Antivenoms for the Treatment of Spider Envenomation†

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†This review is dedicated to the memory of Dr. Struan Sutherland who’s pioneering work on the development of a funnel-web spider antivenom and pressure immobilisation first aid technique for the treatment of funnel-web spider and Australian snake bites will remain a long standing and life-saving legacy for the Australian community.
ABSTRACT

There are several groups of medically important araneomorph and mygalomorph spiders responsible for serious systemic envenomation. These include spiders from the genus Latrodectus (family Theridiidae), Phoneutria (family Ctenidae) and the subfamily Atracinae (genera Atrax and Hadronyche). The venom of these spiders contains potent neurotoxins that cause excessive neurotransmitter release via vesicle exocytosis or modulation of voltage-gated sodium channels. In addition, spiders of the genus Loxosceles (family Loxoscelidae) are responsible for significant local reactions resulting in necrotic cutaneous lesions. This results from sphingomyelinase D activity and possibly other compounds. A number of antivenoms are currently available to treat envenomation resulting from the bite of these spiders. Particularly efficacious antivenoms are available for Latrodectus and Atrax/Hadronyche species, with extensive cross-reactivity within each genera. In the case of Latrodectus antivenoms this is of considerable importance in countries where antivenom is unavailable or where certain antivenoms are associated with an unacceptably high risk of adverse reactions. Moreover, Latrodectus and Atrax antivenoms appear to be effective in the treatment of envenomation by closely related Steatoda spiders (family Theridiidae) or the un-related spider Missulena bradleyi (family Actinopodidae), respectively. The effectiveness of Loxosceles antivenom in the treatment of the necrotic arachnidism resulting from the bite of recluse spiders is less clear mainly due to late presentation of victims. Antivenom is also available for Phoneutria envenomation but is reserved only for severe cases.

Key Words: Envenomation; Spiders; Antivenom; Latrodectus; Phoneutria; Steatoda; Atrax; Hadronyche; Missulena; Loxosceles.
**INTRODUCTION**

Although most cases of spider bite result in minimal if any significant clinical consequences, there are a small number of spiders that may produce either serious systemic clinical envenomation syndromes or significant local reactions. The true incidence of spider bite, spider envenomation and death resulting from spider bite in humans world-wide is unknown and more than likely under-represented due to the voluntary nature of most reporting processes. This review will discuss the role and effectiveness of spider antivenoms for treatment of envenomation by medically important spiders of the genera *Latrodectus*, *Loxosceles*, *Phoneutria* and the subfamily Atracinae (genera *Atrax* and *Hadronyche*).

**HUMAN ENVENOMATION BY THERIDIID SPIDERS**

**Distribution of *Latrodectus* Species**

Arguably the most clinically significant group of spiders are the widow spiders (Araneae: Araneomorphae: Theridiidae), of the genus *Latrodectus*. This genus is comprised of multiple species found on all continents excluding Antarctica (Bucherl, 1971) (see Figure 1). Little is known about the true incidence of envenomation following the bite of Widow spiders due to a lack of organized data collection in most regions of the world. In Australia, an estimate of two to three thousand *L. hasselti* (Red-back spider) bites per year has been made. Clinically significant Red-back spider envenomation requiring antivenom therapy occurs in around 20% of these cases (Jelinek et al., 1989; White, 1998). In the United States, reports to the American Association of Poison Control Centers in 1997 revealed 2757 cases of Widow spider bite, but with only 0.004% defined as having a ‘major outcome’ (Litovitz et al., 1998).
Latrodectism

Although rarely fatal, envenomation by Latrodectus spp. may result in an incapacitating syndrome of severe local, regional, or systemic pain and autonomic features called ‘latrodectism’ which, if left untreated, may last for several days or weeks (Maretic, 1983; White et al., 1995). The syndrome may vary in severity depending on the species and size of the spider, the season of the year, and the amount of venom injected but appears to be similar regardless of the geographic location of the spider (Bogen, 1926; Keegan et al., 1960; Maretic, 1983; McCrone, 1964; Moss and Binder, 1987; Muller, 1993; Sutherland and Trinca, 1978; Wiener, 1961a; Zukowski, 1993).

