Scorpion sting and its complications are quite common in South India especially during summer months. When children happen to be the victims, majority of them exhibit not only local symptoms of pain and irritation of short duration but also symptoms of peripheral failure within 15 minutes following the sting. At times they do have significant ECG changes suggestive of myocarditis. Rarely they develop seizures and hyperpyrexia. If these children are not treated adequately in an energetic manner they are likely to die of these complications. It is interesting to note that the type of complications following scorpion sting seen in Tamil Nadu, has not been reported elsewhere. Certain complications like consumptive coagulopathy reported in some districts of Andhra Pradesh (Devi et al., 1970) are not observed with the venom obtained from the species in Tamil Nadu. This strongly suggests that there must be differences in the virulence of the venom of scorpions of the same species in different regions. The most common genera of scorpions prevalent in Tamil Nadu and its neighbourhood are Buthus and Palamneus. In this part of the country,
stings of Buthus Tamulus species are generally met with. The present study was undertaken to find out the toxic manifestations of Buthus Tamulus and Palamneus gravimanus as seen in Tamil Nadu in various experimental animals like the dog, cat, rabbit, rat and frog and also to assess the effects of drugs to counteract the toxic effects of the venom on these animals. Fresh venom of Buthus Tamulus obtained by direct electrical stimulation of the telson was diluted with normal saline so as to produce a strength of 1 mg per 1 ml. This solution was stored at 4°C in a refrigerator and at this temperature, the potency of the toxin was maintained over a period of 6 to 9 months. Dried, lyophilised venom available elsewhere was not used in this particular study, since the venom was not obtained from the local species of Buthus Tamulus.

Acute toxic effects were studied in dogs, cats, rabbits and frogs. In dogs, the minimal lethal dose is 3.2 mg per kg body weight and the LD₅₀ for the venom of Buthus Tamulus works out to 2.65 mg per kg body weight (Reed Muench, 1938). The venom of Palamneus gravimanus is less toxic and the MLD is 4.8 mg per kg body weight and LD₅₀ works out to 3.9 mg per kg body weight. It appears
that the toxic symptoms related to Buthus species, are more severe than that of Palamnous gravimanus. The minimum lthal dosage of the venom obtained from very young scorpions was 12.9 mg per kg body weight. The venom obtained from the younger animals is less virulent and hence the toxic effects are not commonly met with. In cats, the minimum lthal dosage for Buthus Tamulus is 4.4 mg per kg body weight. In rabbits, the MLD is 3.3 mg per kg body weight. Obviously the toxin of Buthus Tamulus is more potent and the dog seems to be more sensitivo to this toxin when compared to other laboratory animals.

In dogs, doses ranging from 1 to 3.5 per kg body weight elicit symptoms like salivation, aversion for food, restlessness, increased respiratory distress and finally death due to respiratory failure. When doses ranging from 4 mg per kg body weight and above were administered intravenously, death of the animals occurred in 10-15 minutes, as a result of respiratory arrest.

In cats, similar effects were observed with doses ranging from 1 to 3 mg per kg body weight. A dose of 4.4 mg per kg body weight administered intravenously caused death in 10 minutes, due to respiratory failure. In the
case of rabbits when the venom was given intravenously in
doses of 3.3 mg per kg body weight through the marginal
ear vein it caused initially vasodilation of blood vessels,
warmth and tachycardia. After 15 minutes blanching of the
pinna, fall in body temperature, depressed activity and
flaccidity of limbs were observed. Respiratory failure and
death occurred in 30 minutes. Surviving animals do not exhibit
any other symptoms when observed over a period of 1 to 2 weeks.
Post mortem examination was done on all the dead animals.
The gross and histological appearances of various organs
were studied.

In the present study, changes in the heart rate and
blood pressure were the most important observations, soon
after injection of the venom of Buthus Tamulus in dogs and
cats. Cardiovascular changes are the most serious complications in experimental animals and human beings. The heart
rate varied with the dosage of venom. Though the heart
rate was unaffected with low dosages up to 100 \( \mu \)g per kg body
weight, there was mild to moderate tachycardia with doses
of 1 to 3 mg per kg body weight. With increasing doses,
there was a tendency towards bradycardia instead of tachy-
cardia. The response of the venom in isolated frog’s heart
experiments, suggests that changes in heart rate depend on the dose of the venom. Periodic addition of the venom in increasing doses into the cannula attached to the isolated frog's heart, exhibited initially an increase in force and amplitude of systolic contraction with an increased phase of relaxation followed by a gradual decrease in amplitude and irregular beat.

