

PRELIMINARY REPORT ON THE MEDICAL IMPORTANCE OF *SICARIUS* (ARANEAE: SICARIIDAE) AND THE ACTION OF ITS VENOM

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ABSTRACT: Following a report of a person who suffered very serious tissue loss after being bitten by a spider which answered to the description of *Sicarius spatulatus* Pocock, I decided to investigate the matter. Specimens of *S. albospinosus* Purcell were used for envenomation experiments with rabbits in order to document the clinical signs and symptoms, histopathological, chemopathological and haematological consequences of the bite. In the laboratory the bite of *Sicarius* proved to be far worse than those of South African species of *Loxosceles* and the behaviour and distribution of these spiders is thus of relevance in terms of their epidemiological importance. Species of *Sicarius* occur in the less densely populated areas of South America and southern Africa. The restricted distribution in low human density areas means that human accidents are likely to be rare. The bite of *Sicarius* results in an intensely necrotic and haemorrhagic lesion locally and systemic symptoms attributable to disseminated intravascular coagulation.

INTRODUCTION

Spiders of the genera *Sicarius* and *Loxosceles* are closely related and share many morphological and behavioural similarities. Both are primitive six-eyed spiders with simple and similar male and female genitalia. Furthermore, species of both genera stridulate by the same unique mechanism (rub scrapers on the palpal femurs against stridulatory files on the outer surface of the chelicerae) and both spiders bury their egg sacs in sand (no other spiders do this). Accordingly, when a human accident was reported to me and involved considerable tissue destruction following a bite by a spider answering to the description of *S. spatulatus* Pocock and in an area where it is common, I decided to investigate the matter toxicologically.

To date, all the published accounts of *Sicarius* species have been of a taxonomic and behavioural nature. Of the 23 species currently

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accepted (Gerschman de Pikelin & Schiapelli, 1979) 15 were described between 1849 and 1900. It is clear that the genus needs revision, especially in South America where most of the species occur and where the published distributional records are out of date. Three works on the behaviour of South American species have been published (Levi, 1967; Levi & Levi, 1969 and Reiskind, 1965) but an extensive manual and computer search of the literature failed to reveal any clinical or toxicological studies on these spiders.

Zoogeographically, the disjunct distribution of *Sicarius* species in the arid parts of the widely separated Neotropical and Afrotropical regions is interesting (fig. 1). Clearly, ancestors of present day species were separated by continental drifting following the break-up of Gondwanaland in Cretaceous times. It is most unlikely that these primitive spiders could have been dispersed by any other means since the continental displacement. Spiderlings of sicarid species do not balloon as do many of the more advanced web-bound labidognath spiders such as *Latrodectus* species. Because of their xerophilous, rupicolous way of life, sicarids are extremely unlikely candidates for dispersal by the normal agencies such as accidental carriage with human trade goods and travel, with migratory animals or by rafting on driftwood, which are normally implicated in the intercontinental dispersal of invertebrates. Regarding the disjunct distribution of *Sicarius* in terms of continental displacement, there is one anomaly viz *S. utriformis* (Butler) recorded from the Galapagos Islands which are unrelated to continental drifting in that they are of relatively recent volcanic origin. To the best of my knowledge, *S. utriformis* is known only from the types described in Victorian times and it is possible that the record is inaccurate.

METHODS

The *in vivo* envenomation studies were conducted with the approval of the Witwatersrand University Animal Ethics Committee. Rabbits were given tetracycline antibiotics by subcutaneous injection 24 hours prior to envenomation and daily thereafter to reduce the chances of artefacts due to secondary infections. Hind quarters of adult Californian white rabbits were depilated by means of an electric shaver and a proprietary depilatory cream. Adult spiders were induced to bite at the centre of the depilated area by pressing the spider into contact with the rabbit's skin. As *Sicarius* bites with reluctance, the spiders normally had to be annoyed by pulling their pedipalps with fine forceps to induce biting. The clinical appearance of the skin was monitored and changes were photographed in colour and with Kodak High Speed Infrared Film using a Kodak Wratten Filter 87C over an electronic flash and a dark red filter over the camera lens. Infrared film was used to monitor extravasation in the upper and middermis. Blood samples for haematological and biochemical study were taken with a No. 23 (0.6mm) Butterfly disposable needle inserted into the median artery of the ear or by cardiac puncture with a No. 18 needle on a 50 cm³ syringe. Aliquots

