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SNAKE TOXINS AND VENOMS: AN EVOLUTIONARY PERSPECTIVE

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ABSTRACT: The medical meanings of the terms "toxic" and "venomous" to describe health risks from snakebite make these same terms ineffectual when used in evolutionary studies of snake oral secretions. From the snake's standpoint, a venom is certainly toxic, but a toxin is not necessarily a venom. The term toxin describes only a property of the oral secretion, its laboratory pharmacology; the term venom describes its biological role, how it is actually used by the snake in its natural environment. Failure to distinguish an oral secretion's property from its actual adaptive role has led unnecessarily to confusion when interpreting snake behaviors, feeding strategies, and evolutionary events. This has been especially true in colubrid snakes where the Duvernoy's gland has often been considered to be little more than a poorman's venom system. In fact, the Duvernoy's system in most colubrids may not be a venom system at all, at least not primarily, and its role in the biology of these snakes may be related instead to problems of prey handling and/or digestion. Even in truly venomous snakes, what is called a venom is in fact a mixture of oral secretions with multiple functions. Therefore in functional and evolutionary studies of snake oral secretions, it is not sufficient nor useful to make conclusions about the biological roles of these secretions from their pharmacological and physiological properties alone (e.g. toxicity, color, viscosity). This can be done safely only by examining the survival consequence (if any) of the oral secretion when actually deployed by the snake in its natural environment.

Key words: Duvernoy's systems; Venom systems; Oral secretions of snakes

HUMAN saliva injected cutaneously into the dorsum of the hand may produce local pain, erythema, and edema leading to marked swelling accompanied by restriction of function (Stough et al., 1989). Some components of human saliva are toxic and exhibit a notable LD_{50} (Bonilla et al., 1971). Yet despite these effects and these properties, few people would be so cavalier as to suggest that *Homo sapiens* is a venomous species. Humans consume no food requiring envenomation to make it safe to eat, nor are enemies thwarted by the threat of saliva injection. Physicians administering to patients injected with human saliva (usually incarcerated persons seeking a

medical pass to the relative comfort of a prison hospital) treat the proximate manifestations and need be little troubled as to whether this should be characterized as a "bite" by a "venomous" animal. However, anthropologists examining human origins are not distracted by such properties of human saliva and do not leap to the conclusion from such evidence alone that our own phylogenetic history includes the evolution of a venom system contributing to our biological success! We keep straight the difference between a property of saliva (e.g., toxicity) and its actual deployment by humans (e.g., ecology). The toxicity of our own oral secretions is an incidental property. Human saliva can cause medical signs and symptoms, and a physician must respond. However, if our saliva is toxic does that make us a venomous animal? Of course not.

Property Versus Biological Role

Unfortunately, biologists have not always used the same precautions and common sense when examining oral secretions in advanced snakes. Often based only on a secretion's pharmacology or medical effects, an investigator will note that a snake's oral secretion is toxic, stop there, and declare from this alone that the snake is venomous. Formally such a hasty conclusion results from confusing a secretion's properties with its biological roles, a troubling confusion not restricted to herpetologists nor to snake oral secretions (Bock, 1980). The properties of an oral secretion include its descriptive characteristics, its color, chemical composition, viscosity, protein content, and toxicity. They are usually determined under laboratory conditions. Properties may suggest, but alone they certainly do not confirm, whether these characteristics have any biological significance whatsoever. For example, a pink oral secretion may imply something about the pharmacology of the secretion, but is the color pink biologically significant? Perhaps biologists are led to speculate about an adaptive contribution the color pink makes to survival, but they cannot safely conclude anything about biological significance from the pharmacology alone. The properties of an oral secretion, therefore, should be distinguished from its biological roles. The biological roles, or just roles, of an oral secretion refer to the contribution the secretion plays in the survival and natural life-history of the organism (Bock, 1980). The biological role(s) is determined within the natural context in which the secretion actually serves. Observation of the free ranging animal in its natural habitat is usually or ideally the basis for concluding whether a secretion is (or is not) biologically adaptive, that is whether (or not) it contributes to the successful performance of the snake and therefore contributes (or not) to the snake's chances of survival.