The present study reveals that the heart rate is greatly influenced by the dose of the venom and bradycardia is often related to larger doses of the venom. Cardiac arrhythmias may be attributed to several factors. Sinus tachycardia and ectopic beats are influenced by the activation of the beta adrenergic receptors in the heart and bradycardia may be due to the release of acetyl choline by the toxin. Activation of the sympathetic system by the toxin may also be responsible for the production of cardiac arrhythmias, since those are controlled with beta adrenergic blocking agents.

Hypotension is a major complication observed in this study with Buthus Tamulus whereas hypotension is the most common observation in many of the published reports so far. (Freire-Maia et al., 1974; Mosch Werth, 1970; Poonking, 1963)
Caius and Mashkar (1932) and Freire Maia et al., (1974) have reported both hypertension and hypotension in their study with the venom of different species. According to Caius and Mashkar (1932) the venom of different species, depending on the dose, exhibit remarkable discrepancies in the intensity of toxic effects. Larger doses of the venom of certain species of Buthus Tamulus, Buthus rugiscutis and Buthus alticola produce hypertension whereas the venom of Buthus australis and Buthus pachyrurus produce hypotension; Buthus pachyrurus produces hypertension only after a short interval. Hypotensive response is attributed to the release of free catecholamines from the adrenal glands and post ganglionic sympathetic nerve endings (Freire Maia et al., 1974). On the other hand, observation in children at Madras (Santhanakrishnan et al., 1972) showed only hypotension as one of the most frequent clinical signs following scorpion sting and these children did not exhibit any increase of catecholamine metabolites in the urine. The hypotensive response may be related to the degree of shock to which the animals are exposed following venom injection; sinoatrial and atrioventricular blockade might also contribute to hypotension (Freire-Maia et al., 1974). The possibility that the toxin can release a hypotensive substance in addition, cannot be ruled out.
Marked changes in the electrocardiogram are observed following the infusion of the venom of Buthus tamulus. After infusion of the venom in doses of 2 mg per kg body weight, serial electrocardiogram studies showed an increase in heart rate, depression of ST segment, depression of T wave leading to inversion, QTc prolongation, supraventricular premature beats and junctional rhythms. With a dose of 4 mg per kg body weight and above, sinus bradycardia and prolongation of PR interval were observed and there was marked reduction in the amplitude of QRS complex.

Elaborate electrocardiogram studies in experimental animals have been made by few authors. Froare-Maia et al., (1974) have studied the electrical activity of the heart, only in rats. They reported only changes like tachycardia, bradycardia, ventricular ectopic beats, incomplete or complete AV block and sinus arrhythmia. No previous detailed reports are available regarding changes in QRS complex and T wave, in animal experiments. Many reports of electrocardiographic changes following scorpion sting in human beings are available (Poonking, 1963; Patterson, 1966; Gueron et al., 1970 and Santhanakrishnan et al., 1970).
Poonking (1963) reported typical changes in electrocardiogram suggestive of myocarditis persisting for 3 to 6 days mostly in adults. Gueron et al., (1970) observed similar electrocardiogram changes associated with hypotension.

They attributed hypotension and myocarditis to the increased circulating catecholamines as a result of direct effect of the venom on the sympathetic system. In Tamil Nadu, Santhanakrishnan et al., (1975) have reported certain changes in the electrocardiogram in children. These children had only hypotension following scorpion sting and not hyper-tension. They also did not observe any increase in the circulating catecholamines in these patients.

Further supporting evidence for changes in the electrocardiogram was presented by Shaw et al., (1972); Kothari et al., (1976); Alagesan et al., (1977). Unusual electrocardiographic changes were observed in a few cases and they manifested in the form of curricular fibrillation paroxysmal tachycardia and complete right bundle block. Electrocardiographic changes observed in these subjects were transient and returned to normal within a week. Very rarely, the ECG changes persisted for more than three weeks (Jain et al., 1970). Experimental study on animals has confirmed that ECG
changes are transient and reversible. Some changes like the modification of T wave may occur as a result of electrolyte imbalance, particularly of potassium. Mohammed et al., (1954) in their study have shown some hyperkalemia in certain experimental animals following venom administration; but there was no significant change in potassium levels in the present study. Hence electrolyte imbalance might not be the cause for T-wave changes. Santhanan Krishnan et al., and Poonking in their respective studies have also observed no significant change in serum potassium levels which could contribute to ECG changes.