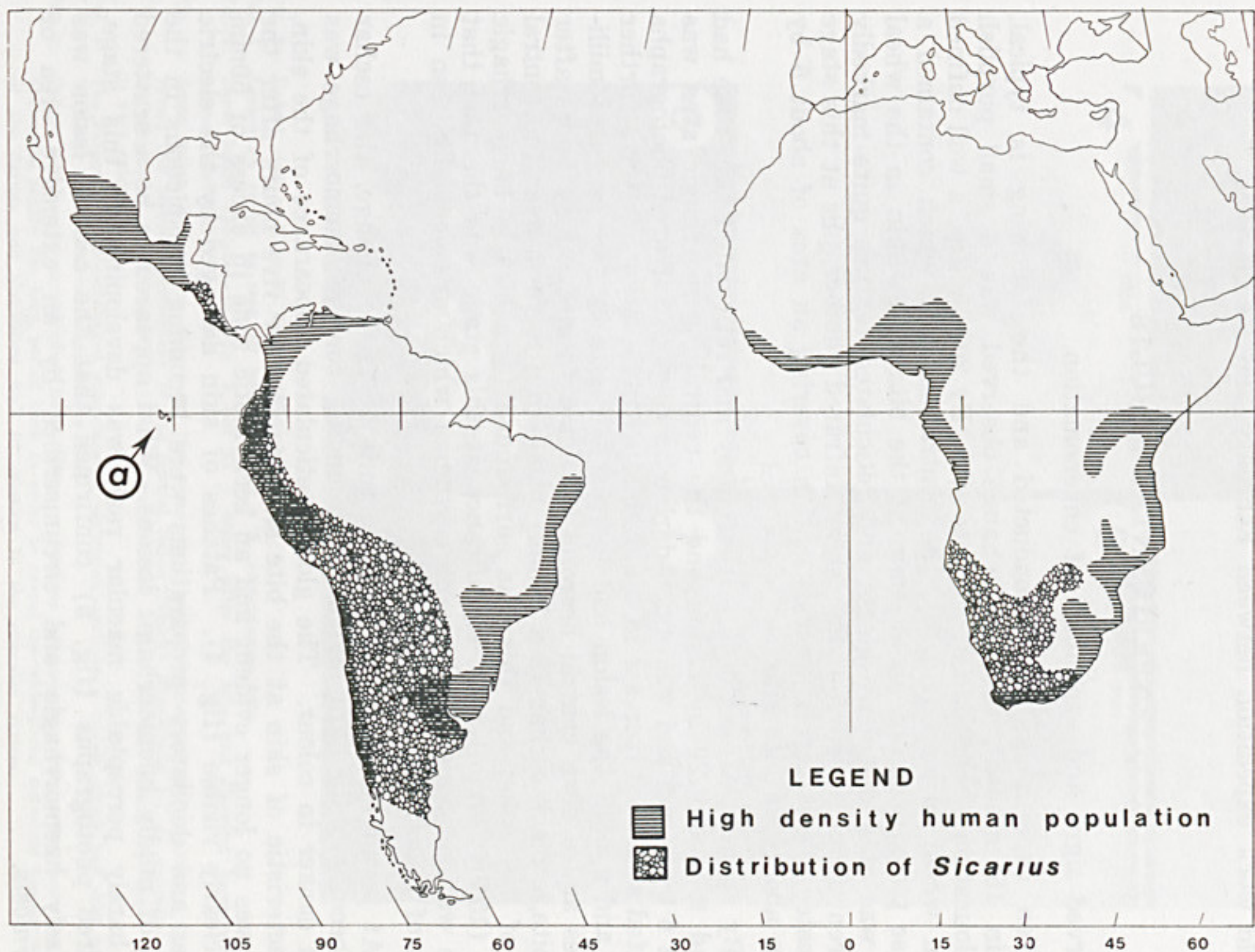


Fig. 1. Distribution of *Sicarius* species in relation to the high density human populations, viz more than 10 people per km². All areas where distributions overlap should be regarded as the most likely regions for human accidents with these spiders. The species *S. utirformis* (Butler) was described from the Galapagos Islands (a) in 1877.

for histological study were removed post-mortem in the usual way. The aliquots were machine processed and the sections were stained with haematoxylin and eosin. The majority of blood and serum samples were machine analysed as routine clinical specimens in the standard manner. A Beckman 1260 autoanalyser was used for the serum biochemistry screening. Venom was tested for proteolytic activity by the method of Rinderknecht *et al.* 1968 in which a hide powder azure was used as a chromogenic substrate.

