
Snake Venom

Snake Venom and its Effects on The Body

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Life Science 4M03

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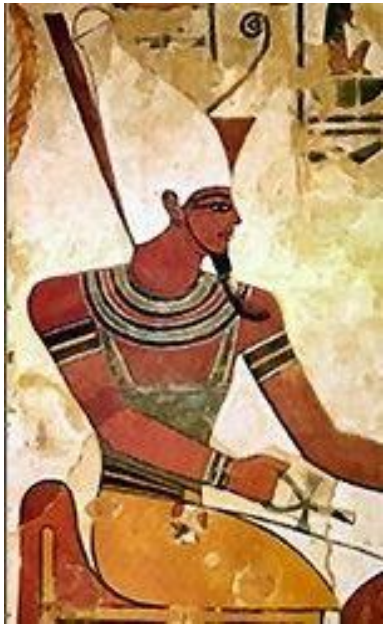
History and Evolution

- Culturally significant

Egyptians – Atoum | Greek – Acheloos

Hinduism – Kaleyeni | Christianity – Devil

- Venom genetically ancestral to snakes



https://www.pinterest.fr/sbastienquercy/pith%C3%B4m-pi-atoum-tjekou/

(Boquet, 1979; Fry, 2005; Fry 2012)

Interesting Venom/Snake Facts

- 8000 venomous snake bites are reported in USA every year (Copperhead Most)
- India - most affected (35000-50000 deaths/year)
- Prey includes fish, frogs, snails, lizards, chickens, mice, other snakes
- Venom is primary offensive weapon
- Belcher's Sea Snake Bite = **Can Kill 1000 Humans**

Known by its triangular head. The venom from the Russel's viper causes renal failure within hours

Cobra's are some of the largest and deadliest snakes in the world

(Nielson, n.d; Kang et al., 2011)

More Interesting Venom/Snake Facts

(Nielson, n.d; Kang et al., 2011)

How to Identify Venomous Snakes

- **Three** families of venomous snakes
  - **Atractaspidids**
    - Colubridae family
    - Lightly toxic venom
      - tissue necrosis
  - **Elapids**
    - Neurotoxin (central nervous systems/respiration)
  - **Viperids**
    - Hematoxic venom (tissue or blood)
- Based on **colours, triangular head, elliptical pupils, rattles, skin pattern etc.**

https://1.bp.blogspot.com/-w2PccrKd2xk/WS1i_wEkBXI/AAAAAAAAPDI/_G2buHWOxc9g0QLU6pck8bGt77LLvbFACLcB/s1600/Common%2BVenomous%2BSnakes.JPG

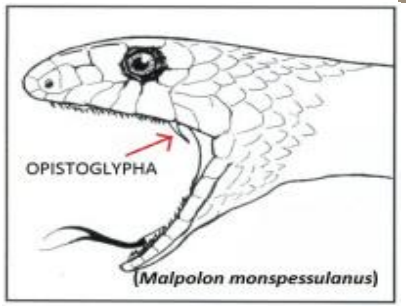
(Underwood, 1979; Savage & Slowinski, 1992 and Reed, 2003)

Fang Structures

- **Three** fang structures
  - **Proteroglyphous**
    - Elapid Family
    - Fixed to the jaw and cannot fold up
  - **Solenoglyphous**
    - Viper family
    - Attached to the jaw by a hinge and can be folded up against the roof of the mouth
    - Longest
  - **Opisthoglyphous**
    - Colubrid family
    - At the back of the mouth

https://upload.wikimedia.org/wikipedia/commons/thumb/8/87/Ophiophagus_hannah_skull.jpg/220px-Ophiophagus_hannah_skull.jpg

https://upload.wikimedia.org/wikipedia/commons/thumb/f/ff/Crotalus_skull.jpg/220px-Crotalus_skull.jpg



https://allyouneedisbiology.files.wordpress.com/2015/02/malpolon-bo.jpg?w=204&h=176

(Vonk et al, 2008 and Warrell, 2010)

Classification of Snake Venom

- Five different types of snake venom:
  - **Hemotoxic Venom**
    - RBCs or other tissue
    - Hemolysis, disrupts blood clotting etc.
    - Tissue Damage are permanent
  - **Myotoxic Venom**
    - Muscle tissues or kidney
    - Paralysis, loss muscle contraction etc.
    - Benefits for the snakes to eat and leave the prey flaccid
  - **Neurotoxic Venom**
    - Nervous system, respiration
    - Vomiting, droopy eyelids etc.
  - **Cytotoxic Venom**
    - Destroy and attacks the living cells of all sorts
    - Bleeding, swelling etc.
  - **Haemorrhagic Envenoming**
    - Bleeding in multiple organs

(Chang, 1979; Karlssoni, 1979; Ohsaka, 1979 and Russell, 1980)

