Dear Sir:

I appreciate the comments of Isbister and others in their Letter to the Editor regarding my review article,¹ and emphasize that we are all in agreement on most of their points raised, especially with regards to 1) the complexity of a confusing topic supported mainly by case reports and not by more scientifically robust studies, 2) the exaggeration of bite severity and tissue necrosis, 3) the confusion created by the term “necrotic arachnidism,” 4) the lack of scientific support for necrotic bites by *Tegenaria agrestis* in the United States, and 5) the occurrence of geographic differences in the clinical presentation of envenomings by widow spiders. I will address each point of agreement first and note that my purpose in the review was to create more clarity out of complexity by stratifying spider bites by syndromic presentations. In addition, references by Isbister and others provided 16 (20%) of the 80 references cited.

This review was not a meta-analysis or a descriptive epidemiologic analysis. A proper meta-analysis would have required a statistical analysis of a consolidated collection of similarly conducted, well-designed, prospective cohort investigations, few of which exist on the topic. This review was simply a compilation of case reports, case series, and retrospective reports of witness-confirmed and unconfirmed spider bites, with and without expert identification of suspect spiders by arachnologists. The few well-recognized spider bite syndromes, including latrotoxicism, loxoscelism, phoneurism, funnel web neurotoxicity, and minor spider envenomings, were further expanded to include the newly recognized ste-
atodism, a milder form of latrodectism, a miscellaneous category for spider part and content exposures, and a type of spider-bite induced tissue necrosis not related to *Loxosceles* species spider bites. The methodologic and analytic weaknesses of previous investigations of spider envenomings were stressed throughout the review and introduced as follows:

“The epidemiologic analysis of spider bites is confounded by several factors including the extensive differential diagnosis of dermal bite-like lesions, suspected versus definite spider bites, and precise identification of biting spiders by arachnologists. To date, most studies of spider bites have been retrospective, bites have not been confirmed by eyewitnesses, and spiders have not been kept alive for identification, or identified incorrectly. Only prospective studies of definitely confirmed spider bites with expert identification of the envenomings species will contribute to the development of evidence-based methods to precisely describe venomous spiders and the outcomes of their bites.”

The term “necrotic araneism” was not invented by me, but adopted from publications in the South African literature by Newlands and Atkinson as a more precise term that did not include necrotic envenomings by other arachnids, such as scorpions, mites, and ticks.²,³ An Internet search of the world’s scientific literature from 1966 to the present on the subject of “necrotic arachnidism” yielded 90 references, nearly half of which treated stings and bites by scorpions (37 references), mites (2 references), and collective envenomings by scorpions and other venomous animals, including reptiles (3 references). In addition, the differential diagnosis of necrotic araneism incorrectly ascribed to *Loxosceles* species spider bites was also emphasized in the review, and the work of Vetter and Vetter and Bush was cited repeatedly:

“The differential diagnosis of necrotic araneism, often incorrectly ascribed to *Loxosceles* spider bites, is extensive. Vetter and Bush have emphasized repeatedly that the diagnosis of brown recluse (*Loxosceles reclusa*) bites is frequently overused for dermonecrotic lesions of uncertain etiology, especially in locations in the United States where the spider is not even endemic.⁴,⁵ In a retrospective analysis of suspected brown recluse bites in four western American states over a 41-month period, Vetter and others collected 316 diagnoses of brown recluse spider bites, but could only confirm 35 recluse sightings in those same four states over the study period.”⁶

“Ulcerating or necrotic wounds from a myriad of other insect-induced, infectious, or physical sources are often misdiagnosed as *Loxosceles reclusa* bites with necrotic araneism in the United States. Systemic loxoscelism is also rare in the United States, with a 3% incidence rate and no deaths in a population of 111 patients with expert-confirmed brown recluse (*Loxosceles reclusa*) bites in a 1997 survey in the United States.⁷ Systemic loxoscelism is much more common following South American Loxosceles species bites (*L. laeta, L. laeta, L. intermedia*) with a prevalence rate of 13.1% and a case fatality rate of 1.5% in 267 cases of expert-confirmed *L. laeta* or *L. intermedia* bites.⁸

“Unsuspected patients with diabetes may develop neuropathic foot ulcers or soft tissue infections following minor trauma that may be misdiagnosed as *Loxosceles* bites.”

