

## COLUBRID SNAKES AND DUVERNOY'S "VENOM" GLANDS

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### Abstract

One of the largest groups of snakes is the family Colubridae. This is a paraphyletic assemblage that includes a few venomous species, but most pose no special health risk to humans. Thirty to forty percent of colubrids possess a Duvernoy's gland, a specialized oral gland located in the temporal region. Although it is a homologue to the venom glands of viperid and elapid snakes, the Duvernoy's gland is anatomically and functionally distinct. Generally it lacks a large internal reservoir of secretion, emptying is under low-pressure flow, and the secretion is not delivered via hollow fangs. In contrast, true venom glands hold a large store of ready venom, expel the venom under direct action of striated muscles, and inject it as a high-pressure pulse via hollow fangs. Both the Duvernoy's gland and the venom gland are part of a snake's trophic system, involved primarily in predatory behavior. True venoms are composed of potent toxins whose main biological role is to bring about rapid prey death. Although the secretion from the Duvernoy's gland may include toxins, surprisingly only a few colubrids deploy it similarly to kill prey quickly. In fact, the biological role(s) of Duvernoy's secretion remain today largely unknown. Therefore, it is misleading, in a functional and evolutionary context, automatically to call Duvernoy's secretion a venom (biological role) when only its pharmacology (property) is known. Although Duvernoy's secretion has some components in common with true venoms, some may be fundamentally different in chemical composition, likely because it is involved in different biological roles than a true venom. This means it likely includes novel chemical components with a promise of interest to human medicine.

### Introduction

Pharmacologists and biologists interested in colubrid snakes often work at cross purposes, especially when discussing "venoms" in these snakes. Understandably, pharmacologists focus on the medical significance of these snakes, and the risks they pose to humans. On the other hand, biologists usually focus on the natural history of these snakes, their evolution, and the biological roles in which their "venoms" are involved. Unfortunately biologists have tended, inadvertently, to adopt the convenient, but inappropriate terminology of the medical literature when examining evolutionary and functional questions. And pharmacologists have overlooked some of the clarity biologists recently have provided about colubrid relationships and venom biological roles. For example, many still talk about "rear-fanged colubrids" as if this were a natural group. Instead, this is a heterogeneous assemblage of species, separately evolved with a different assortment of oral secretions. In fact, colubrids as a whole are phylogenetically heterogeneous, a mix of different snake lineages, formally a paraphyletic group. If a pharmacologist discovers that a snake's oral snake secretion is toxic, biologists are apt to call it a venom automatically, without any further documentation or verification that in fact it is actually used by the snake as a venom.

Again understandably, most medical attention given to snakes is centered on the truly venomous groups, the Elapidae and Viperidae (Fig. 1). Each is a monophyletic group, separately evolved. But colubrid snakes are different in important ways. Their "venom" apparatus is different, their "venom" is used in different ways, and their evolutionary history is one in which the "venom" apparatus evolved several times in different colubrid groups. The purpose of this paper is 1) to review these differences of colubrids and truly venomous snakes, and 2) to examine the consequences of these differences.

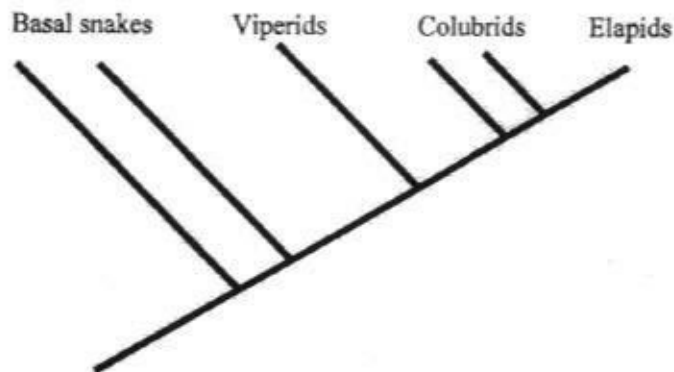


Figure 1. Phylogeny of squamates. Elapids are most closely related to colubrids. From several sources (80, 81).

