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I. INTRODUCTION

Scorpion sting has been known to men since ancient times and its effects and remedies have been described in works on toxicology by Nikadros of Kolophon (275-130 B.C.) in verse! His treatises were preserved in manuscript form throughout the Greco-Roman and medieval periods when they were translated into Latin and in 1904 into German by Brenning, which was reported by Leak (1968).

Standard Text Books refer somewhat disparagingly to scorpion sting as "Painful and inconvenient but hardly dangerous" (Manson-Bahr, 1954), and yet deaths following scorpion sting occur in many parts of the world. In Mexico's Durango state alone, 1600 deaths have been reported in the past 36 years (mainly in children).

In Brazil, scorpion sting carries a 12% mortality and in small children the mortality reaches over 60% (Knight, 1960). The problem of scorpionism in Brazil has been extensively described by Campos (1924), Barros (1937), Magalhães and Guimarães (1940) and Magalhães (1946). The latter authority (1929) estimates the number of accidents by scorpions in Brazil as more than 6,000 annually with over 800 fatalities. In spite of the vast literature on clinical and experimental observations
in this field, the opinions of the various authors on the amount of venom which can be ejected by a scorpion and on the toxicity of this venom are rather discordant. The solution of this question, however, is of great importance for the exact appreciation of the neutralizing and therapeutic capacities of specific antivenins as well as of the value of unspecific measures for the treatment of scorpion stings.

II. HISTORY

The scorpion, by the terror which it inspires as well as the strangeness of its form, has struck the imagination of the people of the orient and of the Mediterranean since ancient times and has been mythicized in the legend of Mithras. When Mithras sacrificed the bull, the first being created whose blood was to fertilize the universes, a scorpion was sent by Ahriman, the Genie of Evil, to destroy the sources of life by attacking the testicles of the animal. Scorpions are prominent in monuments pertaining to the mysteries of Mithras, whose cult was prolonged until the second and the third centuries of our era, especially in North Africa. In ancient Egypt, also scorpions were frequently represented on monuments. They are mentioned in the Ebers Papyrus and in several passages in the book of the Dead. Numerous Incantations had the reputation of
protecting against the sting of the scorpion.

Many Greek and Latin classics mention scorpion. Aristotle wrote that their harmfulness was not the same in all lands, their sting was inoffensive in some lands, but always fatal in others (especially in Caria, South of Antolia). Most authors shared this opinion, and thought, Africa to be the country of origin of scorpion. Earlier references which are beyond the scope of this review can be found in the Encyclopedia of Pauly (1929).

The belief in fables, and ancient proverbs is still great in the primitive populations of North Africa. A study of these legends is found in a work of Pallary (1936). The first investigation of scorpions, free of popular beliefs, superstitions was performed by Francesco Redi (1668), considered one of the methods of Descartes. Redi studied the scorpions of Italy, which he declared not venomous, the scorpions of Egypt, and specially those of Tunisia, whose sting, he declared often lethal. The illustrations in Redi's work show that the Tunisian scorpions studied were Androctonus australis.

Until the beginning of our century, there have been very few investigations of poisoning by scorpions. De Mau Pertuis (1731) experimented on dogs and Chickens, Maccary (1810) tried the stings of Buthus iccitanus on himself, Bert (1865), & (1885),
Jousset de Bellesme (1872, 1874), Valentin (1876), and Joyeux-Laffuie (1882, 1883) also contributed to the literature.

III. BIOLOGY

(A) Morphology:
Scorpions range in length from 1/4 inch to as much as 8 inches. The main body of the scorpion is divided into trunk and tail. The trunk is subdivided into cephalothorax and pre-abdomen (Fig.1). The thorax has four segments, each with a pair of walking legs on the under surface. The abdomen has six segments tapering to a single sharp sting at the end of tail, with a small opening supplied by two relatively large venom glands. Such animals as 8 inches African scorpions have a very large sting and their venom is dangerous to humans. The loser scorpion of Sumatra is even larger but, as it lives in dense forest, it is not often encountered by man. There are as many as 650 species of scorpions in the world (Frazier, 1968).

(B) The Life of Scorpions:

(a) Prey: Scorpions prey by night. Their prey consists almost entirely of insects and spiders. They seize a victim with their large claws and tear it to pieces or crush it, extracting its body juices. If prey offers any resistance, the scorpion may then, and only then, use its sting by bringing its abdomen forward over the body and thrusting the poison-
Scorpion, labelled to show the main anatomical features.
bearing tip into its prey. The prey is then slowly eaten, an hour or more being spent, sometimes in consuming a single beetle. Scorpions can survive long periods without eating and it is said that they never drink, getting all the moisture they need from their food or from dew.

(b) Domicile: It is curious that only the desert or semidesert scorpions all over the world, in Mexico, Brazil, the Sahara regions, in Palestine, Yemen, South Africa, Syria, Libya and Arabia are the most dangerous to man, and are representatives of the same family, the Buthidae. It may be curious also that several representatives of this group share the "domiciliary habits." They are found in hill regions and valleys, under stones, rocks, logs, loose bark of trees and around human habitations in gardens, old lumber, boxes and bricks. They also live in old buildings, garages, cellars, wash houses, old chimneys no longer in use, and chiefly under houses. Scorpions also may be found in cement blocks, boards, sacks, porches, floors, eucalyptus trees, chicken houses and couches.

(c) Mating: Normally when the female is responsive, the male first grasps her with his claws and then manoeuvres to face her, gripping her claws with his own. Sometimes, when
the female is not submissive and tries to pull away, the male raises his sting almost straight above his claws and the female does the same. It happens very rarely and then only for a few seconds. Having grasped the female, the male drags or pushes her to a suitable place where he scrapes away the soil with his feet and deposits his spermatophore. Then, still holding her by her claws, he manoeuvres her over it, so she can take up the spermatophore with her cloaca. The two animals remain together for about 5 to 6 minutes before breaking away. Sexual behaviour of the scorpions has been described by Büchel (1955), and Zolessi (1956) in detail.