Specimens of *S. albospinosus* for the study were collected beneath rocks in the Namib desert at Awasib, Tsondab vlei and Lüderitz during a field work expedition between February and March 1981.

EXPERIMENTAL RESULTS

Observed signs and symptoms of envenomation.

Ten experiments were conducted and the following is typical. Within 15 minutes, the first change observed was a small purplish discolouration of the skin at the bite site. By 20 minutes, a well defined 25mm wheal formed (fig. 3), the central area of which contained a diffuse purple zone of about 4mm at the bite site. Skin in the wheal area was of a distinctly glossy and reticulated texture quite markedly different from the surrounding area. Infrared photographs at this stage suggested slight dermal extravassation covering an area of about 5 by 11mm about the bite site.

By an hour after the bite, the glossy and reticulated skin zone had spread to about 20 by 30mm and the central haemorrhagic area was about 6 by 25mm and was much darker in colour. Infrared photographs depicted a marked increase in the dermal extravassation. After a further hour and a half, the lesion had increased in size by two or three millimetres and a dark central necrotic zone had formed. Five hours after the bite, a black eschar (8 x 15mm) had begun to form over the central area of the lesion and this was surrounded by a clearly haemorrhagic zone (15 by 20mm). Of significance at this stage was the fact that there was no evident oedema or erythema which are normally seen in cases of loxoscelism.

At seven hours, the clinical picture began to change, the eschar had become quite hard and the surrounding zone of haemorrhage was much darker in colour. The glossy reticulated appearance of the skin, characteristic of skin at the bite site for four or five hours after the bite, was no longer evident and an ecchymotic zone in excess of 50mm was clearly visible (fig. 4). Patches of skin damaged by the electric shaver and depilatory preparations were becoming conspicuous in the form of mildly haemorrhagic lesions. What appeared to be a scattered and barely perceptible macular rash was developing at this stage. Infrared photographs (fig. 5) confirmed that the central lesion was intensely haemorrhagic and circumscribed by an extensive area of ecchymosis.