Whether or not necrotic araneism following spider bites by non-*Loxosceles* species occurs, it has been described following both *Tegenaria agrestis* bites in the United States and *Cheiracanthium* species spider bites in Africa. The term “non-*Loxosceles*” was not used as a new taxonomy, but simply as a means to separate the well-recognized dermonecrosis following *Loxosceles* spider bites from the insufficiently supported dermonecrosis following spider bites by genera other than *Loxosceles*. In the southern African experience, Newlands and Atkinson noted that *Cheiracanthium* species spiders were responsible for most of the dermonecrotic lesions following confirmed spider bites in their analysis of 39 spider bites.² Conversely, the lack of epidemiologic support for the necrotic araneism purportedly caused by *Tegenaria agrestis* spider bites in the United States was emphasized throughout the review and introduced and developed as follows:

“In a retrospective analysis of spider bites in the Pacific Northwest (1988–1995), the CDC subsequently reported that a non-native species, *Tegenaria agrestis*, the hobo spider, introduced into the area from western Europe in the 1930s, was possibly responsible for an increasing number of unidentified spider bites with extensive dermal necrosis and permanent scarring.⁹ Nevertheless, *Tegenaria agrestis* has never been conclusively identified as the cause of necrotic araneism in the Pacific northwest of the United States because the CDC report was based on retrospective telephone reports of suspected bites without expert identification of biting spiders.”

“*Tegenaria agrestis*, also known as the hobo spider or “aggressive” house spider, is a relatively recent Western European émigré to the United States, settling comfortably in the Pacific northwest of the United States and the Canadian Pacific circa around 1936.¹⁰,¹¹ Since other spiders capable of inducing necrotic araneism are rare to non-existent in the colder climates of the North American Pacific coast, such as *Loxosceles* and *Cheiracanthium* spiders, the hobo spider may be the principal cause of necrotic araneism in the colder latitudes of the North American Pacific coast.⁴,⁶ Since the hobo spider is considered innocuous in Europe, however, it remains unclear and unproven whether the US hobo spider is really the major cause of necrotic araneism in the North American Pacific Northwest."⁴,⁶,¹⁰,¹¹

“In an elegant laboratory investigation designed to compare the venom toxicities of hobo spiders from the United States and Europe, Binford analyzed the venoms of *Tegenaria agrestis* spiders from Washington, the United Kingdom, and Switzerland by both liquid chromatography and insect bioassays.¹³ Chromatographic profiles were different between the sexes, but similar within sexes between hobo spiders from the United States and the United Kingdom. Insect toxicity studies showed no differences between venom potencies in spiders from the United States and the United Kingdom, but female venoms were more potent than male venoms.¹¹ Binford concluded that these results did not support the common claims that hobo spiders, particularly the larger males, commonly cause necrotic araneism in the northwestern United States.¹¹ In several recent studies of necrotic araneism and spider ranges, Vetter and others concluded that the majority of dermonecrotic lesions in the United States are misdiagnosed as necrotic araneism from spider bites, particularly *Loxosceles reclusa* and *Tegenaria agrestis* bites, especially in regions where such species are either not endemic or rarely reported.”⁴,⁶

It was not my intent to exaggerate the topic of necrotic araneism, especially “non-Loxosceles” araneism, but to present the controversy in an unbiased manner. History will
recall a rather embarrassing situation in Australia, where for a decade or so, the white-tail spiders of the Lampona species were wrongly accused of causing dermonecrotic bites, until the “myth was debunked” by Isbister and Gray in 2003. History may be repeating itself in the experience in the United States of continuing to ascribe necrotic araneism to Tegenaria agrestis spider bites in the Pacific northwest. To their credit, Isbister and Gray in Australia and Vetter and Bush in the United States have pursued a well-published crusade of “de debunking the mythology” of necrotic araneism improperly ascribed to Lampona and Loxosceles spider bites in Australia and the United States.

In addressing the many conflicting descriptions of latrodeictism from throughout the world, I was careful to list all of the reported observations and clinical manifestations of Latrodectus species spider bites and to emphasize the geographic variations in presenting features and the controversies in treatments, such as with intravenous calcium gluconate in the United States:

“The notorious Latrodectus biters include L. mactans, L. hasselti, L. curacaviensis, L. geometricus, L. hesperus, L. indistinctus, L. lugubris, L. menavodi, L. tredecimguttatus, and L. variolus. Although the clinical picture of latrodeictism caused by different Latrodectus species is similar, there are unique features that characterize the initial clinical presentation of widow bites in different countries.”

“In a prospective analysis of 68 red back spider (L. hasselti) bites in Australia, Isbister and Gray reported pain after all bites, severe pain in 42 cases (62%), prolonged (more than 24 hours) pain in 45 cases (66%), pain-associated insomnia in 22 cases (32%), and systemic effects in 24 cases (35%), notably local or regional diaphoresis in 23 cases (34%).”

“In a retrospective study of 45 black (L. indistinctus) and brown (L. geometricus) bites in South Africa, Muller reported that black widow bites (n = 30) were twice as common and more severe than brown widow bites (n = 15), and were characterized by generalized muscle pain and cramps, abdominal muscle rigidity, profuse sweating, hypertension, and tachycardia. Conversely, brown widow bites were associated with markedly less pain and muscle cramping, always localized to the bite extremity.”

