CHAPTER II

Background Information

The Russell's viper and Its Venom

There are about 2000 species of snake in the world. They are divided, according to their poison, into 2 types: poisomous and non-poisonous snakes. The poisonous snakes have fangs at the front of their mouths which enable them to inject venom efficiently. The poisonous snakes are divided into 3 families: Colubridae, Elapidae and Viperidae; and only Elapidae and Viperidae are found in Thailand (Benyajati, B.E. 2517). The elapinae in Elapidae family have neurotoxic poison, and the hydrophiinae or seasnakes have myotoxic poison. Snakes in Viperidae family have haematotoxic effect. They have long erectile fangs, triangular heads, and usually short fat bodies. Vipers have 2 subdivision, first: crotalins or pit vipers, having a thermo-sensitive pit between eye and nose, which detects warm-blood prey in the dark; and second: viperine vipers, without pits. Among the viperine vipers, one of the most common and widely distributed species is the Vipera russellii or Russell's viper. It is found throughout the plains of India, Burma, Ceylon, Thailand, Sumatra and Java. The Russell's viper is generally of quiet and peaceful habits. It prowls about at night in search of prey which consists of mice, rats, frogs, etc. It attacks man for self-defence and

only when provoked. When ready to attack, it produces a loud hissing sound which can be heard from a distance of 20 to 25 feet.

The snake venom is secreted from the salivary glands which can be considered as a mixure of physiologically and toxicologically active substances. The preliminary studies was done on indian snake venoms (Ganguly and Malkana, 1936), and found that the Russell's viper venom contains the elements of C, H, N, S and O. Iwanaga and Suzuki (1979) recently found that the organic components of the Russell's viper venom are lipid, carbohydrate, amino acid, nucleosides, nucleotides and organic phosphate compounds. Many enzymes including phospho diesterase, ATPase, hyaluronidase also can be found in this venom.

Earlier studies by Lamb and Hanna in 1903 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 process in others. Tailor, Mollick and Ahuja (1935) subsequently found that intravascular coagulation and incoagulability of the blood 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 in vivo while slower action produced invisible coagulation, and occured with fine deposition of fibrin in the wall of the blood vessels. Finally blood was defibrinated and in consequence incoagulable.

It has been known for many years that the venom of Russell's viper has powerful coagulant properties. Several investigators have suggested that the venom could be used as a substitute for tissue thromboplastin in the determination of the prothrombin time (Lee et al., 1955; Macfarlane, 1967). This venom could convert autoprothrombin III (factor X) to autoprothrombin C (factor Xa) which occured rapidly (Esnouf and Williams, 1962), and also could be used for differentiation of bleeding from factor VII and from factor X deficiency (Quick, 1971).

The Cardiovascular Effects of the Russell's viper venom

The action of Russell's viper venom on the circulartory system was extensively studied by Chopra and Chowhan (1934). They found that the venom had a tendency to produce thrombosis and grangrene at the bitten site. The extensive phenomena appeared at the outset of the poisoning. The systemic blood vessels, especially the peripheral ones, was found to be contracted but those of the splanchnic areas were widely relaxed in the same way as shown in histamine shock. The symptoms of shock were due to local dilatation of capillaries of the splanchnic area because enormous engorgement of the abdominal viscera was presented. This could be proved by the fact that when they clamped mesenteric artery, quite large dose of the venom could not produce any marked effect in the blood pressure. They suggested that circulatory shock might not relate with reflex impulse and the nervous centers were not much affected, because the

similar results were produced in decerebrated animals.

The paralytic action of the venom on blood vessels was shown to be confined only in the capillaries in the perfusion experiment. The veins and arteries were not dilated, and showed a tendency to constrict. Capillaries paralysis following venom perfusion has been 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, will potentiate the action of the venom. Adrenaline and pituitrin which tone up the capillaries; glucose, gelatine and gum saline which increase total blood volume and blood viscosity; tend to revive the blood pressure after envenomation (Chopra and Chowhan, 1934).

The haemorrhagic tendency and enormous leakage of the plasma from the capillaries was supported respectively by the fact that the coagulation time was increased and the red cell count was also increased after envenomation in large doses. Death was preceded by spasmodic and irregular respiration, convulsion and asphyxia, indicated the involvement of the vagal center owing to deficient blood supply (Chopra and Chowhan, 1934).

Lee (1948) studied the circulatory action of the venom of Vipera russellii formosensis, a subspecies of Russell's viper, in rabbits. He found that the venom had coagulant

action and produced intravascular clotting. An immediate fall in mean arterial blood pressure and an increase in heart rate were observed. But injection of adrenaline, transfusion of normal saline, or artificial respiration faied to restore the blood pressure. Vagotomy and atropinization could not alter the venom action. In the animal pretreated with heparine (25 mg./kg.bw.) before injection a large dose of the venom, or in the animal injected a large dose of heated venom (80°C, 30 minutes), which the coagulant and most other enzyme activities were destroyed; no sudden death was observed. But the heated venom still produced a transient fall in the arterial blood pressure (Lee, 1944).