The initial bite of a Widow spider is often described as initially feeling like a bee sting (Bogen, 1926; Ingram and Musgrave, 1933; Maretic, 1983; Sutherland and Trinca, 1978). Most commonly local pain, sweating, erythema, and piloerection are noted at the bite site within 1 hour of exposure (Maretic, 1983; Muller, 1993; Sutherland and Trinca, 1978; Zukowski, 1993). Clinical features may remain isolated to the site of the bite or less commonly progress to become regional or systemic (see Table 1). Progression to systemic toxicity may occur at a variable rate either rapidly or over a few hours (Clark et al., 1992; Jelinek et al., 1989; Maretic, 1983; Timms and Gibbons, 1986; White et al., 1995). The risk of systemic toxicity is greater in the very young, the very old, and those with any preexisting chronic medical illnesses. The natural progression of envenomation is a gradual diminution of symptoms and signs over several days to weeks although, uncommonly, features of envenomation may persist for months. Fortunately, however, there have been no reports of death from widow spider envenomation in the medical literature in the last 40 years. This is probably related to both an improvement in medical supportive and resuscitative therapies as well as the development of specific antivenom therapies (see Treatment and Management of Latrodectism).

Table 1. Summary of the local, regional, and systemic features of latrodectism.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
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<tbody>
<tr>
<td>Local and</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Erythema at bite site</td>
</tr>
<tr>
<td>regional(^a) effects</td>
<td>Systemic effects</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>• Piloerection</td>
<td>• Muscle fasciculation</td>
</tr>
<tr>
<td>• Sweating</td>
<td>• Regional lymphadenopathy and tenderness</td>
</tr>
<tr>
<td>• Regional sweating to limb or specific region of body</td>
<td></td>
</tr>
<tr>
<td>• Generalized muscle pain</td>
<td>• Vomiting</td>
</tr>
<tr>
<td>• Abdominal pain mimicking acute abdomen</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Muscle fasciculation and tremor</td>
<td>• Dizziness</td>
</tr>
<tr>
<td>• Generalized sweating</td>
<td>• Dyspnea</td>
</tr>
<tr>
<td>• Tachycardia</td>
<td>• Restlessness</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Mild pyrexia</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Paresthesia</td>
</tr>
<tr>
<td>• Priapism</td>
<td>• Pavor mortis(^b)</td>
</tr>
<tr>
<td>• Muscle fasciculation</td>
<td>• Facies latrodectismica(^c)</td>
</tr>
<tr>
<td>• Regional lymphadenopathy and tenderness</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Includes bitten limb and can also occur in contralateral limb.  
\(^b\)Feeling of impending doom.  
\(^c\)An unusual pattern of facial muscle grimacing, trismus, blepharoconjunctivitis, and facial flushing.  


The venoms of all *Latrodectus* species are thought to contain similar toxic components.  This assertion is based on two significant observations. 1) Envenomation resulting from the bite of any Widow spider results in a similar clinical picture regardless of the species of spider. 2) Widow spider antivenoms produced using the venoms of specific *Latrodectus* species reverse the effects of envenomation from other Latrodectus spiders both in experimental animal models and in the clinical setting (see Antivenom Cross-Reactivity with Other *Latrodectus* Venoms). The toxin believed to be responsible is the vertebrate-specific, \(\alpha\)-latrotoxin (\(\alpha\)-LTx), a 120 kDa toxin that acts selectively on presynaptic nerve endings causing massive release of neurotransmitters by synaptic vesicle exocytosis (for a review see Sudhof (2001)).
Treatment and Management of Latrodectism

Treatment with locally produced species-specific antivenom is regarded as the principal therapy in countries where antivenom is available. Specific antivenoms raised against the venoms of various *Latrodectus* species have been developed in many regions of the world (Theakston and Warrell, 1991) (see Table 2). Nevertheless, there are large areas where no local antivenom is available. These include Central Asia, the Middle East, northern Africa and Southeast Asia, and also Europe where antivenom production ceased with the outbreak of the Balkan conflict in the 1990s.