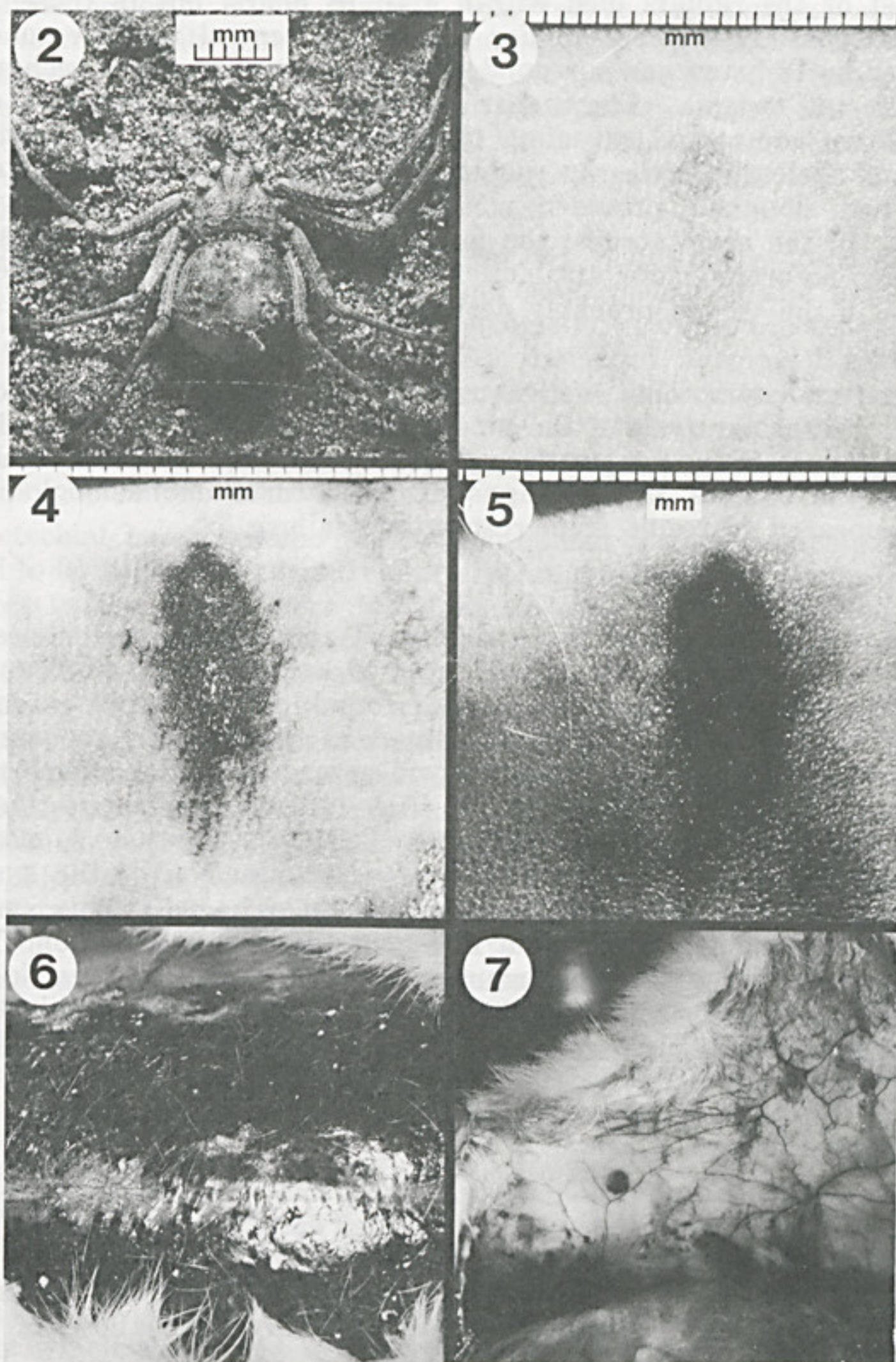


Fig. 2. Dorsal view of *Sicarius hahnii* (Karsch) 1878.

Fig. 3. Lesion on rabbit as seen 20 minutes after a *S. albospinosus* bite.

Fig. 4. Same lesion depicted in Fig. 3 but at 7 hours after the bite and showing haemorrhage, necrosis and eschar formation.

Fig. 5. Same lesion depicted in fig. 4 at the same time but photographed with infrared film to reveal the severe haemorrhage of the central lesion (black) surrounded by an extensive area of echymosis (dark grey area). The gravitational effect on the spread of the lesion is very evident.

Fig. 6. The extensively haemorrhaged subcutaneous abdominal wall of a rabbit which had died within 16 hours of a *Sicarius albospinosus* bite.

Fig. 7. Rabbit which was sacrificed 6 hours after a *Sicarius albospinosus* bite. Skin covering the abdominal region has been peeled back in order to reveal the widespread petechial haemorrhages of the dermis and abdominal wall in relation to the vascular system.

Most of the rabbits died within 4 to 16 hours, but in those which survived (possibly received milder bites), the central necrotic zone was depressed by 18 hours and surrounded by an extensive area of ecchymosis, erythema and oedema. The eschar sloughed in 9 days, leaving a crater up to 60mm across and revealing tremendous damage to the subdermal tissue and skeletal muscle. In rabbits, the lesion healed rapidly after the eschar had sloughed, provided no secondary infection was allowed to develop. In the early stages, the lesion was always found to be sterile, even when no prophylactic antibiotics had been administered. Proteolytic enzymes in the venom probably destroyed bacterial contaminants in the early stages.

Signs and symptoms seen in rabbits prior to death were those of collapse. Slight paralysis of the hind limbs, generalised cyanosis, shallow breathing and body temperatures as low as 34,7°C were measured. None of the rabbits showed signs of haematuria or haemoglobinuria. Death appeared to result from respiratory failure.