Enzyme estimations in the present study showed significant elevation of LDH, SGPT and SGOT enzymes following venom administration. ECG changes associated with enzyme elevation strongly suggest the possibility of a direct effect of the venom on the myocardium. Devi et al., (1970) have reported disturbance in the coagulation mechanism suggestive of consumptive coagulopathies and they concluded that cardiovascular changes are
due to consumptive coagulopathies. The present study as well as the observation of Santhanakrishnan et al., (1972) in children of Tamil Nadu, have failed to confirm any significant disturbance in coagulation mechanism, thereby ruling out consumptive coagulopathy as the cause for cardiovascular abnormalities and ECG changes. These findings strongly suggest that the toxic effects of the venom may vary with different species of scorpions the mode of action also may vary with the venom of different species.

Autopsy studies in experimental animals fail to confirm any significant hemorrhagic manifestations as reported by Reddy et al., (1972). They noticed in their necropsy studies on dogs and human beings, subendocardial haemorrhages, occlusion of capillaries in the heart with thrombi and haemorrhages. Thus, though many authors, Patterson (1960) Bose et al., (1966), Jain et al., (1970) and Freire-Maia et al., (1974) have reported electrocardiogram changes in adults and children the exact mechanism of these changes is not fully understood. The possible explanation from the present study, is that either the ionic exchange mechanisms
at the myocardial cellular membrane level is responsible for these ECG changes, or alternatively, the autonomic imbalance leading to arrhythmias might have caused the changes in the ECG.

Changes in respiration following the administration of the venom of Buthus Tamulus to mongrel dogs are manifested in the form of gasping or rapid breathing initially, leading to periodic breathing and apnoea after forcible expiration, depending on the dosage of the venom. Bilateral vagotomy did not modify the respiratory apnoea. Autopsy study of these dogs showed only mild congestion of the lungs in one animal and minimal subpleural haemorrhages with patchy areas of collapse and emphysema were observed on histopathological study. These findings are at variance with that of Reddy et al., (1972) and Devi et al., (1970). They have observed in their autopsy study on dogs, as already pointed out, massive haemorrhages in the lungs as well as other organs. Lima et al., (1975) reported pulmonary edema following the injection of Tityustoxin into the lateral ventricles of rats. In the present study pulmonary edema was a rare observation. Mundel (1961) has reviewed 78 cases of scorpion sting in Manga
taluk(Maharashtra) and observed that pulmonary edema sets within
2 to 10 hours, invariably leading to death. Gaitonde et al., (1978) reported that 50% of patients especially the young had pulmonary edema following red scorpion sting (Buthus Tamulus of Bombay) and many succumbed despite vigorous treatment. But pulmonary edema as such was rarely observed in adults and children of Tamil Nadu and Pondicherry (Santhanakrishnan et al., 1974; Singh et al., 1979) thereby confirming the present observation of species variability on the induction of toxic effect. When compared with cardiovascular complications, pulmonary manifestations are less significant in these cases and the possible explanation is that the effect of the venom on different organs is variable.

Del Pozo et al., (1945) observed, after administering crude venom of Tityus Serrulatus, to cats, respiratory paralysis in the inspiratory phase. Freire Maia et al., (1970) in their study on rats using purified toxin reported apnoea in the expiratory phase. It has been claimed that respiratory paralysis is due to central action (Megalhaes; 1938). Immediately after the administration of the venom, a gasping type of breathing and irregular rhythm were observed and this may be medullary in origin (Hoff and Breckenridge; 1952),
or may be due to the involvement of "higher" centres. However, the toxin can also produce arrhythmias by blocking peripheral neuromuscular transmission, Adam and Weiss (1959).