**Antivenom Effectiveness**

Antivenom therapy is considered the most effective treatment for the symptoms and signs of latrodectism (Bogen, 1926; Clark et al., 1992; Russell et al., 1979; Sutherland and Trinca, 1978; Wiener, 1956; Wiener, 1961a). Patients receiving antivenom therapy are more likely to be discharged home directly from emergency departments and have much shorter hospital stays than those receiving supportive measures alone (Clark et al., 1992). Additionally, relief of symptoms usually occurs within 1 to 2 hours of antivenom administration with all available antivenoms (Clark et al., 1992; Maretic, 1983; Muller, 1993; Sutherland and Trinca, 1978).

Table 2. Cross reactivity of *Latrodectus* antivenoms.

<table>
<thead>
<tr>
<th>Venom that antivenom is raised against</th>
<th>Source</th>
<th>Composition</th>
<th>Clinically</th>
<th>Mice (in vivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. mactans</em></td>
<td>Merck &amp; Co., Inc., West Point PA, USA</td>
<td>Equine IgG</td>
<td><em>L. hesperus</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Instituto Nacional de Microbiologia, Buenos Aires, Argentina</td>
<td>Equine IgG</td>
<td><em>L. variolus</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Instituto Bioelcón, Calzada de Telalpan, Mexico D.F.</td>
<td>Polyvalent Equine F(ab)2 IgG</td>
<td><em>L. bishop</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td><em>L. indistinctus</em></td>
<td>South African Institute for Medical Research, Rietfontein, Edenvale, Transvaal, South Africa</td>
<td>Equine IgG</td>
<td><em>L. geometricus</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td><em>L. hasseltii</em></td>
<td>Commonwealth Serum Laboratories, Melbourne, Australia</td>
<td>Equine F(ab)2 IgG</td>
<td><em>L. katipo</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fragment</td>
<td><em>L. tredecimguttatus</em>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steatoda grossa&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>L. mactans</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>L. hesperus</em>&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>L. tredecimguttatus</em>&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>L. lugubris</em>&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-L.Tx&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–</td>
</tr>
</tbody>
</table>
Generally, the dose of Widow spider antivenom required to treat envenomation is reported as one to two ampoules of antivenom for most formulations (Clark et al., 1992; Jelinek et al., 1989; Maretic, 1983; Sutherland and Trinca, 1978; Wiener, 1956; Wiener, 1961a). Uncommonly, some patients have required up to 8 vials of Australian red-back spider antivenom to reverse the features of L. hasselti envenomation (Graudins et al., 1999). Importantly antivenom may reverse envenomation presenting to hospital many days or even weeks after exposure (Allen and Norris, 1995; Banham et al., 1994; Wiener, 1956).

### Antivenom Side-Effects

The incidence of severe anaphylactic reactions occurring with different antivenom formulations appears to vary. This has resulted in an inconsistency in the threshold for use of antivenom from region to region. In the United States, there appears to be the greatest reluctance by physicians to use specific immunotherapy. This is most likely due to isolated case reports of death following administration of North American widow spider antivenom (Clark et al., 1992) and an extrapolated risk of anaphylaxis calculated from the use of crotalid polyvalent snake antivenom (Spaite et al., 1988). Clark et al. observed an 8% incidence of allergic reactions (urticaria and bronchospasm) with North American widow spider antivenom use (Clark et al., 1992). This has resulted in alternative therapies being employed however large case studies have shown that these are not as effective as antivenom therapy (Clark et al., 1992). Manufacturer recommendations for the use of this
Antivenom suggest that it should be reserved for ‘severe cases’ of envenomation or those occurring at the extremes of age. However, these recommendations are conservative and could result in a significant number of patients suffering from prolonged envenomation if left untreated.