Post-mortem Findings

Autopsy examinations were conducted immediately after death in most cases. In two animals which had died a few hours before autopsy, the sub-dermal abdominal wall was found to be very extensively haemorrhaged (fig. 6). In all freshly dead rabbits, the abdomen and inside surface of the skin displayed widespread petechial haemorrhages associated with the vascular supply (fig. 7) which is suggestive of a disseminated intravascular coagulopathy (DIC). Further support for the diagnosis of DIC was forthcoming on examination of the systemic organs, many of which were petechially haemorrhaged. This systemic pathology was evident from about five hours after envenomation. Organs generally affected were the alimentary canal and mesenteries, kidneys, liver, spleen, lungs, heart and the subconjunctiva of the eye. During the autopsy, aliquots of systemic organs were taken for histological investigation.

Histological Findings

Skin punch biopsy aliquots removed from the lesion at the bite site three hours after envenomation, revealed early vasculitis accompanied by massive extravassations throughout the depth of the collagen layer. Very little inflammatory reaction and oedema could be detected at this early stage, a finding which contrasts markedly with those of South African loxosceline envenomation lesions.

By six hours after envenomation, the epidermis at the bite site had completely disappeared, probably due to a direct proteolytic effect of the venom. This lysed tissue overlaid a collagen layer which was intensely haemorrhaged and necrotic (fig. 8). Occasional polymorphonuclear leukocytes and eosinophils were seen throughout the dermis. The dissolution of the epidermis must have been the result of a proteolytic enzyme in the venom as this was too early after the bite to be an ischemic effect caused by the vasculitis. Studies conducted with hide-powder azure substrates confirmed that *Sicarius* venom has a strongly

proteolytic action. Other changes observed in the skin at six hours were, fibrin-thrombi clots partly occluding the lumens of blood vessels and necrosis of the muscle layers at the dermal-muscle interface (fig. 9). It must be stressed that as the skin and systemic organ aliquots were removed from the freshly dead rabbit, the fibrin-thrombi clots seen in most of the sections were not necessarily attributable to a diffuse intravascular coagulation syndrome.

Changes seen in the kidneys after six hours were focal areas of inflammatory cells in the medulla, congested glomeruli and evidence of necrosis (fig. 10). No evidence of haemoglobin casts in the renal tubules could be detected. Vorse et al (1972) described haemoglobin casts in renal tubules in a fatal case of loxoscelism with disseminated intravascular coagulopathy. This finding was in keeping with the fact that no evidence of haemoglobin could be detected in rabbits which died within 12 hours of envenomation.

Petechial haemorrhages seen on the small intestine during autopsy proved to be slight extravassation of erythrocytes into the lamina propria. Changes in the spleen were found to be very slight congestion and a slight inflammatory infiltrate into the red pulp region accompanied by areas of necrosis with pycnosis and karyorhexis of the nuclei. Likewise, changes in the adrenal glands were not marked; slight extravassation of erythrocytes into the periadrenal fat accompanied by congestion were the only detectable abnormalities. The heart displayed areas of subendocardial haemorrhage and mononuclear cell infiltrates between the striated muscle of the heart giving rise to foci of interstitial myocarditis (fig. 11). Eosinophilic micro-abscess formation, small areas of necrosis and fibrin thrombi in the portal vessels were the main histological findings in the liver (fig. 12). Lungs of all the rabbits exhibited marked changes such as pulmonary oedema, widespread inflammatory cell infiltrates and areas of eosinophilic micro-abscess formation (fig. 13). Changes seen in the other organs were either slight such as the perivascular cuffing seen in the brain or possible artefact related to some other cause such as one rabbit which had a well formed granuloma in the cerebellum.

Serum biochemistry and haematological findings

Generally, the serum biochemical and haematological findings concurred with the histopathological findings. Higher levels of the circulating enzymes alkaline phosphatase, alamine transaminase (ALT) and aspartate transaminase (AST) suggest massive hepatocellular damage which was noted in the histology at an early stage (Table 1). Increases in the creatine phosphokinase (CPK) normally suggest muscle trauma and myocardial infarction and it is possible that skeletal muscle damage at the bite site, and the histological changes seen in the heart muscle (possibly due to DIC) are causes for the high CPK levels detected in the serum within 8 hours of the bite (Hyde and Driasey, 1974). The precise cause of the higher level of serum glucose are not determinable at this stage as heart failure, malfunction of the kidneys, thyroid, liver and pancreas cause glucose increase. Of these organs changes were seen histologically in the heart, kidneys and liver which may explain the increased glucose levels at an early stage.