In the present study, the effect of scorpion venom on the skeletal muscle (gastrocnemius and hyoglossal) has revealed certain interesting findings. The venom increased the excitability and contractility initially as evidenced by the asynchronous twitchings of the muscle. In the muscle pretreated with venom, the time taken for fatigue (on repeated stimulation) was prolonged as compared with the control. Excitability to scorpion venom was not prevented in frog's gastrocnemius, when pretreated with d.Tubocurarine - a skeletal muscle relaxant. Patterson (1960) observed no significant direct effect of the venom obtained from C. Sculpturatus on the skeletal muscle. But in the present study it has been observed that the venom of Buthus Tamulus elicits a direct stimulant effect on the skeletal muscle. Patterson (1960) failed to elicit symptoms of envenomation with C. Sculpturatus species in curarised frog muscle preparation. Acute toxicity studies in frogs have revealed similar responses previously reported by Caius and Mashkar (1952). Electrical stimulation of the sciatic nerve did not
elicit any marked response either in the isolated or intact skeletal muscle preparation. The preparations when pretreated with venom of Buthus australis and Buthus europeus exhibited increased susceptibility to electrical stimuli when applied for more than an hour. Similar responses were elicited on the preparation pretreated with the venom of Buthus Tamulus.

The effect of venom on the plain muscle was studied in the isolated guinea pig or rat ileal preparation. When the tissue was exposed to the venom there was an increase in tone and amplitude on contraction which was dose dependent. Very large dose of the venom exhibited no response. These observations have been corroborated by Caius and Mashkar (1932). Since the preparation pretreated with atropine does not give any response to the venom of Buthus Tamulus it is presumed that the response is mediated through the parasympathetic (Cholinergic). On the other hand, Patterson (1960) observed that the normal peristaltic activity in the intact preparation (cats and rabbits) was inhibited by the venom of C. Sculpturatus. Perhaps, the difference in activity observed on the plain muscle may be due to change in the chemistry of the venom from different species of scorpions.
Animal studies have shown a significant rise in serum amylase levels after venom administration. Though naked eye appearance of pancreas was normal, histopathological study revealed focal haemorrhages. These findings were strongly suggestive of pancreatitis. Similar observations were made in human beings, both adults and children. Severe abdominal pain and tenderness were frequently observed in adults (Poon King T., 1963; Bartholomew, 1970) but not in children (Santhana-krishnan et al., 1974) and most of them had raised serum amylase levels.

Central nervous system involvement is rarely observed in experimental animals. In the present study, edema in both extracellular and intracellular spaces of the brain was observed in the sections. No haemorrhages were seen either in macroscopic or microscopic examination. Except for the findings
of Reddy et al., (1972) who described extensive hemorrhagic lesions in the human brain, no similar observation was made by other authors in their study (Mosch Gueron et al., 1970; Garcia et al., 1978).

Neurological manifestations following scorpion sting have been occasionally reported in literature. Occasional episodes of seizures or hemiplegia have been mentioned both in adults and children (Prasad et al., 1974; Lath et al., 1969). Cerebral edema may be the cause for seizures. Garcia et al., (1978) have reported that a neurogenic permeability factor is released by the sensory nerves when kept in contact with tityustoxin thus inducing an inflammatory reaction.

Treatment of insect bites and stings is always beset with problems. There is no specific antivenin available for poisonous stings except for the few like snake venom poisoning. An attempt was made in Cairo (1909) to prepare an effective serum for the treatment of scorpion venom complications but unfortunately the preparation was not potent enough to counteract the toxic effects of the venom.
In practice, large doses of the venom are required to immunise horses over a long period to obtain an effective and potent serum for treating the complications associated with scorpion sting (Jadhav; 1977) and hence the attempt for the production of a specific antivenin has been given up.

Since there is no specific antivenin available for management of these cases, efforts were mainly concentrated in the management of complications only. In the literature reported from the West, hypertension, congestive heart failure and toxic myocarditis have been observed as serious complications (Patterson, 1960; Mohammed, 1956; Gueron et al., 1970; Freire Maia et al., 1974). In Andhra Pradesh, consumptive coagulopathy has been observed as a serious complication following scorpion sting (Devi et al., 1970). In such cases, heparin has been recommended to reverse the clotting mechanism. In Tamil Nadu, complications associated with scorpion sting are mainly confined to hypotension, and toxic myocarditis. The same observations were observed in experiments conducted on laboratory animals. To combat shock and hypotension, various methods were adopted (Ross et al., 1956; Simbhi et al., 1962; Jay et al., 1965). Santhanakrishnan et al., (1972) and Naghelyi (1962) observed that the administration of
chlorpromazine along with certain drugs in the form of lytic cocktail was found to be effective in combating shock associated with different clinical conditions.

