

Question 3: Why are there so few venomous mammals and no birds, whereas there are so many venomous reptiles?

Convergent evolution is the process in which organisms from different lineages independently evolve similar features, such as venom. Venom is one of the most widespread, convergent functions in the animal kingdom and is used by some animals for killing or disabling prey, defending themselves from predators, or competing with other members of their species. Evidence suggests that these animals have independently evolved an apparatus that synthesises, stores, and secretes a mixture of toxic compounds to the target animal through the infliction of a wound¹. This phenomenon is noted in *On the Origin of Species*², where Darwin states, "I am inclined to believe that in nearly the same way as two men have sometimes independently hit on the very same invention, so natural selection, working for the good of each being and taking advantage of analogous variations, has sometimes modified in very nearly the same manner two parts in two organic beings, which owe but little of their structure in common to inheritance from the same ancestor." —Darwin (1859, pp. 193–94)

Animals have repeatedly evolved specialised organs and anatomy to produce and deliver a concoction of potent toxic molecules to subdue prey or predators - venom. The most well-studied venom systems are those of snakes, which evolved from a venomous lizard ancestor 200 million years ago³. It has been hypothesised that, like snakes, a common venomous ancestor links the venomous mammalian lineages. This contrasts the alternative hypothesis: several mammalian lineages have independently evolved venom, displaying an example of convergent evolution. Venom, however, is much more common among reptiles, amphibians, and fish than among mammals and birds^{4,5}. Venom's complex evolutionary history, diverse functions and costs to the organism may aid to explain this bias.

Venomous snakes predominantly use their venom to assist with the acquisition of prey, but they may also deploy it in defensive bites to deter potential predators and aggressors⁶. According to the widely accepted venom optimisation hypothesis⁷, venom production carries a high metabolic cost to the organism, suggesting that these snakes would be reluctant to use it unless to capture prey. In all known venomous species, the wet weight of venom never exceeds 0.5%⁸ of the total body mass of the animal. Replenishing venom raises basal metabolic rates by up to 40%⁸, making it a valuable resource.

In 2001, Young and Zahn investigated the functional morphology of venom injection in the Western Diamondback Rattlesnake (*Crotalus atrox*). They explored this by using high-speed digital videography combined with direct recording of venom flow using perivascular flow probes⁹. Although venom flow was variable, in most strikes the onset of venom flow was coincidental with fang penetration, and retrograde flow (venom suction) was observed prior to fang withdrawal. The duration of venom flow was consistently less than the duration of fang penetration. The occurrence of retrograde flow, "dry bites", accounted for 35% of the strikes⁹. The duration of venom flow, maximum venom flow rate and total venom volume were all significantly lower in predatory than in defensive strikes⁹. It has also been observed that depending on, e.g., prey size, the venomous animal injects only once versus several times¹⁰, and thereby carefully regulates the total amount of venom spent⁹. This is known as venom metering¹¹ and may have evolved as a mechanism to avoid injecting larger volumes of venom, consequently minimising both metabolic and ecological costs of venom depletion.

Ecological costs are a possible rationale for not wasting venom; this relates to the multi-functionality of most venoms¹¹. Schendel, V. et al suggest that overspending venom on one purpose represents a needless depletion of valuable tools for other purposes. For example, unnecessarily depleting venom reservoirs in a defensive situation also means that there has been an unnecessary depletion of not just defensive but also predatory toxins, or vice versa¹¹. It can take up to several days or weeks for some venom components to be regenerated¹¹ and during that time of regeneration, the venomous animal is likely to be both more vulnerable to predators or competitors and less able to capture prey¹¹.

Therefore, the importance of saving the metabolic cost of producing venom, as seen in venom metering and ‘dry bites’ in snakes, has driven the evolution of venom delivery mechanisms in reptiles. This is evidence to show that, due to the costs of venom, maintaining a venom reservoir may not be worth the energy investment for mammals and birds, which are endothermic and have high metabolic rates. Reptiles, which are ectothermic and have lower metabolic rates, may have greater metabolic potential to produce venom and maintain a supply of it.

