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Introduction to the special edition of *Journal of Toxicology - Toxin Reviews*

Included within this issue are eight articles which cover specific aspects of the architecture of the venom glands, current taxonomy, biochemistry of the venoms and effects of envenomation on humans by snakes generally included in the heterogeneous family of advanced snakes, the Colubridae. This family is often referred to as rear-fanged snakes because of the common occurrence of one or more enlarged teeth on the rear of the maxilla; however, colubrids with a Duvernoy's gland (a homolog of the venom gland of front-fanged snakes) may or may not have enlarged maxillary teeth. The "Colubridae" is exceptionally diverse and includes the majority of living snakes, and various members may be completely non-venomous, capable of producing venoms which facilitate handling prey, or capable of producing highly toxic venoms which can kill not only prey, but also unwary human handlers. Estimates of venom-producing species exceed 700 worldwide, but our knowledge of even the most rudimentary aspects of the venoms exists for only a handful of species. The general state of the biochemistry and toxinology of most colubrid venoms is somewhat comparable to that which existed for front-fanged snake venoms in approximately 1960, before analytical techniques allowed for extensive work with these complex secretions. Application of many methods to colubrid venoms has been further hampered by the small amount of secretion typically produced, but this limitation has now been addressed (1-2). An increase in the amounts of crude material available and the widespread use of many microanalytical techniques can allow preliminary analysis of venoms from even the smallest species (see 3), but a lack of commercial availability of most colubrid venoms still represents a barrier to widespread analysis. However, as will be developed in the following essays, these venoms represent a vast source of novel biological compounds, and it is hoped that this issue will stimulate interest in the venoms of these diverse and widespread snakes.

Definition of a venom

Historically, venoms have been differentiated from poisons by the route of entry into a recipient organism: venoms are injected or introduced into a wound produced by the delivering organism, and poisons are ingested (accidentally or intentionally) by the recipient organism. The term venom typically is applied to simple to complex secretions (usually containing multiple toxins) produced in a specialized gland which cause deleterious effects and/or death when injected into a recipient organism (e.g., 4). A toxin, on the other hand, is a biologically produced unique molecular entity, which can damage or kill an organism through its action on specific tissues (e.g., 5). Unfortunately, even in the scientific literature, one still occasionally encounters the description of a venom as a "neurotoxin" or a "hemotoxin", particularly in reference to the venoms of front-fanged snakes (families Atractaspididae, Elapidae and Viperidae). The term "hemotoxin" is really a misnomer, because there are no venom toxins, which specifically target the blood *per se*. Though the dominant pharmacological effect of a venom may be described superficially as "neurotoxic" or "tissue-damaging", no snake venom described to date contains only a single molecular or pharmacologically-active component. Toxinologists, herpetologists and other should therefore refrain from using such obfuscating language, because these errors become propagated by the lay press and could lead to inappropriate management of human envenomations by a "hemotoxic" snake. For example, in the United States, the general public considers rattlesnakes to produce "hemotoxic" venom; however, venom of the Mojave rattlesnake, *Crotalus scutulatus* (as well as several other species), often contains Mojave toxin, a potent homolog of the presynaptic neurotoxin crotoxin, and bites by this species can rapidly become life-threatening.

Venoms of colubrid snakes

Arguments have been put forth that secretions from the Duvernoy's gland of snakes in the family Colubridae *not* be termed venoms (6; also see Kardong, this issue), because this label could obscure attempts to ascertain the biological roles of these secretions (but see 7). I consider colubrid Duvernoy's gland secretions to be venoms, because the Duvernoy's gland is homologous with the venom gland proper of front-fanged snakes (8), some components common in front-fanged snake venoms are also found in colubrid venoms (3) and it appears that these secretions serve a role which is similar to the venoms of front-fanged snakes (particularly facilitation of prey handling: e.g., 7). Additionally, colubrid venoms contain numerous components with both enzymatic and toxic activities, and as protein sequence data becomes available, it is apparent that several colubrid venom proteins show homologous sequences with front-fanged snake venom proteins. However, as detailed in following papers, there may be important biological roles for venom components which are unique to the Duvernoy's gland secretion of colubrids.

A general pattern emerging from the consideration of colubrid envenomations is that in general, colubrid bites are not a significant source of human morbidity and mortality. The reasons for this are numerous, including an injection system which is not as efficient as that seen in front-fanged snakes, leading to the requirement (generally) of long contact time for delivery of amounts of venom sufficient to cause problems in humans. From a public health perspective, this is good news, as it means that colubrids are not likely to become a significant health threat to humans. However, for individuals suffering from serious envenomations, this means that efficient treatment (such as antivenom administration) is not available, and fatal results may ensue. Due to the extensive international trafficking of reptiles in the pet trade, serious envenomations due to colubrid bites are likely to increase but are still unlikely to become a significant problem. This should *not* discourage our interest in these venoms, however. From a toxinologist's perspective, colubrid venoms represent a largely unexplored source of biochemically and pharmacologically interesting compounds, and basic research into these venoms should be encouraged. Results from such lines of query will have interesting and potentially important applications to many areas of biology.

The first paper in this volume (K. V. Kardong) provides information on the structure and function of the Duvernoy's gland of colubrid snakes, and important differences in architecture from the venom glands of front-fanged snakes are detailed. The taxonomy and classification of the advanced snakes has been in a state of flux for some time. Many phylogenetic relationships have been reanalyzed using DNA molecular data, and the next paper (by N. Vidal) provides up-to-date information for toxinologists on systematics and relationships among the snakes lumped into the polyphyletic family "Colubridae". The third paper (S. P. Mackessy) focuses on aspects of biochemistry and pharmacology of colubrid venoms, and it will become apparent to the reader how much work remains in these areas of toxinology. The next paper (D. Chiszar and H. M. Smith) provides information about the occurrence of bites by colubrids in humans in the United States which have resulted in localized or systemic symptoms. Similarly, the paper by J. M. Gutiérrez and Sosa documents cases of envenomation by colubrids in Mexico and Central America. Review of cases of human envenomations by colubrid snakes in the Americas is completed with the paper on South American cases by J. Prado-Franceschi and

S. Hyslop. A review of colubrid snakebite in Europe and Africa (Kuch and Mebs) is the last paper on human envenomations by this group of snakes. The final paper (Sawai et al.) reviews the effects of bites by and the production of antivenin for the yamakagashi (*Rhabdophis tigrinus*) in Japan. An obvious gap in this collection is a review of the effects of colubrid snakebites in Asia, and it is hoped that a future author will fill this void. All in all, this collection of papers contributes greatly to our understanding of this diverse group of largely unexplored snakes and venoms, and it is hoped that this volume will stimulate further research into colubrid venoms and envenomations.

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Extraction of venom from a large brown treesnake (*Boiga irregularis*) from Guam. The capillary tube is placed over the enlarged rear maxillary tooth to collect venom as it is expressed.