Injection Tactics

- **Purposes of bite**
  - Inject the venom into their prey (immobilize and or kill)
  - Defend against attack by potential predators and antagonists
- **Fang Contact**
  - **Viperid snakes**
    - Strike and release targets for both predatory and defensive bites
  - **Elapid snakes**
    - more inclined to hold after biting
      - more chance to delivery of more venom
    - more sophisticated delivery system
      - spit small fractions of venom for defensive purposes repeatedly

https://www.youtube.com/watch?v=srZmEsidcDE

(Malasit et al., 1986)

Chemical Make-up of Venom

- Venom gland = modified version of salivary gland
- Different toxin encoding genes = different venom
- Primary constituents: proteins and peptides (aka toxins)
- Contains 30 to >100 protein toxins
- Common enzymes
  - Phospholipase A2s (PLA2s)
  - Serine proteinases
  - Metalloproteinases
  - Acetylcholinesterases (AChEs)
  - l-amino acid oxidases

http://www.sundayguardianlive.com/sites/sundayguardianlive.com/files/styles/article_page_image_895x550/public/

(Johnson, 2012; Casewell et al., 2014; Kang et al., 2011)

Factors Determining Venom Quantity

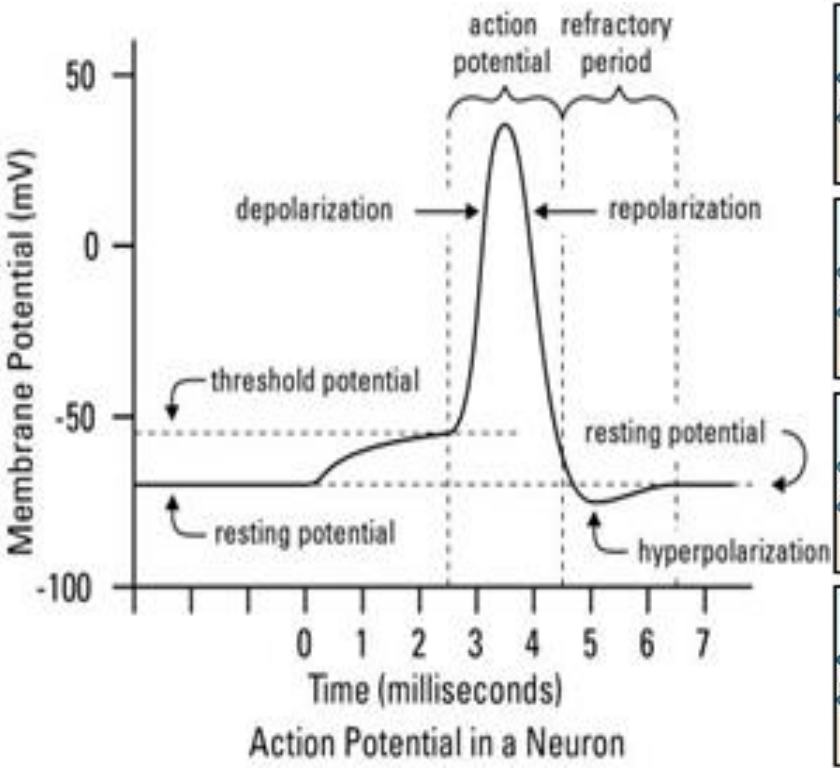
- Correlates to snake's size
  - Increases exponentially with snake size
- Ranges from 1 mg to 850 mg
- Accurate assessment of prey before venom injection
  - Situation + (Size/Type of Target)
- Uses chemosensory, visual and thermal cues
- Rattlesnakes increase venom quantity based on target size

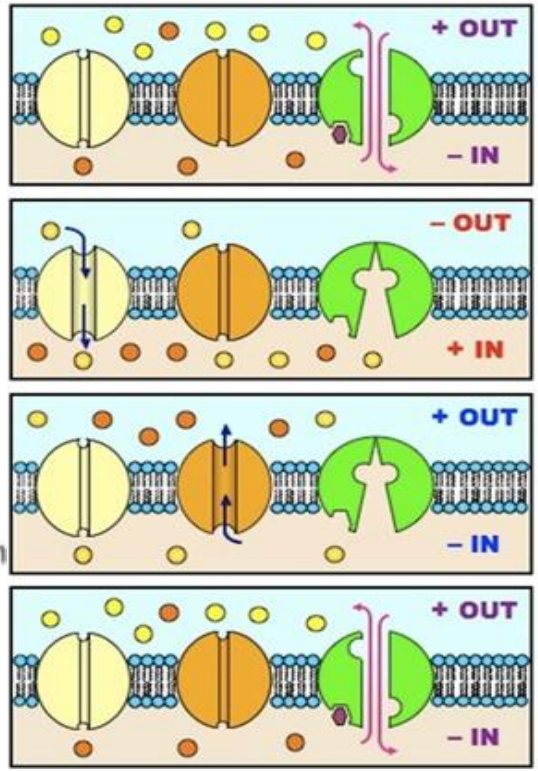
https://www.youtube.com/watch?v=GYmU_wyQxyw