### Oral Secretions

The earliest snakes were non-venomous and date to the time of the dinosaurs, about 70 million years ago (1). Snakes we might recognize as belonging to the colubrids appeared later, during the early Cenozoic. The first members of the Viperidae and Elapidae are known first from

the middle Cenozoic, about 20-25 million years ago (2). Part of the evolution of snakes has included the rich suite of oral glands (Fig. 2). They are found in, under and next to the tongue; they lie in strips along the upper and lower lips and release their secretions into the oral cavity. Not all those shown (Fig. 2) are present in each species. But reptiles generally, and snakes in particular, usually come equipped with many of these distinct oral glands which generally lubricate and condition prey. Even snakes with well developed venom glands are likely to possess

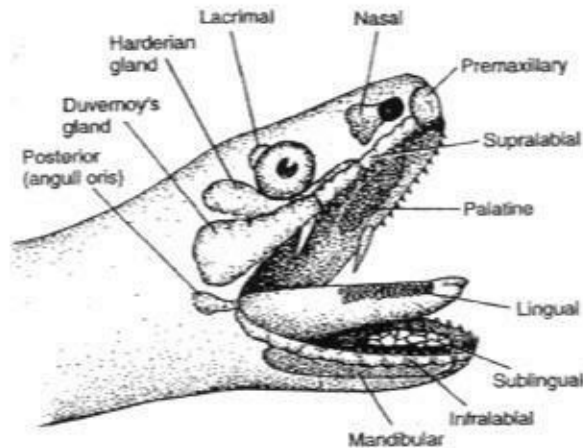


Figure 2. Oral glands of reptiles. Not all oral glands are present in all reptilian species. The venom gland of viperids and elapids is a phylogenetic derivative of the Duvernoy's gland. Based on Kochva (3).

many of these other glands as well. Amongst these glands is the Duvernoy's gland, common in colubrids and the homologue of the venom gland in truly venomous groups. Therefore, the venom glands and the Duvernoy's glands are just two of several oral glands.

#### **Anatomy: Duvernoy's Gland vs. Venom Gland**

The Duvernoy's gland is found only in some groups of colubrids. Its distinctive anatomy distinguishes it from the venom gland, and as such the Duvernoy's gland is not found in viperid or elapid snakes. Several reviews are available (3,4).

#### *Duvernoy's gland*

When present, the paired gland is located behind the eye, in the temporal region, often crowding the supralabial gland along its ventral border (Fig. 3A). The parenchyma is composed of serous cells arranged in lobules that open into lobular ducts, in turn joining common lobular ducts downstream. In the brown tree snake, where the duct system has been studied, common lobular ducts empty into a central cistern on the medial wall of the gland (Fig. 3A). From here a single, main duct departs, reaching to and emptying into the area immediately adjacent to the most posterior, and grooved, maxillary tooth (5). Oral epithelium forms a pocket around the maxillary tooth (Fig. 4A), into which secretion is delivered from the main duct (6).

*Venom Gland*

The venom gland is homologous to the Duvernoy's gland (7-14). However, the paired venom gland, characteristic of viperid and elapid snakes, is anatomically quite different from a Duvernoy's gland. It is defined by a capsule of connective tissue that holds the secretory parenchyma within. Considerable space within the gland is dedicated to extracellular storage of venom, providing a large reservoir of ready venom. In viperid snakes, venom exits the gland via the primary venom duct, passes through a smaller accessory venom gland, and continues as a secondary venom duct that makes contact with the base of the fang (Fig. 3B). In elapid snakes, the main venom gland also includes a large extracellular storage area. Venom, upon exiting from the main gland, immediately passes through the accessory venom gland, which may be quite large, before continuing to the base of the fang (15, 16).