By "toxic", one refers to a property of a secretion, meaning that relative to a particular organism, usually laboratory animals, and whether or not it is lethal in that organism. This is usually expressed as the secretion's LD_{50}. By using the term "venom", one makes claims about the contribution that the secretion makes to survival of the organism producing the secretion.

What is a Venom?

Venoms are found throughout the animal kingdom, but they serve in a variety of biological roles. Many are part of feeding systems. Cnidarian nematocysts are laced with venoms lashed into prey; the gastropod *Conus* delivers venom on injected projectiles, modified radula (Halstead, 1988). Scorpion venoms initially immobilize prey; venom of the solitary braconid wasp acts selectively on segmental body muscles of insect larvae and paralyzes them, but it does not kill the prey, which remain alive until the wasp's eggs hatch and feed on the larvae (Minton, 1974). Salivary glands of shrews, *Blarina*, produce venom that flows along a groove between median pair of teeth into a prey, apparently immobilizing it (Pearson, 1950).

Many venoms serve in digestion, either in a primary or secondary role. Spider venom exhibits proteolytic (Mebs, 1970) and lytic activity (Norment and Vinson, 1969). As a digestive secretion, perhaps their first role (Minton, 1974), spider venoms liquefy

tissues of prey that can then be ingested by a muscular stomach.

Many venoms serve defensive roles. Social bees, wasps, or ants may act collectively by inflicting hundreds of stings in defense of a colony; bony fishes include species, such as the lionfishes, *Pterois*, and scorpionfishes, *Scorpaena*, with spines, sometimes grooved, associated with venom glands that penetrate tissues of an adversary and that introduce venom into wounds; cartilaginous stingrays deliver venom on caudal spines driven into tissues by whipping their tails; the gila monster, *Heloderma*, feeds on eggs and litters of endotherms and may use a venomous bite when deterring attacks by defending parents (Minton, 1974); the male platypus possess a horny spur on its hindlimbs, modified into a venom apparatus (Hill, 1822; Martin and Tidswell, 1895) perhaps used in intraspecific social conflicts.

Venoms have evolved independently in many different animal groups and serve in a variety of adaptive roles. Venom is a broad term under which is subsumed many distinct biological roles—immobilization, paralyzing, killing, liquefying prey, and deterring adversaries. The anatomical instruments associated with venoms are as varied as the biological roles—stingers, spines, and teeth. Behavior deploying the venom apparatus may be passive (e.g., spreading spines and awaiting the adversary to collide with or step on some sea urchin) or active (e.g., biting adversaries).

In the medical literature, the term may even be used more broadly. Venom becomes a general term serving to denote a substance of biological origin that kills, injures, deters, or impairs an organism into which it is injected. Venoms are mixtures of components (among them toxins), produced in specialized glands (venom glands), that are injected into other animals (Mebs, 1978). Some scientists would even extend the term venom to plants, defining a venom as any "toxic substance produced by a plant or animal in a highly developed secretory organ or group of cells, and which is delivered during the act of biting or stinging . . ." (Russell, 1980:3).

I do not wish to treat this larger issue of venom in animals and plants. Instead my purpose is to identify the problems introduced in evolutionary studies of snake venoms when the selective regime is defined too broadly. The danger of doing so has been discussed by Lauder et al. (1994:297) who pointed out that a selective regime defined too broadly prevents recognition of specific selective factors responsible for the evolution of a trait. In snakes, different and specific possible selective factors must be recognized so that one does not preclude the possibility of identifying the immediate factors causally responsible for the evolution of their venom systems in snakes. This cannot be done effectively if snake oral secretions are seen only as "venoms".

Although various biological roles of snake oral secretions have been proposed long ago (Zeller, 1948), the tendency in examining the evolution of or the performance of snake oral glands is to think of them generally, only or primarily as prey killing adaptations (e.g., Meier, 1990). However, this falls into the trap of hiding various roles under one general selective regime. Perhaps nowhere in discussing evolution of snake venom systems has this been a more difficult problem than with Duvernoy's gland of colubrid snakes.

