CONCEPTS

Sensationalistic Journalism and Tales of Snakebite: Are Rattlesnakes Rapidly Evolving More Toxic Venom?

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Recent reports in the lay press have suggested that bites by rattlesnakes in the last several years have been more severe than those in the past. The explanation, often citing physicians, is that rattlesnakes are evolving more toxic venom, perhaps in response to anthropogenic causes. We suggest that other explanations are more parsimonious, including factors dependent on the snake and factors associated with the bite victim’s response to envenomation. Although bites could become more severe from an increased proportion of bites from larger or more provoked snakes (ie, more venom injected), the venom itself evolves much too slowly to explain the severe symptoms occasionally seen. Increased snakebite severity could also result from a number of demographic changes in the victim profile, including age and body size, behavior toward the snake (provocation), anatomical site of bite, clothing, and general health including asthma prevalence and sensitivity to foreign antigens. Clinical management of bites also changes perpetually, rendering comparisons of snakebite severity over time tenuous. Clearly, careful study taking into consideration many factors will be essential to document temporal changes in snakebite severity or venom toxicity. Presently, no published evidence for these changes exists. The sensationalistic coverage of these atypical bites and accompanying speculation is highly misleading and can produce many detrimental results, such as inappropriate fear of the outdoors and snakes, and distraction from proven snakebite management needs, including a consistent supply of antivenom, adequate health care, and training. We urge healthcare providers to avoid propagating misinformation about snakes and snakebites.

Key words: snake, snake envenomation, rattlesnake, venom, Mojave toxin, biochemistry, antivenoms, mass media, evolution

Introduction

The media loves a sensational story, and when scientists and health professionals are quoted, the public will believe almost anything heard or read. Recently, in 2008, we witnessed a flurry of media stories perpetuating the notion that rattlesnakes—particularly those native to southern California, Arizona, and Colorado (Table 1)—were rapidly evolving more toxic venom.1–4 These stories cited speculation by physicians reporting an unusual number of severe snakebite cases in recent years. Published opinions that snakes are rapidly evolving more toxic venom are not new. A popularized view, for example, was published in an article in Natural History nearly a decade ago.5 Regrettably, a new round of similar media stories emerged with the onset of snakebite season in 2009.6–8 The speculation appears to have arisen from a combination of sensationalistic journalism and a general lack of knowledge by attending physicians regarding the numerous effects underlying the presentation of severe envenomation in patients.

Could more toxic venoms really be evolving rapidly among rattlesnakes? To answer this question, we need to consider both the basis of the claim—observations of increased snakebite severity—and alternative explanations that provide more parsimonious reasons why some bites seem more severe. In this article, we point out that there are 2 important variables in the equation for explaining snakebite severity: the snake and its venom, and the human snakebite victim’s response to the venom. Major factors influencing the severity of a rattlesnake
bites are summarized in Table 2 and discussed in more detail below. We suggest that there are many explanations providing a far more likely scenario to account for an increase in envenomation severity, rather than rapidly evolving venom composition. We also question the supposition that snakebites have become more severe, and point out the serious difficulties involved with testing the hypothesis that more toxic venoms are evolving among snakes. We conclude by drawing attention to some of the dire consequences of misinformation about snakes, their venom, and envenomations.

The Snake Factor: Biology and Properties of Venom

With regard to the snake and its venom, there are two major factors that could influence the severity of a bite: the amount of venom injected and biochemical composition (including relative toxicity) of the venom.

AMOUNT OF VENOM INJECTED

The amount of venom injected by a rattlesnake when biting varies with many factors, but the most important appears to be size of the snake (Table 2 lists several factors pertinent to defensive bites). As snakes grow, the quantity of venom stored in the paired venom glands increases exponentially. Contrary to popular opinion in the United States, larger rattlesnakes inject substantially more venom than smaller snakes, as documented for both predatory and defensive contexts. Young rattlesnakes, like adults, also appear capable of controlling, or metering, how much venom they inject. Moreover, clinical studies confirm that larger rattlesnakes

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California

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<td>Sistrurus catenatus edwardsii</td>
<td>Desert massasauga</td>
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Hayes and Mackessy

Table 1. Rattlesnakes native to selected regions of the southwestern United States
inflict more dangerous bites than smaller snakes. 18,19 If demographic changes in the local snake population resulted in proportionally fewer young snakes, then a greater proportion of bites would be inflicted by larger, more dangerous snakes, and clinicians would observe a corresponding increase in snakebite severity. Would there be any reason to expect such demographic changes in snake populations? Indeed, the recent drought in the Southwest, 20 has almost certainly dampened the reproduction of rattlesnakes, 22–24 yielding a relative paucity of small snakes. Thus, an increase in snakebite severity could be attributed to an increase in the size of the snakes that are biting humans.

