Chapter II

Background Information

Snakes possess a serious health hazard to the inhabitant of tropical and subtropical region of the world. The problem is not limited to that region alone. The world mortality from snake bites has been estimated at 30,000 to 40,000 annually (Chugh et al., 1975). In Thailand alone, the mortality rate from snake bites is about 0.9 per 100,000 population (Trisnananda, 1979). High mortality figures have also been reported from Burma, Cylon and India. Several kinds of snake venom have been reported. The snake of families Elapidae, Viperidae, Crotalidae and Hydrophidae are found in this region.

The elapid snakes are land snakes with relatively, short fixed, front fangs. These include Crobra, Kraits etc.

The viperid snakes are land snakes with long erectile fangs. The body is often short and relatively fat. The head is triangular in shape and there is a distinct neck. The viperid snakes are divided into two groups; the pit or Crotaline viper, which has a thermosensitive pit between the eyes and nostrils. Among others, the group includes, Malayan pit viper, Green pit viper and the pitless viper such as the Russell's viper.

The Hydrophidae consists of many species of sea snakes with small head, long thin body and prominent fattened tail.

Russell's viper is found in some areas. It is very common in Thailand. Russell's viper is generally quiet and peaceful by habit. It prowls about at night in search of prey which consists of mice, rats, frogs etc. It attacks man in self defense only when provoked. The snake venom is secreted from the salivary gland. It can be considered a mixture of physiologically and toxicologically active substances. In preliminary studies on Indian snake venom, the Russell's viper venom were found to contain the elements of C, H, N, S and O (Ganguly and Malkna, 1935). Iwanaga and Suzuki, (1979) recently found that the organic component of Russell's viper venom are lipid, carbohydrate, amino acid, nucleosides, nucleotides and organic phosphate compounds. Many enzymes including phosphodiesterase, ATPase, hyaluronidase are found in this venom. The Russell's viper venom consists of a mixture of toxic protein and necrotizing properties. A bleeding manifestation which occurred frequently following a bite was reported (Chugh et al., 1975). Early signs of systemic poisoning were blood stained spit, non-clotting blood and other hemorrhagic signs, bleeding from gums, ecchymosis and positive tourniquet test follow in 1-3 hours. Hematemesis, hemoptysis, hematuria and shock developed in severe cases with the bite of Russell's viper (Trisnananda,1979). These signs were also reported in experimental animals injected with Russell's viper venom (Tungthanathanich, 1983). It has been known for many years that the venom of Russell's viper has powerful coagulant properties. Morever it can be used as a substitute for tissue thromboplastin in the determination of the prothrombin time (Kleinman et al., 1945). Lee et al., (1955) demonstrated that the Formosan daboia (Russell's viper) venom had a potent coagulant action in vivo as well as in vitro and its

action resembles that of thromboplastin but not that of thrombin.

Many conflicting observations exist regarding the clinical features and correlations between local and systemic poisoning. Despite the frequency of a variety of medical complications after snake bite, including acute renal failure (ARF), however the pathogenesis of ARF is uncertain (Arthur at al., 1976).

Effects of Russell's viper venom on cardiovascular functions

The action of Russell's viper venom on the circulatory system was extensively studied by Chopra and Chowhan (1934). A small doses of venom was injected intravenously into the cat produced a slight initial rise in blood pressure followed by a gradual fall, When given a large dose the fall was more pronounced and blood pressure remained permanently at low level. Rapid administration of large dose of snake venom produced a sudden fall in blood pressure and the animal sometimes died suddenly from convulsion and heart failure. Lee (1944) proved that the sudden death produced by Russell's viper venom was due to intravascular clotting. Ahuja et al., (1946) has also reported that Russell's viper venom has a marked tendency to produce thrombosis and gangrene at the site of the bite and death is due to secondary shock. The systemic blood vessels especially the peripheral ones, are found to be contracted and those of the splanchnic area are widely dilated as in histamine shock. The nervous center is not much affected after envenomation. It has been shown that in decerebrated animals exactly the same results are produced (Lee, 1948). The symptoms of shock in daboia (Russell's viper) poisoning are not due to reflex impulses, but are due to the

local dilatation of the splanchnic area. There is enomous engorgement of the abdominal viscera and hyperemia of the splanchnic area. If the mesenteric arteries are clamped, large doses of the venom do not produce any marked effect in the blood pressure. The paralytic action of the venom seems to be confined to the capillaries only (Lee, 1948). In the perfusion experiment it was observed that the veins and arteries were not dilated, instead they showed a tendency to constrict. The paralytic action of the venom on the capillaries was observed to be similar to that of histamine, since the venom did not give any fall of blood pressure after large doses of histamine and vice versa (Ishwariah and David, 1932; Chopra and Chowhan, 1934). Drugs like ether and chloroform which depress the capillaries, potentiate the action of venom. Adrenalin and pituitrin, which tone up the capillaries while glucose, gelatin and gum - saline, which increase the total volume and the viscosity of the blood tend to increase the blood pressure. The hemorrhagic tendency and enomous leakage of plasma from the capillaries is further supported by the fact that the coagulation time the red cell count are also increased after large doses of the venom (Tungthanathanich, 1983).