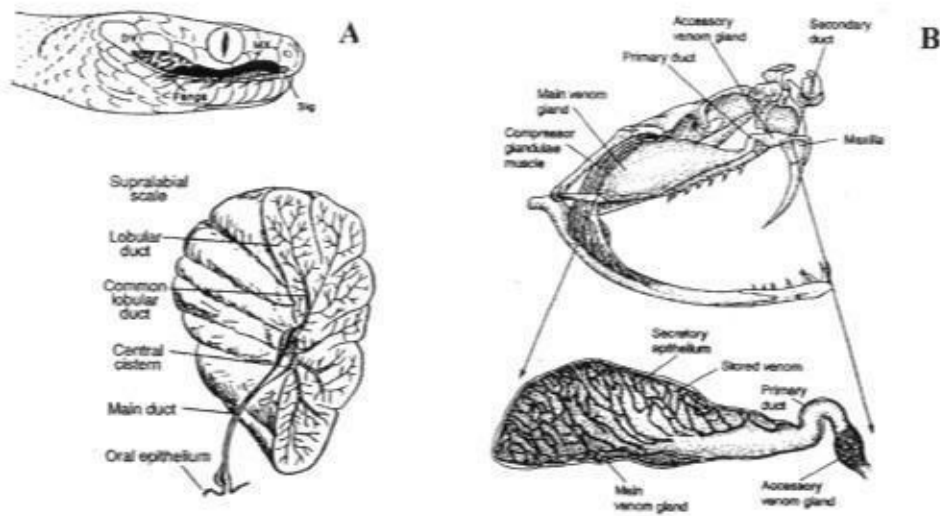


Figure 3. Duvernoy's gland (left) and viperid venom gland. A) Duvernoy's gland (DV) is shown in cutaway view revealing the duct system draining the lobules. Based on *Boiga irregularis*. B) Venom gland includes considerable storage space, a primary duct and an accessory gland. Based on *Crotalus viridis*. Abbreviations: MX, maxilla; Slg, supralabial gland. Based on Zalisko and Kardong (5).

**Emptying Mechanism***Venom Gland*

In viperids and elapids, skeletal muscles, derived from jaw adductors, insert on the capsule of the venom gland. Upon contraction, these compressor muscles act directly on the main venom gland. It is hypothesized that they impart forces directly to the gland, raising intraglandular pressure and thereby causing venom expulsion (15). In viperids, the main compressor is the *M. compressor glandulae* (Figs. 3B & 4C), aided or supported in some species

by the *M. pterygoideus glandulae*. In elapids, the main compressor may include several subdivisions that insert on the main venom gland (17).

When venom is expelled, the venom duct is drawn into tight contact with the base of the erected fang (Fig. 4D), discharging the venom under pressure into the venom channel through the core of the fang, and out the exit orifice at its apex into the prey. Full replenishment of venom stores in an emptied gland may take several days or more (3). However, viperids apparently meter venom during normal feeding (18, 19), drawing selectively on the venom stores to inject in proportion to prey size. They can manage multiple strikes within a few minutes of one another without decrease in envenomation effectiveness (20).

#### *Duvernoy's Gland*

In colubrids with Duvernoy's glands, seldom do jaw muscles or their derivatives insert directly on the capsule of the gland (21). More commonly, skeletal muscles, part of the jaw adductors, pass medial to Duvernoy's gland, but do not insert on it (Fig. 4a). Upon contraction, these muscles may bulge and exert some pressure on the adjacent gland (22), but they do not produce a sudden, high-pressure surge within the Duvernoy's gland. The main duct delivers secretion under low pressure to a cuff of oral epithelium surrounding the base of the posterior maxillary tooth (Fig. 4B), which may convey the secretion into or onto the tissues of the prey (5). During the strike of brown treesnakes (*Boiga irregularis*), almost half of the secretion may not reach tissues beneath the skin (23).