Duvernoy's Gland of Colubrids

Progress in examining the form and function in the evolution of advanced snakes has lagged in part because biologists have sought easy answers to difficult and complex events. We have accepted too quickly the view that if its toxic then its venomous, and therefore avoided the difficult task of looking for other possible biological roles for oral secretions within advanced snakes. Implicit in many such arguments is what I have termed and criticized as the "snowballing hypothesis", wherein oral secretions are first mild venoms, then more so, and then very toxic (Kardong, 1982*a*). The problems with such an argument are many, but among them is a failure to examine experimentally and closely their biological roles.

The issue of property versus biological

role seldom comes up when discussing snakes belonging to the Elapidae (here including sea snakes) and Viperidae, because for most of these advanced snakes there is a clear relationship between their venom systems and the role performed in quickly dispatching prey. Most herpetologists would concede that these venom systems have played a substantial role in the respective evolutions of elapids and viperids. The prey sought by these snakes may exhibit specific antipredator behaviors (Owings and Coss, 1977; Poran and Coss, 1990; Poran et al., 1987; Rowe and Owings, 1990), often accompanied by immunological resistance to snake venoms (Coss et al., 1994; DeWit, 1982). When tables are turned and venomous snakes are themselves preyed upon, their predators may develop immunological resistance to venoms used defensively (Weinstein et al., 1992).

Usually the contentions over the role of oral secretions center on members of the Colubridae. Many oral glands are present within snakes (Kochva, 1978), but most controversy about "venomous" snakes centers on one gland in particular, the Duvernoy's gland, present in many colubrids (Taub, 1966). To complicate matters, Duvernoy's gland is homologous to the venom gland of elapids and viperids (Cans and Elliott, 1968; Kochva, 1978; Kochva and Gans, 1970) as suggested by similar embryonic development (Gygax, 1971; Kochva, 1965; Kochva and Wollberg, 1970; Martin, 1899*a*,*b*,*c*). Further, secretions isolated from Duvernoy's gland may exhibit mild (Burger, 1975; Grogan, 1974; Hayes and Hayes, 1985; Rosenberg et al. 1985; Vest 1981*a*,*b*) or even alarming toxicity (Fukushima, 1986; Kikuchi et al., 1987; McKinstry, 1983; Sakai et al., 1983, 1984), with reports of human deaths following bites by some of these colubrid species (FitzSimons and Smith, 1958; Minton, 1990; Mittleman and Goris, 1974; Ogawa and Sawai, 1986).

Certainly some colubrids with Duvernoy's glands can kill prey rapidly (e.g., *Thelotornis, Dispholidus,* and *Rhabdophis*) apparently under natural conditions. In such colubrid species, Duvernoy's secretion plays a biological role similar to the complex oral secretions of most viperids and elapids, but these are exceptions. When present, the Duvernoy's gland of most colubrids is quite unlike the venom glands of elapids and viperids. Most Duvernoy's glands are not compressed by specialized striated jaw muscles to shoot a charge of venom into prey during a brief bite, and the large luminal reservoir holding a ready supply of venom in venom glands is usually small or absent in Duvernoy's gland (Taub, 1966, 1967). In contrast, the true venom glands of elapids and viperids are acted upon directly by specialized striated jaw muscles (McDowell, 1968), hold a large reservoir of ready venom, and possess a duct system connected to hollow fangs that hold a pressure head so that during the strike a charge of venom is injected quickly and deeply into tissues. The Duvernoy's system of colubrids is not designed to discharge a pulse of venom under pressure (Kardong and Lavin-Murcio, 1993; Zalisko and Kardong, 1992;). No colubrid possesses a hollow fang (Young and Kardong, unpublished), so that Duvernoy's secretions are conveyed along the sides of teeth or within an open tooth groove (Meier, 1990). This means that as the tooth pierces prey, the tooth surface or its open groove is susceptible to occlusion by the pliable prey tissues penetrated (Kardong and Young, 1991), therefore impeding the flow of the secretion deep into tissues of the prey. As a result, relatively low quantities of secretion are delivered and up to half of the secretion remains on or in the skin and does not act significantly on the systemic system during prey capture (Hayes et al., 1993). This makes the Duvernoy's system a very inefficient killing system.

