3 Reptile Venom Glands
Form, Function, and Future

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CONTENTS

True venom systems evolved at least twice in extant reptiles—once early in helodermatid lizards and second much later in advanced snakes (colubrids, viperids, elapids, and atractaspidids). In helodermatids, the venom gland lies along the lower jaw and empties near grooved, multiple teeth within the mouth. As these slow-moving lizards feed largely on eggs and nestlings, this venom system is probably part of a defensive strategy. Within venomous snakes, the venom gland lies in the temporal region. In viperids and elapids it consists of a main venom gland, pressurized during the strike by directly attached striated muscles, and an accessory gland with connecting ducts eventually emptying into a hollow fang. Atractaspidids possess only a main venom gland, although it too is pressurized by striated muscles. These venom systems are closed, producing a sudden, high-pressure discharge of the venom bolus drawn from a reservoir within the gland. In contrast, many colubrid snakes possess a relatively lower-pressure system based on a Duvernoy's gland lacking a large reservoir, which releases secretion ("venom") more slowly into oral epithelia adjacent to teeth that are sometimes deeply grooved but never hollow. Consequently, predatory systems based on a Duvernoy's system may employ an adaptive strategy different from that of front-fanged venomous snakes. In viperids, elapids, and atractaspidids, the venom system discharges a bolus of venom quickly, dispatching the prey (or thwarting a predator). Such differences in deployment of these oral glands in an adaptive context account for variation in gland structure and in the composition of their secretions. Although early research has focused on the toxic properties of these oral secretions, it is

now clear that venom components, including those of Duvernoy's glands, perform multiple biological functions. However, biological roles must be based on experimental evidence, not conjecture, where it is shown that the oral secretions in fact are injected at levels capable of producing favorable prey capture results. Elucidating these neglected adaptive roles of reptile oral secretions will significantly improve our understanding of the evolution of the complexity of composition and function of these secretions.

I. INTRODUCTION

True venom delivery systems have evolved in several living groups of reptiles: advanced venomous snakes (e.g., colubrids, atractaspidids, vipers, pit vipers, cobras, and allies) and helodermatid lizards (Gila monster, *Heloderma suspectum*, and beaded lizard, *Heloderma horridum*) (Kochva, 1978; Minton and Minton, 1980; Zug, 1993). These squamate groups, as well as other reptiles, possess an extraordinary variety of oral glands (Gabe and Saint-Girons, 1969) and accompanying secretions with an incompletely characterized variety of functions. Some snakes have independently evolved an oral system capable of producing medically significant bites; others are completely harmless to humans. Understandably, investigation of these systems has focused on medically relevant effects of the oral secretions. Consequently, the vast majority of research (approximately 95%) on reptile oral secretions has emphasized the medical and pharmacological effects of these complex mixtures (Kardong, 2002a). This is largely due to practical considerations, as snakebite is a serious public health problem in many regions, especially in underdeveloped countries (White, 1995; see also Section IV, this volume). Estimates of worldwide snakebite incidence range up to 2.5 million bites/annum (Chippaux and Goyffon, 1998).

Many studies of squamate oral secretions have determined lethal potency and experimentally assessed additional deleterious biological effects. Unfortunately, as relatively little attention has been given to the functional and evolutionary roles (sensu, Bock, 1980) of these substances, some aspects of the basic biological significance of these oral secretions remain speculative (Weinstein and Kardong, 1994; Kardong, 1996b; Aird, 2002). Resolving the adaptive significance of venom components requires experimental investigation of the role of specific squamate oral secretions in survival strategies. Presumptive assignment of biological significance without such verification (e.g., Fry et al., 2006) only confounds the study of adaptive processes (Leroi et al., 1994).

Here, we first consider the comparative structure of oral glands. With this anatomical grounding in hand, we will then examine the diversity of secretory products, the functional and evolutionary significance, and a proposal for a richer and more promising research paradigm.

II. STRUCTURE

A. Phylogeny

The sister group to the squamates (lizards and snakes) is Sphenodontida, which dates to at least the Late Triassic, about 230 million years ago (mya). The oldest lizard dates to the Late Jurassic (160 mya), and oldest snakes to the Middle Creataceous (100 mya), although these groups are now extinct. The most ancient group of extant lizards is the Gekkota (Middle Cretaceous), while that of extant snakes is the Aniliidae (Late Cretaceous). Helodermatid-like lizards extend back 98 mya, at least to the Late Cretaceous and perhaps earlier (Gilmore, 1928; Gao and Hou, 1996), but these earliest groups may lack grooved teeth, as are present in later helodermatids (Nydam, 2000). Fossil evidence of boids also dates to the Late Cretaceous. All venomous snakes belong to the advanced snakes, the Caenophidia (Colubroidea), which includes most extant snakes (Figure 3.1). The Caenophidia include three separate lineages, the Atractaspididae, Elapidae, and Viperidae, which have been recognized as dangerously venomous snakes because of their clinical significance and capacity to produce human morbidity and mortality (Warrell, 2004; Kuch et al., 2006). This

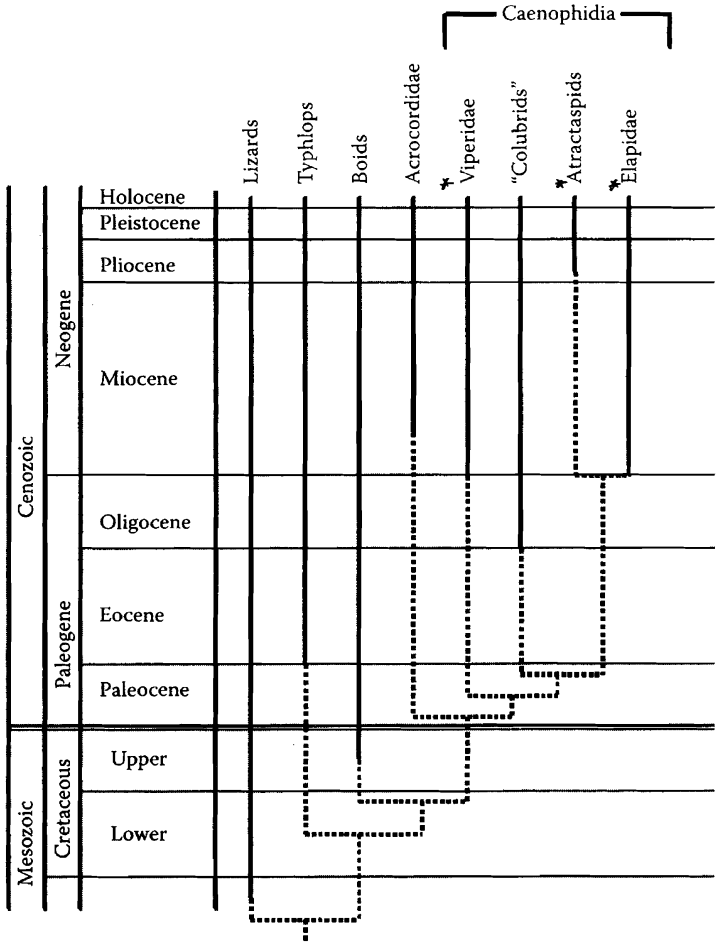

FIGURE 3.1 Stratogram. Stratographic occurrence and phylogenetic relationships of selected squamate groups. Lizards and basal snakes (Typhlopidae, Boidae) appear early, followed by aquatic species (Acrochordidae), and then in the Cenozoic by the advanced snakes. An asterisk (*) denotes clades with a front-fanged venom system, tubular fangs, and specialized venom apparatus. "Colubrids," in parentheses to recognize their paraphyletic feature, have an earlier stratographic debut than the front-fanged venomous snakes. Note that front-fanged venom systems evolved once in viperids and again in atractaspidids and elapids. (Phylogeny based on Benton, 1997; Kuch et al., 2006; Vidal et al., 2007.)

recognition is based also on biological function, as their venom apparatus is designed to bring about rapid prey death (Kardong, 2002a). Other lineages within the Caenophidia are currently incompletely resolved (but see Vidal et al., 2007; Chapter 2, this volume) and their taxonomy unsettled, but for convenience are referred to as colubrids (i.e., members of the unresolved family Colubridae). The colubrids are a paraphyletic group that includes several independent clades. A few species may cause severe human envenomations and even fatalities (FitzSimons and Smith, 1958; Mittleman and Goris, 1978; McKinstry, 1983; Ogawa and Sawai, 1986; Minton, 1990; Kuch and Mebs, 2002), but most colubrids do not represent a significant risk to humans (Kardong, 2002a).

Living families of advanced snakes all debut in the fossil record in the Cenozoic, beginning with the colubrids (Oligocene, 34 mya), followed by elapids (cobras and allies) and viperids (vipers and pit vipers), both at about the start of the Miocene (23 mya). Currently, viperids are thought to derive early within the radiation of advanced snakes, and elapids more directly from colubrids (Figure 3.1).