(d) Development: The young scorpions are born alive, one or two at a time, over a period of some weeks. The young may be called larvae, because their external and internal morphological constitution is not complete. After birth, the baby scorpions ride around on their mother's back. Only after their first moult do they leave the mother and become independent. Some scorpions are known to live for as long as 5 years. The scorpion leads a solitary life and does not like the company of his colleague. Sometimes it has been seen to devour its own partner after mating!
(e) The venom apparatus: The paired poison glands of scorpions are situated in the last segment of the post abdomen with two ducts which join just in front of the point of the sting. The sting faces upward when the tail is extended but downwards when the scorpion poises for attack or defence, the entire tail like abdomen being curved dorsally and forwards. The victim is struck quickly and repeatedly. The thrust being made forward over the scorpions' carapace. When a scorpion strikes, the muscles simultaneously squeeze the glands, so that the fluid is forced into the wound. This reflex also occurs when the point of the sting is not embedded in any victim, the liquid is then ejected may be shot over 2 feet in front of the animal.

(f) Sting: Most scorpion stings occur during summer months and in the months following the monsoon. Scorpion stings though decrease in frequency due to rapid urbanisation is still very common in the villages and hilly areas of India. Scorpion sting almost always occurs under accidental circumstances more often at night. In South India, particularly in Madras city, the peak incidence of scorpion sting is around April to June (Gajalakshmi, 1979). In Gujarat particularly in V.S. General Hospital, Ahmedabad, total 15 cases of scorpion
sting were admitted during July 1974 to October 1974.

(C) Classification:

Unlike snakes, all scorpions are venomous. The venom is injected by means of a stinger found at the tip of the telson, the terminal structure of the tail. Scorpions belong to the class Arachnida and Order scorpionida. The following is a brief classification of scorpions:

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buthidae</td>
<td>Buthus, Androctonus, Buthotus,</td>
</tr>
<tr>
<td></td>
<td>Parabuthus, Leiurus, Isometrus,</td>
</tr>
<tr>
<td></td>
<td>Centrurus, Centruroides, Hadrurus,</td>
</tr>
<tr>
<td></td>
<td>Tityus, Heterometrus.</td>
</tr>
<tr>
<td>Diplocentridae</td>
<td>Nebo</td>
</tr>
<tr>
<td>Scorpionnidae</td>
<td>Scorpio, Opisthopthalmus,</td>
</tr>
<tr>
<td></td>
<td>Palamnaeus, Pandinus.</td>
</tr>
<tr>
<td>Vejovidae</td>
<td>Vejovis</td>
</tr>
<tr>
<td>Chactidae</td>
<td>Euscorpius</td>
</tr>
<tr>
<td>Bothriuridae</td>
<td>-</td>
</tr>
</tbody>
</table>

The most common species of scorpions in the United States are centruroides gertschi and C. Sculpturatus (Stahnke 1966). Androctonus in Africa, Buthus in Asia, Leiurus in Middle East and Tityus in South America (Vachon 1966).
IV. EPIDEMIOLOGY:

In many areas of the world scorpion sting is a public health problem of some magnitude. Areas particularly affected are Africa, the Middle East, India, Mexico, the West Indies (Particularly Trinidad), Central America, South America (Particularly Brazil and Argentina) and South Western United States. In United States and Mexico it is estimated that more people are killed by scorpions than by snakes.

In a town in Brazil with a population of only 2,00,000 in 1954 alone, nearly 200 people needed emergency hospital treatment for scorpion stings. What was described as a 'Casual hunt' there, revealed nearly 15,000 scorpions in an area inhabited by only 13,000 people!

Five types of species are considered to be most dangerous. They are all belonging to the family of scorpions called Buthidae. Their sting can be fatal to man. These are: Centruroides of central America, Androctonus of Africa, Buthus in Asia, Leiurus of Middle East and Tityus of South America. Well documented accounts of serious scorpionism refer almost exclusively to North Africa, the Middle East, South Africa, Brazil, Trinidad, Mexico or to the state of Arizona in U.S.A. To a great extent this undoubtedly reflects the distribution of
dangerous Buthidae producing neurotoxic venom, although it would seem that in many regions the problem has yet to be properly appraised. In India, for example, reports on the effects of scorpion stings are to some extent conflicting and reliable data on the identity of species involved in accidents are lacking. Cains and Mahaskar (1932), while reporting a number of fatalities in children (attributed mainly to species of Buthidae), concluded that scorpions in the subcontinent were no more dangerous to human beings than bees or wasps. Basu (1939) reported that during the period 1928-1937, 19 scorpion sting cases were treated at the calcutta medical college hospital. Five cases (all children) were fatal. It appears that a scorpion involved in one accident may have been Buthus tamulus (Fabricius) but whether this species was responsible for one of the fatalities is not clear. More recently Mundle (1961), without noting the species involved, reported that out of 78 cases of scorpion sting seen over a period of 14 years in Bombay State, 23 were fatal and 9 of these fatalities were in adults. According to P.C.Sahu (1982) of Orissa, amongst 86 known species of scorpion in India, Buthidae family is common in South Orissa. Out of two locally available varieties, the small, white one is dangerous for the dreaded complications
and death encountered by its sting.

On the other hand, Roantree (1961), whilst noting that the annual numbers of scorpion sting cases treated in a hospital in Southern India were between 800 and 1000, reported no fatalities, and suggested that many of Mundle's fatal cases may have been due to snake bites.