Perhaps, an explanation for the disproportionate prevalence of venom in reptiles opposed to its infrequency in mammals is that mammals do not possess the genetic ability to evolve venom. However, we find that animals, including mammals, have evolved venoms at least 101 independent times and that venoms play at least 11 distinct ecological roles in addition to predation, defence, and feeding⁶ (shown in figure 1).

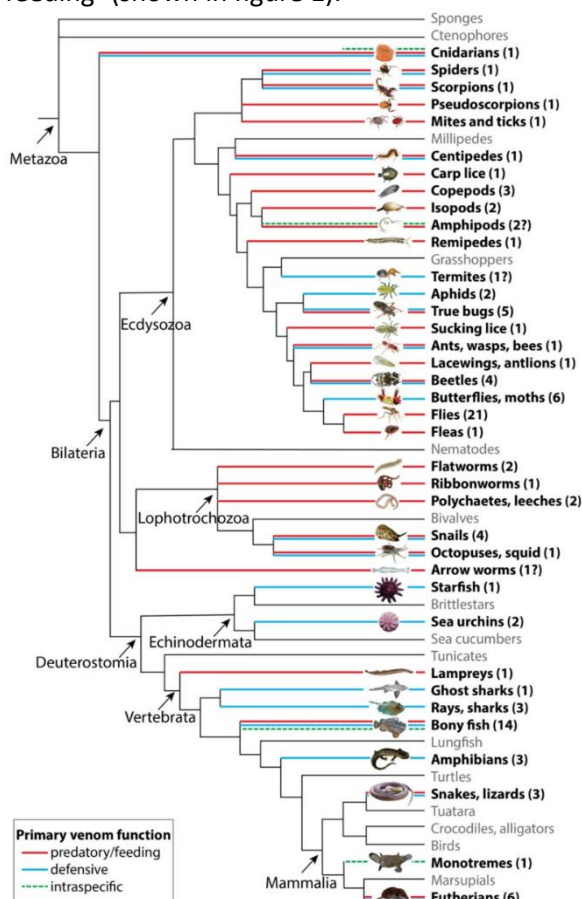


Figure 1 (Source: Casewell, N.R. et al. 2020) Taxonomic diversity and the main primary functions of venom⁶. A phylogenetic tree of venomous animals modified after Casewell et al. illustrating the frequency with which venoms have evolved within the animal kingdom¹². Coloured branches highlight venomous lineages, with red branches indicating a predatory/feeding venom function, blue branches indicating a defensive function and dashed green branches indicating a role in intraspecific competition¹¹.

Barua et al.¹³ has found that venoms found in snakes and mammals share a common origin. This was explored by tracing the origin of a class of toxins, called kallikrein serine proteases, to a salivary protein found in a common ancestor¹³. Results from the evolutionary tree also showed that non-toxic salivary kallikreins in mammals, including those found in mice and human saliva, also evolved from the same ancestral gene¹³. The study provides evidence for the hypothesis that venom evolved from a common group of genes with toxic potential that existed in the ancestor of snakes and mammals¹⁴.

Moreover, they found that snake venom kallikrein serine proteases and mammal salivary kallikreins did evolve from the same ancestral gene¹³. These non-toxic kallikreins in mammal saliva were more closely related to the venomous toxins found in snakes than to other kallikreins found within mammals¹³.

As a result, evidence suggests that there was no direct venomous ancestor between mammals¹⁵, alternatively proposing that salivary kallikrein proteins in mammals, including humans, only have the evolutionary potential to become toxic. Barua et al. have shown in their study that venom in mammals and reptiles originated multiple times in parallel by modifying the same gene family despite 300 million years separating these lineages¹³. However, simply because mammals have the building blocks to evolve venom does not suggest this will occur¹³. This echoes the notion that venom is energetically expensive to make, thus a strong ecological pressure for it is necessary, which humans and most mammals do not have¹³. Therefore, the energy investment of synthesising venom in mammals would not be worthwhile.

Nevertheless, although examples are scarce, venom is found in four mammalian orders: Eulipotyphla, Monotremata, Primates and Chiroptera. Intriguingly, most venomous mammal species belong to Eulipotyphla, and multiple representatives of eulipotyphlan mammals (shrews, hedgehogs, moles, and solenodons) are venomous¹⁶. This suggests that venom in mammals may be advantageous in certain circumstances, despite the high metabolic cost to the organism.