(Johnson, 2012; Young, Lee, & Daley, 2002)

Toxins (Mechanism of Action) - Normal

http://www.dummies.com/education/science/understanding-the-transmission-of-nerve-impulses/

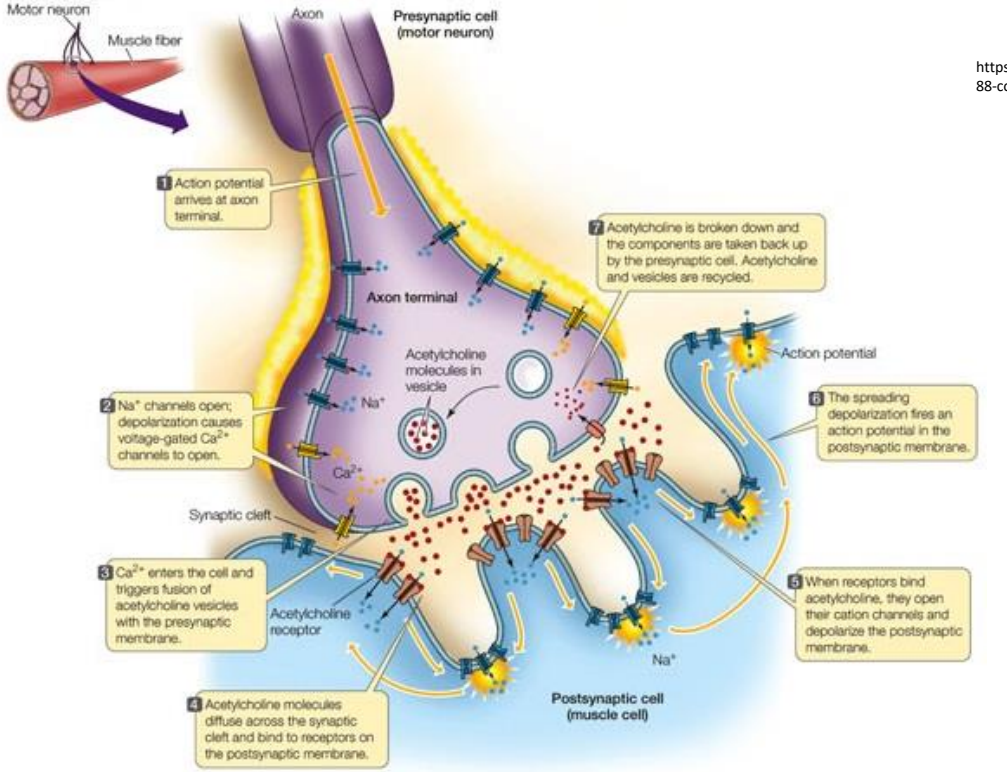




1. **Resting Potential**
   Na^+/K^+ pump
2. **Depolarisation**
   Voltage-gated Na^+ channel
3. **Repolarisation**
   Voltage-gated K^+ channel
4. **Resting Potential**
   Na^+/K^+ pump

(Gong et al., 2008)

Toxins (Mechanism of Action) - Normal

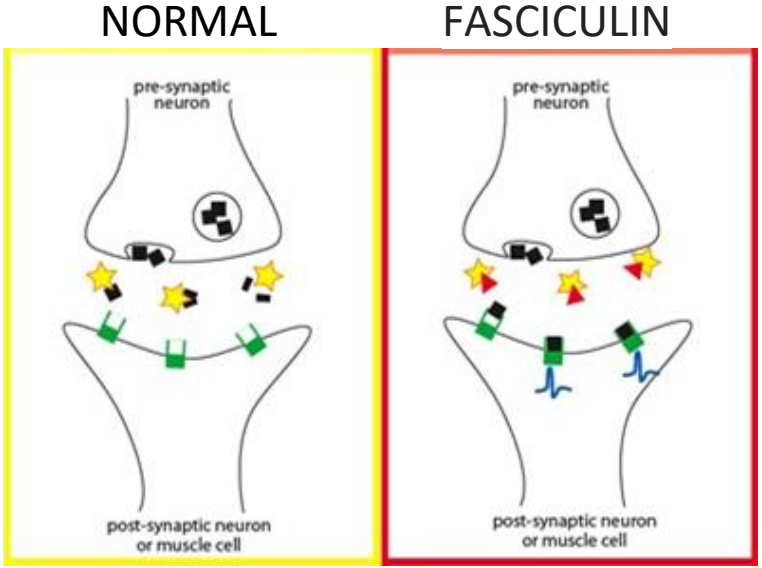


https://universe-review.ca/I10-88-connSynapse.jpg

(Rossetto et al., 2008)