In Australia, on the other hand, Red-back spider antivenom, an equine derive F(ab)$_2$ fragment, is the most commonly used antivenom in the country (Ho et al., 1999; Sutherland and Trinca, 1978; White, 1998). Clinicians will commonly administer antivenom to any patient with persisting local features of envenomation, regional symptoms or signs and any case of systemic envenomation. Mild allergic reactions are reported to occur in 0.54% of cases (half of these were the result of administration of undiluted antivenom intravenously), with a 1.4% incidence of serum sickness (Sutherland and Trinca, 1978). Severe anaphylaxis or death has not been reported following Red-back spider antivenom use. The reported incidence of allergic reactions is probably over-represented with this antivenom as it is based on voluntary reporting of antivenom use to the manufacturer (Ho et al., 1999).

Antivenoms in general contain a significant amount of protein with anti-complement activity that may result in anaphylactoid reactions if infused rapidly (Sutherland, 1977). This activity is reported to be reduced in trypsin-digested antivenoms such as Red-back spider antivenom. It may be much greater in antivenoms produced as crude hyperimmune equine sera, such as North American widow spider antivenom (Sutherland, 1977). Little is documented about the use of antivenom and the incidence of adverse reactions with antivenom formulations in other parts of the world.

**Antivenom Cross-Reactivity with Other *Latrodectus* Venoms**

Widow spider antivenoms are commonly produced from animals exposed to one specific *Latrodectus* venom. Nevertheless, it has been observed that species-specific antivenoms
are capable of treating envenomation from more than one kind of Widow spider. Indeed clinical observations of antivenom use around the world and in vivo studies in mice suggest that it may be possible to use antivenom raised to the venom of related widow spiders, from other continents, to treat widow spider envenomation (see Table 2). These observations suggest that all Widow spider antivenoms may be capable of reversing clinical envenomation by any other Latrodectus species worldwide. This is supported by the observation that L. hasselti antivenom can neutralize the toxicity of α-LTx derived from L. tredecimguttatus venom (Graudins et al., 2001).

Use of Widow Spider Antivenom in the Treatment of Envenomation by Related Theridiid Spiders

The ‘Cupboard’, ‘Brown house’, or ‘False widow’ spider are all descriptive terms used to encompass various species of Steatoda (Araneae: Araneomorphae: Theridiidae), close relatives of widow spiders. They are found worldwide and are endemic to most continents (Cavalieri et al., 1987; Korszniak and Story, 1994; Main, 1984; Rutherford and Sutherland, 1989; South et al., 1998; Warrell et al., 1991). In general, bites from Steatoda spp. result in minor local symptoms not requiring any specific intervention. However, they have been implicated in a small number of cases of systemic envenomation in humans, also called ‘steatodism’ (Graudins et al., 2002a; Rutherford and Sutherland, 1989; South et al., 1998; Warrell et al., 1991). The envenomation syndrome observed in these severe cases is similar to that of latrodectism adding further support to in vitro observations of an α-LTx-like effect by Steatoda venom (Einhorn and Hamilton, 1973; Einhorn and Hamilton, 1974; Frontali et al., 1976; Gorio et al., 1978; Graudins et al., 2002a; Korszniak and Story, 1994). Red-back spider antivenom has been successfully administered in two cases of systemic steatodism with resolution of all features of envenomation (Graudins et al., 2002a; South et al., 1998). In vitro toxicity data supports this clinical observation, and suggests that S. grossa venom is immunogenically and
chromatographically similar to *Latrodectus* venoms (Graudins et al., 2002a).