The point is this: if Duvernoy's system evolved to kill prey, then in most colubrids it is a very inefficient prey-killing system! It does not have the ability to generate and hold a high pressure charge of venom, the open "fang" is easily blocked by the integument of the prey, most secretion does not immediately reach deep tissues, and

induced prey death (if at all: Rochelle and Kardong, 1993) is slow, leaving the snake open to retaliation by the prey. The reason the Duvernoy's system is a poor prey-killing system is because in most colubrids its primarily biological role is not to bring about rapid prey death at all. Its primary roles are centered on other aspects of prey capture, control, and preparation for swallowing. Yet this confusion is inevitable if one calls the oral secretions of viperids and elapids venoms and also calls the Duvernoy's secretions of colubrids venoms. To do so suggests similar biological roles when in fact this may not always be the case. The primary roles of most Duvernoy's systems may be quite different from the oral systems of viperids and elapids. Further, subsumed under the term venom are quite different possible biological roles. Venoms may include any secretion that, for example, quiets or immobilizes prey, promotes prey death, quickly kills prey, or defends snakes from their own threats, (various authors). So broadly used, the term venom in the end defines nothing, or more generously it overlooks the subtle and distinctive multiple ecological roles of snake oral secretions and their consequences for the snake's survival.

This is why it is not useful in evolutionary studies to use the general term "venom" to cover the multiple roles for oral secretions of snakes. One term will not fit all. If initially one sets aside the bias that Duvernoy's system is primarily a prey killing system, then one might be more inclined to discover the full range of roles played by the suite of chemicals composing Duvernoy's secretion (Weinstein and Kardong, 1994, Weinstein et al., 1993). With this, biologists might also develop a terminology that more accurately describes this variety of biological roles.

In viperids and elapids, the toxicity of their oral secretions and the immediate medical danger that this presents to humans has understandably led to a preoccupation with the clinical significance of these secretions. Even the proteolytic components, which from the snake's standpoint are usually part of its digestive system and not part of its prey capture strategy, have been largely treated as a clinical problem in human medicine. That approach has been carried back into the analysis of Duvernoy's systems. However, if one steps outside the medical context, outside of preoccupation with the "human health risks", and outside the medical terminology that has grown up around these oral secretions, then one might turn to the issue from the snake's point of view. Why did these oral secretions and their various properties and biological roles evolve? These oral secretions evolved in the service of a variety of biological roles, and so they serve many functions other than to kill prey quickly. Calling such a secretion a "venom" may underscore the medical significance of the secretions, but it is a term too vague and inclusive by itself to be useful in examining the evolutionary significance of these various oral secretions.

Venom

Biological Role of Duvernoy's System

Predominantly, the venom systems of viperid and elapid snakes serve to kill prey quickly, but few colubrids possess a venom system that chemically acts similarly or is anatomically designed similarly. If the Duvernoy's system in most colubrids is not an equivalent venom system, then what is its biological role? For the most part, the role is unknown. I (Kardong, 1982*a*) and others (Gans, 1978; Jansen, 1983; Rodriguez-Robles and Thomas, 1992) have speculated on possible roles and hypothesized contributions that the gland might make in the hopes of encouraging further research to test these hypotheses. Duvernoy's secretion may contribute to capture of prey by improving prey handling, by immobilizing, quieting, incapacitating struggling prey. It may contribute a digestive role. Certainly in viperids, the proteolytic enzymes accompanying the other toxins contribute directly to accelerating digestion of bulky prey (Thomas and Pough, 1979), and this may have had a phylogenetic significance in the evolution of some snake faunas (Savitzky, 1980). Duvernoy's

secretion may act similarly (Finley et al., 1994), but, because comparatively little of the secretion penetrates beyond the integument (Hayes et al., 1993), little enters to start directly digestion within. This has led to the hypothesis that it might chemically enlarge or maintain the holes mechanically punctured in prey integument by teeth during the strike or during swallowing, thereby opening routes for entry of digestive enzymes released later by the digestive tract of the snake (Hayes et al., 1993). Other hypothesized roles are imaginable (Kardong, 1982*a*). With a more open minded view of Duvernoy's gland, these hypotheses should receive the testing that they deserve. There is some evidence that the Duvernoy's gland evolved and has been lost frequently within colubrids (Underwood and Kochva, 1993). If these evolutionary events are to be evaluated, then biologists will need to understand more about Duvernoy's system than its occasional role in a few exceptional species as a prey killing system.