Toxins (Mechanism of Action) - Neurotoxins (Fasciculins)

- Target is Acetylcholinesterase
- Acetylcholine NOT broken down
- Overstimulation of postsynaptic neuron
- Causes tetany (involuntary muscle contraction)



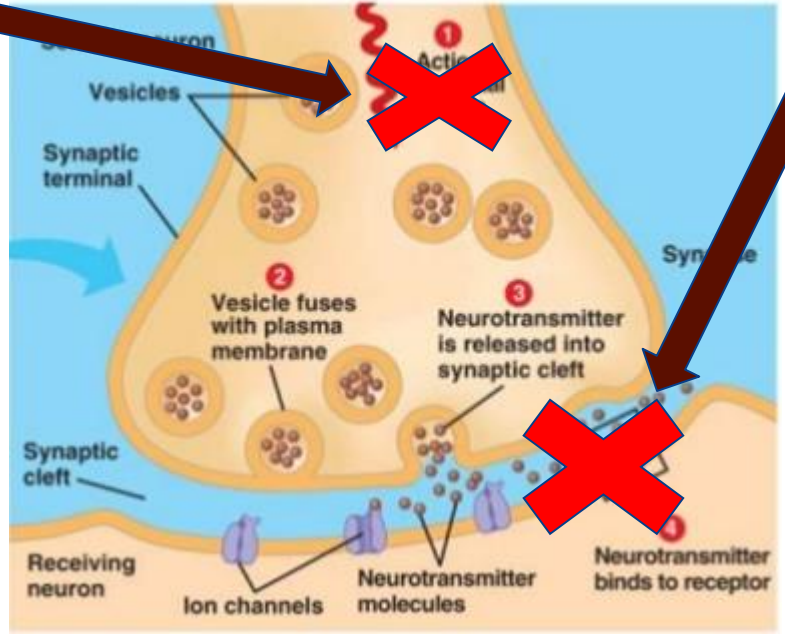
https://sites.google.com/a/macalester.edu/nerve-agents/home/acetylcholine-and-vx

(Lauridsen et al, 2016)

Toxins (Mechanism of Action) - Neurotoxins (Dendrotoxins/α-neurotoxins)

Dendrotoxins

- Target is K+ channels
- Action Potentials NOT completed
- No relay of message
- Causes paralysis of nerves



https://www.epilepsyresearch.org.uk/about-epilepsy/background-to-seizures/

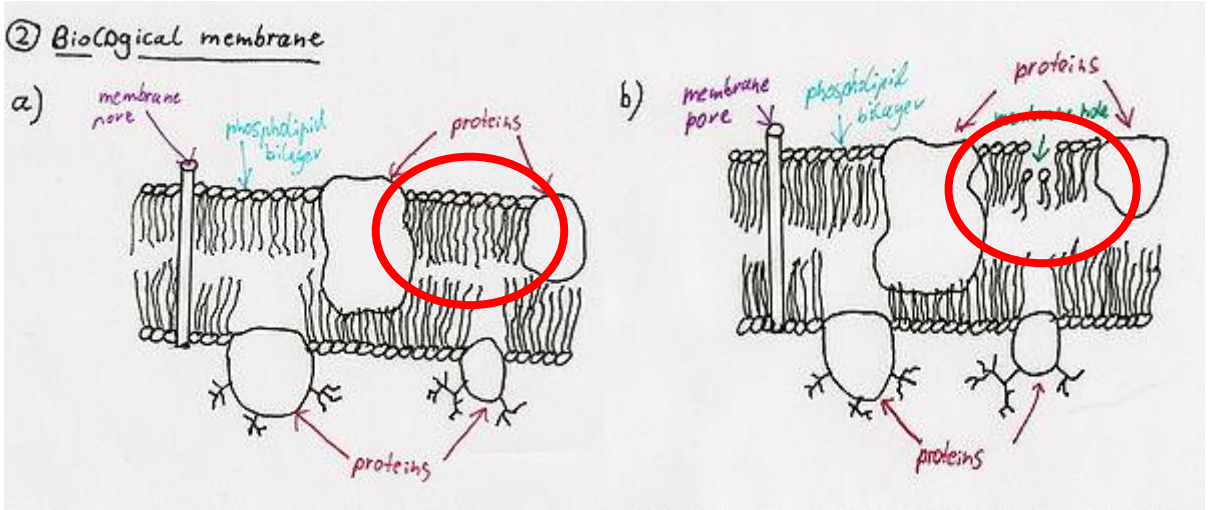
α-neurotoxins

- Target is nicotinic acetylcholine receptors
- Antagonistic
- Acetylcholine cannot bind
- Causes paralysis of nerves