Rattlesnakes potentially adjust the amount of venom injected with level of perceived threat. Snakes of several viperid and elapid species inject more venom when physically grasped than when unrestrained. 14,15,25 With the recent popularity of snake television programming, one might anticipate an increasing number of bites to humans who are inspired by or imitating the snake-handling celebrities. If so, one could expect a higher proportion of bites to result in serious envenomation. However, the only data available for rattlesnakes suggest that they inject similar quantities of venom in both low- (not grasped) and high-threat (grasped) contexts. 14,25 Nevertheless, as we point out later, interaction with the snake often dictates the site of the bite on the human, which could, in turn, affect envenomation severity.

Because clothing can physically disrupt the kinematics of venom injection by snakes, 11,16 changes in the dress style of humans could influence the quantity of venom injected and, hence, severity of bites. For example, an individual bitten in the lower extremity has a greater likelihood of receiving an unimpeded and potentially more serious bite if shorts are worn instead of long pants. We are unaware of any data to address the possibility that clothing worn by snakebite victims has changed in recent years. Such a shift could result from cultural changes in preferred clothing, or an age-related shift in victim profile associated with age-related clothing differences.

### BIOCHEMICAL COMPOSITION (TOXICITY) OF VENOM

Rattlesnake venoms are complex mixtures of compounds, primarily proteins and peptides, which belong to approximately 13 different protein families. 26–29 However, because many of these protein families have multiple isoforms and homologs, there may be well over 100 different protein components in the venom of a given rattlesnake species, 26,30,31 Therefore, the complete protein complement of a venom (the venom proteome) can be quite complex, and it can vary with snake species, age, population location, and other factors (see Table 2). As a suite of genetically determined and heritable traits, the venom proteome can evolve and has done so. 32 However, there are numerous problems with the notion that more toxic venom is rapidly evolving in rattlesnakes. For reasons described below, it is highly unlikely that venom toxicity could change within a few years or decades, and this explanation for any observed increase in

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**Table 2. Major factors potentially influencing the severity of rattlesnake bites to humans (with select references)**

<table>
<thead>
<tr>
<th>Factors associated with the snake and its venom</th>
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| 1. Amount of venom injected  
   a. Size of snake—larger snakes inject more venom than smaller snakes 10,13  
   b. Level of threat—snake may inject more venom when it perceives greater threat 14,15  
   c. Kinematics of bite—human clothing can interfere with bite and disrupt venom injection 16  |
| 2. Biochemical composition and toxicity of venom  
   a. Snake species and venom composition—some snake venoms have more toxic proteins than others 28,44  
   b. Size of snake—young are more toxic in some but not all species 12,41  
   c. Population-level variation—some snakes of the same species show defined geographic variation in toxicity 29,50,51 |

<table>
<thead>
<tr>
<th>Factors associated with the human and its response to the venom</th>
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<tbody>
<tr>
<td>1. Size of human—smaller individual is more vulnerable to venom 19,52 (some studies do not show this 57,104)</td>
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<tr>
<td>2. Interaction with snake—snake provoked to bite may deliver more venom 10,15</td>
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<tr>
<td>3. Site of bite—dictated largely by human behavior, potentially influences bite severity 18,19,60,65</td>
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<tr>
<td>4. Clothing—physical disruption of bite kinematics can reduce amount of venom snake injects 16</td>
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<td>5. General health—elderly, asthmatics, and other health-compromised individuals more vulnerable 60,76,77</td>
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<tr>
<td>6. Hypersensitivity to foreign antigen—inappropriate immune response, usually in previously exposed individuals 60,85–88</td>
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| 7. Treatment  
   a. First aid—when rendered, is often detrimental 89,90  
   b. Antivenom—type and amount of antivenom administered 81,91  
   c. Institution and physician(s)—institutional policies and physician experience will vary  
   d. Time elapsed before treatment—the sooner the treatment, the better 52,81,82  |

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snakebite severity must not be propagated without foundation in fact.