The endangered solenodon is found on the Caribbean islands of Hispaniola (*Solenodon paradoxus*) and Cuba (*Atopogale cubana*). A study conducted by Casewell et al.¹⁶ investigating the origin and evolution of *S. paradoxus* has shown that venom has evolved independently on at least four occasions in eulipotyphlans, and that molecular components of these venoms have also evolved convergently, with kallikrein-1 proteins coopted as toxins in both solenodons and shrews following their divergence from all other mammals over 70 million years ago¹⁶.

Casewell et al. has shown that solenodon venom consists of multiple paralogous kallikrein 1 serine proteases, making them new and arising from mutation independently. These kallikrein 1 serine proteases cause hypotensive effects *in vivo* and seem likely to have evolved to facilitate vertebrate prey capture¹⁶. By inducing hypotension, the prey's brain would receive less blood causing the animal to slow. Therefore, it can be concluded that the solenodon venom system likely evolved for overpowering, slowing, and subduing vertebrate prey, therefore reducing the energy expended by the solenodon in hunting. The small venomous water shrew (*Neomys fodiens*) also utilises their venom for overpowering vertebrate prey (shown in figure 1) much larger than they would otherwise be able to feed upon¹⁶ (e.g., similar mass to themselves) and for paralysing invertebrate prey for long-term storage purposes ("prey caching")¹⁶, presumably to provide a continual resource to help offset the extreme metabolic demands of these small animals¹⁶. Venomousness helps the shrew optimise its foraging as it reduces prey handling time, enables it to gain larger energy portions, and facilitates food hoarding, which reduces foraging time¹⁷. This highlights a clear evolutionary advantage for these small mammals to produce venom but suggests that for most larger,

carnivorous mammals, the high metabolic cost would be unjustified as they can overcome prey more easily.

To extend, Dufton¹⁸ argues that venom was more widespread in eulipotyphlans, as these animals were small and imperfect endotherms with unfavourable surface area to volume ratios¹⁸. Since this “would place a very high premium on the efficiency of food capture and mastication”, these could have been the very circumstances in which producing venomous saliva arose as a selective advantage^{15,18}.

Another hypothesis, proposed by Folinsbee et al.¹⁹ is that snakes use venom to stun their prey long enough for ingestion because their lightly built skulls and lack of limbs for grasping effectively requires dependence on an alternate form of prey control¹⁹. Mammals, on the other hand, have forelimbs with which to grasp prey while inflicting bites, much sturdier skulls capable of holding and tearing prey, and large chewing muscles and muscular attachments on both the jaws and skull¹⁹. In the case of small venomous mammals, mild venom may serve to stun prey that might otherwise evade capture¹⁹. *N. fodiens* needs to eat its own weight in food in a 24-hour period to maintain a high metabolic rate²⁰. Presumably, it uses venom to stun prey quickly for rapid ingestion and to reduce prey escapes²⁰. Larger mammals would be unlikely to benefit from venom in this case, as they are stronger and have lower basal metabolic rates per gram.

To conclude, the ability to secrete and inject venom into prey is rare, yet has convergently evolved multiple times in different lineages and in different anatomical areas. Most venomous mammal species belong to the order Eulipotyphyla, and venom was likely selected for due to the high metabolic rates of eulipotyphlans, thus requiring a high rate of prey acquisition with minimal energy expenditure. Alternatively, many other small mammals evolved the ability to enter torpor to cope with high metabolic rates; this is not observed in eulipotyphlans²¹. Perhaps, torpor is a more successful and efficient strategy to reserve energy and so has been selected for more frequently in mammals than venomous saliva.

Relating to the venom optimisation hypothesis, venom is most widespread and specialised in reptiles due to the energy investment of toxin synthesis being efficient overall. Both snakes and eulipotyphlan mammals commonly use venom to overpower prey (shown in figure 1), reducing the net energy expended in hunting. However, venom production is so expensive that it is often more profitable to invest energy in less costly mechanisms of defence or hunting; instead of venom, most mammals evolved to be large, fast, and powerful which negates the need for venom to capture prey or defend themselves. Consequently, it is more probable that reptiles will benefit from using and synthesising venom than mammals.