Vick et al. (1967) concluded that Russell's viper venom produced a pooling of blood in the hepato-splanchnic bed of the dog, followed by a decline of arterial blood pressure, a narrow pulse pressure and also a decrease in heart rate. Evisceration could prevent the initial hypotension and bradycardia. Vagotomy could not prevent the sharp fall in arterial blood pressure, whereas bradycardia was prevented and a significant increase in heart rate occured.

It has been believed that intravascular clotting due to the coagulant enzyme in the venom causes the acute sudden death (Lee, 1944; Ahuja et al., 1946). The thermostable vasculotoxin produced a sustained hypotension leading to delayed circulatory failure (Lee, 1944). It was believed that hypotension caused by the vasculotoxin was not central in origin, since it could be seen in both decerebrated and

despinated animals (Chopra and Chowhan, 1934; Chopra et al., 1935) or after elimination of the brain circulation (Lee, 1948). The initial arterial hypotension appeared to be due to peripheral vasodilatation, especially capillary dilatation in the splanchnic area. The volume of the intestine was markedly increased while the limb vessels remained unaffected or even contracted (Chopra and Chowhan, 1934; Chopra et al., 1935; Lee, 1948).

Acute Renal Failure Caused by the Russell's viper Venom

The clinical syndromes which associated with snake bite are variable. The kidney is one of the organs frequently involved in snake bite patients. It is well known that acute renal failure is an important cause of death in patients who survive from the early effects of the severe viper envenomation (Aung-Khin, 1978). There is not many case reports of the Russell's viper bite. Most of reports have presented only the clinical signs and symptoms of bleeding such as haematemesis, haematuria, etc., and oliguria or anuria. Some cases were noted a decrease in blood platelets and increase fibrinolytic activity, probably from intravascular coagulation (Sitprija et al., 1973). There are little direct morphological evidences attributing intravascular coagulation as a cause of renal damage in viper envenomation (Aung-Khin, 1978). No correlation is found between the severity of renal failure and haemostatic abnormality (Shastry et al., 1977).

Aung-Khin (1978) has studied histological and

ultrastructural changes of the kidney in patients, rabbits and rats. General features of disseminated intravascular coagulation, consumption coagulopathy and paradoxic haemorrhage have been seen as a result of the strong coagulant effects of the venom. The salient features in the kidney were intra-glomerular deposition of fibrin, fibrin degradation products and coagulation. The obstruction of glomerular capillaries by coagulated material was the most likely cause of reduction of blood supply to the renal tubules. This tubular ischaemia might be resulted in tubular necrosis and subsequent renal failure. And also, there are some reports about the close association between tubular necrosis and intravascular coagulation (Mckay and Margaretten, 1967; Clarkson et al., 1970).

Intravascular haemolysis has been observed in Russell's viper bite (Peiris et al., 1969). In severe haemolysis, tubular obstruction by haemoglobin casts may cause renal failure. Intravascular clotting can enhance intravascular haemolysis (Brain et al., 1957) and intravascular haemolysis can also cause intravascular clotting (Deykin, 1970). These changes can create a vicious cycle which enhance the cause of renal failure (Sitprija and Boonpucknavig, 1979).

Sitprija et al. (1974) reported necrotizing arteritis in patients bitten by the Russell's viper. There was deposition of β-1 C globulin in the arterial wall but no immunoglobulins were noted in the lesions. This finding suggested the nonimmunologic activation of the complement

system through the alternate pathways. The venom might activate this by its direct injurious effect to the artery. Arteritis cause narrowing of the arterial lumen, and can further accelerate intravascular coagulation. Both can cause a decrease in renal blood flow, and acute renal failure can be occured.

Many investigators believed that the snake venom had direct cytotoxic effect on renal tubular cells (Raab and Kaiser , 1966; Hadler and Brazil, 1966). Sitprija (1976) suggested that renal failure probably due to the direct nephrotoxicity of the Russell's viper venom. Varagunam and Panabokke (1970) also postulated that the direct nephrotoxic effect was presumbly due to absorption of the venom from the site of the bite into the blood stream and a very high concentration being achieved by the kidney because of their profuse blood supply.

Hypotension from cardiovascular effects of the Russell's viper venom can cause the sudden decrease in renal blood flow which may induce ischaemic renal failure. However, renal failure has been noted in some cases of Russell's viper bite without hypotension (Sitprija and Boonpucknavig, 1979).