Chapter II

# Background Information

## Thyroid Hormone

It is well known that in the cardiovascular system the cardiac output tends to be proportional to the metabolic rate, being low in hypothyroidism and high in thyrotoxicosis. One of the most distinctive findings in hyperthyroidism is a moderate elevation in systolic blood pressure with little change in diastolic, or a marked increase in pulse pressure. This is often associated with vigorous, brisk and rapid contractions of the heart, which are in contrast with the weak heart beat of hypothyroidism. The arm-to-lung or arm-to-tongue circulation time is prolonged in hypothyroidism and shortened in hyperthyroidism.

There are two thyroid hormones with biologic activity in vivo. One of them, thyroxine ($T_4$), is produced only by thyroid gland. The other, 3.5,3'-triiodothyronine ($T_3$), is produced largely by deiodination of $T_4$ at extrathyroidal sites (Cavalieri and Rapoport, 1977 ; Schimmel and Utiger, 1977). Peripheral tissues, particularly kidney, contain a deiodinase enzyme complex that converts $T_4$ to the metabolically more active $T_3$ (Chiraseveenuprapund et al., 1978). Abnormality of thyroid hormone level was found in acute renal failure, total $T_4$ and total $T_3$ decreased while thyroid stimulating hormone was normal (Utiger, 1980 ; Kaptein, 1981 ;

Chopra, 1983). The same pattern was found in chronic renal failure (Finucane et al., 1977 ; Weissel et al., 1979 ; Kosowicz et al., 1980; Utiger, 1980). A significant inverse relationship between the serum concentration of total $T_4$ and total $T_3$ and the degree of renal failure was apparent (Joasoo et al., 1974 ; Finucane et al., 1977; Kaptein, 1981).

In hyperthyrcidism, a hyperdynamic circulation characterized by an elevation in cardiac output, tachycardia, diminished peripheral vascular resistance and a tendency to a rise in arterial pressure appears to be associated with an increase in renal blood flow. Measurement of para-aminohippuric acid (PAH) clearance in hyperthyroid patients have been found to yield results well above normal (Bradley, 1971). In both hyperthyroidism and hypothyroidism, glomerular filtration rate has usually been found to change, rising above normal in the former and falling in the latter (Corcoran, 1947 ; Ford et al., 1961; Bradley, 1971). Under normal circumstances, animals and men appear to regulate body electrolyte composition within normal limits despite thyroid abnormality as Bradley (1978), Williams (1981) and Chaiyabutr (1981) have shown the normal level of plasma sodium, potassium calcium and phosphorus in both hyperthyroidism and hypothyroidism.

The early reports have been shown that the urinary excretion of sodium and calcium were increased in hyperthyroid patients (Williams, 1981; Resnick and Laragh, 1982) and dogs (Pronina, 1971; Chaiyabutr, 1981), in the opposite, were decreased in hypothyroid patients (Williams, 1981) and dogs (Chaiyabutr, 1981).

It has been consistently reported that concentrations of angiotensin-converting enzyme are increased in patients with hyperthyroidism and the increment may be due to a direct effect at the cellular level (gow and Roulston, 1987). Earlier investigators found that plasma renin activity and plasma renin substrate decreased in thyroidectomized rats, and after $T_3$ injection, the change in the plasma renin-angiotensin system in the rat were corrected within 20-40 hours (Bouhnik, 1981).

Many papers has reported about the beneficial effect of thyroxine on recovery from toxic and ischemic acute renal failure. Potassium dicromate injected rats treated with thyroxine had significant better in inulin clearance, improved fractional excretion of sodium and increased urine osmolarity as compared to animals given only normal saline (Siegel et al.,1984). Thyroxine was protective also against gentamicin nephrotoxicity (Cronin and Newman, 1985). Gaudio et al.(1984) evaluated the efficacy of thyroxine in ischemic acute renal failure, rats were treated with thyroxine after 45 minutes of renal ischemia. The results showed that postischemic treatment with thyroxine accelerated the recovery of glomerular and tubular function.