**HUMAN ENVENOMATION BY AUSTRALIAN FUNNEL-WEB SPIDERS**

**Distribution of *Atrax* and *Hadronyche* Species**

Australian funnel-web spider venom probably represents one of the most toxic spider venoms known to affect humans. Australian funnel-web spiders (Araneae: Mygalomorphae: Hexathelidae: Atracinae) are a relatively large group of spiders that include the genera *Atrax* and *Hadronyche*. These genera comprise of over 35 different species of that are mainly located along the southeastern seaboard of continental Australia and Tasmania (Gray, 1987; White et al., 1995) (see Figure 2).

**Clinical Features of Envenomation by *Atrax* and *Hadronyche* Species**

The medical literature contains numerous reports describing severe male *Atrax robustus* envenomation and death in humans (Sutherland, 1983a; Torda et al., 1980; Wiener, 1961b). Life-threatening envenomation indistinguishable to that of *A. robustus* resulting from the bite of *Hadronyche* species has also been observed and appears to be becoming more common due to rapid population spread (Dieckman et al., 1989; Harrington et al., 1999; Miller et al., 2000). These reports suggest that the envenomation syndrome is similar between species and all Funnel-web spiders are thought to have venom potentially toxic to primates and man (White et al., 1995). Despite this, Funnel-web envenomation remains an uncommon phenomenon. An estimate of envenomation occurring in one out of ten bites has been made and that there are approximately 30 to 40 funnel-web bites with 3 to 4 cases of envenomation per year (White et al., 1995).

Systemic envenomation, while rare, may develop extremely rapidly and has been reported as quickly as 10 minutes following a bite (White et al., 1995; Sutherland, 1983a). Children may deteriorate rapidly and death may result in 1 to 2 hours if left untreated.
(Sutherland, 1983a). Death usually results from progressive, irreversible hypotension, or possibly raised intracranial pressure resulting from cerebral edema (Fisher et al., 1980; Torda et al., 1980) (see Table 3).

The envenomation syndrome is due to the presence of δ-atractoxins (formerly robustoxin and versutoxin) that are 4–5 kDa peptide neurotoxins found in Funnel-web spider venoms (Brown et al., 1988; Sheumack et al., 1985; Szeto et al., 2000). These all act by slowing sodium current inactivation (Nicholson et al., 1994, 1996, 1998; Szeto et al., 2000) resulting in spontaneous repetitive firing of action potentials (Grolleau et al., 2001). Ultimately, excessive neurotransmitter release results in muscle fasciculation and autonomic effects on the cardiovascular system and exocrine glands.

Table 3. Summary of clinical features of funnel-web spider envenomation.

<table>
<thead>
<tr>
<th>Local effects</th>
<th>Systemic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• pain</td>
<td>• sweating</td>
</tr>
<tr>
<td>• piloerection</td>
<td>• muscle fasciculation</td>
</tr>
<tr>
<td></td>
<td>• tachycardia</td>
</tr>
<tr>
<td></td>
<td>• hypotension</td>
</tr>
<tr>
<td></td>
<td>• non-cardiogenic pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>• dyspnea</td>
</tr>
<tr>
<td></td>
<td>• confusion</td>
</tr>
<tr>
<td></td>
<td>• coma</td>
</tr>
<tr>
<td></td>
<td>• cerebral edema</td>
</tr>
<tr>
<td></td>
<td>• metabolic acidemia.</td>
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<table>
<thead>
<tr>
<th>Systemic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• circumoral paresthesia</td>
</tr>
<tr>
<td>• tongue fasciculation</td>
</tr>
<tr>
<td>• salivation</td>
</tr>
<tr>
<td>• lachrymation</td>
</tr>
<tr>
<td>• sweating</td>
</tr>
<tr>
<td>• nausea</td>
</tr>
<tr>
<td>• vomiting</td>
</tr>
<tr>
<td>• generalized muscle fasciculation and weakness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late effects¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• persistent hypotension</td>
</tr>
<tr>
<td>• unremitting coma</td>
</tr>
<tr>
<td>• coagulopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late effects¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• disseminated intravascular coagulation</td>
</tr>
<tr>
<td>• rhabdomyolysis</td>
</tr>
</tbody>
</table>

¹Commonly not seen in patients receiving early treatment with antivenom.