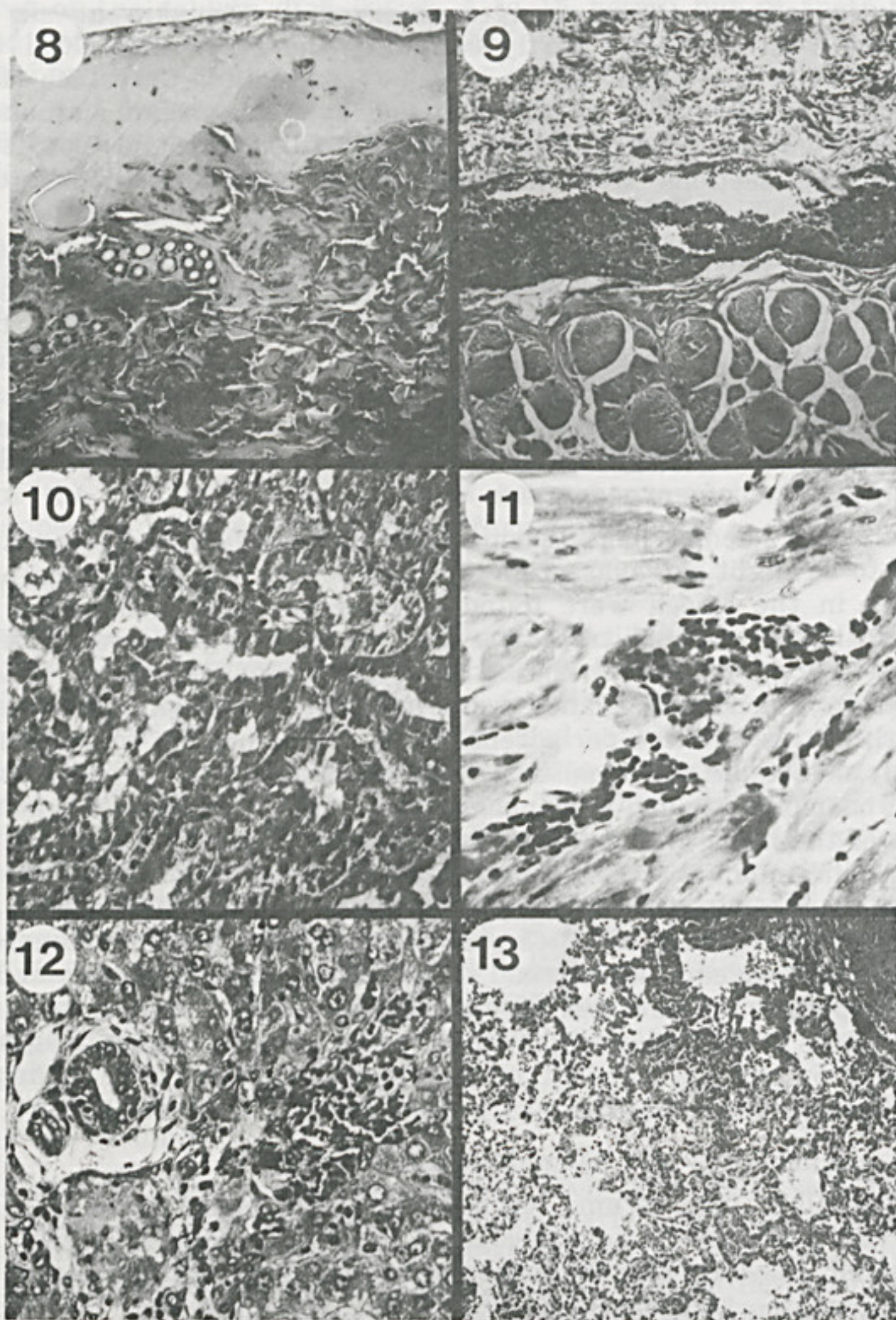


Fig. 8. Section of skin from the bite-site 6 hours after envenomation. The epidermis is completely lysed by this stage and overlies a collagen layer which is intensely haemorrhagic and necrotic. (H & E, 150 x).

Fig. 9. Evidence of vasculitis 6 hours after the bite. The vessel (cut longitudinally) is partly occluded by fibrin thrombi clots and inflammatory cells. The collagen above the vessel is haemorrhaged and slightly oedematous. The muscle beneath the vessel is necrotic with karyolysis of the nuclei (H & E, 160 x).