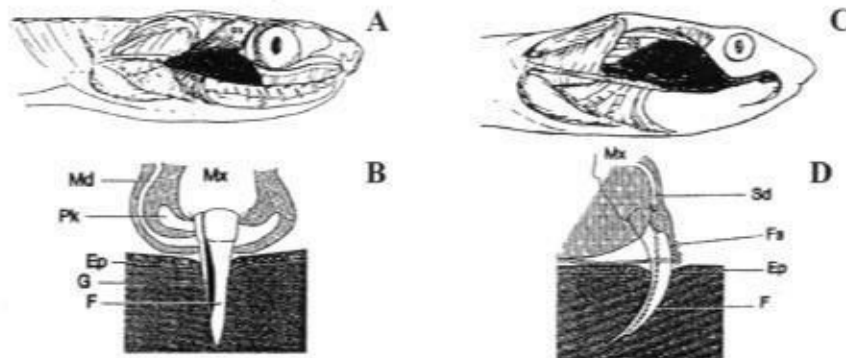


Figure 4. Secretion delivery in Duvernoy's gland compared to venom gland. A) Duvernoy's gland (based on *B. irregularis*), located in the temporal region, empties into a cuff of tissue surrounding the maxillary tooth. Note that the jaw muscle, adductor mandibulae externus superficialis (as) passes medial to the gland but does not insert on it. B) Enlargement of position of main duct (Md) emptying into the pocket of oral epithelium (Pk) around the base of the posterior maxillary tooth (F). C) Venom gland (based on *Trimeresurus*), located in the temporal region, empties into the base of the hollow fang. Note that the jaw muscle, compressor glandulae (cg) directly inserts on the venom gland. D) Enlargement of position of secondary venom duct (Sd) as it is held tight to and empties into the base of the hollow fang (F). Abbreviations: Jaw muscles, adductor mandibulae externus superficialis (as) and compressor glandulae (cg). Other abbreviations: Ep, epithelium of prey; Fs, fang sheath; G, groove in maxillary tooth; Mx, maxilla. Based on Weinstein and Kardong (4).

The Duvernoy's gland and the venom glands are, respectively, low-pressure and high-pressure systems of secretion delivery onto or into prey. The low pressures of secretion flowing from Duvernoy's gland may be little more than capillary pressures, and the high pressures from the venom gland are substantially greater (6). No extensive reservoir is typically present within the Duvernoy's gland, and secretion is released slowly. Venom glands hold a large store of ready venom, and it is injected in a sudden pulse, under pressure.

#### Phylogenetic Distribution of Duvernoy's Gland

Estimating the occurrence of Duvernoy's gland in colubrid snakes is difficult, because no single general survey that includes examination of the duct system and histochemistry, has been conducted. Based on a histological study of colubrid snakes, primarily from museums (24), presence of a Duvernoy's gland was implied if an oral gland included predominantly serous cells. Upon such a basis, about 70 percent of Natricinae snakes sampled possessed a Duvernoy's gland, compared to about 10 percent of other colubrid snakes. Such a criterion occasionally can be unreliable, as mucous cells sometimes are intermingled with serous cells. Often a Duvernoy's gland is associated with a distinctly grooved posterior maxillary tooth. A large survey of snakes and scoring of their tooth morphology (25) revealed that a distinctly grooved posterior maxillary tooth, and by implication a Duvernoy's gland, was present in 21 percent (Xenodontinae) to 88 percent (Homalopsinae) of colubrid snakes examined, with an average of all colubrids sampled around 30 percent. These would be minimum numbers, as not all Duvernoy's glands are served by a grooved tooth (26).

#### Biological Roles of Snake Oral Secretions

Although particular functions are less well known, the suite of oral glands in snakes contribute to successful prey capture, swallowing, and digestion. All are therefore part of the trophic system in snakes. Amongst these, the functions of the oral secretions produced by the Duvernoy's gland and by the venom gland of truly venomous snakes are best known. Often these are thought of as primarily prey killing adaptations (27). But the wider range of biological roles has been proposed long ago (28, 29).