Russell's Viper Venom

The Russell's viper venom were found to consist of a mixture of toxic factors, coagulation factors and a number of enzymes which contribute to the pathophysiologic actions including phospholipase $A_2$,

phosphodiesterase, adenosine triphosphatase, hyalurodinase, kininogenase, thrombinlike enzyme, factor X activator, factor IX activator, factor V activator and prothrombin activator (Lindquist et al.,1978 ; Morris et al., 1978 ; Iwanaga and Suzuki, 1979 ; Kisiel, 1979 ; Teng et al., 1984). Earlier studies had found that the coagulant action of the Russell's viper venom both in vitro and in vivo showed different results. An intravascular clotting had been noticed in some cases and complete failure of blood clotting had process in others (Lamb and Hanna, 1903). Intravascular coagulation and incoagulability both were manifestations of action of the venom which differed only in degree and rapidity. The rapid action of the venom produced massive clotting of the blood while slower action produced invisible coagulation and occurred with fine deposition of fibrin in the wall of the blood vessels. Finally blood was defibrinated and in consequence incoagulable (Taylor et al.,1935). General features of disseminated intravascular coagulation have been seen as a result of the strong coagulant effects of the venom (Aung-Khin, 1978). The prothrombin inhibitors, platelet aggregation inhibitors and an anticoagulant protein have also been purified from the venom (Teng et al.,1984). Interference in blood coagulation by the venom would aggravate bleeding, and acceleration of blood coagulation by the venom might cause intravascular coagulation or bleeding after consumption of the coagulation factors (Teng et al.,1984). The obstruction of glomerular capillaries by coagulated material was the most likely cause of reduction of blood supply to the renal tubules, this tubular ischemia resulted in tubular necrosis and subsequent renal failure (Chugh et al.,1975 ; Aung-Khin, 1978).

Intravascular hemolysis is observed in Russell's viper bite (Peiris et al.,1969 ; Chugh et al.,1975 ; Mahasandana et al.,1980), it can be evaluated by the degree of hemoglobinuria (Condrea,1979). The study by Sitprija et al.,(1985) showed hemoglobin casts in the lumen of distal convoluted tubules and collectng tubules of kidney. Phospholipase $A_2$ in the venom was responsible for hemolytic effect (Mckay et al.,1970 ; Russell and Puffer,1971 ; Tu,1969 ; Iwanaga and Suzuki,1979). Condrea (1979) showed that the major red cell phospholipids are phosphatidylcholine, springomyelin and phosphatidylethanolamine. All of these phospholipids are good substrates for phospholipase. In severe hemolysis, tubular obstruction by hemoglobin casts may cause renal failure (Peiris et al.,1969 ; Chugh et al.,1975).

The action of Russell's viper venom on the circulatory system has been reported by many investigators. Two phase of changes in cardiovascular system were observed in the experimental dog (Tungthanathanich,1983 ; Tongvongchai,1984 ; Chaiyasest,1986 ; Meeratana,1986 ; Kingkheawkanthong,1987). In the first phase, the venom produced a marked reduction in mean arterial blood pressure. In the second phase, mean arterial blood pressure recovered to control level. The pattern of changes in the first phase are similar to that of study in rats (Chaiyabutr et al.,1985). There is evidence obtained by Huang and Lee (1984) that most phospholipase $A_2$ subfractions of the venom had hypotensive effect in rats given 0.1 mg/kg BW intravenously. Huang (1984) suggested that phospholipase $A_2$ fractions in the venom released thromboxane $A_2$, prostacycline and histamine from the perfused guinea-pig lungs which might

cause vasodilation in the periphery, combined with pulmonary vasoconstriction, restriction blood return to the heart, leading to a decrease in cardiac output and induced hypotensive effects. The rise in mean arterial blood pressure following the transient decrease after envenomation and restored to normal level in the second phase has explained by the effect of vasopressive mediator such as renin-angiotensin system (Chaiyabutr,1985) and catecholamine (Chaiyabutr et al.,1984).