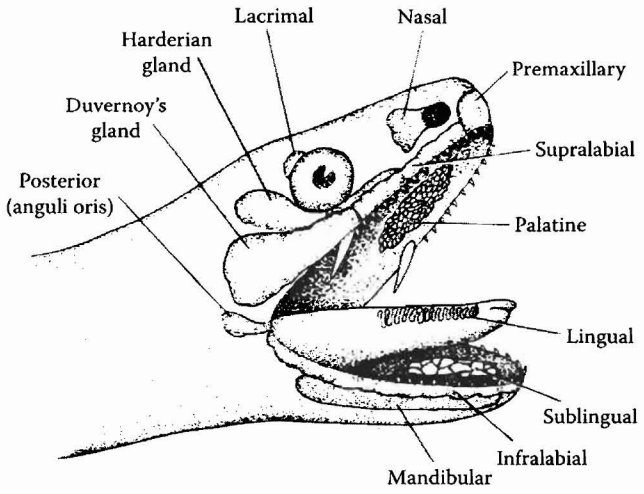

FIGURE 3.2 Oral glands of reptiles. Not all oral glands shown are present in all squamates. The venom gland of advanced snakes is a phylogenetic derivative of the Duvernoy's gland, located in the temporal region behind the eye. (From Kardong, 2002b, after Kochva, 1978. With permission.)

Thus, within the snake radiation, modern venomous snakes appear late, derived from the more basal and nonvenomous snakes, and they in turn from the even earlier lizards.

B. Anatomy of Reptilian Oral Glands

In reptiles, a great variety of glands are present in and around the oral cavity (reviewed by Kochva, 1978). Some are in the tongue, along the upper and lower lips, near the nasal cavity, or near the eye; others are specialized to contribute selective secretions to the mouth (Figure 3.2). Those associated with the nasal cavity and eye bathe these structures, keep them moist, and perhaps perform related functions yet undiscovered. Those that release products immediately into the oral cavity similarly lubricate the oral cavity, but also lubricate food to ease its passage during swallowing.

1. Lizards

a. Helodermatid Lizards

The reptilian oral glands that have received the most attention are those of the venomous helodermatid lizards and venomous snakes. In the helodermatids, the venom apparatus apparently serves a defensive function, as these lizards are slow moving, with the lowest metabolism of any lizard studied to date (Beck, 2005), and feed largely upon prey (e.g., bird eggs, fledglings, juvenile mammals, reptile eggs) swallowed with little resistance (Herrel et al., 1997). Alternative or additional roles for the venom system have not been sufficiently considered. For example, the specialized diet of helodermatids suggests that food is available for a limited part of the year, thereby placing a premium on efficient digestion of gathered prey. Their venom may contribute to heightened digestive processing of prey during this brief period, similar to that proposed in some populations of North American rattlesnakes, which often face a similar brief abundance of prey availability in the early spring (Thomas and Pough, 1979; Kardong, 1986b; Beck, 2005).

Venom secretion in helodermatids likely evolved independently from that in snakes. Unlike venomous snakes, the venom gland, a specialized mandibular gland, lies along the lower jaw, opening into multiple ducts (*Heloderma suspectum*) (Stahnke et al., 1970) or a single duct (*H. horridum*) (Kochva, 1978) that conduct venom to the mandibular tooth row (Figure 3.2). Mandibular and

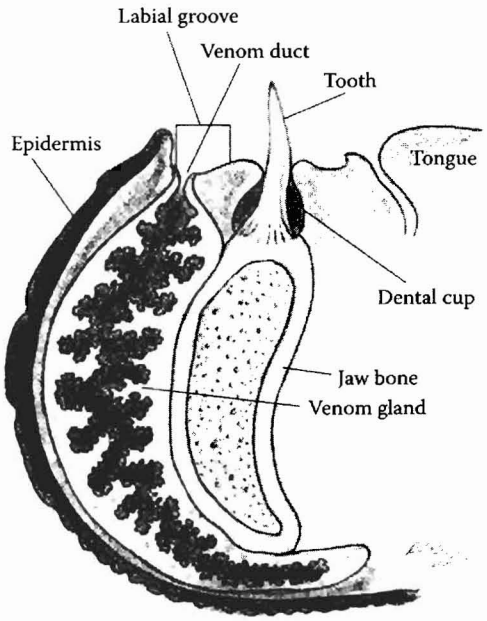

FIGURE 3.3 Venom gland of a helodermatid lizard. Cross section of one of the sacs emptying near a dentary tooth. (After Beck, 2005. With permission.)

maxillary teeth are grooved, but not tubular, perhaps aiding flow or distribution of oral secretion. The venom gland encapsulates multiple lobules emptying into a slightly expanded central lumen (Figure 3.3), but there is no evidence of storage of large volumes of venom in reservoirs, as in many venomous snakes (Bogert and Campo, 1956).

Thus, grossly, the structure of the helodermatid venom gland is readily distinguishable from venom systems in snakes. The complexity of helodermatid venoms is comparable to many snake venoms, and similarly, helodermatid venom biochemistry is reasonably well known. Numerous toxins and other biologically active polypeptides have been isolated from *Heloderma* venoms. These include hemorrhagins, gilatoxin (a kallikrein-like component; Utaisinchaeroen et al., 1993), vasomotor-active peptides (helodermins; Uddman et al., 1999), cell-specific ion channel toxins (helothermine; Nobile et al., 1996), and numerous enzymes and biogenic amines (Mebs and Raudonat, 1967; Hendon and Tu, 1981). The glycoprotein gilatoxin exhibits a murine i.v. lethal potency similar to that of the crude venom (2.7 mg/kg; Hendon and Tu, 1981). Several glucagon-like peptides (i.e., exendin-4) have been isolated from *Heloderma* venoms, and a derivative of these components, Byetta® (exenatide), has been added to the pharmaceutical armamentarium for management of type II diabetes mellitus. These venoms are antigenically distinct from snake venoms. *Heloderma suspectum* and *H. horridum* venoms showed no reactivity in immunodiffusion against twenty-four different monovalent and polyvalent antivenins against snake venoms (Minton, 1974). Interestingly, *Heloderma* venoms exhibit marked thermostability, retaining toxicity after autoclaving at 100°C for 20 minutes (Mebs, 1972). A snake venom with similar documented thermostability is that of Wagler's pit viper, *Tropidolaemus wagleri* (Weinstein, 1991). Although the literature pertaining to *Heloderma* venoms has been comprehensively reviewed (Russell, 1980; Tu, 1991; Mebs, 2002; Campbell and Lamar, 2004; Beck, 2005), the biological role of helodermatid venom has received little attention (Beck, 2005).

Envenomations inflicted by helodermatids produce recognizable clinical poisoning characterized by severe pain, hypotension (and hypotensive shock), nausea/vomiting, diaphoresis, and local edema (Hooker et al., 1994; Roller, 1977; Strimple et al., 1997; Cantrell, 2003; see also Chapter 23).

Myocardial infarction and consumptive coagulopathy following *Heloderma suspectum* envenomation have been reported (Bou-Abboud and Kardassakis, 1988; Preston, 1989), indicating that these envenomations can be life threatening.

b. Other Lizards

Although there is a report of toxic components and transcripts encoding several classes of toxin-like proteins in oral secretions of non-helodermatid lizards (Fry et al., 2006), such as iguanids, agamids, and varanids, there is no current evidence that these proteins are introduced into prey in the wild at levels significant enough to produce rapid subjugation or immobility. Instead, complications of these bites are more likely the result of secondary bacterial infection. Isolated reports of patients bitten by varanids (particularly the desert monitor, *Varanus griseus*, Sopiev et al., 1987) and presenting with clinically significant envenomations or "toxic effects," such as dysphagia, dyspnea, chest discomfort, and other signs/symptoms (Ballard and Antonio, 2001), have been published. However, these and similar cases require careful evidence-based and physician-based evaluation. This is particularly important because there are enormous numbers of varanid, agamid, and iguanid lizards in captivity, and bites from some of these are probably common. However, there are no noteworthy recent reports from medical facilities documenting the clinical evolution of such episodes. Instead, well-documented clinical sequelae of varanid and iguanid bites feature mechanical trauma (severity may be related to the involved anatomical region) and infectious complications. Presentations may include severe lacerations, extensive soft tissue injury, type I hypersensitivity, and cellulitis (Kelsey et al., 1997; Hsieh and Babel, 1999; Merin and Bush, 2000; Bibbs et al., 2001; Levine et al., 2003). Typically, larger specimens inflict correspondingly more serious wounds.

Selection in lizards favors increased relative bite performance associated with increasing cranial size as well as ontogenetically related growth of jaw adductors (Herrel and O'Reilly, 2006). Over one dozen bites inflicted by large varanids (*V. niloticus*, *V. bengalensis*, *V. salvator*, *V. varius*) either personally experienced, medically managed, or observed firsthand by one of the authors (SAW), presented as purely lacerations with reactive erythema and edema. In these cases, increased size of the varanid was associated with increased severity of the resulting injury. Broad-spectrum antibiotic coverage (amoxicillin/clavulanate, 875 mg, b.i.d.) was prescribed in one of three cases managed by SAW. None of these three cases, or the bites experienced personally, had any clinically significant sequelae.