(Laustsen et al, 2015; Lauridsen et al, 2017)

Toxins (Mechanism of Action) - Cytotoxins (Phospholipases)

- Hydrolyze phospholipids
- Several physiological systems affected
- Integrity of the membrane lost
- Cell membrane ruptures

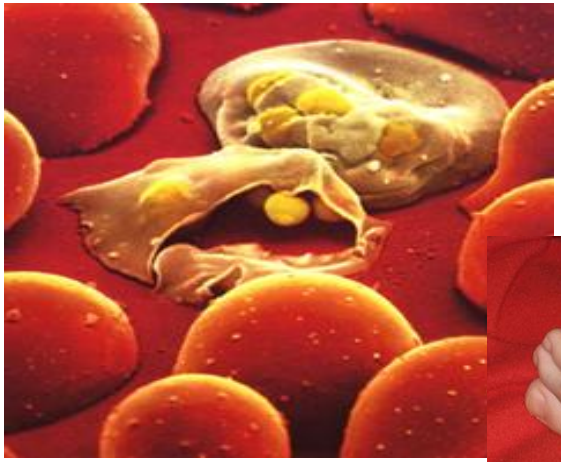


https://en.wikipedia.org/wiki/Snake_venom#Neurotoxins

(Valdez-Cruz et al, 2007)

Toxins (Mechanism of Action) - Cytotoxins (Hemotoxins)

- Causes hemolysis
- Induce excess blood coagulation
- Result is vast internal bleeding
- Death (Most Deadly Snake Toxin)



http://www.zo.utexas.edu/faculty/sjasper/images/malariaRBC.jpg

http://www.newhealthguide.org/Internal-Bleeding-Symptoms.html

(Tang et al, 2016)

Determining Venom Toxicity

- LD-50 test
- Find the required dose that will kill half of the population of species
- Not considered a biological constant

http://trinities.org/blog/wp-content/uploads/1-Person-in-2-natures.png

http://www.occupyforanimals.net/uploads/7/7/3/5/7735203/1065327.jpg?362

(Elli, 2017; Kini & Evans, 1990)

Physiological Effects

- Different species, different symptoms
- Common Symptoms:
  - Swelling and redness
  - Pain around the area
  - Difficulty breathing
  - Nausea
  - Blurred vision
  - Sweating
  - Salivating
  - Numbness
- Interference in platelet aggregation

https://www.mesotheliomalawyercenter.org/site/wp-content/uploads/2013/05/symptoms.jpg

(Elli, 2017; Kini & Evans, 1990)

Use of Snake Venoms to Treat Disease

- Venoms consist of:
  - Complex proteins, peptides, enzymes, etc.
- Use in cancer
  - Inhibit cell proliferation and promote cell death
    - Occur because of increased/decreased expression of proteins that control the cell cycle, apoptosis induced cancer cells, etc.
- Create drugs involved with:
  - Thrombin inhibition, blood thin, etc.

http://news.mit.edu/sites/mit.edu.newsoffice/files/images/2012/20121003154740-0_0.jpg

(Elli, 2017; Kini & Evans, 1990)

Snake Bite Venom Management

- Common hazard in some places of the world
- Snake bite venom management:
    1. First aid
    2. Hospital emergency care
    3. History and physical examination
    4. Laboratory tests
    5. Targeted therapy (anti-snake venom)

https://www.offgridweb.com/preparation/infographic-snake-bite-first-aid/

(Ahmed et al., 2008)