There was high incidence of acute renal failure following Russell's viper bite (Chugh et al.,1975 ; Sitprija et al.,1976 ; Shastry et al.,1977) and it was frequently cause of death. The study by Than et al.(1985) showed that the greater fraction of administered venom was taken up by the kidney. Many papers reported about the effects of Russell's viper venom on the renal functions but the mechanisms responsible for development of acute renal failure are still unclear. Pathophysiological studies of this venom on renal function in human is usually undertaken by observation patients in hospitals. In experimental dogs injected with the venom, there were marked reductions in renal blood flow and glomerular filtration rate while renal vascular resistance increased. There were marked alterations in general circulation ; decreased in blood pressure, heart rate and cardiac output while total peripheral resistance increased (Tungthanathanich,1983 ; Tongvongchai,1984 ; Chaiyabutr,1985 ; Meeratana,1986 ; Kingkheawkanthong,1987). The blood pressure gradually increased and approach the control level within 2 hours. However, renal blood flow, glomerular filtraton rate were decreased throughout the period of the experiment (Tungthanatanich et al.1986). They proposed to be due to local

vasoconstrictor released in the kidney which associated with an increased in renal vascular resistance. The renin-angiotensin system was proved to be responsible for renal vasoconstriction after envenomation since in rat studies, when the formation of angiotensin II was blocked by the converting enzyme inhibitor (MK-422, enalapril maleate), the result showed the increase in renal blood flow, glomerular filtration rate and urine flow (Chaiyabutr et al.,1985). The mechanism for renin release may be involved by acute plasma volume expansion (Roy et al.,1981).

Direct nephrotoxicity of Russell's viper venom was demonstrated by Ratcliffe and Pukrittayakamee (1985). They eliminated the systemic effects by isolated functioning rat kidney and perfused at constant pressure with a blood free recirculatory medium. After a baseline period Russell's viper venom was added to the perfusate, the venom produced a dose dependent fall in inulin clearance and rise in fractional exoretion of sodium. Varagunam and Panabokke (1970) postulated that the direct nephrotoxic effect is presumably due to the absorption of the venom from the site of the bite into the blood stream and a very high concentration being achieved in the kidneys because of their profuse blood supply.

It has been shown by Vick et al.(1967) that Russell's viper venom produced a pooling of blood in hepato-splanchnic bed in dog, following by a marked reduction of arterial blood pressure. However this conclusion may not apply to recent results, since in dogs either splenectomy (Tongvongchai,1984) or intravascular volume expansion with dextran solution (Chaiyasest,1986), a marked decrease in blood pressure and cardiac output

were still apparent after envenomation. Chaiyasest (1986) concluded that without splenic and intestinal blood circulation, there was no compensation of the hypotensive effect of the venom. The hypotensive effect after venom injection in volume expanded animals indicated that organ and/or venous vascular bed other than spleen or intestine circulation may play a role in pooling the blood volume shift (Chaiyasest,1986).

Meeratana (1986) studied the factors responsible for the hyperphosphaturia and mechanism of acute renal failure following Russell's viper envenomation. He concluded that the phosphaturic effect of the venom was independent on parathyroid hormone, hypocalcemia and extracellular volume expansion. The hyperphosphaturia was most likely mediated by an inhibition on sodium-inorganic phosphate cotransport system in the renal tubule. His data indicated that thyroparathyroidectomy alleviated the effect of Russell's viper venom on general circulation, renal hemodynamics and tubular function as compared to the intact animals.

The study by tongvongchai (1984) concluded that Russell's viper venom caused direct effect to produce hypotension due to decrease renal functions and the mechanism of the action appeared to be mediated by prostaglandin synthesis. Since the envenomated animals showed a decrease in renal hemodynamic and renal function while the animal pretreated with indomethacin, an inhibitor of prostaglandin synthesis, exhibited the improvement of the changes. The specific prostaglandin can not be indicated since indomethacin inhibits the conversion of arachidonic acid to prostaglandin at cyclooxygenase pathway. It is possible that

thromboxane $A_2$ may take part in alteration leading to the insults of renal function. The study by kingkheawkanthong (1987) showed that the intrarenal arterial continuous infusion of imidazole , an inhibitor of thromboxane synthesis, aggravated renal function of envenomated animals which correlated to an increase in renal vascular resistance. She suggested that imidazole may enhance effect of Russell's viper venom by interfering tubular cell function, effects of imidazole other than thromboxane synthetase inhibitor such as cyclooxygenase inhibitor and sympathomimetic activity may mask the beneficial effect of thromboxane synthesis blocker.