Fig. 10. Kidney showing necrosis at 6 hours after the bite but no evidence of haemoglobin casts. (H & E, 400 x).

Fig. 11. An infiltrate of mononuclear cells and slight extravasation in between the striated muscle fibres of the endocardium. (H & E, 400 x).

Fig. 12. Eosinophilic micro-abscess formation near portal vessels in the liver. (H& E, 400 x).

Fig. 13. Pulmonary oedema, eosinophilic micro-abscess formation and widespread inflammatory cell infiltrates are clearly visible in this section of the lung, 6 hours after the bite (H & E, 160 x).

TABLE 1

Serum biochemistry results following *Sicarius albospinosus* bite in rabbits. The results reflect the pre-bite values (viz. normal) at time 0 and the findings at 4 and 8 hours after envenomation.

Time (hours)	Glucose	Alkaline phosphatase	ALT	AST	CPK	Amylase
0	7,2	43	79	25	343	506
4	9,9	85	156	144	496	456
8	16,1	292	760	1360	2018	436

ALT = alanine transaminase
 AST = aspartate transaminase
 CPK = creatinine phosphokinase

Paralysis of the hind limbs was thought to be due to a possible neurotoxic component in *Sicarius* venom. Neurotoxins which stimulate the adrenal, autonomic and sympathetic nervous systems generally give rise to very high levels of circulating catecholamines. High levels of catecholamines can induce cardiac arrest as is the case in scorpion envenomation but in the experiments I conducted, I got the impression that the rabbits died of respiratory failure rather than cardiac arrest. Catecholamine levels in a rabbit challenged with the venom of *Sicarius* was found to be greatly reduced prior to its death within eight hours of envenomation. The possible neurotoxic properties of *Sicarius* venom shall soon be studied in detail.

Besides the serum biochemical changes, discovered, numerous clinical tests revealed little or no abnormality, viz total protein, albumin, calcium, cholesterol, uric acid and bilirubin.

The haematological changes seen clearly suggest a DIC in my opinion. The diagnosis of DIC is confirmed by thrombocytopenia, depletion of fibrinogen, the activity of the clotting factors, accumulations of fibrin and fibrinogen degradation products (FDP) and prolonged prothrombin (PT) and partial thromboplastin (PTT) times (Bradlow, 1981). Rabbits subjected to the bite of *S. albospinosus* fulfilled all these requirements except increased levels of FDP (Table 2). The reason for this is not clear for in a single experiment conducted with the bite of *S. hahni*, the FDP levels in the blood rose dramatically within 6 hours of envenomation. This could be due to species specific differences in the action of the venom. An interesting feature of *Sicarius* envenomation was that clotting factor VIII is affected and drops to 16% of its activity within seven hours of the bite. When the activity of factor VIII drops below about 30%, systemic haemorrhaging is possible and this may account for the petechial haemorrhage seen in many of the visceral organs. Bradlow (1981) points out that factor VIII deactivation is rarely seen in DIC cases. Accordingly, the deactivation of factor VIII may be a unique feature of *Sicarius* envenomation. In my opinion the

DIC seen in the rabbits was a direct result of the effect on the clotting factor and not due to some secondary cause such as vasculitis or skeletal muscle damage.

TABLE 2

Clotting study on the blood of rabbits subjected to the bite of *Sicarius albospinosus*. Pre-bite values (viz. normal) are given at times 0 and the effect of the venom on the coagulation potential of the blood was assessed at various intervals after envenomation.

Time (hours)	PT (sec)	PTT (sec)	Fibrinogen (mg/dl)	FDP ($\mu\text{g}/\text{cm}^3$)	Factor VIII (% coagulent activity)
0	12,0	24,6	219	<10	100
1	—	—	199	10-40	75
2,5	—	—	210	<10	70
5	—	—	251	<10	38
6	—	—	139	<10	20
7,5	29,5	55,5	160	10-40	16

PT = prothrombin time
PTT = partial thromboplastin time
FDP = Fibrin degradation products