In the present study, the role of these drugs in modifying the hypotensive response was studied in dogs. Based on the reports that administration of adrenergic blocking agents reverse the hypotensive response in case of shock, chlorpromazine, an adrenergic blocking drug was infused into dogs in the form of lytic cocktail. The venom was given in doses ranging from 2.5 to 4 mg per kg body weight to produce a proportionate fall in blood pressure. The fall in blood pressure was dose-dependent as already observed. Concomitant with the fall in blood pressure, there was associated tachycardia with doses ranging from 1 to 3 mg per kg body weight and with larger doses of venom, there was an associated bradycardia.

The hypotensive effects were effectively reversed after the infusion of lytic cocktail. The heart rate also gradually returned to normal. On the other hand, lytic cocktail when infused into healthy anaesthetised dogs, produced a gradual fall in blood pressure, reduction in heart
rate, and fall in body temperature (Hypothermia). There seems to be paradoxical reversal of hypotensive response with lytic cocktail in animals pretreated with scorpion venom. This observation has been corroborated clinically in children by Santhanakrishnan et al., (1972). Thus, administration of chlorpromazine in the form of lytic cocktail seems to be beneficial for the reversal of shock like states following the sting of Buthus Tamulus species. This form of treatment has considerably reduced the mortality and morbidity in children (Santhanakrishnan et al., 1974).

Animals pretreated with reserpine or guanethidine are more resistant to the toxic effects of Buthus Tamulus. This is corroborated by the observations of Subbu (1971) that sympathetic blockade with guanethidine enables the animal to tolerate circulatory stress to a greater extent. Administration of Beta adrenergic blocking agents like propranolol was effective in blocking the arrhythmias especially persistent tachycardia induced by the scorpion venom in experimental animals. Likewise atropine was found to be useful in correcting bradycardia.
From this study, it could be definitely concluded that the beneficial effects of the administration of drugs like lytic cocktail and beta adrenergic blocking agents in cases of toxicity due to scorpion venom are primarily due to the adrenergic blockade caused by these compounds. Masco et al., (1970) studied the effect of hypnotic drugs like barbiturates chlorpromazine etc. in cases of scorpion sting. They observed improvement of clinical symptoms only with chlorpromazine and not with any other hypnotic agent. This report was confirmed in laboratory animal studies. The beneficial effect of chlorpromazine is mainly due to its adrenergic blocking action.

There are many reasons for selecting lytic cocktail therapy instead of chlorpromazine in the treatment of complication following scorpion sting. Sine quo non of the lytic cocktail drugs therapy is to achieve deconnection and thereby alter the course of lethal shock (Veghelyi, 1962). The deconnection effectively achieved by the lytic cocktail decreases the cerebral metabolism and this in turn has an oxygen sparing effect thereby decreasing the oxygen demand of the brain cells. A number of experiments have shown that
chlorpromazine is capable of exerting an improved dibenamine like effect with the additional advantages of depressing cerebral activity, a quality common to all compounds mitigating the force of shock (Hershey et al., 1955). The superiority of lytic cocktail over chlorpromazine alone or any other drug combination was investigated in some experimental animals and it was proved that lytic cocktail offers the best protection in shock like condition. Although primarily chlorpromazine exerts its major beneficial effects, side effects like tachycardia is a rare occurrence with lytic cocktail than with chlorpromazine alone. Further the cerebral blood flow is significantly decreased with lytic cocktail than with chlorpromazine alone, and thus the therapeutic effectiveness is further enhanced and the deconnection is effectively maintained.

The present experimental study provides ample evidence about the role of symptomatic treatment of the complications following scorpion sting. The drug combination in lytic cocktail provides an effective measure in arresting the hypotensive effects though individually each drug may have a paradoxical effect. Likewise, any abnormal rhythm can be
reversed by the judicious use of certain drugs after blood pressure is adequately maintained. Atropine helps in reversing the bradycardia and propranolol in counteracting any persistant tachycardia. These drugs may play a very vital role in the treatment of complication of scorpion sting in human beings as seen in Tamil Nadu.

The present experimental work amply justifies the therapeutic effectiveness of lytic cocktail in reversing the shock like syndrome in children following scorpion sting. Thus the treatment of complications associated with scorpion sting depends upon the species of the scorpion and the clinical manifestations.