The most widespread of the medically important scorpions of the Mediterranean region is Buthus occitanus. Other dangerous buthids, occurring in Israel-Jordan region are Androctonus crassicauda and Leiurus quinquestriatus. A crassicauda is common in the South eastern provinces of Turkey and its distribution extends eastwards to India and southwards through Syria, Israel and Jordan to Arabia. It is not found in Egypt. L. quinquestriatus, on the other hand, which has a venom 4 to 5 times more toxic to rats than A. Crassicauda, is widespread in the eastern part of North Africa and its distribution extends through Israel and Syria to eastern Turkey and through Sinai peninsula to the shores of Red sea. In an early account of L. quinquestriatus in Egypt, Wilson (1904) noted that it was common throughout the country but especially in upper Egypt. It was frequently found in houses and he considered that it was probably responsible for the numerous scorpion sting
fatalities. Amongst children in this region Todd (1909) observed that fatalities were particularly numerous in the town of Assouan, where, over the seven year period 1901-1907, the annual death rate due to scorpion sting was 0.64/1000 of the population. This represented 1.67% of the total death rate. More recently, Shulov (1939) and Efrati (1949) have reported fatalities due to this species amongst children in Israel.

Grasset, Schuafsma and Hodgson (1946) observed that in South Africa, scorpion stings, although painful and responsible in some cases for severe symptoms of intoxication, are seldom fatal, even among children whose symptoms are more severe. They reported that the few scorpion sting fatalities that occurred amongst children appeared to be due mainly to species of Parabuthus and noted that the toxic action of the venom of these scorpions was similar to that of B. occitanus and L. quinquestriatus in north Africa.

In Brazil, two species of the genus Tityus, T. serrulatus Lutz Mello and T. baheinsis are extremely dangerous and both have been responsible for fatalities in adults as well as in children. T. Serrulatus is commonly found in centres of population and frequently invades houses and outbuildings, while T. Bahiensis, which geographically is rather more widely
distributed is essentially a scorpion of fields and plantations.

Waterman (1938) reported that in Trinidad 698 scorpion sting cases were treated in one hospital in a cane-growing district during the five year period 1929-1933. Thirty three of these cases were fatal - a case mortality rate of 4.7% and, in a later paper (Waterman, 1939), it was implied that the species involved in these accidents was Tityus trinitatis pocock.

An annual scorpion sting fatality totalling well over one thousand has been reported from Mexico. Fatalities are more frequent in the one to four year old age group, and the principal offending species are centruroides noxius and C. suffus, Pocock, although in this region other species of centruroides, including C. limpidus karsch, are also considered to be dangerous.

From the public viewpoint, scorpions are regarded as the most important venomous insects and in some places, during certain months, scorpion sting has been listed as the most important cause of death.

Two very dangerous species, C. sculpturatus Ewing and C. gertschi stahnke, are found in United States although their
distribution is restricted to the southern half of Arizona and to small areas in neighbouring states. Stahnke (1963) reported that during the period 1929 to 1948 these scorpions were responsible for twice as many deaths in Arizona than all other venomous animals combined.

V. EXTRACTION:

The simplest method for obtaining scorpion venom is to kill the scorpions, cut up the telsa, crush it, make a maceration in physiological saline solution or in distilled water and purify the solution.

The second method to obtain directly the crude venom consists in a proper manual technique, described by Bücherl (1953).

Pure venoms can be obtained also with electric stimulus first described by Bücherl (1953), by provoking the contraction of the venom gland muscularis with a high frequency electric current about 5 V current obtained from a transformer or a battery, latter on the same method was redescribed by Lissitzky and Mirander in 1956. From 1951 to 1953 Bücherl collected the first 309 mg of dry Tityus serrulatus venom, obtained after 4,105 electric extractions of several hundred specimens and 697 mg of dry venom of Tityus bahiensis after
6,148 extractions from 1,112 individuals.

The first drops of venom are commonly limpid and transparent, the following being more and more opalescent and viscous. The fresh, natural venom has a pH from neutral to alkaline, while immature venom is acid to litmus. Both have a foamy whitish aspect, with astringent properties and without any taste on the tongue. The vacuum-dried venom is of whitish-grayish color, hydroscopic, and may be stored perfectly in a vacuum dessicator, over calcium chloride, at room temperature and in the dark or in a small vacuum glass, without apparent change of activity after 3 or 5 months.

The first electric extractions give a higher quantity of venom. After 10 or 15 extractions, repeated with the same individuals every 3 or 4 weeks, the venom quantities decrease until they reach about 0.03 to 0.04 mg per specimen. Several scorpions have much more venom than 0.62 or 0.39 mg. About 2 mg per specimen may be the maximum of venom that a Tityus scorpion can inject in a victim.

VI. CHEMISTRY:

(A) Toxic Principles:

(a) Stability: The stability of the neurotoxins of Androctonus australis toward denaturing agents such as temperature and variations in pH has already been noted.
(Rochat et al., 1967). After a solution of 1 or 2 mg of toxin in 1 ml of Tris acetate (pH 8.6), 8 M urea has been left standing for 5 hr at 20°, no loss of toxicity was observed, after 18 hr at 50° in the same solvent 18% of the initial toxicity was still present. This stability is primarily due to the low molecular weight of the toxins and their compact secondary structures. The toxicities of the venoms of centruroides sculpturatus and Leiurus quinquestriatus are moderately stable to heat treatment, suggesting that the toxic proteins are stable, low molecular weight polypeptides (Watt, 1964, Nitzan, 1970). Further evidence of the low molecular weight of the toxic fraction of scorpion venom is the dialyzability of the toxin (Kamon, 1965). The lethal toxins of the venoms of the scorpions Leiurus quinquestriatus (Nitzan et al., 1963, El-Asmar et al., 1972) and centruroides sculpturatus (Watt, 1964) are dialyzable.