Some investigators have noted the regional beliefs that have anecdotally assigned toxicity to varanids (Smith, 1935). Rarely observed clinical effects of bites inflicted by the Komodo monitor (*Varanus komodoensis*) have been ascribed to pathogenic serotypes of *Staphylococcus* sp. or various Enterobacteriaceae. *Escherichia coli* was the most common bacteria isolated from saliva of wild *V. komodoensis*, while *Staphylococcus capitis* and *S. caseolyticus* were most common in saliva from captive specimens (Montgomery et al., 2002). These investigators identified over fifty taxa of pathogenic organisms in *V. komodoensis* saliva. Interestingly, *Pasteurella multocida* was isolated from the blood of mice succumbing to injections of saliva from wild specimens. The wild *V. komodoensis* studied also had plasma antibody against *P. multocida*. The wounds inflicted by *V. komodoensis* are likely associated with sepsis (Montgomery et al., 2002). In addressing the potential infectious sequelae of *V. komodoensis* bites, Auffenberg (1981) weighed his own extensive experience with anecdotal reports collected in the Flores Islands. He reported two uncomplicated aseptic bites inflicted by 1.0–1.2 m specimens. Reports from islanders described variously severe outcomes from bites inflicted on humans, including rare fatalities. Some included reported predatory behavior. Culture of oral secretions collected from wild lizards yielded *Staphylococcus* sp. and several taxa of Enterobacteriaceae. Persistence of specific populations of oral bacterial flora may depend on re-inoculation from carrion (Auffenberg, 1981).

Many lizards possess a mandibular gland parallel with the infralabial gland along the lower jaw (Figure 3.2). However, outside of helodermatids, the mandibular gland exhibits no distinctive, large

lumen or specializations for venom production and storage. In varanids, teeth are not grooved (or tubular) but are typically serrated. In the absence of any scientific confirmation and clinical verification to the contrary, medical manifestations following bites are most parsimoniously attributed to bacterial infection (Gillespie et al., 2002).

2. Front-Fanged Venomous Snakes

a. Elapids and Viperids

In contrast to helodermatid lizards, venom of elapid, viperid, and atractaspid snakes is produced in and delivered by a specialized venom apparatus along the upper jaw that includes specializations of glands, muscles, teeth, venom, and behavior (Kochva, 1978; Kardong, 1979, 1980, 1982; Jackson, 2003). The venom glands of elapid (including sea snakes and allies) and viperid snakes exhibit some variability in morphology and size, but all share a similar basic design in that there is a main venom gland and an accessory gland. In viperids, the main venom gland empties via a single primary duct into the accessory gland, and from here via a secondary duct into the base of the tubular fang (Figure 3.4). In most elapids, the accessory gland is next to the main venom gland and surrounds the primary venom duct emptying the main venom gland (Figure 3.5) (Rosenberg, 1967). In some sea snakes, the main and accessory glands do not abut one another but instead are separated, connected by the primary venom duct (Gopalakrishnakone and Kochva, 1990, 1993). The main venom glands of both viperids and elapids consist of clumped tubular cisternae lined with secretory cells (Kochva and Gans, 1966), although elapid venom

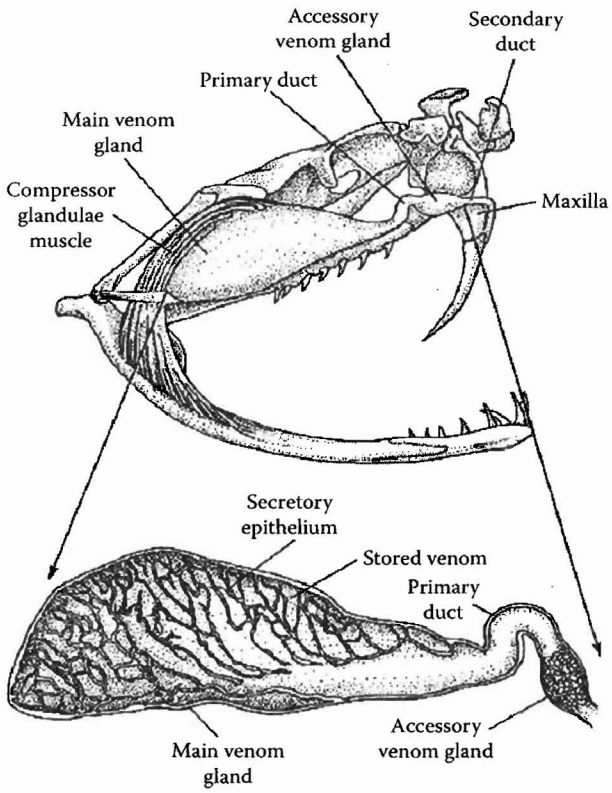

FIGURE 3.4 Viperid venom gland. The secretory epithelium releases venom stored in the collective lumen of the gland where large quantities accumulate, ready for an envenomating strike. During the strike, contraction of the compressor glandulae muscles pressurize the gland, forcing a bolus of venom through the ducts and into the prey. (From Kardong, 2002b, after Mackessy, 1991. With permission.)

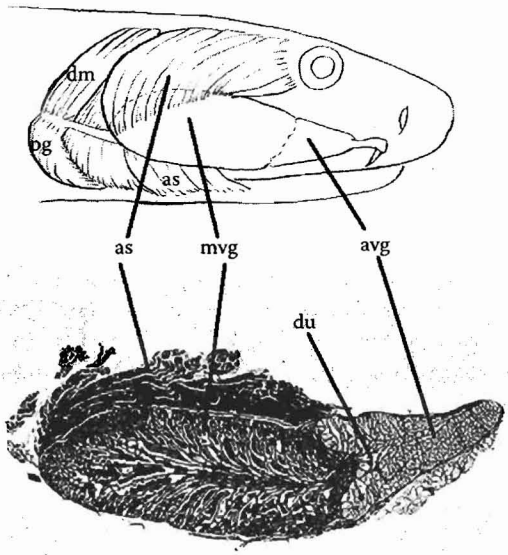

FIGURE 3.5 Elapid venom gland. Head of a representative elapid snake. Note presence of adductor superficialis (as) muscle, which inserts directly on the venom gland (mvg), pressurizing it during the strike. Accessory venom gland (avg), venom duct (du), depressor mandibulae (dm), pterygoidus (pg). Histomicrograph is of *Walterinnesia aegyptii* (kindly supplied by E. Kochva).

glands tend to have longer secretory tubules than those observed in viperid glands (Rosenberg, 1967). Slowly cycling columnar cells with apical granular secretory activity and mucous secretion contribute to venom formation. A diverse cellular population contributes to a wide array of venom components. Recent data support previous studies and hypotheses regarding the origin of venom components as derived molecular species encoded as a consequence of conserved physiological functions (Kochva, 1987; Ho et al., 1997; Cousin et al., 1998; Fry, 2005). The viperid and elapid gland compressors are, respectively, the compressor glandulae muscle, derived from the adductor externus profundus, and the superficialis muscle, derived from the adductor externus superficialis (Jackson, 2003). Further subdivision of the crotaline compressor glandulae into fascicular columns may endow finer control over the volume of expressed venom (Young et al., 2000).

Venom glands reside next to the upper jaw behind the eye, not along the mandible, as in helodermatid lizards. In viperid snakes, venom is produced in a specialized gland and stored extracellularly in a large basal lumen (Figure 3.4) (Mackessy, 1991). Venomous snakes hold stored venom during extended periods of fasting, but it remains ready when feeding resumes after hibernation or in defense; there is no reported turnover of the stored venom protein (Mackessy and Baxter, 2006). If manually depleted (extracted, or "milked"), the secretory epithelium of the main venom gland exhibits rapid protein synthesis (Kochva et al., 1980; Carneiro et al., 1991; Mackessy, 1991) with subsequent exocytosis replenishing venom stores in the ductules and large lumen. This process is completed in about 16 days (Kochva, 1987). However, when expending venom during natural strikes, venom is replenished more rapidly, or less total venom is expended initially, as judged by the rapid recovery of lethal envenomation of prey (Kardong, 1986b).