Venomousness in mammals is poorly investigated but, if offered greater attention, would grant enhanced understanding of evolutionary relationships and ecology. The enormous diversity of venomous animals means venoms are excellent models for studying questions in evolutionary biology through comparative methods, and at the same time represent a rich source of novel molecular tools with therapeutic potential²³.

Word count: 1,999

Bibliography

1. Surm, J.M.S. and Moran , Y. (2021) *Insights into how development and life-history dynamics shape the evolution of Venom*, *EvoDevo*. Available at: <https://pubmed.ncbi.nlm.nih.gov/33413660/> (Accessed: 21 April 2024).
2. Darwin, C. (1859) 'On the Origin of Species', in *On the origin of species: By means of natural selection or the preservation of favoured races in the struggle for life*. London: Sirius Publishing, pp. 193–194.
3. Zimmer, C. (2005) *Which came first, the snake or the venom?*, *Science*. Available at: <https://www.nationalgeographic.com/science/article/which-came-first-the-snake-or-the-venom> (Accessed: 31 March 2024).
4. Surm, J.M. and Moran, Y. (2021) *Insights into how development and life-history dynamics shape the evolution of Venom - Evodevo*, *BioMed Central*. Available at: <https://evodevojournal.biomedcentral.com/articles/10.1186/s13227-020-00171-w> (Accessed: 31 March 2024).
5. Zancolli, G. *et al.* (2021) *Convergent evolution of venom gland transcriptomes across metazoa*, *bioRxiv*. Available at: <https://www.biorxiv.org/content/10.1101/2021.07.04.451048v2.full> (Accessed: 31 March 2024).
6. Casewell, N.R. *et al.* (2020) *Causes and consequences of snake venom variation*, *Trends in pharmacological sciences*. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7116101/> (Accessed: 31 March 2024).
7. Morgenstern, D. and King, G.F. (2012) *The Venom Optimization Hypothesis revisited*, *Toxicon : official journal of the International Society on Toxinology*. Available at: <https://pubmed.ncbi.nlm.nih.gov/23266311/> (Accessed: 31 March 2024).
8. Williams, J. (2023) *The value of Venom*, *RSB*. Available at: <https://www.rsb.org.uk/biologist-features/the-value-of-venom> (Accessed: 31 March 2024).
9. Young, B.A. and Zahn, K. (2001) *Venom flow in rattlesnakes: Mechanics and metering*, *The Company of Biologists*. Available at: <https://journals.biologists.com/jeb/article/204/24/4345/33062/Venom-flow-in-rattlesnakes-mechanics-and-metering> (Accessed: 31 March 2024).
10. Nelsen, D. and Kelln, W. (2016) *265. poke but don't pinch: Risk assessment and defensive behaviors of the western widow spider (latrodectus hesperus)*, *Toxicon*. Available at: https://www.academia.edu/22658480/265_Poke_but_Dont_Pinch_Risk_Assessment_and_Defensive_Behaviors_of_the_Western_Widow_Spider_Latrodectus_hesperus (Accessed: 31 March 2024).
11. Schendel, V. *et al.* (2019) *The diversity of Venom: The importance of behavior and Venom System Morphology in understanding its ecology and evolution*, *Toxins*. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6891279/> (Accessed: 31 March 2024).
12. Casewell , N.R. *et al.* (2012) *Complex cocktails: The Evolutionary Novelty of Venoms*, *Trends in ecology & evolution*. Available at: <https://pubmed.ncbi.nlm.nih.gov/23219381/> (Accessed: 31 March 2024).
13. Barua, A., Koludarov, I. and Mikheyev, A.S. (2021) *Co-option of the same ancestral gene family gave rise to mammalian and reptilian toxins - BMC biology*, *BioMed Central*. Available at: <https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-021-01191-1> (Accessed: 31 March 2024).
14. Okinawa Institute of Science and Technology Graduate University (ed.) (2022) *Common origin: Venoms in snakes and salivary protein in mammals evolved from the same ancestral gene*, *SciTechDaily*. Available at: <https://scitechdaily.com/common-origin-venoms-in-snakes-and-salivary-protein-in-mammals-evolved-from-the-same-ancestral-gene/> (Accessed: 31 March 2024).