(b) Isolation and Properties: Scorpion venoms, like snake venoms consist of a mixture of many pharmacologically active proteins. Some proteins are enzymes, and others are nonenzymatic. At least 16 bands can be observed in electrophoresis for the venom of pandinus exitialis (Ismail et al., 1974 a).
Ultracentrifugically homogeneous toxins of Buthus occitanus and Androctonus australis were isolated. The yield of the first toxin, which has an LD 50 level of 0,15 ug g⁻¹, is 7%. The other one has an LD50 of 0,05 ug g⁻¹ in mice (Miranda et al., 1964 a-c). Because of the high content of ionizable groups in the neurotoxins, they tend to make nonspecific associations with other proteins (Miranda et al., 1966 ). Both Buthus and Androctonus scorpions are found in North Africa. Several neurotoxins have also been purified from the venom of the South American scorpion Tityus serrulatus (Miranda et al., 1966 ). Rochat et al, (1967) initially isolated two neurotoxins and later another toxin was isolated (Miranda et al, 1970), from the venom of Androctonus australis. Buthus occitanus venom contains three neurotoxins, and Leiurus quinquestriatus venom has five (Miranda et al., 1970). The yields of the various toxins are as follows:

<table>
<thead>
<tr>
<th>Toxin</th>
<th>A.australis</th>
<th>B.occitanus</th>
<th>L.quinquestriatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>11.3</td>
<td>4.1</td>
<td>1.8</td>
</tr>
<tr>
<td>II</td>
<td>52.6</td>
<td>2.2</td>
<td>7.5</td>
</tr>
<tr>
<td>III</td>
<td>03.0</td>
<td>10.0</td>
<td>2.2</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>V</td>
<td></td>
<td></td>
<td>20.6</td>
</tr>
<tr>
<td>Total %</td>
<td>66.9</td>
<td>16.3</td>
<td>36.4</td>
</tr>
</tbody>
</table>
The total amino acid residues of scorpion toxins are in the range of 57 to 78 residues, but most of these toxins have 62 to 66. None of the toxins contains methionine residues.

Pure toxin obtained from Heterometrus scaber venom has a molecular weight of 15,000 and is a glycoprotein (Nair et al., 1975). It contains 1.74% glucosamine, 0.31% sialic acid, 3.25% fucose, and 0.45% of an unidentified neutral sugar. It does not show any enzyme activities, hemolytic activity, or inhibition of succinate dehydrogenase activity, but it produces hyperglycemia in sublethal dose. Zlotkin et al., (1972a) separated pure neurotoxins from the venom of the scorpion A. australis and found highly toxic to mammals. He showed that its toxicity was destroyed by trypsin digestion.

(c) Sequences: The complete amino acid sequences of toxin I and II of Androctonus australis venom (Rochat et al., 1970, 1972a,b) and toxins of centruroides sculpturatus venoms (Babin et al., 1974, 1975), partial sequences of the toxins of Buthus occitanus tunetanus and Leiurus quinquestriatus venoms (Rochat et al., 1972a,b) have been described in detail.

As mentioned earlier, the total number of amino acid residues in scorpion toxins is usually in the 62 to 66 range, which is similar to the values for neurotoxin type I of Elapidae.
and Hydrophiidae. All scorpion toxins contain four double bridges. The location of the disulfide bridges in scorpion toxins is quite different from that in snake toxins, and the two types of toxin they do not cross immunologically. The similarity between scorpion and snake toxins is not great. These structural differences also reflect the different modes of neurotoxic action of venoms of these two totally different animals.

(d) Structure-Toxicity Relationship: Toxicity was destroyed when the toxins from the venoms of Androctonus australis and Buthus occitanus were subjected to chymotryptic and tryptic digestion (Miranda et al., 1964b). This suggests that small fragments do not have biological activity.

Toxin I of A. australis has three tyrosines in positions 5, 8 and 14. Iodination of the toxin resulted in iodinated tyrosine at all positions. However, the tyrosine at position 8 contained 51% of the total iodine incorporated. As there was no change in toxicity it was concluded that Tyr-8 is not involved in the toxicity of the molecule (Rochat et al., 1972c).

(B) Enzymes:

The enzyme seems to be commonly present in venoms of scorpions (Mohamed et al., 1969). Phospholipase A₂ from the
venom of Heterometrus scaber (Kurup, 1966), acetylcholinesterase from Hadrurus arizonensis (Saunders and Johnson, 1970), Hyaluronidase from scorpionsaurus palmatus (Zlotkin et al., 1972a) and Heterometrus scaber (Nair et al., 1973) have been found.

Nair and Kurup, (1973b) have reported that phosphomonoesterase and 5-nucleotidase are present in the venom of Heterometrus scaber. However, Russell et al., (1968) reported that venom of Vejovis spinigerus does not contain phosphodiesterase, amylase or L-amino oxidase activity.

(C) Non-protein components:

Scorpion venoms consist primarily of protein but also contain nonprotein material that give strong interference in the Biuret test (Rosin, 1973). A number of free amino acids were detected in the venom of Buthus minax (El-Asmar et al., 1973a), and free tryptophan was found in the venom of Heterometrus scaber (Nair et al., 1973). Histamine, which is a hypotensive agent is present in the venom of palamæus gravimanus (Ismail et al., 1975a). 5-Hydroxytryptamine can be found in the venoms of Leiurus quinquestriatus (Adam and Weiss, 1956) and Heterometrus scaber (Nair et al., 1973).
VII TOXICOLOGY:

(A) Clinical Symptoms and Case Reports:

Clinical studies of over 1000 randomly selected persons indicate that envenomation by the scorpion centruroides margaritatus produces such symptoms as pain, local edema, and fever 1 to 20 hr after the sting (Marinkelle and Stahnke, 1965).

Human volunteers receiving Nebo hierichontictus venom injections in the arm reported local burning pain and the formation of a small papilla, surrounded by an edematous area developing around the site of injection (Rosin, 1969b).

Watt et al. (1974) summarized the responses in man to scorpion envenomation. The constitutional symptoms include severe local pain and swelling and occasional discoloration, sweating, pallor, restlessness, anxiety and confusion, salivation, nausea, abdominal cramps, chest pains, and headaches are also evident. There is sensation of choking, muscle weakness, and twitching. Initial tachycardia changes to bradycardia and initial hypertension to hypotension. There are respiratory distress and subsequent cyanosis. Death results from cardiovascular collapse and pulmonary edema. The time to death varies from less than 1 hr to several days.
The pathological findings reveal elevated urinary excretion of catecholamine and their metabolites. Serum potassium is elevated, and serum sodium is lowered. Congestion and hemorrhages are evident in various organs, along with pulmonary edema. The effect on the heart is focal myocardial necrosis, infiltration with monocytes and lymphocytes, and deposition of fat droplets.