First, selection and genetic drift act much too slowly for rattlesnake venoms to evolve substantial changes within a handful of years. A single generation time for rattlesnakes is in the range of 3 to 7 years, and individuals of most species have a potential lifespan of 20 to 30 years. Evolutionary change requires many generations, as epigenetic (environmental) influences on venom via diet appear to be negligible. To account for hypothesized changes in venom toxicity in different geographic regions (southern California, Arizona, and Colorado), the changes would need to be parallel (toxicity consistently increasing) and take place simultaneously among several unrelated species (Table 1) and in many rattlesnake populations that differ substantially in climate, habitat features, prey base, and predation pressure. Unfortunately, what is meant by “rapid evolutionary change” to scientists (often, thousands to hundreds of thousands of years) is quite different than that perceived by the lay public (typically less than 1 human generation).

Second, although coevolutionary “arms races” between rattlesnakes (evolving more toxic venom) and their prey (evolving venom resistance) have been invoked to explain rapid venom evolution, biochemical changes in venom associated with ontogeny suggest that adult rattlesnakes generally do not benefit from more toxic venom. Many (perhaps most) North American rattlesnake species have more toxic venom as neonates than as adults. As the snakes grow, the toxicity of their venom declines, presumably because they have more venom to inject and the need for proteolytic (digestive) activity increases. In spite of having more toxic venom, the neonates cause less severe envenomation because neonate snakes produce, store, and inject when biting 20 to 50 times less venom than adults. If the snakes were “behind” in the coevolutionary arms race with the prey they have consumed for many thousands of years, why would the venom need to “evolve” suddenly—within the duration of an individual snake’s lifetime, according to popular press reports—to become more toxic? When the snake already has genes to produce more toxic venom, yet reduces the toxicity of its venom as it grows, it makes little sense to argue that the snakes are quickly evolving to “catch up” with their prey. Further, there are very few data on toxicity of venom to native prey species, and there are no data to suggest that snake prey utilization has changed significantly over the last several decades. It has been suggested that “dormant genes” could be expressed in response to greater prey resistance. However, although some genes in the venom proteome are known to be transcribed but not transcribed, there is no evidence that this repression of expression is reversible in response to prey base changes or any other factors.

Third, although hybridization has been invoked as a mechanism for rapid venom evolution, hybridization among rattlesnakes in nature is exceptionally rare. Any introduction of new genes into a species via hybridization would be quickly swamped out unless there was exceptional selection favoring retention of those genes. In rattlesnakes, all species that produce highly toxic venom are known to express the gene for crotoxin/Mojave toxin homologs. This presynaptic neurotoxin is quite potent, and it is the main lethal component that gives these venoms their toxic “punch.” However, there is no evidence, despite persistent media reports, that hybridization of Mohave rattlesnakes (Crotalus scutulatus) with neurotoxic venom components has had any influence on the less toxic, predominantly tissue-damaging venom of southern Pacific rattlesnakes (Crotalus oreganus helleri) in California. In the paper that examined the distribution of these neurotoxins in C oreganus helleri venom, Mojave toxin was identified only in specimens from an isolated mountain range far removed from any population of potentially hybridizing Mohave rattlesnakes. There may well be an unidentified neurotoxin in the venom of some southern Pacific rattlesnakes, if inferences based on human snakebite victims are meaningful, but the majority of snakes tested throughout the species’ range, particularly in the densely populated areas where bites more commonly occur, appear to lack neurotoxicity. Further, the vast majority of envenomings by this species do not present with clinical neurotoxicity.

Apart from the rates and mechanisms of change, the link between venom toxicity and envenomation severity may not be as strong as commonly assumed. Severe symptoms of envenomation (eg, hemorrhage, tissue necrosis, coagulopathy, hypovolemia) can be produced by venoms that are of lower lethality, and highly toxic venoms may not induce lasting tissue damage.