Data taken from Fisher et al. (1980), Sutherland (1983a), Torda et al. (1980).
Treatment and Management of *Atrax* and *Hadronyche* Envenomation

First-aid for Funnel-web spider bite may be a life saving maneuver in patients who will require transport to hospital. Application of a pressure immobilization bandage inhibits the development of envenomation and has been proven to be clinically effective in the prevention of Funnel-web spider envenomation (Sutherland and Duncan, 1980; Sutherland et al., 1980). Prolonged application of a pressure immobilization bandage for up to 24 hours may result in apparent local neutralization of venom (Sutherland et al., 1980). It is hypothesized that the venom is slowly inactivated in the tissues, possibly by hydrolysis (Sutherland et al., 1980).

Antivenom Effectiveness

In view of the life-threatening envenomation syndrome that may result from the bite of Funnel-web spiders, a purified rabbit IgG antibody to the venom of the male *A. robustus* was developed in 1980 by Commonwealth Serum Laboratories in Melbourne, Australia (Fisher et al., 1981; Hartman and Sutherland, 1984; Sutherland, 1980; Sutherland et al., 1981). Antivenom therapy has markedly shortened the course of envenomation and resulted in reduced hospital stay as well as reduced the morbidity and mortality from funnel-web spider envenomation (Fisher et al., 1981; Sutherland, 1983a). Antivenom treated patients are commonly discharged from hospital within 1 to 3 days of antivenom treatment. Prior to antivenom availability the average length of hospital stay for severe, non-fatal cases of envenomation was 14 days (Torda et al., 1980).

The antivenom has also been reported to be effective in reversing envenomation from other species of Funnel-web spider including *H. formidabilis, H. infensa, H. species 14, H. cerberea* and *H. versuta* (Dieckman et al., 1989; Harrington et al., 1999; Miller et al., 2000). More recently, Graudins et al. (2002b) have shown that Funnel-web spider antivenom can neutralize the toxicity of a number of other *Hadronyche* and *Atrax* spp. venoms from both male and female spiders in vitro.

Antivenom Side-Effects
Although figures are unavailable, the incidence of allergic reactions to funnel-web antivenom appears to be low. Only one case of delayed serum sickness has been documented one week following treatment with Funnel-web spider antivenom (Miller et al., 1999).

**Use of Funnel-Web Spider Antivenom for the Treatment of Envenomation by Mouse Spiders (Genus Missulena)**

There are currently 11 recognized species of mouse spider in the genus *Missulena* (Araneae: Mygalomorphae: Actinopodidae) with a wide-spread distribution over mainland Australia (Faulder, 1995; Main, 1985; Main, 1996). Envenomation is uncommon but may resemble systemic funnel web spider envenomation in severe cases (Faulder, 1993). Funnel-web spider antivenom has been used to successfully treat an envenomation syndrome from the bite of a male Eastern mouse spider (*Missulena bradleyi*, see Figure 3) (Underhill, 1987). Subsequently a δ-atracotoxin-like action of the venom to slow sodium channel inactivation has been identified and the action of antivenom to neutralize the venom confirmed in isolated nerve-muscle preparations (Rash et al., 2000).

**HUMAN ENVENOMATION BY LOXOSCELES SPIDERS**

The second most medically important group of spiders are from the genus *Loxosceles* (Araneae: Araneomorphae: Loxoscelidae) otherwise known as ‘recluse’, ‘violin’ or ‘gaucho’ spiders. These spiders can cause necrotic arachnidism, otherwise known as loxoscelism, a form of necrotic cutaneous lesion. Less commonly they can cause a systemic illness that is sometimes fatal.

**Distribution of Loxosceles Species**

They are distributed in the southern states of North America, as well as Central and South America, Europe, southern Africa, Middle East and parts of Asia and have been
accidentally introduced into Australia and some other countries (see Figure 4). Although there are over 50 species only a few have been implicated in loxoscelism.