In a clinical analysis of 698 cases of scorpion sting, admitted in Trinidad Hospital over a period of five years, from 1929 to 1933, Waterman (1938) found that the heart beat was generally slow but forceful and extrasystoles were frequent. Mundle (1961) gave a detailed report on 78 cases of scorpion sting observed over a period of 14 years in Manguan Taluka (Kolaba), Bombay. Twenty three patients including 9 adults died either following bradycardia (26/min), fall of body temperature, pulmonary edema and profuse perspiration. Roantree (1961) has reported that in Kolar Gold Field Hospital prior to 1952, nearly 800-1000 cases had scorpion sting per annum, but he did not come across a single fatal case.

Poon King (1963) studied 45 patients of scorpion bites, 39 had abnormal electrocardiographic tracings. Ectopic beats
were observed in 11 and electrical alterations in 6, incomplete right bundle branch block in 4 and an abnormal Q-wave in AVL in one case, inverted T-waves in several leads in 31, prolonged QT interval in 24 cases with biphasic T-wave. Shah et al (1972) have reported transient auricular fibrillation and paroxysmal supraventricular tachycardia in one patient each.

Purshowtham Rao et al (1969), have reported, from the records of Karnool Medical College Hospital, Madras, that each year nearly 40-50 children in lower age groups die due to scorpion stings. Jain et al (1970) corroborated myocardial injury with elevated enzymes and ECG changes in patients with scorpion sting. Bose et al (1966) observed ECG changes in one out of 11 cases of peripheral circulatory failure following scorpion sting.

The cases of hemiplegia (Lath, 1969, Solanki et al, 1981), gangrene of finger (Prasad et al., 1974), myocarditis (Yajanik, 1972, Ramachandra, 1981, Shah et al., 1972) and transient complete right bundle branch block (Alagesan, et al., 1977) following scorpion sting have been reported.

One thousand one hundred and seventy three patients stung by scorpions were admitted at the hospital Joao XXIII,
in Belo Horizonte, between January 1972 and December 1978 (an average of 168 cases per year). From the total number of patients, 323 were children, out of, 40 severe cases were treated at I.C.U. (Campos et al, 1979).

(B) Yield and Toxicity:

The amount of venom that can be obtained from a scorpion is very small, usually less than 1 mg per specimen. There is considerable variation in the toxicities of scorpion venoms, depending on the species of animal used as subjects, the route of injection, and the species of scorpion, as follows:

Table 1.

<table>
<thead>
<tr>
<th>Scorpion</th>
<th>LD50 (Ani)</th>
<th>Route</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androctonus australis</td>
<td>0.019</td>
<td>Mice</td>
<td>Rochat et al, 1967</td>
</tr>
<tr>
<td>- Toxin I</td>
<td>0.010</td>
<td>Mice</td>
<td>Rochat et al, 1967</td>
</tr>
<tr>
<td>A. mauretanicus mauretanicus</td>
<td>0.170</td>
<td>Mice</td>
<td>Chemolet et al, 1974b</td>
</tr>
<tr>
<td>Buthotus Judaicus</td>
<td>8.46</td>
<td>Mice</td>
<td>Nitzan &amp; Shulov, 1966</td>
</tr>
<tr>
<td>Buthus Occitanus</td>
<td>0.15</td>
<td>Mice</td>
<td>Miranda et al, 1964a</td>
</tr>
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<td></td>
<td>1-1.2</td>
<td>Mice</td>
<td>Nitzan &amp; Shulov, 1966</td>
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<td>Centruroides Sculpturatus</td>
<td>1.1-1.9</td>
<td>Mice</td>
<td>Johnson et al, 1966</td>
</tr>
<tr>
<td></td>
<td>1.46</td>
<td>Mice</td>
<td>Watt, 1964.</td>
</tr>
<tr>
<td>Species</td>
<td>Species</td>
<td>Route</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>1.12 Mice</td>
<td>Stahnke, 1963</td>
<td></td>
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<td>0.59 Rabbits</td>
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<td>1.00 Rats</td>
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<td>0.09 Rats i.m.</td>
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<td>0.33 Rats i.p.</td>
<td>Patterson, 1964</td>
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<td>2.36 Cats</td>
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<td></td>
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<td>2.62 Dogs</td>
<td>Stahnke, 1963</td>
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<td>168 Mice i.p.</td>
<td>Johnson et al, 1966</td>
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<td>Cheymol et al, 1974b</td>
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<td>H. Scaber</td>
<td>0.72 Rats i.v.</td>
<td>Nair et al, 1975</td>
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<td>Gotlieb, 1966</td>
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<td>Nitzan &amp; Shulov, 1966</td>
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<td>-Fraction 1</td>
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<td>El-Asmar et al, 1972</td>
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<td>-Fraction 3</td>
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<td>Pandinus exitialis</td>
<td>40 Mice i.p.</td>
<td>Ismail et al, 1974a</td>
<td></td>
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<td>0.3 Mice s.c.</td>
<td>Nitzan &amp; Shulov, 1966</td>
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<td>Scorpio maurus palmatus</td>
<td>11.1 Mice</td>
<td>Zlotkin et al, 1972a,b</td>
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<td>Tityus Serrulatus</td>
<td>0.66 Mice i.v.</td>
<td>Brazil et al, 1973</td>
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<tr>
<td>Vejovis Spinigerus</td>
<td>4.87 Mice i.v.</td>
<td>Russell et al, 1968</td>
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</table>
VIII  PHARMACOLOGY :

Scorpion venom affects many parts of the body. The distribution of Leiurus quinquestriatus venom in the rat was investigated by Ismail et al., (1974b), who found the highest radioactivity in the Kidneys and the lowest radioactivity in the brain. The high venom content in the kidneys suggests the rapid excretion rate of the venom. The venom does not appear to penetrate the blood-brain barrier, thus confirming an earlier findings (Osman et al., 1973). Relatively high radioactivity in the lungs and heart may be due to the fact that the primary sites for the action of the venom may be in these organs.