Vick et al., (1967) concluded that Russell's viper venom produced an immediate and irreversible decline in arterial blood pressure. Pulse pressure narrowed and heart rate decreased as arterial pressure fell. Respiration was not affected during the initial postinjection period. But after approximately 10 minutes, respiratory movement ceased abruptly and profound bradycardia was noted. Evisceration prevented the initial hypotension and bradycardia. Vagotomy did not prevent

the sharp fall in arterial blood pressure. However, bradycardia was prevented and a significant increase in heart rate occurred.

Effects of Russell's viper venom on renal functions

The kidney is among the organs frequently affected in snake bites. It is well known that ARF is an important cause of death in patients who survived the early effects of a severe viper bite. (Aung-Khin, 1978). Many investigators believed that snake venom had a direct cytotoxic effect on renal tubular cells (Schreiner and Maher, 1965; Hadler and Brazil, 1966; Raab and Kaiser, 1966). Among the large organs of the body, the kidney receives the largest amount of blood per unit weight of tissue (Starling and Lavatt, 1962). It is probable that vascular necrosis, 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 kidney (Varaguman and Panabokke, 1970). Hypotension due to the cardiovascular effect of the Russell's viper can cause the sudden decrease in renal blood flow which may induce ischemic renal failure. However, renal failure has been noted in some cases of Russell's viper bite without hypotension (Sitprija and Boonpucknavig, 1979).

The pathological findings in the kidney following a snake bite was acute tubular necrosis, bilateral diffused cortical necrosis, proliferative glomerulonephritis, hemorrhagic glomerulonephritis and hemorrhagic interstitial nephritis (Oram et al., 1963; Sant and Purandare, 1972; Sitprija and Boonpucknavig, 1977). The pathogenesis of acute renal failure following a bite has been generally attributed to hemorrhage leading to circulatory failure, shock, collapse, acute

intravascular hemolysis and disseminated intravascular clotting (Oram et al., 1963; Reid, et al., 1863).

Sitprija and Boonpuchnavig (1974) reported necrotizing arteritis in patients bitten by the Russell's viper due to the deposition of β - 1 C globulin in the arterial wall. No immunoglobulins were noted in the lesion. Fibrin deposition was not seen. The vein showed necrosis of the wall and luminal occlusion by platelet thrombus. Arteritis was present at the level of interlobar and arcuate arteries. The arterioles and capillaries showed no changes. Deposition of complement in the arterial lesion without immunoglobulins suggested a non-immunologic activation of the complement system through an alternate pathway (Bruninga, 1971; Ruddy et al., 1971).

Sarangi et al., (1980) indicated that after Russell's viper bite the most common type of renal function impariment was a reduction in urinary output with an incidence of hematuria. Tungthanathanich (1983) recently studied the effects of Russell's viper venom on renal function in dogs. The decrease in renal function, such as renal plasma flow, renal blood flow, glomerular filtration rate and urine flow rate were observed after venom injection. There was a incomplete revival of renal function and renal vascular resistance was still higher than normal.

Acute renal failure in splenetomized animals

Whitaker et al., (1969) have shown in monkeys and rabbits that epinephrine infusion produced coagulation in the peritubular capillaries with consequent ischemia. Mandal et al., (1978) studied the changes in

renal morphology induced by epinephrine infusion between intact and splenectomized dogs. The splenectomized dogs had significantly less tubular and glomerular damage with renal congestion and no evidence of coagulopathy as compared to intact dogs. This suggested that the spleen might play a role in the pathogenesis of ARF. It was found that the intact animal had more severe ARF than splenectomized animal and also had a higher packed cell volume. The higher packed cell volume might be the significant factor responsible for the renal lesion. Bell et al., (1981) confirmed that an intravenous infustion of epinephrine caused acute tubular necrosis by approximately 75% of intact, but only 13% of splenectomized dogs. It is well known that spleen contains large amount of erythrocytes, leukocytes, plateletes and other clotting factors. Sympathetic stimulation causes intense splenic contraction and release of its contents. This effect causes to increase in packed cell volume, blood viscosity an 'blood coagulability. Epinephrine infusion in intact dogs was sustained depression of renal blood flow and urine flow. It has been suggested that the protective effects of splenectomy may involve by a reduction of blood coagulability or facilitaion of renal prostaglandin release (Bell et al., 1981). The experiment of Mandal (1982) supported the hypothesis that renal protection might mediated by an effective vasodilator prostaglandin attested by reversal of the renal protection after pretreatment with indomethacin in splenectomized animal.