The action of metalloproteases can produce autolysis of the venom constituents. Stabilization of venom components appears to be accomplished by regulation of pH levels. This is accomplished by mitochondria-rich cells of the main venom gland that acidify the mixture, and by endogenous inhibitors that inhibit enzymatic activity of venom during storage. When injected, activation is spontaneous (Mackessy and Baxter, 2006). These mitochondria-rich cells are morphologically similar to parietal cells of the gastric pit in the mammalian stomach. In the stomach, acidification activates

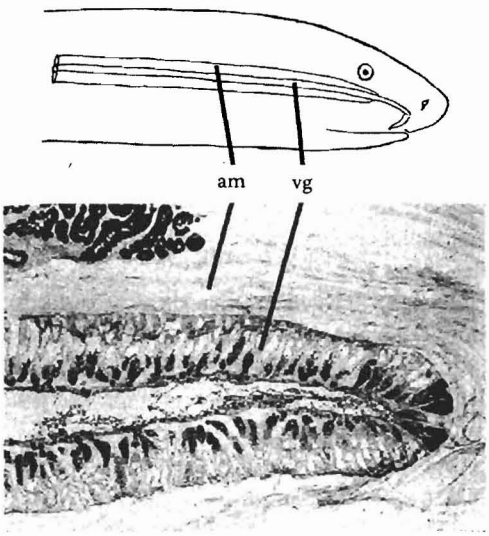

FIGURE 3.6 Atractaspidid venom gland. (a) This venom gland (vg) is elongate, typical of some atractaspidids. (b) Longitudinal section of venom gland. The specialized adductor externus medialis (am) muscle runs parallel with and inserts on the venom gland, presumably pressurizing it during a bite. Note lumen (lu) into which the radially arranged secretory tubules empty. An accessory gland is absent. Histomicrograph is of *Atractaspis engaddensis* (kindly supplied by E. Kochva).

digestive enzymes, but in the venom gland acidification inhibits venom enzymes (Mackessy and Baxter, 2006).

b. Atractaspidids

Atractaspidids have a different venom gland arrangement (Kochva et al., 1967). The centrally located lumen is elongated and surrounded by spoke-like tubules. In some species the gland may be located in the temporal region, but in other species it extends posteriorly out of the region and along the sides of the body (Figure 3.6). It is accompanied by striated compressor muscles involved directly in emptying the gland. In this variation of venom gland topography, it is similar to *Causus* and *Maticora*. Unlike elapids and viperids, the venom gland of atractaspidids lacks a discrete accessory gland and possesses a different histochemical profile (Kochva, 1978). The gland compressor muscle, also unlike viperids and elapids, is derived instead from the adductor externus medialis (Jackson, 2003).

The Duvernoy's gland (see below), a common oral gland in colubrids, is homologous with the true venom gland (Gygax, 1971; Kochva, 1965, 1978; Kochva and Wollberg, 1970). In some atractaspid species, in addition to a venom gland, a Duvernoy's gland is claimed to be present, diagnosed by its macroscopic appearance (coarsely lobulated) and position (dorsolaterally, at the corner of the mouth) (Haas, 1931; McDowell, 1986; Greene, 1997). However, such an interpretation is problematic (Wollberg et al., 1998; Underwood, 2002), and its hypothesized presence may actually be a misinterpretation of the rictal gland. If it is present, the simultaneous presence of a venom gland and a Duvernoy's gland in some atractaspidids has unknown significance. Possibly, the specialized venom gland now adds the role of producing a venom, and other oral gland functions are retained by the persistent Duvernoy's gland (McDowell, 1986).

c. Accessory Glands

The accessory gland, smaller than the main venom gland, consists of two parts recognized by histochemical (Kochva and Gans, 1965; Mackessy and Baxter, 2006) and ultrastructural (Hattingh et al., 1984; Mackessy, 1991) profile. An extract of *Agkistrodon piscivorus* accessory gland injected

intraperitoneally in mice is essentially nontoxic, with doses of up to 100 mg/kg resulting in no ill effects (Gennaro et al., 1963). Its function may be to condition or activate venom passing through during injection (Gans and Elliott, 1968). The presence of serous cells caudally followed rostrally by mucus-secreting epithelium (Hattingh et al., 1984; Mackessy, 1991) implies that lytic venom components passing through are activated by the caudal portion (Mackessy and Baxter, 2006). The accessory gland, especially the rostral part, may contribute substances to the venom during injection. However, electrophoresis and RP-HPLC analysis find no peptide or protein components added to the venom bolus exiting the intact apparatus, compared with main venom gland alone (Mackessy and Baxter, 2006).

As mentioned above, the accessory gland in viperids is separate from but connected via a primary duct to the main venom gland, encircles the venom duct in elapids, and is absent in atractaspidids. The relative size of the accessory gland may vary considerably, especially in specialized species (Gopalakrishnakone and Kochva, 1990).

3. Colubrid Snakes

The structure of venom glands in viperid and elapid snakes is considerably different than the jaw and gland apparatus of colubrids (Figure 3.7), and many species even lack its homologous counterpart, the Duvernoy's gland (Taub, 1966). About 17% of colubrid snakes lack evidence of a Duvernoy's gland, although in some groups as many as 90% of those examined were without a Duvernoy's gland (Taub, 1967). Those colubrids with a Duvernoy's gland exhibit a gland with structure significantly different from the venom gland of front-fanged snakes (Zalisko and Kardong, 1992). Although Duvernoy's glands may show variation, especially in size, they typically do not have any significant storage reservoir, possess a duct system readily distinguishable from that of venom glands of front-fanged

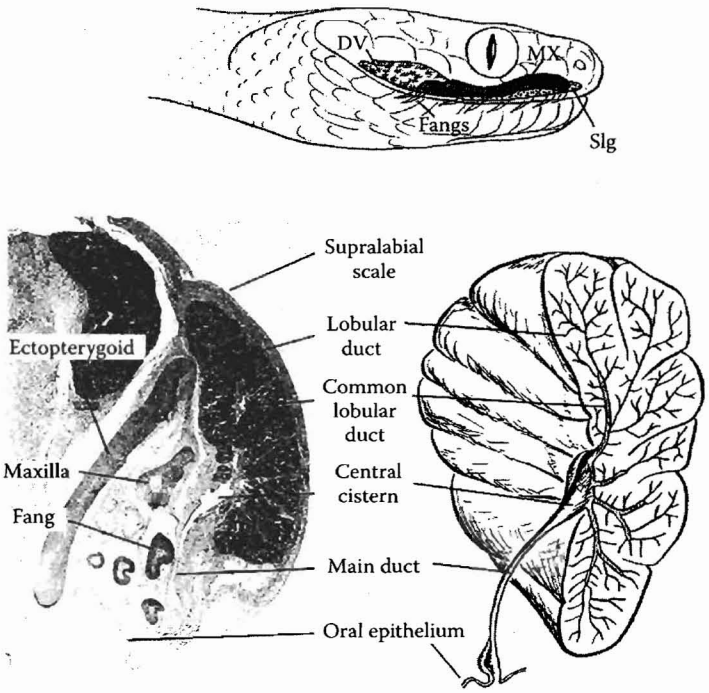

FIGURE 3.7 Duvernoy's gland, *Boiga irregularis*. Top: Duvernoy's gland (DV) lies within the temporal region posterior to the maxilla (MX) and is distinct from the supralabial gland (slg). Lower left: Cross section of right upper labial region to show internal structure of the Duvernoy's gland (lobular duct, common lobular duct, central cistern, main duct) and relationship to adjacent structures. Lower right: Schematic illustration of Duvernoy's gland and its duct system. (After Zalisko and Kardong, 1992.)

snakes, and usually have no direct striated muscle insertion to pressurize the gland (Taub, 1967). The gland, composed primarily of serous cells, is encased in a capsule of connective tissue (Taub, 1967). Teeth associated with Duvernoy's gland are never tubular (hollow) but instead are solid, often enlarged, and sometimes deeply grooved (Weinstein and Kardong, 1994; Young and Kardong, 1996). Rather than pressure discharge of a bolus by mechanical action of striated muscles, release of secretion appears to be primarily via autonomic stimulation (Rosenberg, 1992). The gland is tightly adhered to the overlying skin, and a ligament runs from the posterior end of the gland and inserts on the distal end of the quadrate bone. Contraction of the jaw adductor muscles may therefore contribute to gland pressurization. Released secretion is conveyed by a duct into a loose cuff near or around rear, often enlarged, maxillary teeth (Zalisko and Kardong, 1992). Alternatively, several ducts may carry secretion to the vicinity of various maxillary teeth (Fry et al., 2007).

These basic structural and functional features of Duvernoy's gland are also present in some colubrid species that are known to cause severe bites in humans (e.g., *Dispholidus* and *Thelotornis*; Fitzsimmons and Smith, 1958; Pope, 1958). The Duvernoy's gland is enlarged, but the departing duct serves a grooved maxillary tooth, not a hollow fang (Kardong, 1979; Young and Kardong, 1996). This means that in these venomous colubrids, as in all others with a Duvernoy's gland, the delivery system is necessarily low pressure. The venom system of these colubrids is built on a different morphology than the venom systems of viperid, elapid, and atractaspid snakes. Various caenophidian snakes exhibit atypical or specialized gland morphologies (e.g., *Causus*, *Aipysurus*; Fry et al., 2007), including some colubrids (e.g., *Dasypeltis*; Gans, 1974), some with derived specialized functions (e.g., *Dispholidus*; duToit, 1980). Recognizing these differences in morphology (Duvernoy's vs. front-fanged venom gland) and delivery (low vs. high pressure; McDowell, 1986, 1987; Greene, 1997) may help clarify differing biological roles and evolutionary strategies within caenophidians possessing different venom systems.