**Loxoscelism**

There are two basic forms of loxoscelism: cutaneous (the more frequent form) and viscerocutaneous which is relatively uncommon to rare (see Table 4). Diagnosis of envenomation is usually based on clinical presentation since the spider is not usually available for identification. Despite this enzyme immunoassay ELISAs have been successful in detecting *Loxosceles* venom in necrotic skin lesions (Cardoso et al., 1990) and specific IgG antibodies in patients (Barbaro et al., 1992a) although the latter has not proved effective so far. In addition a passive haemagglutination inhibition assay for *L. reclusa* venom appears to show promise for the confirmation of loxoscelism (Barrett et al., 1993).

Sequelae of the cutaneous form include disfiguring scars (Schenone et al., 1989), persistent damage to underlying nerves, hyalinizing panniculitis and myonecrosis (Bascur et al., 1992), pseudoepitheliomatous hyperplasia and pyoderma gangrenosum (Ingber et al., 1991). In the rare cases of lethal envenomation, typically in children, death is associated with acute renal failure mainly due to hemolysis (Futrell, 1992).

Table 4. Summary of the clinical features of cutaneous and viscerocutaneous loxoscelism.

<table>
<thead>
<tr>
<th>Form of loxoscelism</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>• painless bite with pain intensifying (probably due to ischemia)</td>
</tr>
<tr>
<td></td>
<td>• itching and tenderness</td>
</tr>
<tr>
<td></td>
<td>• nonspecific erythema</td>
</tr>
<tr>
<td></td>
<td>• local edema</td>
</tr>
<tr>
<td></td>
<td>• hemorrhagic mottling areas with regions of ischemia</td>
</tr>
<tr>
<td></td>
<td>• fever</td>
</tr>
<tr>
<td></td>
<td>• dry necrosis with underlying ulceration</td>
</tr>
<tr>
<td>Viscerocutaneous</td>
<td>As above plus:</td>
</tr>
<tr>
<td></td>
<td>• fever</td>
</tr>
<tr>
<td></td>
<td>• intravascular hemolysis</td>
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</table>
The dermonecrotic, platelet aggregative and intravascular hemolytic activity of Loxosceles spp. venom is due to the presence of 31–35 kDa sphingomyelinase D that can account for death of laboratory animals (Babcock et al., 1981; Barbaro et al., 1992b; Futrell, 1992; Kurpiewski et al., 1981; Tambourgi et al., 1998). Polymorphonuclear leucocytes are also important in the development of the necrotic lesions (Smith and Micks, 1979; Young and Pin, 1988) and appear to be related to the presence of circulating complement (Ward and Cochrane, 1965) although the extent of complement pathway involvement is still uncertain (see Futrell (1992)).

**Treatment and Management of Loxoscelism**

The Instituto Butantan (Sao Paulo, Brazil) has developed a specific antivenom to *L. reclusa* (soro-antiloxoscelico) that is used routinely in patients with acute cutaneous lesions and/or signs of systemic toxicity. Nevertheless the antivenom has shown limited success in reversing symptoms, mainly due to late presentation of victims (Futrell, 1992). However, a recent study employing polyclonal anti-*Loxosceles* Fab fragments indicated that administration of antivenom within 4 hours reduced Loxosceles-induced dermonecrotic lesions in rabbits (Gomez et al., 1999). This maybe why the effectiveness of the antivenom is poor clinically. A polyvalent antivenom (soro-antiarachnidico polyvalente) is also available for bites of other species of *Loxosceles* found in Brazil including the three most common and clinically important species *L. intermedia*, *L. gaucho* and *L. laeta* (Braz et al., 1999; Mota et al., 1995). However antivenom is not available in most regions where these spiders are found.