Finally, as human populations expand into formerly remote areas, they are encroaching upon and displacing rattlesnake populations, some of which could conceivably show higher levels of venom toxicity or contain venom components that cause the angioedema and respiratory distress described in the more serious snakebite cases. Population-level or regional variation in venom biochemistry is well documented for many snake species worldwide, including rattlesnakes, but there is no evidence to suggest that this variation has occurred recently.
The Human Factor: Biology and Response to Snake Venom

When ascribing a cause to any observed change in snakebite severity, the human factor should be given equal consideration to that of the snake and its venom. We propose 7 primary factors related to the human and the human’s response to venom that could influence snakebite severity (Table 2). Complex relationships among these factors require that many, if not all, should be taken into account in any formal analysis of snakebite severity and its changes over time.

SIZE OF HUMAN

As expected for many drugs or toxins, the effect of venom on a snakebite victim is dependent in part on the victim’s body mass. That is, smaller (younger) humans are more vulnerable to the effects of venom than larger (typically older) humans. Age and body size do not necessarily correspond well, as young teenagers can have greater body mass than many adults. Any shift in the body size profile of snakebite victims could lead to a change in observed snakebite severity. Shifts in demographic properties of those most at risk of snakebite, for example, could plausibly result in smaller (younger) humans being bitten with increasing frequency, thereby leading to more severe envenomations. Recent increases in the proportion of Americans overweight and obese could also result in an increase in snakebite severity, despite larger body size, due to the increased risks of obesity-related health disorders. Human age- and gender-related behaviors could also potentially influence snakebite severity, as adults and males are more likely to interact with snakes (see below) and be bitten by larger snakes.

INTERACTION WITH SNAKE

In North America, the majority of snakebites inflicted upon humans (children and females being exceptions) now result from human interactions with the snake. As discussed above, snakes of some species grasped by a human and provoked to bite inject more venom than when they are unrestrained, although the only available data for rattlesnakes suggest otherwise. However, provocation and/or handling of a snake could certainly influence the anatomical site of the bite (eg, digit, limb, torso; lower vs. upper extremity), which in turn might affect the severity of the bite (see below). Interactions with the snake can also lead to multiple bites and additional envenomation. Whether the proportion of bites resulting from human interactions has increased in recent years or decades remains to be seen, but it certainly is a possibility.

SITE OF BITE

The anatomical site of the bite could influence the bite’s severity, and it is the human’s behavior that generally dictates the site of the bite. Those suffering an accidental bite are typically bitten on a lower limb during an encounter with a snake while walking. In contrast, those who interact with snakes, often under the influence of alcohol, are typically bitten on an upper limb. Available analyses suggest that bites to lower and upper extremities cause similar envenomation severity. However, 1 study suggested that bites to the distal digits are less severe than bites to the proximal digits or limbs. Another study controlling for multiple factors, including snake size, snake species (5 taxa from southern California), site of bite (distal digit, proximal digit, limb), number of fang marks, and human body size, showed that only 2 of these variables were significant: snake size and human body size. Larger snakes delivered the most severe bites and smaller snakebite victims suffered the most severe envenomations. The site of the bite (almost always upper limbs in this data set) did not influence severity. Moreover, smaller snakes more often bit distal digits whereas larger snakes more often bit limbs, perhaps explaining the milder bites to distal digits reported earlier. Finally, smaller (younger) people were more often bitten by smaller snakes, and larger (older) people were more often bitten by larger snakes. Clearly, analyses that address multiple variables simultaneously are essential to identify the most important contributing factors to snakebite severity, and more such studies are needed to confirm these findings.

Although site of bite may not be a strong explanatory factor, studies are needed comparing envenomation severity of bites to lower and upper extremities that also control for snake size and patient mass. We also need to learn whether the victim profile, behavior in particular, is changing in ways that might influence the site of the bite.

CLOTHING

Although snake fangs readily penetrate ordinary clothing, the clothing itself can physically disrupt the kinematics of venom injection by snakes, potentially reducing envenomation severity. In a study using model human limbs (warm saline solution-filled gloves), a cloth (denim) covering significantly reduced glove envenomation, with a 60% reduction in venom injected by small snakes and 66% by large snakes. More than half of the venom expended by snakes was lost harmlessly on the clothing. Thus, the wearing of long pants, as an alternative to shorts, potentially provides effective, low-cost protection from snakebite when in the habitat of venomous snakes. Although we are unaware of any data on the
type of clothing worn by snakebite victims, a change in dress style of snakebite victims could influence the severity of envenomation.