Snake Venom Immunity

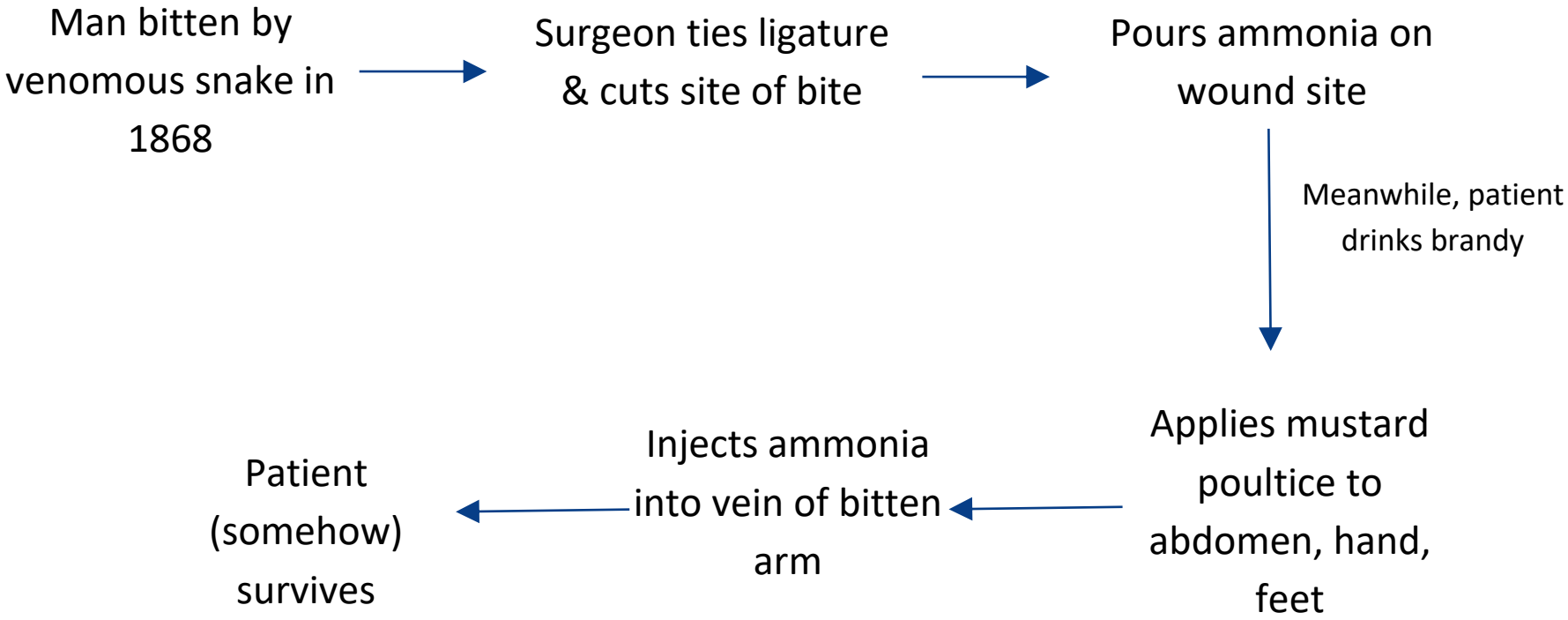
- Immunoglobulins from immunizing horses with snake venom
- Antivenom created from horse serum
- Sole effective antidote

- Steve Ludwin…snake venom immunity? (www.cnn.com/.../snake-venom-self-immunization-steve-ludwin-...)

http://uk.businessinsider.com/a-man-who-injects-himself-with-snake-venom-says-it-is-keeping-him-young-and-could-save-thousands-of-lives-2016-7

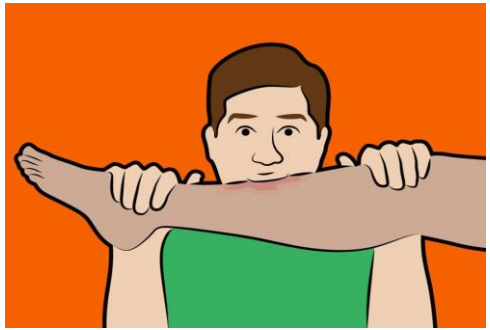
(Ahmed et al., 2008; Froissart, 2017)

Venom Treatment (1868 case)

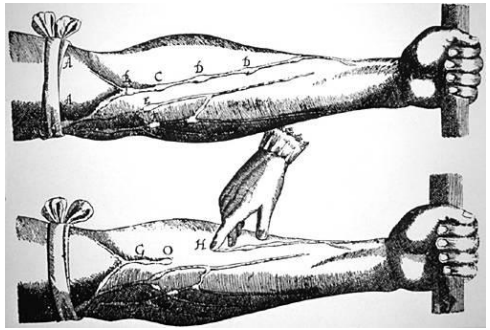


(Hobbins, 2017)

Other Traditional Venom Treatments



http://www.iflscience.com/editors-blog/10-survival-myths-that-might-get-you-killed/



http://web.ecs.baylor.edu/faculty/newberry/myweb/gtx%20os%20files/f05%20student%20pages/morehouse-basinger/Harvey%207.htm