- 1) *Rapid prey death.* The most evident function of a venom is to kill prey rapidly. Prey captured by snakes may retaliate while struggling to escape or actually inflict wounds. Many non-venomous snakes use mechanical means to control these risks, employing strong jaws or body constriction to immobilize the prey. In truly venomous snakes, the injected venom quickly kills the prey. The strike may be targeted to the most vascularized part of the prey (20) where potent toxins within the venom are injected, quickly spread, and rapid death of prey occurs. In some viperid snakes, the prey may be released immediately after envenomation, thereby reducing further the risk of injury from prey retaliation (30). Elapids snakes commonly hold prey, unless the prey is successful in returning a bite, and then the snake may release the prey (31, 32). Prey capture in venomous snakes is built around chemical means of predation, replacing mechanical means of previous snake groups.
- 2) *Quiescence/Immobilization of Prey.* Oral secretions, introduced during the bite by a snake, may not actually kill prey but instead relax or immobilize prey. Unlike rapid death, immobilization does not eliminate the possibility of retaliation, leaves the possibility of eventual prey escape, and requires continued metabolic investment in wrestling with and holding the prey. The advantage is that prey struggle is reduced. This

may be especially important with "cold blooded" prey where venom toxins, promoting rapid death, may be less effective within such an ectothermic physiology. Upon capture, lizards may turn to bite and hold the neck of the attacking snake, producing a stalemate. Under such conditions, injection of immobilizing secretions relax the lizard's grip and permit the snake to complete swallowing (33, 34).

- 3) *Lubrication.* Oral secretions, placed on the surface of the prey, reduce surface friction and help during subsequent intraoral transport and swallowing. Although seldom recognized as an important biological role, oral secretions nevertheless help prepare the prey for ingestion. Snakes do not masticate nor do they bolt food (inertial feed) (35). Instead they use reciprocating advances of the independent left and right sides of the jaws, unilateral feeding (36), to walk their jaws over prey. Once at the back of the oropharyngeal cavity, action of the esophagus aided by axial musculature slides the prey along into the stomach (37). This passage is facilitated by a lubricating coat of oral secretion spread across the prey.
- 4) *Digestion.* In addition to toxins, oral secretions injected deep into prey also carry proteolytic enzymes. These may contribute to the internal breakdown of tissues, and thereby promote the chemical digestion of prey (38). Where the diet of snakes changes as they grow, for example from ectotherms (amphibians, reptiles) to endotherms (rodents), they are faced with unfavorable changes in surface to volume ratios presented by bulky rodents (39). An ontogenetic change addressing this is to increase proteolytic enzyme components in the oral secretion with the dietary shift to rodent prey (20).
- 5) *Poststrike Tracking.* Following an envenomating strike, prey may be quickly released (40), removing the snake from the vicinity of the prey, and allowing the prey to die from the venom injected. However, this predatory behavior requires that the released prey be relocated. To do that, the prey can not scamper beyond a recovery range, the distance the snake can safely and effectively search. Reducing the recover range is a role played by the venom, which does so in two ways. First, it eventually kills the prey. But second, before that, some venom includes components that specifically disrupt the locomotor ability of the prey (20), literally knocking it down (41) before death occurs. Time to death may take several minutes, but knockdown time may be only a few seconds (42), shortening the poststrike recovery distance proportionately.  
Release of envenomated prey poststrike also requires that the particular struck prey be discriminated from competing environment odors, such as from other rodents. It also means that the snake be able to discriminate the trail of the same mouse arriving (non-struck) from its departing odor (struck) (42). Snakes that quickly release struck prey form chemical search image of the prey, unique to the struck prey. This chemical image includes odors gathered from the prey upon contact at the strike. But it also includes odors induced by the process of envenomation. The process of envenomation itself increases the perceptibility of the poststrike prey trail (43), (44), (45), (46). Although some small quantity of venom remains on the surface of the struck prey (18), (19), it is not the venom per se that carries the enhancing odor (47). Instead components of the venom, when injected into prey, induce secreted odors that produce a scent trail, enhance its perceptibility, and give its odor trail a unique chemical character, used by the snake to relocate it.
- 6) *Defense.* Secondary, and the biological role most likely to draw the attention of medical community, is the use of venom in defense. Venom injected during a defensive bite carries all of its trophic components, mentioned above, into the threatening animal or

human. In some venomous snakes, these trophic components are joined by other chemical components to enhance its effectiveness in defense.