“In a 10-year (1980–1990) retrospective analysis of latrodeictism in Brazil, Lira da Silva and others reported that most widow bites occurred in cities (57%), affected men predominantly (70%), and were most commonly inflicted by L. curacaviensis. The clinical presentation was characterized by limb pain (29%), tremor and rigidity (29%), generalized sweating (28%), distal paresthesias (21%), and abdominal cramping (17%). Although treatment was mainly supportive (67%), 21% of widow bite victims required antivenom therapy, with most patients (64%) discharged within 24 hours.”

“In a 10-year (1984–1994) latrodeictism study in Spain, Diez-Garcia and others reported only 12 confirmed Mediterranean black widow (L. tredecimguttatus) bites, most characterized by generalized pain and abdominal rigidity and cramping (n = 10), and local pain (n = 8) and erythema (n = 10) at the bite sites. Laborator abnormalities were unusual and included leukocytosis (n = 4), elevated creatine kinase (n = 4), and proteinuria (n = 3). Latrodectus antivenom therapy was not indicated in any case.”

“In an American retrospective chart review of 163 black widow bites in Arizona, Clark and others reported that the most common initial manifestations included generalized abdominal, back, and leg pain. The extremities were the most common bite sites. Intravenous calcium gluconate was ineffective for pain relief compared with a combination of intravenous opioids and benzodiazepines, and antivenom as indicated by severity of envenomings. The investigators concluded that although calcium gluconate had been recommended for analgesia in the past, it was ineffective compared with intravenous opioids and benzodiazepines, and that antivenom therapy significantly shortened the duration of symptoms in severe black widow envenomings.”

“In their letter, Isbister and others have accused me of intentionally misleading readers by stating that red back spider antivenom was among the most frequently used spider antivenoms and that funnel-web spider antivenom was among the least frequently used spider antivenoms in Australia. In this case, I simply described Sutherland’s reported experience with antivenom use in Australia as follows: “In a retrospective analysis of all antivenom use in Australia over a one-year period, Sutherland reported that red back spider (L. hasselti) antivenom was the most common antivenom administered (n = 258), followed by Sydney funnel-web antivenom (n = 3), and that serum sickness occurred in only three patients receiving red back spider antivenom. In severe envenomings, especially in children, antivenom may be effective in reversing latrodeictism up to 90 hours after an envenoming bite.”

A frequency ratio in the administration of red back to funnel-web spider antivenom of 86:1 would indicate that red back antivenom is administered much more frequently on an annual basis in Australia than funnel-web antivenom.

With regard to bites by the grass spider (Agelenopsis aperta), and other infrequently envenoming species, Isbister and others have accused me of exaggerating the severity of these bites and any associated systemic manifestations. I addressed this topic without exaggeration and with caution as to the rarity of such events as follows:

“Other species of spiders may cause medically notable human bites with mild envenomings, local pain and erythema, and without necrosis or significant systemic manifestations other than regional lymph node tenderness, contagious arthralgias, malaise, nausea, and low-grade fever. On rare occasions, spidresses previously considered completely harmless, such as the grass spider (Agelenopsis aperta), may inflict severely envenoming bites, especially in children. Miscellaneous spider bites are a frequent source of telephone calls to poison information centers, especially in Australia, South America, and the United States.”

In the case report on envenoming by Agelenopsis aperta, Vetter described “the first report of clinically significant bites by the grass spider.” Two cases of envenomings in southern California were reported. In one case, a child exhibited several envenomation symptoms. Vetter concluded that although the grass spider may be innocuous generally, it should be considered a venomous creature of occasional medical importance.

I do not feel that my concluding comments represented misinformation or exaggeration in any way and only served to alert clinicians to the extensive differential diagnosis of purported spider bites and necrotic araneism:

“Most spiders are venomous, but cannot inflict serious bites
on humans due to delicate mouthparts and fangs. The differential diagnosis of spider bites is extensive and includes other arthropod bites, skin infections, and chemical and physical agent exposures.”

In conclusion, my recent review article on spider envenoming in the American Journal of Tropical Medicine and Hygiene was carefully peer-reviewed by several outside experts, apparently not Isbister and others, who recommended many valuable changes and additions; all of which were incorporated into the revisions leading to the final published manuscript. In my opinion, this review was not alarming, misleading, self-promoting, or self-referring. Isbister and others were frequently referenced throughout the review and given due credit for their valuable contributions to a better understanding of the epidemiology and toxicology of spider envenomings.

Like the Australian experience with the purported necrotic araneism from Lampona species spider bites, American clinicians will likely be similarly fooled by the over-diagnosis of brown recluse spider bites, other “non-Loxosceles” species spider bites, and misdiagnosed Loxosceles species spider bites. The scientific and public health communities have a responsibility to continue to conduct the proper prospective investigations of confirmed spider bites with expert identification of biting spiders to dispel the folklore surrounding spider bites and to further advance knowledge of spider bite epidemiology and outcomes. Until a sufficient number of well-designed studies are conducted, the public and the medical community will continue to seek information on venomous bites and stings from anecdotal reports, sensational media productions, such as non−peer-reviewed textbooks.

REFERENCES