(a) Effect on Nerves :

Scorpion toxins block impulse transmission at presynaptic sites of both cholinergic and adrenergic nerves (Yarom, 1970). Purified toxins of Tityus serrulatus (Gomez and Dinitz, 1966) have been shown to cause both contraction and relaxation of isolated rat ileum. This can be the result of the release of both acetylcholine and catecholamines (Cunha Melo et al., 1970).

(a) Acetylcholine Release : Scorpion venoms release acetylcholine at the neuromuscular junction (Benoit & Mambrini, 1967), from postganglionic parasympathetic neurons (Diniz and -
Torres, 1968), from brain (Gomez et al., 1973) Tetrodotoxin antagonized the spasmogenic action of the scorpion toxin and completely inhibited the secretion of acetylcholine (Tazieff-Depierre and Andrillon, 1973).

When there is a continuous discharge of acetylcholine, normal nerve impulses can not be transmitted to the muscle. Heterometrus fulvipes venom produces a tetanizing effect in isolated frog gastrocnemius muscle. This hastens the onset of fatigue, and the effect is irreversible (Venkateswarlu and Babu, 1975).

The spasmogenic action of the venom on guinea pig ileum was observed only in the presence of Ca ion, which is indispensable to the secretion of acetylcholine (Tazieff-Depierre et al., 1973).

It has been demonstrated that d-tubocurarine antagonizes the effects of Androctomus australis venom on frog striated muscle (Tazieff-Depierre and Nachon-Rautureau, 1975).

Androctonus amoreuxi venom blocks the twitch activity in both phrenic nerve hemidiaphragm of the rat and in cat tibialis anterior preparation (Ismail et al., 1975a,b). This inhibitory activity can be prevented by the specific antivenin.
(b) **Catecholamine Release**: Catecholamine and its metabolites such as vanilmandelic acid can be detected in high content in the urine of patients severely stung by the scorpion *orthochirus* (Gueron and Weizmann, 1969).

Injection of *Tityus serulatus* venom and its purified toxin have been shown to deplete the catecholamine from rat adrenal gland (Henriques et al., 1968).

*Leiurus quinquestriatus* venom increased the serum catecholamine levels in normal and adrenalectomized rats (Moss et al., 1973), probably due to release from the adrenergic nerve endings.

(c) **Nerve Permeability**: Scorpion venoms not only depolarize the neuromuscular junction but also affect axons. When the venom of *Buthus tamulus* was applied externally to squid axon, it caused a gradual depolarization of the nerve membrane (Narahashi et al., 1972). When the venom was applied internally, however, it had no effect on the resting potential. Katz and Edwards (1972) studied the effect of *centruroides suillus* venom on the nerve of isolated frog sartorius nerve-muscle preparation. Single shocks applied to the nerve produced repetitive responses in both nerve and muscle.
Romey et al., (1975) observed that Androctonus australis Hector venom affects the closing of the Na\(^+\) channel and the opening of the K\(^+\) channel in the giant axons of crayfish and lobster nerves.

The venom of Tityus serrulatus and its toxin stimulated the release of acetylcholine independently of K\(^+\), but required both Na\(^+\) and Ca\(^{++}\).

(B) **Effect on Cardiovascular System**:

Scorpion venom possesses potent neurotoxic activity, and strong cardiovascular responses also cannot be over looked (Gueron et al., 1967, Patterson, 1960).

(a) **Pathology**: Yarom et al., (1970) examined the heart tissue of a 2 year old child who had died of a Buthus quinquestriatus sting. The postmortem examination indicated that there was myocardial degeneration. Increased calcium deposits have also been reported in the area of myofibrilar destruction in the heart of a dog envenomated with Leiurus quinquestriatus (Yarom and Braun (1971b).

The similarity of the histological change following scorpion venom injection to those produced by excessive noradrenaline and other adrenergic amines, especially isoproterenol, was striking (Rohayem, 1954, Gueron et al.,
The sympathomimetic nature of scorpion venom injury was further confirmed by the effect of pretreatment with adrenergic blocking agents.

Gueron and Yarom (1970) examined 34 patients with severe stings from the scorpion Buthus quinquestriatus and observed that the electrocardiograms of some victims showed myocardial infarction-like patterns. They also examined urinary catecholamine metabolites and found that vanilmandelic acid was elevated in 7 patients, and total free epinephrine and nor-epinephrine in 8. Nine of the patients died, and pathological lesions of the myocardium were observed in 7. It is clear therefore, that the venom's effects on the cardiovascular system are related to the level of circulating catecholamines produced by direct action on the sympathetic system.

(b) Physiology: Injections of Buthus tamulus venom into dogs produced dramatic changes in the electrocardiogram, indicating that the venom has a pronounced cardiac effect (Purshotham Rao et al., 1969).

The initial effect of Tityus serrulatus and T. bahiensis venoms is bradycardia, followed by an increase in the force and frequency of the heartbeat (Corrado et al., 1966, Diniz et al., 1966). Bradycardia is blocked by atropine and tachycardia
is blocked by dichloroisoproterenol and is absent in reserpine treated animals (Corrado et al., 1968).

It has also been demonstrated (Cheymol et al., 1974a) that toxins I and II of Androctonus australis release catecholamines from nerve endings, resulting in hypertension, peripheral vasoconstriction, lachrymation, salivation, breathing spasms. Subsequent ganglionic blockade produced a block of the vascular tone, leading to hypotension.

Androctonus mauretanicus venom also induces changes in the electrocardiogram, characterized as disorders of cardiac rhythm and conduction (Roch-Arveiller et al., 1974).