These biological roles are not mutually exclusive, nor do all snake oral secretions perform all these roles. Nevertheless, a venom is not only a cocktail of chemicals (48), it is also a cocktail of functions. Further some components may not directly participate in a particular biological role, but instead act synergistically to enhance the effectiveness of other venom principals. These have been termed synergins (*sensu* Slowinski, personal communication).

Snake venoms evolved in trophic roles, part of their prey capture and predatory strategy. These are multiple functions addressing the difficult problems of securing, controlling, and often relocating prey. The complex chemical arsenal that comprises the venom is to be understood within this evolutionary context, and the current and multiple biological roles in which it is involved. Because true venoms include fast acting toxins, they were preadapted for deployment secondarily in defense. Many have been further modified to fit this defensive role.

### Conclusions

#### Colubrid "Venom" and "Venom" Apparatus

##### *Venom*

It is rare to find a colubrid species wherein its Duvernoy's gland releases a secretion that produces rapid prey death (biological role one, above). *Dispholidus*, *Rhabdophis*, *Philodryas* and *Thelotornis* are some of the exceptions, and their Duvernoy's secretion produces relatively rapidly prey death. When biting defensively, severe reactions and even some human deaths have been reported (49-53). But such extreme consequences are rare in bites by colubrids, especially when compared to the common and widespread medical risks from truly venomous snakes such as viperids and elapids (48).

Toxicity of the secretion provides some indication of the health risks should bites occur. Secretions isolated from the Duvernoy's gland may exhibit mild (54-58) or even alarming toxicity (59-62). But toxicity, *per se*, is not a good indicator of the biological role played by the secretion. For example, the Duvernoy's secretion of the brown tree snake, *Boiga irregularis*, is toxic (63, 64) and may produce clinical symptoms (65), yet this snake apparently does not use this characteristic of the secretion to hasten prey death (66).

The point is as obvious as this: human saliva is toxic (67) with clinical manifestations if injected subcutaneously (68). But from this pharmacological property (toxic) or from these clinical symptoms (erythema, edema) we would not conclude that humans use their saliva as a venom! Toxicity is clearly an incidental byproduct of human saliva, not an indication of biological role. The biological role is determined by how the secretion contributes to an animal's survival, which can be determined only by actual empirical study of its use in the wild (69). Outside of the few colubrids that can rapidly kill prey and defend with oral secretions, the biological role(s) of Duvernoy's secretion are today unknown and unverified (70).



*Venom Apparatus*

Not only is the release of Duvernoy's secretion in most colubrids different from the release of venom produced by viperids and elapids, but the glands themselves are different. Characteristically, the Duvernoy's gland holds a very small reservoir of available secretion; pressure driving secretion release is low; delivery is protracted; teeth conveying the secretion are sometimes grooved but never hollow. In viperids and elapids, the venom apparatus includes a large reservoir of ready venom; high pressure drives release of venom; delivery is in a sudden pulse; hollow teeth (fangs) inject the venom.

*Biological Roles and Medical Significance*

Viperid and elapid venoms serve to kill prey rapidly and do so because of their toxicity. In colubrid snakes, that logic is often turned around, reasoning that if Duvernoy's secretion is toxic then it must be a venom, just as in truly venomous snakes. But as just argued, a biological role cannot be determined from such a chemical property alone. If a venom apparatus is defined as an evolved device designed to inject toxins serving adaptively to produce rapid prey death, then all colubrids (with only a few exceptions) lack a true venom apparatus. Consequently, it is misleading for evolutionary biologists to speak of colubrids as possessing an "inefficient" venom apparatus (in litt.). Most colubrids with a Duvernoy's gland do not employ it in such a way.

The pharmacology of Duvernoy's secretions have become better known, with information now on yields, LD<sub>50</sub> values, protein content, hemorrhagic activity, and other properties (4). Such chemical characterizations may aid in assessing the medical significance of the secretion. Yet for all these descriptive properties, nevertheless the biological role of Duvernoy's secretion still remains largely unknown.