GENERAL HEALTH

Several possibilities exist for changes in human susceptibility to venom. These include demographic changes in allergic disorders, obesity, age, and access to prompt treatment.

For reasons not entirely understood, recent decades have seen a dramatic increase in the United States in the incidence of asthma. Contributing factors are thought to include demographic changes (African-Americans, for example, are more susceptible) and population increases in obesity and hygiene (some evidence suggests that obesity predisposes one to asthma, and exposure to microbes protects against it). Many environmental factors appear to have some association with asthma incidence and severity, including higher air temperatures, pollution levels, wind conditions, and wildfires. Exposure to cigarette smoke, inconsistent medication use, sedentary lifestyle, and transient exercise also exacerbate respiratory conditions.

Severe respiratory problems appear to be a common denominator in the clinical observations suggesting an increase in more severe snakebites. Other allergic disorders may also be increasing in the United States, predisposing snakebite victims to more serious consequences of envenomation. The likely increase in angioedema, for example, is associated with a number of factors including hypertension, use of angiotensin-converting enzyme (ACE) inhibitors, race, and aging. Anaphylaxis also appears to be on the rise, particularly food anaphylaxis and more so among males. These documented increases in allergies, though not directly germane to snakebite, suggest that there are changes occurring within the population at large which could affect envenomation severity. We discuss hypersensitization in further detail below, as certain behaviors are associated with increased risks of hypersensitivity to venom.

Sufficient evidence now supports a strong link between numerous comorbidities and obesity, and obesity is increasing in the United States. These conditions could all contribute to envenomation severity. The changing age demographics may also be a factor in susceptibility to venom, particularly in Arizona where the proportion of elderly people in the population is sharply increasing. Access to prompt treatment may be another factor, particularly in southern California where the proportion of ethnic groups is changing, with accompanying changes in transportation, communication, and other special healthcare issues. It is well established that prompt treatment for snakebite is critical for efficacious results.

HYPERSENSITIVITY TO FOREIGN ANTIGEN

Extreme sensitivity to foreign antigens, with or without prior exposure, may lead to severe reactions upon envenomation. Hypersensitivity to bee and other hymenopteran venoms is well documented, and sensitivity should be expected to the much larger bolus received during snake envenomations, sometimes resulting in rapid, life-threatening anaphylactic/anaphylactoid reactions. Sensitivity to antivenom can also complicate the clinical presentation.

Close contact with snakes, and snake venom in particular, has been implicated as a frequent cause for anaphylactoid/anaphylactic reactions following snakebite. In 1 study of 289 rattlesnake envenomations treated by a medical toxicology service, 10% reported having been bitten previously. Less direct antigen exposure can also lead to IgE-mediated venom sensitization, especially among workers at zoos, venom production facilities, or herpetocultural operations. A history of atopy is also associated with venom sensitization. Collectively, these reports suggest that there is a predisposition among a specific, ill-defined, and potentially growing sector of the population which would make them candidates for severe reactions to envenomation. However, these reactions probably have little to do with the absolute composition of the venom injected, and there is no indication that venom evolution is a contributing factor to such reactions.

TREATMENT

Snakebite treatment evolves perpetually. Over the years, many first aid remedies have been replaced by others, with most eventually being dismissed as ineffective. Their use is often detrimental, such that when applied, envenomation may become more severe. In 2000, a new antivenom (Crotalidae Polyvalent Immune Fab [ovine] antivenom, CroFab; BTG-Protherics, Salt Lake City, UT) began replacing the one used for many decades previously (Antivenin Crotalidae Polyvalent; Wyeth, Madison, NJ). Both polyvalent antivenoms were formulated to treat all North American rattlesnake bites, but the 2 differ substantially in pharmacologic and clinical properties. This major difference renders comparisons of recent snakebites to those from previous decades meaningless. If one chose to study historic changes in the severity of snakebites, one would need to analyze separately the cases treated with the 2 antivenoms, although a validated correction for 1 antivenom could plausibly be applied to a combined data set.

There are additional treatment factors that influence envenomation severity, and these can change with time.
Treatment no doubt varies among institutions and physicians, and evolves with experience and changes in policies. The time course of treatment can influence severity of envenomation, and is subject to victim circumstances (eg, distance from hospital, transportation mode) and decisions made by care providers. Antivenom efficacy could also vary from batch to batch, but we are unaware of data to support this possibility.