The cardiovascular effects of the venom of Pandinus exitialis appeared to be mediated through stimulation of the autonomic nervous system, particularly the sympathetic, with release of tissue catecholamines (Ismail et al., 1972).

Cheymol et al., (1974b) investigated the peripheral effects produced by the venoms of Heterometrus caesar and Androctonus mauretanicus. The marked hypertension induced by the two venoms occurred without latency and was followed by bradycardia. The mechanism of this cardiovascular action involved ganglion stimulation, followed by a ganglioplegic effect.
Centruroides sculpturatus venom produces different physiological responses, depending on the species of animals used. In dogs and cats, it produced hypertension, tachycardia, and delayed cardiac irregularities, whereas in rats the opposite responses, hypotension and bradycardia, occurred (Patterson, 1960).

(C) **Effect on Skeletal Muscle**:

Scorpion venoms have a direct effect on skeletal muscle. For instance, Leiurus quinquestriatus venom induces spontaneous twitches and tetanic contraction of skeletal muscle (Adam and Weiss, 1959, Adam et al., 1966). Parnas and Russell (1967) investigated the effects of venoms of five American scorpions on nerve and muscle, and concluded that they have excitatory, blocking and lytic actions.

Yarom and Meiri (1972) suggest that L. quinquestriatus venom acts directly on frog muscle membrane, altering the calcium flux.

Tityus serrulatus venom elicits spontaneous twitches, potentiates the maximum twitch and causes a delay in its relaxation (Brazil et al., 1973).

(D) **Respiratory Effect**:

Purified scorpion toxin (Tityus serrulatus) either
stimulates or paralyses the respiratory movements of rats (Freire-Maia, 1970). Azevedo et al. (1983) recorded several changes in the respiratory pattern, such as gasping, prolonged and labored expiration, ataxic rhythm and noisy inspiration with the mouth open.

The effect of scorpion venom on respiration and the resulting paralysis may be due to its action on the respiratory centers in the brain stem Balozet (1971).

(E) Metabolic Effect:

Scorpion venoms affect many enzyme activities in various tissues. The activities of succinate dehydrogenase, lactate dehydrogenase and acetylcholinesterase are inhibited to a greater extent in muscle homogenates than in nerve cord homogenates by the venom of Heterometrus fulvipes (Babu et al., 1971). A decrease in succinic dehydrogenase activity was observed in the kidneys, heart and liver of chronically treated mice.

The venom of Buthus minax causes hyperglycemia in rats. Liver glycogenolysis seems to be the major factor contributing to this rise in blood glucose (El-Asmar et al., 1973a).

Heterometrus scaber venom causes a considerable increase in the urinary excretion of vanilmandelic acid, indicating
that the hyperglycemia may be due to an increase in adre­
naline production caused by the venom (Nair and Kurup, 1973c ).

(F) Haematological Effects:

The scorpion venom has been shown to contain coagu­
ulins or agglutinins. These can on occasion, produce intra­
vascular coagulation and thrombosis and present as bleeding
 tendencies. There is sudden onset of haemorrhage from various
sites such as body orifices, venipuncture sites, skin and
mucosa. Venom of Palamneus gravimanus has both procoagulant
and anticoagulant properties (Hamilton et al., 1974).

Haemorrhage can be induced experimentally in different
tissues such as the lungs and heart (El-Asmar et al., 1972),
in the abdominal wall (Rosin, 1969a), in the heart (Yarom
and Braun, 1971b).

(G) Miscellaneous Effects:

Scorpion venoms have diverse actions. They increase
motility of the gastrointestinal tract, visceral hyperaemia,
and gastric hyperdistension (Mohamed, 1950, Patterson, 1960,
Stahnke, 1965a). Patterson (1960) observed that cats and
rabbits injected with venom of centruroides sculpturatus
developed distension of the stomach with gas, possibly due
to carbon dioxide, which progressively extended through the
pyloric sphincter into the small intestine.

The venom of Leiurus quinquestriatus produced a marked increase in the frequency and amplitude of contractions of the uterus. This is in good agreement with clinical observations on abortion induced by the venom (Osman et al., 1972).

Stahnke (1965a,b) reported that changes in the toxicity of centruroides sculpturatus venom occurred when the recipient rats were subjected to change in ambient temperature.

On rat uterus the venom of Pandinus exitialis produced a powerful contraction which was greatly attenuated by methysergide and completely blocked by meclofenamic acid, indicating that the contraction is mediated partly by the serotonin content of the venom and partly by the release of kinins, prostaglandins, and/or slow reacting substance (Ismail et al., 1974a).

IX. IMMUNOLOGY AND PREPARATION OF ANTISCORPION SERUM:

Usually, the closer the phylogenetic relationship of scorpions, the more similar are the immunological properties of their venoms. There are cross-immunological reactions between the antivenin of Hadrurus arizonensis and the venom of Vejovis flavis (Potter and Northey, 1962). There is however, no precipitation with the venoms of centruroides sculpturatus,
C. gertschi, Androctonus australis, Leiurus quinquestriatus, and Vejovis spinigerus. Leiurus quinquestriatus and C. gertschi antivenoms form five and two precipitation bands, respectively, with H. arizonensis venom.

Toxins I and II of Androctonus australis Hector differ immunologically from toxin I of Buthus occitanus tunetatus (Boquet et al., 1972). However, toxin I of A. australis Hector belongs to the same serology group as toxin V of Leiurus quinquestriatus.

The antivenin made for Buthus mibax neutralizes the lethal effect, as well as the hypertensive effect, in rats, but does not prevent the respiratory arrest (El-Asmar et al., 1973b).

Antiserum for a given scorpion venom is usually quite specific. For instance, antiserum for Buthus quinquestriatus shows good precipitation bands with its homologous venom, but weaker and fewer bands with heterologous venoms of B. occitanus and Androctonus aeneas, and no reaction with Pandinus spp. venom (Mohamed et al., 1975).