*Trophic System*

The venom apparatus of viperids and elapids, and probably the Duvernoy's system of colubrids, evolved initially to serve the trophic requirements of these snakes, from death to poststrike tracking of prey. The mix of chemicals that comprise the venom reflect this range of trophic roles in which it is involved. Phylogenetic analyses provide improved taxonomies that should help identify natural lineages with specialized venom systems. Also, the venom evolves adaptively, reflecting changes in diet geographically or with ontogeny (20, 38). Further, there is now evidence that snakes and their prey are in a kind of "arms race". Prey evolve resistance to venom toxins; snakes evolve new toxins, and back and forth (71-74). Simple genetic systems in snakes permit production of quite variable venoms (Slowinski, personal comm.). As a consequence, venoms may be variable within a species, and even within the same population through time.

*Pharmacology of Snake Venoms*

Within the medical literature, the term "venom" is applied very generally to any biological secretion that may, if introduced into a human, produce a health risk. Jellyfish to snails to snakes to shrews are included (75, 76). Even some plants may qualify as producing a venom (48). Certainly it is prudent for the health community to do so. By labeling a

secretion a venom, or the animal or plant producing it as venomous, this issues a public health warning.

The Duvernoy's gland of most colubrid snakes likely is fundamentally different from the venom glands of viperid and elapid snakes. The primary biological roles in which Duvernoy's secretion is involved are also different, at least in emphasis, than a true venom. While Duvernoy's secretion has some components in common with true venoms, more commonly it lacks a number of enzymatic properties characteristic of true venoms (4). Even when toxic components are in evidence (e.g., 63, 64), they may not be produced at physiologically significant levels sufficient to participate in prey killing or even tranquilization (66). In most colubrids, Duvernoy's secretion is fundamentally different from true venoms, probably because it is involved in different biological roles and different prey handling strategies. But as has been noticed (77), this means the secretion likely includes uniquely evolved, novel chemical components with a promise of significance to human health.

#### *Biology of Snake Venoms*

For biologists, with functional and evolutionary questions in mind, the medical definition of a venom is too broad to serve our purposes well. The simple medical equation, "if it is toxic, then it is a venom" would make humans, whose saliva is toxic, venomous animals. An oral secretion may have many properties—viscosity, yield, color, toxicity, enzymatic activity, to name a few. But properties alone, simple chemical characteristics, are not the same as the biological role of a secretion, how it functions to contribute to the survival of the snake. We might guess a biological role for a chemical property, but proper verification must come from laboratory simulations of feeding strategies or better, from actual field studies. Further, oral secretions, at least in snakes, serve multiple and separate biological roles. The multiple biological roles reflect the many environmental factors, and thus the many independent selective forces, affecting the evolution of the snake venom system. The term venom, applied to viperid and elapid snakes, and especially if applied to Duvernoy's secretion, masks the multiple functions in which this complex secretion participates. To do so confounds the study of adaptive processes (78).

Colubrid snakes and their Duvernoy's system offer biologists opportunities as well. But to take advantage of the opportunities, we must recognize that the Duvernoy's system is not just an "inefficient" venom system waiting around evolutionarily to become a good one. In most colubrids, the secretion lacks a number of enzymatic properties characteristic of true venom; most Duvernoy's secretions lack phospholipase A<sub>2</sub>, at physiologically significant levels, a component characteristic of many true venoms (4, 77). High proteolytic activity in rattlesnake venoms may aid predigestion (39) and it has been hypothesized to facilitate digestion of bulky or seasonally abundant prey and allow broader distribution patterns (20, 38, 79).

Several colubrid secretions too contain components with digestive activity. If these prove to contribute to a biological role in digestion, then they should not be called venoms. They should be called digestive enzymes. Similarly, if colubrid secretions lubricate, or aid in tracking prey, or tranquilize, then their biological roles accordingly are lubrication, tracking or tranquilizing. This does not make them a venom. To be useful in evolutionary and functional studies, the term venom should be used in a restricted sense, for components of the secretions that bring about rapid prey death under natural conditions.

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