Multiple Biological Roles

The issue of what constitutes a venom needs some clarification. What may come to mind when thinking of venoms is their lethality used primarily in prey capture and perhaps secondarily in defense. However, a venom is a cocktail of different chemicals with a variety of functions (Russell, 1980). Some are toxic while some enhance or spread other factors (Mackessy, 1988, 1993). Therefore, traveling with the toxic components are additional secretions that may participate in a variety of roles—digestion, immobilization, lubrication—in addition to the toxins that contribute to rapid prey death. This chemical arsenal is usually just called a "venom" in recognition of its most important medical component, but this underestimates the presence and importance of these other chemicals and their other biological roles. It is this variety of roles that makes the venom systems so complex and their evolution less than straightforward. Preoccupation with the toxicity and therefore with the supposed killing role of Duvernoy's secretion has led to a neglect of its other and perhaps more primary roles.

Rapid Prey Death

My own view is that a venom's role in producing rapid prey death during prey procurement is a distinct role from other contributions that a venom may make to survival. Oral secretions injected by snakes into prey during capture and swallowing may quiet or immobilize the prey, or contribute similarly to stilling struggling prey. These are quite different roles than those that bring about rapid prey death. These tranquilizing roles for oral secretions are accompanied by quite different designs and behaviors (e.g., constriction, strong jaws) than those oral secretions that bring about rapid prey death (e.g., solenoglyph systems, poststrike trailing). Scientific terminology should recognize this difference.

Certainly the rate of prey death can be prey dependent (Rodríguez-Robles, 1994; Rodríguez-Robles and Leal, 1993; Thomas and Leal, 1993). For example, some lizards may deliver a strong retaliatory bite to an attacking snake, but often the difficulty for the snake is handling a lizard that may escape before the jaws are positioned to begin swallowing. Sometimes the difficulty arises when handling lizards that reach back to bite and hold the neck of the snake holding the lizard, therefore tying up the snake. The snake must release its grip (risking escape of the lizard) or wait for the prey to release its grip (risking a stalemate). Injection of a tranquilizing or "immobilizing" (Thomas and Leal, 1993) oral secretion into the lizard that caused it to become "still" (Rodríguez-Robles, 1992) would be of clear adaptive advantage. However, this is a quite different prey capture strategy than that found in many truly venomous snakes that may release prey in response to prey retaliation (e.g., Kardong, 1982*b*; Radcliffe et al., 1983) or use a predominantly strike and release predatory strategy without waiting for prey retaliation. Using oral secretions that kill prey quickly, reducing its chance of retaliation (e.g., many elapids), or that quickly kill

prey, preventing its escape after release (e.g., many rattlesnakes), are quite different prey capture strategies with quite different associated behaviors, a different mix of oral chemicals, and different jaw designs.

Unfortunately, the biology of elapids is poorly studied from this perspective and viperids are little better studied. Rattlesnake feeding behaviors are perhaps best understood at present. If following the strike the rattlesnake remains in contact with the prey, then the snake exposes itself to retaliation by the prey until the prey is dead. One answer to this problem has been the evolution of strike and release prey capture strategies among rattlesnakes (e.g., Kardong, 1986; Radcliffe et al., 1980) and release when bitten strategies among some elapids (Kardong, 1982*b*; Radcliffe et al., 1983). The oral chemicals that accompany these predatory strategies are different with different specific biological roles.

Venoms may kill prey, but how they do so varies considerably and therefore their contribution to snake survival varies considerably. At least within the truly venomous viperid and elapid snakes, inducing rapid prey death has been an important feature of hunting performance in the evolution of their prey capture strategies (Chiszar and Scudder, 1980; Chiszar et al, 1977; Furry et al., 1991). However in colubrid snakes, envenomation usually does not produce rapid prey death, and therefore they are exposed to different risks from prey struggle and retaliation. Venoms may participate in prey capture in a variety of ways from rapidly killing prey to tranquilizing prey to a digestive role. Each represents a different role that venom plays under various ecological and predatory conditions. With so many ways to contribute to survival, it is not surprising that many different kinds of venom systems occur within advanced snakes.