III. FUNCTIONS OF THE VENOM APPARATUS

As mentioned above, the functions of oral secretions in reptiles have often been interpreted in their roles in production of clinically significant morbidity and mortality (Meier, 1990), and the pharmacology of these secretions referenced almost exclusively to their supposed significance as a venom system (e.g., Fry et al., 2006). Unfortunately, this has had the effect of underestimating the variety of complex roles played by snake oral secretions in the biology of reptiles, produced a very narrow view of oral secretions, and resulted in misinterpretation of reptilian evolution. In fact, reptilian oral secretions contribute to many biological roles other than to quickly dispatching prey.

A. Delivery of Oral Secretions

Secretions released into the buccal cavity help condition dental structures (Gans, 1978) and certainly coat captured prey with mucus to aid its passage during swallowing (Greene, 1997). Contributions to the mucus are secretions released from supralabial and infralabial glands (Figure 3.2) under autonomic nervous system stimulation, as well as from the mucous lining of the buccal cavity. Depending upon the species, other oral glands may also contribute. These secretions collect relatively slowly as the jaws are walked with reciprocating displacement over the prey (e.g., Kardong, 1986a).

The venom glands of viperids (Kardong and Lavín-Murcio, 1993), elapids (Rosenberg, 1967), and atractaspidids (Kochva, 2002) are part of high-pressure delivery systems. The venom bolus is quickly expelled; rattlesnakes can deliver venom in less than half a second (Kardong and Bels, 1998). Although the specific gland compressor is different in each family (Jackson, 2003), all of these venom systems exhibit notably direct striated muscle insertion. When the gland compressor muscle contracts, the main venom gland is pressurized, producing expulsion of a presynthesized, stored, venom bolus. From venom gland to exit orifice at the tip of the tubular fang, this system is closed when activated, not open to ambient pressures, and therefore can develop, under striated muscle

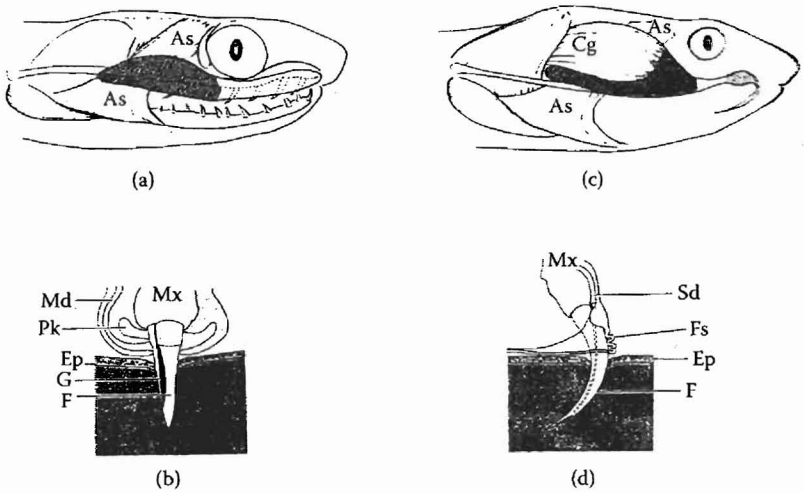

FIGURE 3.8 Duvernoy's gland versus viperid venom gland. (a) The Duvernoy's gland (shaded area), when present in colubrids, is located in the temporal region. The adductor superficialis muscle passes medially to the gland but typically does not insert on the gland, leaving the gland with no direct striated muscle action to pressurize it. (b) The released venom (Duvernoy's secretion) passes into a loose cuff around the posterior maxillary tooth. (c) In the viperid apparatus, the compressor glandulae muscle inserts on the venom gland (shaded) and pressurizes it during the strike. (d) The venom is released under significant pressure and flows through a relatively closed system, enters the erect fang, passes through the fang lumen, and then enters the prey (shaded). As, adductor superficialis; Cg, compressor glandulae; Ep, epidermis of prey; F, grooved maxillary tooth (in b), fang (in d); Fs, fang sheath; G, open groove; Md, main duct; Mx, maxilla; Pk, secretory pocket; Sd, secondary duct. (After Weinstein and Kardong, 1994. With permission.)

action, a sustained high-pressure head until venom enters the prey or predator (cf. Rosenberg, 1967). Penetration of the integument, of prey or predator, by the hollow fang lifts the fang sheath, which remains on the surface of the integument, and thereby opens the route of venom flow, allowing rapid discharge of a bolus of venom (Young et al., 2001, 2003, 2004; Young and O'Shea, 2005).

In comparison with that of a front-fanged venom system, the Duvernoy's gland is necessarily a low-pressure system due to its fundamental anatomical differences and more limited envenomation abilities (Kardong and Lavín-Murcio, 1993). The release of Duvernoy's secretion into a loose cuff of oral epithelium followed by access to a solid or grooved tooth means that this colubrid jaw apparatus is an open, low-pressure system, unable to produce or sustain a high-pressure head (Figure 3.8). In an extensive survey of squamate jaw muscles, Haas (1973) reported that no striated muscles insert directly on the Duvernoy's gland, but as Hass and others (Kochva and Wollberg, 1970) observe, in the colubrid snake *Dispholidis typus* (boomslang) some fibers of the adductor externus superficialis may actually insert on the gland, forming a modest compressor glandulae. Even if not directly attached, the adductor externus superficialis common to colubrids (and all snakes) runs medial to Duvernoy's gland such that when it contracts and bulges, it could theoretically exert a small mechanical lateral force on the nearby gland, further encouraging release of secretion (Jansen and Foehring, 1983).

The special case of *Dispholidus* is an exception among colubrids, and the structure, mechanism of secretion release, and contribution to prey handling distinguish the Duvernoy's gland from the venom gland of front-fanged venomous snakes (Kardong and Lavín-Murcio, 1993). Therefore, interpretation of how such a Duvernoy's system is deployed during prey capture, swallowing, and defense would benefit by recognizing its distinctive structure. Some have been tempted to view the Duvernoy's system as presumably an inefficient venom system (Jackson, 2007). This is unfortunate, but understandable, because its secretions have typically been interpreted in a medical context rather than in a biological one (Kardong, 2002a; but see Mackessy et al., 2006; Pawlak et al., 2006,

2008). Instead, we should consider that its primary biological roles may be those other than producing rapid prey death, and hence interpret its distinctive structural and functional features as serving other survival roles (Kardong, 1996b).

B. Biological Roles of Duvernoy's Secretion (Venom)

The secretions produced by Duvernoy's glands are a highly variable cocktail of chemical entities (primarily proteins), each with individual and synergistic roles. Many of these components exhibit toxicity. Certainly, viperid and elapid venoms provide the biological role of killing prey rapidly, and do so because of toxic components. But the reverse is not necessarily true. If an oral secretion, such as Duvernoy's secretion, is toxic, then we cannot automatically conclude that the secretion is a venom without evidence on how it is utilized during predation. A biological role cannot be determined on the basis of a chemical property alone, but only by directly documenting the role in an organism's survival. Because of the preoccupation with toxicity, alternative functions of Duvernoy's secretion have not been extensively examined and remain largely ignored. However, there are some possibilities, not necessarily mutually exclusive (reviewed in Greene, 1997; Kardong, 2002a; Mackessy, 2002).

During prey capture, the snake must subjugate the prey to prevent its escape and eventually turn it into a meal. The snake also faces the danger of retaliation by the prey, inflicting injury that might injure the snake. Snakes have evolved a variety of mechanisms to deal with these difficulties. Certainly oral secretions function to *kill prey rapidly.* Even some colubrids possess an oral gland system capable of producing secretions with high toxicity (see above) and occasionally human deaths (FitzSimons and Smith, 1958; Mittleman and Goris, 1978; Sawai et al., 1985; Ogawa and Sawai, 1986; Minton, 1990). Certainly this suggests that a few specialized Duvernoy's systems can kill prey rapidly. However, synthesis of such a toxic venom is metabolically costly (McCue, 2006). Other Duvernoy's systems may not rapidly kill but rather immobilize/tranquilize prey (Rodríguez-Robles, 1992; Rodríguez-Robles and Thomas, 1992; Thomas and Leal, 1993). This may reduce prey struggle, but leaves open the possibility of retaliation, escape, and continued metabolic expense. The colubrid snake *Diadophis punctatus* was reported to produce immobility or protracted time to death of squamate prey. This suggests that Duvernoy's secretions are used during prey capture (Gehlbach, 1974; Anton, 1994; Hill and Mackessy, 2000). If oral secretions from the ringneck snake (*D. p. occidentalis*) are injected in high doses intra-abdominally into a natural prey such as the garter snake *Thamnophis ordinoides*, 100% mortality may occur after 3 h (O'Donnell et al., 2007). Unfortunately, such results do not answer the question of whether the ringneck snake in nature actually can or does deliver oral secretions at levels similar to the dose levels used in these laboratory experiments. Without reference to actual prey handling techniques, such toxic effects demonstrated in the laboratory may have no relevance to the actual biological functions. For example, when preying on the black-fronted nunbird (*Monasa nigrifrons*), a green vine snake (*Oxybelis fulgidus*) was observed grasping the bird by the head without constriction. The bird was allowed to hang until immobile. This arboreal snake then swallowed the prey without any sign of struggle (Endo et al., 2007). This could suggest that the properties of Duvernoy's secretion relevant to the snake's survival are the immobilizing properties that incapacitate the bird, not the toxic properties that may immediately kill it.