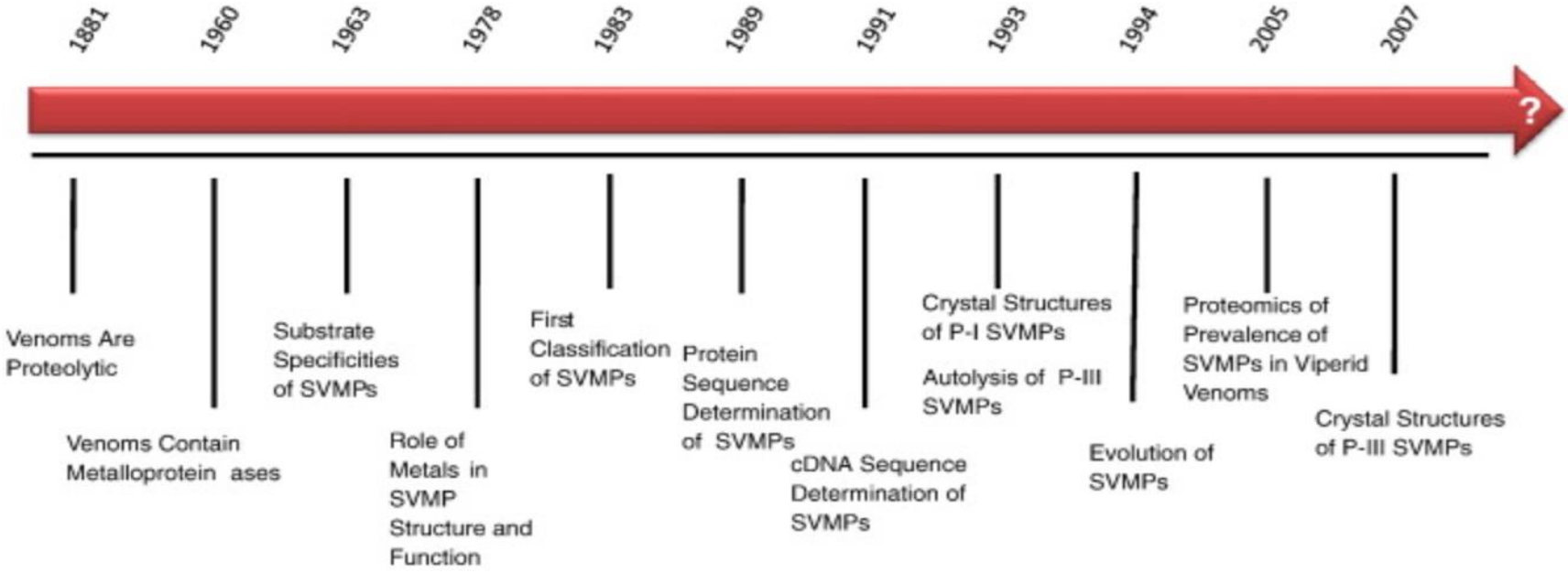
http://www.uniprot.org/taxonomy/29760

- Suction
- Ligature
- Medicinal plants (Vitis vinifera L)

(Hobbins, 2017; Gupta & Peshin, 2012

Current and Future Studies

- Venom used in pharmaceutical research



(Fox and Serrano, 2007)

https://www.factslides.com/s-Snake

Conclusion

- Venom is a defence mechanism/offensive weapon
- Venom quantity increases with snake's size + prey size/type
- Different Toxin, target different body components/processes (action potentials, red blood cells, etc.)
- Different snake bites = different physiological effects
- Venom as cancer treatment (inhibit cell proliferation/promote)cell death
- Snake bite can be treated:
  - First aid
  - Emergent Care
  - Targeted Therapy
  - Anti-venom Treatment

References

Boquet, P. (1979). History of snake venom research. In *Snake venoms* (pp. 3-14). Springer, Berlin, Heidelberg.

Casewell, N. R., Wagstaff, S. C., Wüster, W., Cook, D. A. N., Bolton, F. M. S., King, S. I., … Harrison, R. A. (2014). Medically important differences in snake venom composition are dictated by distinct postgenomic mechanisms. *Proceedings of the National Academy of Sciences*, *111*(25), 9205–9210. https://doi.org/10.1073/pnas.1405484111

Chang, C. C. (1979). The action of snake venoms on nerve and muscle. In *Snake venoms* (pp. 309-376). Springer Berlin Heidelberg.

Fox, J. W., & Serrano, S. M. (2007). Approaching the golden age of natural product pharmaceuticals from venom libraries: an overview of toxins and toxin-derivatives currently involved in therapeutic or diagnostic applications. *Current pharmaceutical design*, *13*(28), 2927-2934.

Fox, J. W., & Serrano, S. M. (2009). Timeline of key events in snake venom metalloproteinase research. *Journal of PROTEOMICS*, *72*(2), 200-209.

Gupta, Y. K., & Peshin, S. S. (2012). Do Herbal Medicines Have Potential for Managing Snake Bite Envenomation? *Toxicology International*, *19*(2), 89–99. https://doi.org/10.4103/0971-6580.97194

Gong, B., Liu, M., & Qi, Z. (2008). Membrane potential dependent duration of action potentials in cultured rat hippocampal neurons. *Cellular and Molecular Neurobiology, 28*(1), 49-56. doi:10.1007/s10571-007-9230-5

Hobbins,P. (n.d.). Hissstory: how the science of snake bite treatments has changed. Retrieved November 25, 2017, from http://theconversation.com/hissstory-how-the-science-of-snake-bite-treatments-has-changed-71408

Jackson, K. (2007). The evolution of venom-conducting fangs: insights from developmental biology. *Toxicon*, *49*(7),975-981.