Are Rattlesnake Bites Becoming More Dangerous?

In reality, there are no published data to support the view that rattlesnakes are becoming more dangerous. Citing individual case reports is inappropriate, as symptoms can be highly case-specific, but these have been relied on too often by physicians and then later quoted in the popular press. General impressions may be influenced by a simple sampling artifact: with an increase in overall incidence of snakebite, an increased number of low-probability events—serious envenomations—will follow. Clearly, a detailed study is essential, with rigorously collected data on snakebite severity within a delimited area across a reasonable span of time (10 to 20 or more years). As described above, however, any such comparison will be severely hampered by changes in snakebite treatment, particularly the recent switch to CroFab antivenom. Further, to identify statistically any cause(s) for increased snakebite severity, the study would need to control for numerous factors, as described above and summarized in Table 2. Accordingly, the study would require an exceptional sample size. We certainly welcome such a study.

Testing the Hypothesis That Rattlesnakes Are Evolving More Toxic Venom

Clearly, clinical data derived from snakebite victims are tenuous at best for testing the hypothesis that snakes are rapidly evolving more toxic venom. The more feasible and appropriate test would be to compare relative toxicity of snake venoms (LD$_{50}$, hemorrhagic activity, enzyme activities, etc) taken from snakes of the same species and body size at the same location across a reasonable span of time (10–20 or more years). Until this happens, and unambiguous changes in venom properties are documented, any assertion that rattlesnakes are rapidly evolving more toxic venom remains conjecture. Although crotaline venoms appear to be stable during storage, any such test will need to consider this potential source of bias as well.

The Consequences of Misinformation

Feared and misunderstood by many, beloved and much sought after by others, rattlesnakes evoke a wide range of emotions in humans. When the risks associated with snakebite are exaggerated, there are many unfortunate consequences. Many people become more fearful of spending time in natural areas where snakes might be found. Those encountering snakes may over-react to the risk of an encounter or bite, resulting in poor decision-making and heightened stress. Physicians may be overly aggressive in treating the bite. Rattlesnakes may be tolerated less and destroyed more readily when encountered. Rattlesnake round-ups, notorious for their inhumane treatment of snakes, may be accepted and justified more readily by the lay public. Perhaps most unfortunate, misinformation, once accepted as fact, becomes exceptionally difficult to displace—a well-studied phenomenon known as “illusion of truth.” All of these undesirable consequences could be avoided if the media and those in position to share opinions were more careful about checking their facts.

From personal experience, we know that media reports are frequently incorrect in spite of accurate information provided to reporters. Omission of correct facts often reflects an inherent bias toward sensationalism, as illustrated by the aftermath of a reasonably balanced story that appeared in 2009, citing expert opinion for and against rapid venom evolution in rattlesnakes. This particular story was immediately picked up by United Press International, which claimed in its version of the story that the southern Pacific rattlesnake in California was becoming more aggressive and lethal, but omitted opposing views cited in the original report. The latter story, in turn, was immediately picked up by other media outlets. We are even more disturbed that a respected scientific venue, like Scientific American, emphasized unfounded speculation in its story and mischaracterized comments from one of us.

Venomous snakebite is fortunately a relatively rare event in the United States, with 3,000 to 8,000 bites per year resulting in 5 to 10 deaths per year. However, in many other parts of the world, it remains a significant source of morbidity and mortality. Recent reports suggest that between 400,000 and 2 million snake envenomations, with 20,000 to 100,000 deaths, occur globally each year. If snake venoms were indeed evolving rapidly, perhaps in response to various anthropogenic changes to their environment, then a truly global crisis could be at hand. But this is not likely to be occurring, and untoward media sensationalism draws attention away from the true needs to address snakebite globally, namely, a consistent supply of safe and effective antivenom, sufficient health care, and appropriate training of healthcare providers. There are many unanswered questions concerning venom evolution, and this is a rich area of basic research.
evidence does not support the much-touted notion that more potent venoms are evolving rapidly among snakes. If any increase in the proportion of severe rattlesnake envenomations truly exists, then the possible explanations offered here are much more likely.

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