Scorpion toxins and Cobra toxins are not similar immunologically (Boquet et al., 1972). This is reasonable, as they are totally different toxins.
Antiscorpion serum was first produced in the old world by Todd in Cairo in 1909, but unfortunately the preparation was found not potent enough to counteract the toxic effects of the venom. Later it was produced in Johannesburg, Algiers (Sergent, 1936, 1938), Tunis (Renoux and Juminer, 1958), Ankara (Tulgat, 1960), and Bombay (Deoras, 1961).

In the Pasteur Institute in Algiers, horses were immunized by injection, twice weekly at first, then once a week, and finally twice a month with increasing quantities of a ground telson preparation from Androctonus australis. Scorpion is a poor antigen, and immunization required at least 8 months, and involves the use of from 400 to 500 telsons. Larger quantities provoke severe reactions, therefore more than 25 telsons were not used at a time. Not all horses produce serum of satisfactory titer. Immunization, moreover is never complete and certain physiological reactions to the venom were never suppressed.

El-Asmar et al.,(1973b) also prepared an antivenom for Buthus minax by hyperimmunizing rabbits.

Hassan (1942) used atropine and ergotoxin in the preparation of antiscorpion serum from horses.
In practice large doses of the venom are required to immunize horses over a long period to obtain an effective and potent serum to neutralize the toxic complications due to scorpion sting (Jadhav, 1977), and therefore the attempt for the preparation of a specific antiscorpion serum has been given up.

An antivenin has been prepared for the first time against the venom for a scorpion, common in West Bengal (Heterometrus bengalensis) by hyper immunization of rabbits having shown a high titre value (1 : 4096) by indirect haemaglutination test (Das Gupta and Lahiri, 1985).

X. TREATMENT :

(A) Specific :

Antiscorpion serum is rather specific treatment for neutralizing the poisoning effects of scorpion venom. Antivenins are produced in most area where scorpion stings are very common, these are only effective when administered early, within 1 to 2 hr of sting and in sufficient quantity approximately 60-80 ml I.M. even in infants. Eventhough complete immunization is not possible, and certain physiological reactions are never suppressed (Sergent, 1947).

The antivenin made for Buthus minax neutralizes the
lethal effect, as well as the hypertensive effect in rats but does not prevent the respiratory arrest (El-Asmar et al., 1973b).

The serum from Algiers affords no protection against venom of Tityus, and the antityus serum from Butantan has a little neutralizing power against A. australis venom (Bücherl and Balozet, 1960).

(B) Non-specific:

(a) Experimental Study: Hassan (1940, 1942) used ergotoxin, antitoxic serum and atropine to neutralize the action of scorpion venom (Buthus quinquestriatus) in dogs and rats. Hassan and Karami (1953) used Bellafoline and dihydroergotamine as antidotes in rats.

The beneficial effects of adrenergic blocking agents, upon the survival rate in shock in experimental animals as well as in clinical trial have been reported by Nikerson (1962).

Sita Devi et al., (1970) used heparine to prevent dissemination of intravascular coagulation in dogs.

Gajalakshmi et al., (1978) used lytic cocktail as an antidote to neutralize the effect of scorpion venom in cats and dogs.
(b) **Clinical Study**: The following general treatment has been described by Chaubal and Misra (1984).

The victim of scorpion sting should be taken to the physician immediately if the victim is under five years of age, has a heart ailment, has been stung on a number of widely distributed places.

The management depends upon the severity of envenomation, in mild cases no specific medical treatment is required. A cube of ice over the site of sting will reduce the pain. Analgesics like aspirin, paracetamol or A.P.C. can be used to relieve pain. Mild sedative is indicated, provided there is no respiratory depression. Morphine and meperidine should never be used as they synergize the effect of venom. Local xylocaine may also be used to relieve pain.

Hassan (1940) had reported successful treatment in the children and saved 3 out of 4 children with Femergin (ergotamine tartrate) and Antiserum.

The destruction of the venom in the vicinity of the sting by cauterization, the use of potassium permanganate, hypochlorites, ammonia, or phenol is useless.

Jadhav (1977) of Haffkins Institute, Bombay, India, has mentioned general treatment like application of tourniquet,
sucking out the poison and infusion of saline.

Ligature-cryotherapy treatment, at least as first-aid measure, is advocated by Stahnke (1956, 1966).

The injection of large volumes (200 to 500 ml) of a physiological saline solution is recommended (Sergent, 1943a), because the solution dilutes the venom transported by the blood and counterbalances sodium elimination. Glucose solution should not be employed as it increases hyperglycemia.

The use of chlorpromazine (i.v.) with phenobarbital to treat 4 yr old girl, having scorpion sting was reported (Masco, 1970).

Santhana Krishnan et al., (1972) have treated about 190 cases of scorpion sting in children having symptoms like peripheral failure and cardiovascular complications, with combination of promethazine, pethidine and chlorpromazine in the form of a drip, and 60 cases only with corticosteroids.

Yajnik et al., (1972) have treated one case of 14 yr old boy having myocarditis following scorpion sting (At M.P. Shah Medical College and Irvin Groups of Hospitals, Jamnagar) with analgesics, antihistaminics, local anaesthetics, steroids, antibiotics, A.T.S., Tetanus toxoid and vaso-pressor drugs.
Rajarajeswari et al., (1979) noted 68 cases of scorpion sting, in the paediatric age group. Twelve percent of children admitted with severe symptoms, died due to toxic myocarditis, congestive heart failure, pulmonary oedema and coma. They used lytic cocktail, digoxin and steroids to treat the patients.

Singh et al., (1979) have reported 20 cases of scorpion sting between the ages of 15 and 40 years. 5 of them had predominant cardiopulmonary symptoms and E.C.G. changes. They used hydrocortisone, digoxin, diuretics, analgesics and oxygen therapy to treat the patients.

A case of hemiplegia following scorpion sting was reported by Solanki et al., (1981). Mechanism of hemiplegia was explained by them to be an effect of peripheral circulatory failure or coagulin on cerebral blood vessels. The patient completely recovered with the treatment with nylidrin hydrochloride.