EPIDEMIOLOGICAL CONSIDERATIONS

Factors to be considered when assessing the medical importance of a highly venomous spider are those behavioural and distributional characteristics which regulate its potential contact with humans. The laboratory study of *Sicarius* envenomation in rabbits certainly suggests that *S. albospinosus* is one of the most dangerously venomous spiders in the world. The reasons for the low human accident levels with spiders of this genus in the past are of importance. In South Africa, I am aware of only two cases of spider envenomation which may have been caused by the bite of *S. spatulatus* (the smallest species in the genus) in the South eastern Cape. All southern African species of the genus except *S. spatulatus* occur in the sandy and extremely arid regions which are virtually uninhabited by humans (fig. 1). The microhabitat of these spiders further reduces the chances of human contact in that these spiders frequently bury themselves in the sand (as described by Reiskind 1965) beneath large rocks. Another habitat is beneath rocks in the twilight zone of caves or rock shelters. The spiders have a positive geotaxis and are never attached to the underside of their rock cover which greatly reduces the chances of accidents when field workers lift rocks. The spiders are very difficult to see when exposed because of their cryptic colouration and self burying behaviour and are thus unlikely to fall into the hands of most specimen collectors.

Besides the habitat choice, there are several unique behavioural attributes of *Sicarius* which greatly reduce their chances of human contact. In the laboratory, specimens of *Sicarius* would rarely leave their shelter and rather than go out in search of food (as in the case of most spiders including *Loxosceles* species) these spiders would wait for the chance encounter of possible prey items wandering beneath their cover. The spiders bury themselves in the sand and then go into a state of diapause and often months go by before they move. Specimens kept in my laboratory refused food offered more frequently than every two or three months and happily survived up to a year without feeding. Nothing is known of their mating frequency in nature and whether males go in search of females or visa versa. I have only once seen specimens of *Sicarius* walking about in the field and this may have been caused by my disturbing their habitat while collecting arachnids in the vicinity. These spiders live a very long time. An adult female *S. albospinosus* I collected at Tsondab Vlei in the Namib during June 1970 died in October 1980 after it had been handled roughly in envenomation experiments. Another idiosyncrasy which reduces the medical importance of *Sicarius* species is the fact that they appear to bite with great reluctance. In all the laboratory tests, the spiders had to be pressed firmly into contact with the rabbit and in most cases, had to be provoked by pulling their pedipalps with fine forceps before they would bite.

On the negative side, because *Sicarius* specimens are normally in a state of diapause, they do not move when disturbed and could easily be mistaken for dead specimens. Anyone handling such a specimen could be bitten when the spider 'awakes'. Furthermore, one species, *S. spatulatus* occurs in the relatively densely populated areas of the south eastern Cape Province in South Africa and this species has possibly been involved in two human accidents in the East London area. In these cases, the spider was not identified but the description provided by one of the victims fit that of *S. spatulatus*. In this particular case the victim lost an arm because of the extensive tissue necrosis. Other areas where *Sicarius* species occur and which have relatively high human population densities are indicated in figure 1. Most of these high risk areas are in Central and South America, viz. El Salvador, Costa Rica, Colombia, Ecuador, Peru, Brazil and Argentina.

CONCLUSION

Laboratory studies have demonstrated that at least two South African species of *Sicarius* are dangerously venomous. Fortunately, the behaviour and ecological background of these species is such that the chances of human accidents in South Africa are slight. However, with the increasing human activities in the deserts of southern Africa, the chances of human involvement with these spiders increases yearly. While species specific toxicological differences were detected in some of the experiments, all species of the genus in southern Africa and the Americas should be regarded as dangerous until proved harmless. There are several areas in South and Central America where species of *Sicarius* occur in relatively

densely populated areas. In South Africa, the high risk areas are Cape Town and the Port Elizabeth-East London areas, where a small species, *S. spatulatus* occurs.

In South America bites of the spider *Loxosceles laeta* are frequently accompanied by serious systemic symptoms (Schenone, 1978), and it is possible that some of these cases diagnosed on signs and symptoms alone, could be confused with cases of *Sicarius* envenomation which is superficially similar.

While the names *S. albospinosus* and *S. hahnii* have been used, great difficulty was experienced in matching specimens with the type species descriptions. Gerschman de Pilken and Schiapelli (1979) encountered the same difficulty in their study of Argentinian species. In view of the fact that the various species I have studied are not equally toxic, a thorough taxonomic revision of the species is urgently required.

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