Conclusions

Property versus Biological Role

The evolution of oral secretions in snakes and of the jaw apparatus that deploys them depends upon the biological roles served. The descriptive pharmacology or clinical effects alone do not allow one to conclude how or even if the property is of biological significance to the snake itself. For evolutionary biologists, an oral secretion is not a venom just because it is toxic or produces clinical symptoms. Such toxicity or genesis of clinical symptoms may be incidental, like the toxicity and clinical signs produced by injected human saliva. Toxicity is a property, a pharmacological characteristic. It may or may not favorably enhance the ecological performance of the snake. A description of pharmacological properties alone is not sufficient to conclude that a toxin is causally responsible for enhancing fitness. To draw such a conclusion, the property of the oral secretion must be demonstrated to be related to the success and survival of the snake in the wild.

Multiple Biological Roles

Venoms are chemical cocktails. They include an assortment of chemicals with many different functions. To sort this out, it is important to identify the biological roles played by each component and the specific selective regime under which each might be of adaptive significance (e.g., Lauder et al., 1994). Venom denotes injected chemicals that are deleterious, but in snakes, this may occur under quite different environmental conditions. Venoms may participate in defense from adversaries. "Spitting" cobras shoot venom from redirected fang tips that is especially effective when striking eyes; the viscosity and chemical composition apparently favors such deployment (Branch, 1988; Devi, 1968). Venoms may participate in prey capture. This may selectively affect, for example, locomotor ability, preventing escape of released prey (Kardong, 1986), immobilization, preventing prey struggle, tranquility, producing relaxation of a prey's return grip on the snake, or rapid killing, preventing loss of released prey. Venoms may participate in digestion. Proteolytic enzymes delivered deep in tissues by long fangs during envenomation accelerate digestion of bulky prey (Thomas and Pough, 1979). Oral secretions remaining in the integument may favorably promote digestion by other mechanisms than by direct

proteolytic digestion (Hayes et al., 1993). Oral secretions may condition teeth and oral membranes or lubricate prey passage (Gans, 1978) or neutralize toxins of ingested prey (Kardong, 1982*a*).

There may be many environmental factors, and thus many selective forces, that affect the evolution of snake venom systems. The term venom is of little service in addressing historical events because it assumes too many and often opposing biological roles. Lumping all such biological roles under one supposed and general selective regime only confounds the study of adaptive processes (Leroi et al., 1994). Unraveling the evolution of venom systems in snakes should include analysis of these multiple roles and the specific selective conditions of each.

Evolution

Venom secretion within snakes occurred late, among derived groups (Greene, 1994), but the evolution of venom secretion includes more than chemical traits. Accompanying the chemical evolution was the morphological equipment to deliver oral secretions (e.g., jaws, fangs, muscles) and the appropriate behavioral patterns. These venom systems are complex and often quite distinct. Fang, jaw, muscle, and venom of elapids (e.g., McDowell, 1968) represent a different suite of derived characters from viperids (e.g., Kardong, 1980, 1982*a*). Colubrid venom systems are distinct even from elapids and viperids (Kardong and Lavín-Murcio, 1993). Within colubrids, the Duvernoy's gland may have arisen and been lost multiple times (Cadle, 1982; Underwood and Kochva, 1993). Fangs and Duvernoy's glands may have arisen initially for reasons unrelated to their eventual incorporation into the venom systems of derived snakes (Kardong, 1982*a*). The history of snake venom systems involves functional integration of changes within an evolving complex adaptation. While it may be convenient initially to examine the evolution of individual traits, eventually understanding the evolution of envenomation must reconcile these related events within the venom apparatus.

With the research still so formative and an understanding of the biological implications so limited, it is neither productive to proliferate terminology nor to impose restrictions on the use of terms by others. Although I shall not try to make such an argument, it is fair to insist on clear reasoning and complete analysis before declaring a species to be venomous, and it is fair to insist that the analysis of Duvernoy's gland include a more rigorous attempt to discover and properly name its full range of roles. One is likely to find that in most colubrids the primary roles of this gland have little to do with true envenomation of prey.

Biologists can still talk about snake venoms, venom systems, and envenomation because that is inevitably the convention handed us by the medical literature. However, one cannot think in these terms only. Thinking of the limits that this terminology imposes and looking to the full range of possibilities served by snake oral secretions can lead to a better understanding of their evolution.

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