Johnson,s. (2012). *Venomous Snake FAQs*. *Ufwildlife.ifas.ufl.edu*. Retrieved 25 November 2017, from http://ufwildlife.ifas.ufl.edu/venomous_snake_faqs.shtml

Kang, T. S., Georgieva, D., Genov, N., Murakami, M. T., Sinha, M., Kumar, R. P., …Kini, R. M. (2011). Enzymatic toxins from snake venom: structural characterization and mechanism of catalysis. *FEBS Journal*, *278*(23),4544–4576. https://doi.org/10.1111/j.1742-4658.2011.08115.x

Karlsson, E. (1979). Chemistry of protein toxins in snake venoms. In *Snake venoms* (pp. 159-212). Springer Berlin Heidelberg.

Lauridsen, L. P., Laustsen, A. H., Lomonte, B., & Gutiérrez, J. M. (2017). Exploring the venom of the forest cobra snake: Toxicovenomics and antivenom profiling of naja melanoleuca. *Journal of Proteomics, 150*(Complete),98-108. doi:10.1016/j.jprot.2016.08.024

Lauridsen, L. P., Laustsen, A. H., Lomonte, B., & Gutiérrez, J. M. (2016). Toxicovenomics and antivenom profiling of the eastern green mamba snake (dendroaspis angusticeps). *Journal of Proteomics, 136*(Complete),248-261. doi:10.1016/j.jprot.2016.02.003

Laustsen, A. H., Lomonte, B., Lohse, B., Fernández, J.,& Gutiérrez, J. M. (2015). Unveiling the nature of black mamba (dendroaspis polylepis) venom through venomics and antivenom immunoprofiling: Identification
of key toxin targets for antivenom development. *Journal of Proteomics, 119*(Complete), 126-142. doi:10.1016/j.jprot.2015.02.002

Malasit, P., Warrell, D. A., Chanthavanich, P.,Viravan, C., Mongkolsapaya, J., Singhthong, B., & Supich, C. (1986).Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *Br Med J (Clin Res Ed)*, *292*(6512), 17-20.

Nielsen, A. Venomous Snakes - facts, species, bites and natural history. Venomoussnakes.net. Retrieved 24 November 2017, from http://www.venomoussnakes.net/

Ohsaka, A. (1979). Hemorrhagic, necrotizing and edema-forming effects of snake venoms. In Snake venoms (pp. 480-546). Springer Berlin Heidelberg.

References

Reed, R. N. (2003). Interspecific patterns of species richness, geographic range size, and body size among New World venomous snakes. *Ecography*, *26*(1), 107-117.

Rossetto, O.,Morbiato, L., Caccin, P., Rigoni, M., Carli, L., Paoli, M., . . . Montecucco,C. (2008). Tetanus, botulinum and snake presynaptic neurotoxins. *RENDICONTI LINCEI, 19*(2), 173-188. doi:10.1007/s12210-008-0010-z

Russell, F. E.(1980). Snake venom poisoning. *Philadelphia*, *18*, 139-234.

Savage, J. M.,& Slowinski, J. B. (1992). The colouration of the venomous coral snakes (family Elapidae) and their mimics (families Aniliidae and Colubridae). *Biological Journal of the Linnean Society*, *45*(3), 235-254.

Tang, E. L. H.,Tan, C. H., Fung, S. Y., & Tan, N. H. (2016). Venomics of calloselasma rhodostoma, the malayan pit viper: A complex toxin arsenal unraveled. *Journal of Proteomics, 148*(Complete), 44-56. doi:10.1016/j.jprot.2016.07.006

Underwood, G.(1979). Classification and distribution of venomous snakes in the world. In *Snake venoms* (pp. 15-40). Springer Berlin Heidelberg.

Valdez-Cruz, N. A.,Segovia, L., Corona, M., & Possani, L. D. (2007). Sequence analysis and phylogenetic relationship of genes encoding heterodimeric phospholipases A2 from the venom of the scorpion anuroctonus phaiodactylus. *Gene, 396*(1), 149-158. doi:10.1016/j.gene.2007.03.007

Vonk, F. J., Admiraal, J. F., Jackson, K., Reshef, R., de Bakker, M. A., Vanderschoot, K.,... & Mirtschin, P. J. (2008). Evolutionary origin and development of snake fangs. *Nature*, *454*(7204), 630-633.

Warrell, D. A.(2010). Snake bite. *The Lancet*, *375*(9708), 77-88.

Young, B. A., Lee, C. E., & Daley, K. M.(2002). Do Snakes Meter Venom? *BioScience*, *52*(12), 1121–1126. https://doi.org/10.1641/0006-3568(2002)052[1121:DSMV]2.0.CO;2