Besides chemical means, there are mechanical means of prey capture. Constriction offers one mechanism whereby coils of the snake's body encircle and compress the prey, preventing its escape, ultimately leading to death by asphyxiation/thoracic trauma and subsequently facilitating ingestion (Greene and Burghardt, 1978). Large snakes simply overpower prey, using strong jaws to do so. After physically subduing prey, by whatever means, they swallow it. Snakes swallow prey whole, without significant mastication. Swallowing whole prey, especially if covered in fur or feathers, presents significant friction, reduced if lubricating oral secretions coat the prey surface (Gans, 1961). If injected deep into prey during capture or swallowing motions, oral secretions may contribute to

the chemical breakdown of tissues (Thomas and Pough, 1979; Kardong, 1986b; Mackessy, 1988; Hayes et al., 1993) and hence aid digestion. Even if deposited only in tooth punctures in the skin, oral secretion components (enzymatic and nonenzymatic) may contribute to opening such breeches in the integument, thereby facilitating entry of digestive enzymes as the prey passes through the gastrointestinal tract (Hayes et al., 1993).

C. Multifunctionality of Venoms

Snake venoms contain numerous components that serve a wide variety of functions (see Sections II and III). For example, many venoms contain antimicrobial components (Stiles et al., 1991; Lu et al., 2002; Gomes et al., 2005; Nair et al., 2007). Some of these, such as L-amino acid oxidase (LAO), exhibit potent catalytic activity as well as notable bacteriocidal potency, and some of the organisms sensitive to the effects of venom LAOs are common pathogens (*Aeromonas hydrophilia*) of reptiles and amphibians (Stiles et al., 1991). Such components likely are multifunctional and may have potent antimicrobial activity as a coincident consequence of the primary action (production of bacteriocidal oxygen radicals, H_2O_2, as a reaction product of the oxidative deamination of L-amino acids to form α-ketoacids and ammonia) of the enzyme. Such secondary effects may contribute to the conservation, genetic diversification, and duplication of venom components that offer multifunctional utilities for survival.

The use of venom for prey capture and defense, which has been the focus of our discussion, represents a complex strategy that involves multiple functions of venom components and specialized predatory behaviors. For example, the rattlesnake predatory strike may target and deliver a venom bolus to a highly vascularized part of the prey, the thorax holding the lungs and heart (Kardong, 1986b). Typically a rattlesnake, once injecting venom, quickly releases its prey (Klauber, 1956), often within less than half a second (Kardong and Bels, 1998). This strike and quick release behavior is attributed to the advantages of removing the rattlesnake's vulnerable head from biting retaliation by the prey (Lee et al., 1988; Furry et al., 1991). But the cost of this behavior from the snake's standpoint is that the envenomated and released prey must be located again, usually by following chemosensory cues (Chiszar, 1978; Chiszar et al., 1992b,c, 1999). Failure to relocate the struck prey means failure to secure a meal, loss of nutritional support to meet the snake's metabolic needs, and a decrease in fitness.

1. Locomotor Inhibition

The chance to relocate the envenomated prey can be improved by reducing the distance the prey travels after being struck by the rattlesnake. A rapid lethal effect is one way to do this. Another is to disrupt the prey's locomotor system immediately, before death occurs. Within a predatory context it has been noted that well before toxic components bring about death, the envenomated rodent exhibits paralysis of its locomotor system, producing "knockdown" and significantly reducing the distance it travels after being struck and envenomated (Minton, 1969). Crotamine or its close homolog in venom has been shown to produce such effects (e.g., Gonçalves, 1956), and hindlimb paralysis has been used for some time as a bioassay for crotamine (Schenberg, 1959). Crotamine, purified from the venom of the rattlesnake *Crotalus durissus terrificus*, is composed of forty-two amino acid residues, three disulfide bridges (Nicastro et al., 2003), and belongs to the highly conserved myotoxin protein family, designated small basic polypeptide myotoxins (SMPMs) (Ownby, 1998). The homolog myotoxin-α is generally present in the venoms of rattlesnakes (*Crotalus* and *Sistrurus*, Bober et al., 1988). Crotamine has moderate toxicity (i.p., LD_{50} = 6.0 mg/kg; Boni-Mitake et al., 2001), produces myonecrosis, and may have analgesic activity. The hindlimb paresis has been attributed to inhibition of voltage-sensitive Na^+ channels (Nicastro et al., 2003; Oguiura et al., 2005). However, some recent data suggest that preferential antagonism of fast-twitch muscles involving an unknown mechanism may account for the observed paralysis (Rizzi et al., 2007). A crotamine homolog is present in the venom of the northern Pacific rattlesnake, *Crotalus oreganus oreganus* (Bober et al., 1988; Ownby,

1998), and we have observed, following an envenomating strike, the rapid onset of this characteristic spastic hindlimb paresis (Kardong, 1986b).

The spastic paretic effect of crotamine was used by Hampe and Belló (1997) as a sensitive bioassay to determine the concentration of crotamine in a solution. By first injecting mice with a series of purified and known crotamine concentrations and then scoring the time onset of hyperextension paralysis in the hindlimbs, they were able to produce a dose-response (time) curve that could detect doses as low as 0.32 mg/kg (Hampe and Belló, 1997). A regression line of this curve produced the equation:

$$\log \mathbf{t} = 3.20 - 0.80 \log \mathbf{D}$$

where the relationship between the log of the time (**t**) to onset of hyperextension and the log of amount of crotamine (mg/kg) injected (**D**) is determined. We used this equation to calculate the amount of crotamine injected by snakes. To do so, we scored the time from strike to first appearance of hindlimb hyperextensive paralysis in mice naturally struck by *Crotalus oreganus*, northern Pacific rattlesnake. Our results indicate **t** = 14.5 sec (1–56 s). This translates into an average concentration of myotoxin injected to **D** = 0.0028 mg/kg, a level well below the LD_{50} (6.0 mg/kg; Boni-Mitake et al., 2001) and certainly well below the ALD_{100} (absolute lethal dose) upon which the snake in the wild depends to consistently kill its prey.

In natural prey such as deer mice (*Peromyscus maniculatus*), the total time to death, strike to last muscular twitch (Kardong, 1986b), may average just under 2 minutes (117.8 s) (Kuhn et al., 1991). Assuming that prey traveled at 3 cm/s poststrike, this could result in the envenomated prey traveling about 3.5 m before toxic effects alone stopped its displacement (based on Kuhn et al., 1991). However, the quicker paralysis of the locomotor system by myotoxin (here 14.5 s average) means that essentially the mouse is stopped, on average, about 43.5 cm from the snake, reducing the poststrike travel distance by about 88%, and leaving it closer to the snake. This increases the chances of poststrike relocation of the prey and reduces the time the trailing snake itself is exposed to its own community of predators. We hypothesize that its primary biological role, rather than lethality, is more likely to be in reducing the escape distance of envenomated and released prey.

We are well aware that this hypothesis is speculative, as it is built on several separate studies. We present it here to illustrate an example of the biological functions that may be addressed more frequently by pharmacological studies. Restricting experimental focus on the toxic effects of venoms tends to limit our understanding of the totality of venom functions. Certainly crotamine may, when injected, have a concentrated effect in critical organs (Boni-Mitake et al., 2006) or play a synergistic role in quickly dispatching prey. Our point is that broadening the pharmacological analysis of venom components would be welcome, including a test of this hypothesis. Such nonlethal functions may be more important than our first estimates suggest. For example, our estimates of poststrike travel distance may be underestimates, as field studies by others have shown considerable travel of prey after being envenomated (Clark, 2004). This would make the inducement of locomotor disruption all the more important as a survival strategy for the rattlesnake. Thus, based on evidence currently available, myoxins and their homologs seem not to play a significant adaptive role in quickly killing prey. Rather, their most obvious effect is in producing spastic paralysis where they play the primary biological role of reducing prey travel postenvenomation.

2. Precipitous Hypotension and Prey Subjugation

The diversity of biologically active components present in venoms affords direct and synergistic mechanisms of prey subjugation/immobilization. Induction of precipitous hypotension provides a means of rapid disruption of prey locomotion, thereby preventing escape. There is a voluminous literature regarding the hypotensive effects of some snake venoms and envenomation-induced hypotension (with a strong experimental bias toward crotaline venoms). The pharmaceutical exploitation of bradykinin-potentiating peptides from *B. jararaca* venom led to the discovery of one of the most commonly used classes of antihypertensive medications, the angiotensin-converting enzyme inhibitors.