15. Rode-Margono, J.E. and Nekaris, K.A.-I. (2015) *Cabinet of curiosities: Venom Systems and their ecological function in mammals, with a focus on primates, Toxins*. Available at: <https://pubmed.ncbi.nlm.nih.gov/26193318/> (Accessed: 31 March 2024).
16. Casewell, N.R. et al. (2019) *Solenodon genome reveals convergent evolution of Venom in Eulipotyphlan Mammals, Proceedings of the National Academy of Sciences of the United States of America*. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6926037/#r13> (Accessed: 31 March 2024).
17. Kowalski, K. and Rychlik, L. (2018) *The role of Venom in the hunting and hoarding of prey differing in body size by the Eurasian water shrew, Neomys fodiens, BioOne Complete*. Available at: <https://bioone.org/journals/journal-of-mammalogy/volume-99/issue-2/gyy013/The-Role-of-venom-in-the-hunting-and-hoarding-of/10.1093/jmammal/gyy013.xml> (Accessed: 31 March 2024).
18. Dufton, M.J. (1992) *Venomous mammals, Pharmacology & therapeutics*. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1641406> (Accessed: 31 March 2024).
19. Folinsee, K., Johannes Müller, J. and Reisz, R. (2007) *Canine grooves: Morphology, function, and relevance to Venom, Canine grooves: morphology, function, and relevance to venom*. Available at: <https://www.researchgate.net/publication/313661568> *Canine grooves morphology function and relevance to venom* (Accessed: 31 March 2024).
20. Cuenca-Bescós, G. and Rofes, J. (2007) *First evidence of poisonous shrews with an envenomation ... , First evidence of poisonous shrews with an envenomation apparatus*. Available at: <https://www.researchgate.net/publication/6765988> *First evidence of poisonous shrews with an envenomation apparatus* (Accessed: 31 March 2024).
21. Mammal Society, (2024). *Species – water shrew*. Available at: <https://www.mammal.org.uk/species-hub/full-species-hub/discover-mammals/species-water-shrew/#:~:text=They%20do%20not%20hibernate%3B%20they%20remain%20active%20all,year%2C%20diving%20for%20aquatic%20prey%20even%20in%20mid-winter>. (Accessed: 21 April 2024).
22. Fitzpatrick, L.L.J., Ligabue-Braun, R. and Nekaris, K.A.-I. (2023) *Slowly making sense: A review of the two-step venom system within slow (nycticebus spp.) and pygmy lorises (xanthonycticebus spp.), Toxins*. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10536643/> (Accessed: 31 March 2024).
23. Vyas, V.K. et al. (2013) *Therapeutic potential of snake venom in cancer therapy: Current perspectives, Asian Pacific journal of tropical biomedicine*. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3627178/> (Accessed: 21 April 2024).
24. King, G.F. (2011) *Venoms as a platform for human drugs: Translating toxins into therapeutics, Expert opinion on biological therapy*. Available at: <https://pubmed.ncbi.nlm.nih.gov/21939428/> (Accessed: 31 March 2024).
25. Conte, G.L. et al. (2012) *The probability of genetic parallelism and convergence in natural populations, Proceedings. Biological sciences*. Available at: <https://pubmed.ncbi.nlm.nih.gov/23075840/> (Accessed: 31 March 2024).
26. Evans, E.R.J. et al. (2019) *Venom costs and optimization in scorpions, Frontiers*. Available at: <https://www.frontiersin.org/articles/10.3389/fevo.2019.00196/full> (Accessed: 31 March 2024).
27. Rosenblum, E.B., Parent, C.E. and Brandt, E.E. (2014) *The Molecular Basis of Phenotypic Convergence, The Annual Review of Ecology, Evolution, and Systematics*. Available at: <https://www.annualreviews.org/content/journals/10.1146/annurev-ecolsys-120213-091851> (Accessed: 31 March 2024).
28. Steiner, C.C. et al. (2008) *The genetic basis of phenotypic convergence in beach mice: Similar pigment patterns but different genes, OUP Academic*. Available at: <https://academic.oup.com/mbe/article/26/1/35/972385> (Accessed: 31 March 2024).