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<table>
<thead>
<tr>
<th>symptoms associated with Loxoscelism</th>
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<tbody>
<tr>
<td>weakness</td>
</tr>
<tr>
<td>nausea</td>
</tr>
<tr>
<td>vomiting</td>
</tr>
</tbody>
</table>

Taken from Bascur et al. (1992), Futrell, (1992), Schenone et al. (1989).
To date the treatment for envenomation consists of general wound management and documentation of the extent of the lesion. Blood and urine tests are also performed to exclude viscerocutaneous involvement that requires supportive measures including blood transfusion and systemic antibiotics. Occasionally antihistamines, dapsone, hyperbaric oxygen and even cautious use of surgical excision have been tried. However systemic corticosteroids are now generally not recommended (for a review see White et al. (1995)).

**ENVENOMATION AND TREATMENT OF PHONEUTRIA BITES**

**Distribution of Phoneutria Species and Clinical Features of Envenomation**

The ‘Banana’ or ‘armed’ spiders of the genus *Phoneutria* (Araneae: Araneomorphae: Ctenidae) are mainly confined to the eastern areas of Central and South America. In particular they represent the most common cause of spider bites presenting to hospitals in Brazil (White et al., 1995). The venom appears to contain many neurotoxins some of which are capable of causing a slowing of inactivation and a hyperpolarizing shift in the voltage dependence of activation of voltage-gated sodium channels (for a review see Cordeiro et al. (1995)). This is thought to result in an increased release of peripheral neurotransmitters, particularly acetylcholine and catecholamines. Pain is the most common symptom of envenomation but autonomic features also predominate (see Table 5).
Table 5. Summary of the clinical features of Phoneutria envenomation.

| Local features | • pain  
|               | • swelling  
|               | • localized vasodilatation  
|               | • profuse sweating |
| Systemic features | • agitation  
|                  | • tachycardia  
|                  | • arterial hypertension  
|                  | • vomiting  
|                  | • excessive salivation  
|                  | • profuse sweating  
|                  | • priapism  
|                  | • bradycardia  
|                  | • hypotension  
|                  | • diarrhea  
|                  | • acute pulmonary edema  
|                  | • shock |

Data adapted from White et al., 1995.

**Treatment and Management of Phoneutria Envenomation**

Treatment is based on the severity of envenomation with symptomatic treatment involving the use of a local anesthetic block to relieve pain. An equine antivenom is available (soro-antiarachnidico polyvalente, Instituto Butantan, Sao Paulo, Brazil) which contains an anti-Phoneutria fraction. However it is reserved only for moderate to severe cases. Therefore in Hospital Vital Brazil in Sao Paulo it is used in less than 5% of patients, being mainly children under the age of 7 and elderly patients (White et al., 1995). Since the antivenom is administered intravenously there is also a high risk of immediate hypersensitivity reactions.

**CONCLUSIONS**

Antivenoms are available and particularly effective for the treatment of bites from
Latrodectus and Atrax/Hadronyche spp. and most likely Steatoda and Missulena envenomation. The cross-reactivity of certain Latrodectus antivenoms is of particular importance especially where antivenoms are unavailable or associated with high risk of adverse reactions. The role of antivenom therapy in the treatment of Loxosceles envenomation, however, is less clear typically due to the late presentation of victims nevertheless it can be useful in severe Phoneutria envenomation.

ACKNOWLEDGMENT

We gratefully acknowledge the financial support of the Australian Rotary Health Research Fund.

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Gray, M. R. Distribution of the funnel web spiders. In: Covacevich, J., Davie, P., Pearn, J.,


Figure 1. Worldwide distribution of some species of *Latrodectus*. Medically important species are highlighted in bold text. Data from Bucherl (1971), Lucas (1988), Maretic (1978), Newlands and Atkinson (1988), Platnick (1990), Sutherland (1983b).
Figure 2. Distribution of Australian funnel-web spiders (*Atrax* and *Hadronyche*). Data from Gray (1987).
Figure 3. The male (left) and female (right) Eastern mouse spider (*Missulena bradleyi*). Scale bar represents 1 cm. Photo courtesy of David Humfrey.