that the decrease in filtration appears to be attributable to intrarenal vasoconstriction rather than to tissue damage, but the vasoconstrict mechanism is not clear (Bradley, 1978).

It has been shown that removal of the thyroid in the full grown dogs causes reduction of maximal tubular excretion (Tm) of Diodrast to 65% of the control level. (White, Heinbecker and

Rolf, 1947). Similar changes are also found in man (Davies, Mackinnon and Platts, 1952). This has suggested that thyroid hormone exerts a primary effect upon tubular transport independently of its action upon renal hemodynamics.

The urine concentration remains within normal limit in patient with myxedema (Bloomer, Canary and Kyle, 1961). A delay in the excretion of water load has been noted by investigators (Crispell, Parson and Sprinkle, 1954, Bleifer *et al*, 1960). Plasma sodium, potassium, calcium and phosphorus levels are normal in hypothyroidism (Williams, 1981). The urinary-sodium loss was lower than the normal level in hypothyroid man (Resnick and Laragh, 1982) and dog (Chaiyabutr, 1981). The urinary excretion of calcium is decreased whereas urinary excretion of phosphorus are variable (Williams, 1981).

Earlier investigators found that plasma renin activity and plasma renin substrate decreased in thyroidectomized rat; and after T_3 - injection, the changes in the plasma renin-angiotensin system in the rats were corrected within 20-40 hours (Bouhnik, 1981).

Renal hemodynamic-saline diuresis

Renal hemodynamic is one of the most important sets of variables in the control of salt and water handling by the kidney Many studies have shown that renal vasodilation alone or together with increased perfusion pressure, decreases renal tubular sodium reabsorption during saline diuresis (Earley and Friedler, 1964, 1965). Martino and Earley (1968) found that in the vasodilated kidney, sodium

excretion rose despite a decrease in renal blood flow whereas both renal blood flow and sodium excretion decreased in the control kidney. Intrarenal venous pressure measurement was found to increase in the dilated kidney and it was either unchanged or fell in the contralateral control kidney. Several investigators have observed increases in urine flow under conditions of water diuresis following increases in perfusion pressure, suggesting an inhibitory effect proximal to the dilating segment (Daugharty *et al*, 1968, Aperia, Broberger and Soderlund, 1971). Many studies have also detected a limitation of free water clearance at high rates of urine flow, suggesting a further effect within the dilating segment (Daugharty *et al*, 1968, Bank *et al*, 1970).

Role of the renin angiotensin system in regulating renal hemodynamics

Angiotensin II is a potent renal vasoconstrictor (Itskovitz and McGiff, 1974). When exogenous angiotensin II is administered into the kidney there is an increase in both afferent and efferent arteriole resistance (Hall *et al*, 1979). It has been reported that an infusion of low doses of angiotensin into the circulation appears to be associated with sodium retention whereas high dose infusions tend to be associated with increases in sodium and water excretion (Barraclough, 1965, Cannon, Anus and Laragh, 1966, Barraclough, Jones and Marsden, 1967, Malvin and Vander, 1967). Under certain conditions (particularly in sodium retaining states), angiotensin II appears to be one of the regulators of renal vascular resistance, since the administration of the angiotensin II antagonist, saralasin is associated with an increase in renal blood flow

(Freeman, 1973). The study on the action of angiotensin by microperfusion techniques in proximal tubule in the rat has shown that low dose administration of angiotensin II in the peritubular perfusion fluid stimulated sodium reabsorption whereas inhibition of sodium reabsorption was seen at much higher doses (Harris and Young, 1977).

There is the evidence that angiotensin may have a direct effect on the glomerulus. Administration of angiotensin II has been shown to alter the dynamics of glomerular filtration (Myers, Deen and Brenner, 1975, Blantz Konner and Tucker, 1976). In addition to altering glomerular capillary pressure, angiotensin II has been shown to decrease the ultrafiltration coefficient of the glomerulus (Blantz, Konner and Tucker, 1976). Some studies have suggested that there are specific binding sites for angiotensin II in glomerulus and that these binding sites may be associated with the surface of mesengial cells (Sraer *et al*, 1974). The effect of angiotensin II on the glomerulus appears to be blocked by the administration of saralasin (Steiner, Tucker and Blantz, 1979). There was evidence that angiotensin II generated locally within the kidney can influence renal function under conditions of sodium and water restriction (Levens, Peach and Carey, 1981). Angiotensin may play an important role in regulating the rate of aldosterone secretion (Laragh, Angers and Lieberman, 1960). One of the most important factors in the control of aldosterone secretory rate is the level of activity of the renin-angiotensin system. In addition to angiotensin II, potassium and sodium concentrations all play important roles in regulating the rate of aldosterone secretion (Dufau, Crawford and Kliman, 1969, Boyd *et al*, 1973). Administration of angiotensin II into blood vessels

supplying the brain results in an increase in peripheral blood pressure (Bickerton and Buckley, 1961). An increase in blood pressure induced by angiotensin administered centrally has been reported in dog and rabbit, these central effects are mediated mainly by increased efferent sympathetic activity (Lowe and Scroop, 1969, Rosendorff *et al*, 1970). There is an interaction between angiotensin II and the sympathetic nervous system in facilitation of adrenergic neurotransmission (Cubbin and Page, 1963, Benelei, Della and Gandini, 1964).
So it appears that the facilitation of sympathetic neurotransmission by angiotensin II is due to an increase in norepinephrine in the synaptic cleft.