Earlier reports (Russell et al., 1962) demonstrated that an intravenous bolus of *C. adamanteus*, *C. atrox*, *C. ruber*, or *C. oreganus* (formerly *viridis*) *helleri* venom caused immediate hypotension and shock. Several studies have provided evidence of species-specific susceptibility to the hypotensive effects of crotaline venoms (Vick et al., 1967; Schaeffer et al., 1973, 1984; Russell, 1980), perhaps due to the vascular dynamics of venous sequestration in the splanchnic-hepatic circulation (Vick et al., 1967; Russell, 1980). The rapid appearance of radiolabeled crotaline venoms in the lungs and the development of shock, independent from changes in cardiac output, suggested a strong pulmonary role in postenvenomation shock (Gennaro and Ramsey, 1959; Bonta et al., 1970; Russell, 1980). This is especially interesting when considering observations that suggest the specific targeting of predatory strikes to the thoracic cavity (see previous section).

Undoubtedly, the immediate hypotensive effects of many venoms are due to multiple venom components acting both individually and in concert. Components such as bradykinin-potentiating peptides (Ondetti, 1971; Greene et al., 1972; Murayama et al., 2000), rhexic hemorrhagins (Ownby, 1982), and other serine proteases and metalloproteases (Hung and Chiou, 2001; Weinberg et al., 2004) have been implicated in venom-induced hypotensive effects. In addition, some studies have suggested a mechanism related to the loss of central nervous system autoregulation after intravenous administration of *Naja nivea* venom (DiMattio et al., 1985). Other contributing mechanisms may include purinergic receptor activation (Aird, 2002; see also Chapter 20, this volume). This mechanism could function on several levels, including stimulating release of vasoactive peptides and autocoids and inhibiting quantal release from presynaptic terminals and central excitatory neurons, as well as interaction with the effects of other venom constituents (Aird, 2002). These proposed mechanisms merit further investigation. It is noteworthy that some clinical studies have considered the role of elevated purines in hypotensive events concomitant with cellular ischemia (Woolliscroft and Fox, 1986).

Therefore, the hypotensive effects that may occur following envenomation likely result from the complex action of a combination of venom components. These effects probably play an integral role in the rapid immobilization of envenomated prey, both reducing the distance traveled after the strike and reducing danger of prey retaliation. Effective delivery of toxins strongly influences the likelihood of successful preimmobilization. For instance, the biological role of hypotensive effects induced by Duvernoy's secretion (venom) from *Rhamphiophis oxyrhynchus* in anesthetized rats (Lumsden et al., 2005) must be considered in relation to the associated secretory delivery system. Successfully dispatching prey is more complicated than just rapidly killing it. From the snake's standpoint, reducing escape distance and retaliation are also adaptive features of prey capture based on primary functions of venom components. Future research investigating the mechanisms of hypotension induced by ophidian venoms (particularly when conducted in prey species correlated with a specific venom of interest) will advance our understanding of the biological functions of these complex substances.

D. Clinical Implications of Colubrid Venoms: Comparable to Elapids and Viperids?

The detection of neurotoxins in Duvernoy's secretions of colubrid snakes requires careful interpretation and reference to similar toxins in other venomous snakes. For example, it is incorrect to compare the toxic potential of elapids such as *Acanthophis* spp., *Naja* sp., etc., with those of colubrids such as *Boiga dendrophila* to humans directly, without specifying the animal model used. Superficial comparison of murine lethal potencies may suggest a similar level of toxicity between secretions of some colubrids and the venoms of some crotaline or elapid snakes. Unfortunately, for the layperson and nonexpert, this implies a similar level of medical importance and equivalent potential human danger that in fact is not present. It is similarly inaccurate to relate the magnitude of antagonism observed from *in vitro* nerve-muscle preparation assays to potential lethal potency *in vivo*. While such observations can reflect the medical importance of highly potent venoms (such as those from the aforementioned elapids) due to the high proportion of toxins and efficiency of venom delivery

systems, it is misleading to compare these with colubrid toxins. For example, the specificity and ontogenetic nature of the acetylcholine receptor (AchR) subunit composition at the murine motor end plate dictate the action of waglerin 1 from venom of the crotaline viperid, *Tropidolaemus wagleri* (Aiken et al., 1992). This peptide exhibits potent activity in the murine nerve-muscle assay; however, the venom has modal lethal potency in mice, and the purified peptide shows no AchR-binding activity when tested in assays using human or avian tissues (Weinstein et al., 1991; McArdle et al., 1999). Human envenomations by *T. wagleri* typically feature mild to moderate local edema and pain without manifestations of neurotoxicity (S. Minton, personal communication, 1984; Cox, 1991). Most colubrid secretions assayed to date exhibit modal or low potencies in the murine model (see Weinstein and Kardong, 1994, for comparison of lethal potencies), but in avian and lizard models, high toxicity and potency have been observed (Mackessy et al., 2006; Pawlak et al., 2006, 2008).

Having a toxin within the oral gland is not the same thing as delivering it, or delivering it at medically significant levels. Therefore, statements insinuating that one colubrid secretion is as potent as a given elapid venom are overreaching and may be incorrect, likely to produce misplaced concerns regarding medical importance. Such statements do not factor in the venom apparatus, mode of delivery, and possible prey specificity of secreted toxins present in venoms of front-fanged venomous snakes and oral secretions of colubrids. Comments clearly comparing magnitude of *in vitro* assay activity could be accurate in conveyance of observations made regarding the similarity of activity of composite neurotoxins in each venom or secretion. However, such comments will likely be misunderstood, unless succinctly qualified. These considerations assume greater importance due to the explosion of herpetofauna popularity in the pet industry. Incorrect information in the popular press only complicates the need to balance caution with reason in considering potential risks to the reptile hobbyist. On the other hand, it is important that medical professionals obtain an increased awareness of the potential importance of colubrid taxa termed "mildly venomous," or of those with unknown toxicity. The toxicity of oral secretions in the vast majority of colubrid snakes remains unknown, but there are likely taxa of several subfamilies that secrete venoms of clinical importance. Some large adult colubrids with modal or low lethal potency may also pose a risk to pediatric or geriatric patients and to those with chronic illness.

All biological toxins introduced into prey or humans exhibit variability in bioavailability and metabolism. This is particularly relevant as a number of *Boiga* sp. oral secretions exhibit markedly variable protein content (Weinstein and Smith, 1993). This may reflect a broad range of toxin content intraspecifically, as is observed in other venomous caenophidians (Bonilla et al., 1971; Minton and Weinstein, 1986; Chippaux et al., 1991). The lack of a significant volume of stored Duvernoy's secretion contributes further to the differences between the dynamics of colubrid oral secretions and delivery, and those of proteroglyphous and solenoglyphous snakes. Also, as mentioned previously, the unpredictable delivery of colubrid toxins due to the low-pressure delivery systems of these taxa (Kardong and Lavín-Murcio, 1993) and probable species-specific toxin susceptibility may figure prominently when considering colubrid secretion potency. Hypotheses regarding species specificity of colubrid toxins (Weinstein and Smith, 1993; Weinstein and Kardong, 1994; Mackessy, 2002) are supported by data demonstrating saurian- or avian-specific toxins present in some colubrid venoms (Mackessy et al., 2006; Pawlak et al., 2006, 2008).

Undoubtedly, there are unstudied colubrid toxins that are medically important. However, claims of medically significant manifestations of a colubrid bite require careful clinical assessments (Warrell, 2004). As mentioned previously, the majority of serious human envenomations resulting from colubrid bites present as consumptive coagulopathies (disseminated intravascular coagulopathy resulting in hemorrhagic diathesis). To date, clinical evidence indicates that life-threatening colubrid envenomings are due to bites inflicted by the Asian natricine colubrids, *Rhabdophis subminiatus* and *R. tigrinus*, as well as the African dispholidines, *Dispholidus typus*, *Thelotornis kirtlandii*, and *T. capensis* (Visser and Chapman, 1978; Atkinson et al., 1980; Aitchison, 1990; Smeets et al., 1991; Minton, 1990; Li et al., 2001; Seow et al., 2000). Possible

neurotoxic colubrid envenomings have few supporting data and may be misinterpretations of symptoms. Unlike the voluminous documentation of neurotoxic envenomings inflicted by many elapid species and a lesser number of viperids, which can include bulbar and extrabulbar manifestations, there are very limited data regarding neurotoxicity as a consequence of colubrid envenomations. Gonzales (1979) reported neurotoxic effects (ptosis, dysphagia, and respiratory distress) of *Malpolon monspessulanus* envenomation. This single report is supported by the recent case documented by Pommier and de Haro (2007), who report ptosis, blurred vision, and oculomotor palsy in a patient envenomated by an adult *M. monspessulanus* in France. The clinical assessment in this case provides a good evidence base, as the patient was evaluated by an ophthalmologist. Reports of ptosis, respiratory failure, and spasticity among a series ($n = 11$) of pediatric patients (all <4 years of age) bitten by *Boiga irregularis* on Guam (Fritts et al., 1994) could represent evidence of neurotoxic envenoming. In this series, all of the patients with the aforementioned symptoms were less than 1 year old (average = 2.9 months of age). However, the predatory behavior of this species and its ontogenetic variation in venom properties complicate interpretation of these limited documented cases.

Studies of primarily captive *B. irregularis* suggest that small prey are swallowed directly while large prey are constricted (Chiszar et al., 1992a; Hayes et al., 1993). Rodents envenomated by captive specimens were found to accumulate a large proportion (46%) of venom in the integument (Hayes et al., 1993). The murine i.p. lethal potency of adult *B. irregularis* secretion (venom) is 10.3 mg/kg (Weinstein et al., 1991). Interestingly, *B. irregularis* venom exhibits an ontogenetically related decrease in postsynaptic neurotoxin content (Weinstein et al., 1993) and concomitantly increased lethal potency in mice. *Boiga irregularis* implicated in serious bites on Guam were large specimens; mean body length was approximately 1.17 m (Fritts and McCoid, 1999). Further, although increasing *B. irregularis* body size correlates with larger secretion yields, small specimens are capable of substantial yields (Chiszar et al., 1992b). Therefore, numerous variables associated with opisthoglyphous colubrids in general, and with *B. irregularis* biology specifically, contribute to the inconsistent clinical presentations resulting from envenomations by this species (Kardong, 1999). But this presents a paradox. Bites inflicted on human neonates and infants by large specimens resulted in the most concerning clinical presentations. Yet, these large specimens produce secretions with lower murine toxicity. The smaller snakes have oral secretions with significant neurotoxin content, a low toxicity, and are not implicated with serious human envenomations. Thus, *Boiga irregularis* presents a risk to neonates and infants; however, the source of the medical sequelae remains unclear and unconfirmed. Fritts and McCoid (1999) considered the possibility that *Boiga* spp. envenomations may be misidentified as bites inflicted by sympatric elapid species such as *Bungarus* spp. in some locations. This accentuates the need for careful documentation, whenever possible, of colubrid envenomations, including information detailing the verified identity (ideally, with deposition of the voucher specimen in a recognized institution), size, weight, and provenance of offending snakes, and presenting history, lab data, investigations, and clinical observations.

IV. DISCUSSION AND CONCLUSIONS

A. Multiple Functions and Biological Roles in the Wild

Oral secretions of squamates are chemical cocktails with a richness and diversity of functions and biological roles. Even a toxic peptide such as crotamine in the venom of some rattlesnakes fulfills a primary role not of initially killing prey. Rather, its probable primary function is to disable the locomotor system of the released prey, preventing its escape beyond a recovery range before death occurs. Some components of venomous snakes may similarly be toxic, but play more primary roles in spreading venoms, disrupting blood supply, or promoting rapid circulatory spread of the venom (Minton and Minton, 1980; Russell, 1980; Mebs, 2002). Certainly squamate oral secretions may be defined as true venoms and promote rapid prey death, but many have additional roles,

such as producing quiescence/immobilization of prey (Rodríguez-Robles, 1992; Rodríguez-Robles and Leal, 1993), lubrication, digestion, poststrike trailing, defense, and others (Kardong, 2002a). Although crotamine and other myotoxins are widely perceived in the biomedical literature as toxins contributing directly to prey death, their primary biological role likely is to reduce prey escape distance traveled by envenomated prey.

In truly venomous snakes, the venom components that cause rapid prey death are pharmacologically toxic. But the opposite is not necessarily true—simply because a given biological substance is toxic should not alone infer that the animal producing it is necessarily venomous. "Venomous" has been interpreted to imply a verified biological role (Kardong, 1996b). Toxicity is a property, like the color yellow, while venomous implies a biological role, how it is used (Bock, 1980; Kardong, 1996b). In fact, such pharmacological data alone can actually be misleading when making inferences about biological role. For example, human saliva contains a complex array of bioactive substances and bacteria. The chemical constituents may include histatins (cationic, histidine-rich, antifungal peptides; Situ and Bobek, 2000, platelet-activating factor [PAF] and PAF inhibitor [Smal and Baldo, 1991], lysozyme, α-amylase, the α-7 acetylcholine receptor antagonist kynurenic acid [Kuc et al., 2006]), as well as numerous mucins, proteases, and protease inhibitors. A recent investigation of the human salivary proteome catalogued 309 proteins from whole human saliva (Hu et al., 2005), some of which are toxic (Bonilla et al., 1971). However, there is no objective or useful sense in which humans can be described as venomous animals. The murine toxicity of human saliva is an epiphenomenon, a secondary characteristic with no adaptive advantage, but an accidental by-product of its biochemistry. While our saliva may be toxic (i.e., a property), humans are not venomous (biological role).

Squamate secretions injected into laboratory animals may show pharmacological effects of toxicity or deleterious physiological responses. Such results may interest toxinologists, but without further examination, they shed little light on how the lizard or snake actually uses, or does not use, these features of its oral secretion. For example, the colubrid snake *Boiga irregularis* possesses grooved rear teeth (Young and Kardong, 1996) and delivers a pharmacologically toxic (Weinstein et al., 1991) oral secretion (Duvernoy's secretion) (Zalisko and Kardong, 1992) to its prey (Hayes et al., 1993). But if delivery of this secretion is experimentally blocked, there is no significant effect on its prey capture abilities or defense (using mice), suggesting that this "toxic" secretion plays no significant biological role in prey capture or defense (in captive scenarios) in the life of the snake (Rochelle and Kardong, 1993). However, the observation that venom from this species is much more toxic to lizard prey than to mice, coupled with the behavioral differences of the snakes toward these prey (lizards are held until quiescence, while mice are constricted), strongly suggests that snakes utilize different predatory modes, envenomation or constriction, toward different prey (Mackessy et al., 2006). By comparison, if the glandular secretion (venom) of a viperid snake (which does not also constrict) is blocked, prey capture ability may be severely disrupted (Kardong, 1996a). A snake must possess the specialized venom equipment that is sufficient to deliver, in a timely manner, large enough quantities to give the toxin biological significance. Otherwise, the pharmacological properties may be epiphenomena and may mislead interpretation of actual biological roles. Stated another way, an oral secretion may be pharmacologically toxic, but biologically inconsequential if the snake lacks the venom system to inject it at levels sufficient to contribute to prey capture.

B. "Protovenoms": Preadapted for Later Roles

Evolutionary biologists long ago recognized that features in derived species make their debut in basal species, although often in a different biological role. This evolutionary phenomenon is exaptation (preadaptation) (Gould and Vrba, 1982). Paraphrasing Stephen J. Gould, this involves previous characters of ancestors in one biological role being co-opted to new biological roles in later descendants (Gould, 2002). Toxic oral substances, when biochemically documented in colubrid snakes and basal squamates, do not automatically qualify the reptile as venomous. Instead, these toxins may be

involved in different biological roles in basal groups, later to be co-opted into a new role in the true venom system of derived snakes. Herein, genes and their products (toxins) are exapted from earlier phylogenetic roles into new derived roles (Arthur, 2002). The only way to confirm a toxin's biological role in basal squamates is by experimental confirmation.

Taking all the varied and diverse toxic components of squamate oral secretions and collapsing them into a venom system can mask, not illuminate, the variety of specialized morphologies, functions, and biological roles (Leroi et al., 1994) present in squamate reptiles. Such an expansive use of the term *venomous*, even mapped on a robust phylogeny, simply repeats past mistakes. What some have described in basal squamates as a venom system (Fry et al., 2006) is likely not an early evolution of a venom system at all, but an example of chemical preadaptation within oral secretions of a clade of squamates. Calling all in this clade venomous implies an overall potential danger that does not exist, misleads in the assessment of medical risks, and confuses the biological assessment of squamate biochemical systems.

If used in a more restricted sense, we see that venom systems in squamates in fact evolved independently multiple times. Each includes specializations of glands, muscles, teeth, oral secretion (venom), and behavior sufficient to deploy this jaw apparatus in effective defense or in the rapid dispatch of prey. One such venom system is found in helodermatid lizards that includes enhanced activity of the mandibular gland along the lower jaw, teeth, and venom secretion. In a few colubrids, a venom system arose that is built upon the Duvernoy's gland that releases and can deliver surprisingly toxic, occasionally even medically important, secretions. Within the front-fanged advanced snakes, three high-pressure venom systems have apparently independently evolved among atractaspidids, elapids, and viperids. The different structural and functional features of these venom systems suggest that they represent different solutions to environmental challenges of prey capture or defense. The evolution of venom systems in squamates is complex, which is why we urge greater experimental attention to actual prey handling techniques in order to verify natural biological functions, rather than claims based on extrapolation or conjecture. Such an experimental approach, building a better understanding of their varied functions and biological roles, will help to clarify this complex evolution of venom systems. Finally, this overview of venom gland form and function highlights the importance of interdisciplinary research that defines contemporary toxinological investigation. It is likely that future research will provide discoveries useful to basic biomedical science, expand comprehension of the basic biology of venomous reptiles, and contribute to clinical and laboratory medicine.

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