NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Snakes in a Storm!

A Herpetologist's Struggle with Hemostasis

by

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Introduction

The National Weather Service stated that "Molly" had gone from a tropical storm to a full-blown hurricane. And she had veered; she was now headed straight for the Atlantic coast of Florida. It was 11:15 PM and some of the staff of the Alexander Zoo, located on the coast, had been called in for storm preparation. They needed to relocate the animals to designated concrete structures within the facility. The zoo was undergoing renovations and some of the temporary holdings were not suitable to weather a storm, thus the staff wanted to secure the animals before the hurricane made landfall. This was an important move as the zoo housed a record number of animals, including several rare and venomous amphibians and reptiles. Additionally, given the increase in non-native invasive species in Florida, the zoo's staff wanted to keep their animals contained.

Joseph Summers, a zookeeper's assistant, was a new father and had been getting two to three hours of sleep at a time since his daughter, Priyanka, was born two months earlier. But he was dedicated to his job and had a passion for reptiles. When he was notified about the emergency he raced out of his house to help, even though he had just crawled back into bed after feeding Priyanka. Joseph lived only a few miles from the zoo and was thus the first from the herpetology team on the scene. When Joseph arrived, he soon discovered Dr. Janet Norton, the head herpetologist (reptile specialist), whom Joseph has been working under for the past year, was stuck in evacuation traffic. Joseph, a little unsettled by the idea of moving multiple exotic snakes by himself, called Dr. Norton and asked about the relocation protocol. Zoo policy required two people to be present when transporting venomous snakes, but the snakes could be lost if the rapidly intensifying storm destroyed the building. Joseph and Dr. Norton decided he should start moving the snakes immediately. Dr. Norton directed Joseph to follow all the zoo's typical handling guidelines and to make note of the time he handled and secured each snake. In addition, Dr. Norton also sent a brief email to remind Joseph about the venomous snakes in the exhibit (see next page).

As the sirens blared in the distance, Joseph began his task of removing the 20 snakes from their temporary exhibits and placing them in their designated transport boxes. He was careful to write the time at which he handled each snake, and to note the number transported. After he finished moving the snakes from Exhibit Room 1, Joseph heard a loud crash coming from the next room. Cautiously Joseph opened the door to investigate and found the severe winds had sent a tree flying into the side of the temporary Exhibit 2, breaking the window and glass tanks, thus releasing the snakes from their enclosures. Frantically Joseph made sure the newly breached hole in the wall was covered and began the process of rounding up the snakes. He briefly thought about grabbing some protective gear for himself but decided there was no time. The wind was howling outside, and he heard branches cracking; the storm was getting worse. He checked the registry to determine what snakes should be in Exhibit 2 and attempted to move the snakes to their transport boxes. There were a total of ten snakes in this exhibit and Joseph was careful to continue his logging. After finding two of the escapees—one black mamba and one tree boa—Joseph attempted to find the others. As he bent down to move some debris, Joseph felt a sharp pain from his lower left leg and instantly withdrew from what he was doing to see what had happened. As he rolled up his left pant leg he noticed two undeniable puncture marks from a snake bite. After looking around, Joseph couldn't see the snake that bit him. He was instantly overcome with fear;

Summers, Joseph
From: Norton, Janet
Sent: Tuesday, October 2, 2019 11:28 PM
To: Summers, Joseph
Subject: Snake movement instructions

Joseph,

Sorry I can't be there, but I feel comfortable with you moving our 10 snake species. You may not need this but I'm attaching information for each venomous species in Exhibit 1 and 2. Make sure to keep an active log and refer to the snake registry if needed. Please call me if there are any issues! I am trying to get there as fast as possible.

- Green Mamba *(Dendroaspis angusticeps)*
  This snake's venom is known to carry toxin called fasciculins, which works by inhibiting acetylcholinesterase, a vital enzyme used to breakdown acetylcholine (ACh) in the neuromuscular junction (NMJ). This venom causes an increased amount of ACh in the NMJ, which results in multiple and sustained muscle contractions. Human accounts of green mamba bites have reported headaches and slight tremors followed by involuntary skeletal muscle contractions and eventually paralysis.
- Boomslang *(Dispholidus typus)*
  The venom of the boomslang contains toxins that affect the body's coagulation cascade. These toxins work to activate prothrombin to its usable form thrombin without the need of additional cofactors. They also increase activity of Factor X in the clotting cascade. By manipulating clotting in this way, small clots form at a rapid rate and use up clotting factors found in blood, preventing the body from clotting after further injuries. Those affected by the boomslang venom first experience discomfort and fatigue, soon followed by fever, vomiting, bloody urine, severe hemorrhaging (excessive bleeding) through the eyes, mouth, and other bodily orifices.
- Black Mamba *(Dendroaspis polylepis)*
  The venom of the black mamba has been found to contain a specific neurotoxin called dendrotoxin. This toxin has a high affinity for voltage gated potassium channels and inhibits their function. Blocking these channels affects the repolarization of motor neurons thus impeding their action potentials. Individuals affected by the black mamba's venom first experience confusion and headaches followed by a loss of motor control.
- Common krait *(Bungarus caeruleus)*
  The venom of the common krait contains a specific neurotoxin, β-bungarotoxin. This neurotoxic protein affects the presynaptic neuron by inhibiting the release of acetylcholine (ACh) from the synaptic terminals, but the exact mechanism by which this occurs in not fully known. By limiting release of this neurotransmitter, neuronal communication is disrupted. Symptoms of the bite include drowsiness, abdominal pain, numbness, and paralysis.
- Fer-de-lance *(Bothrops atrox)*
  The fer-de-lance has been considered one of the deadliest snakes. Although the mechanism of the fer-de-lance's venom is not completely understood, its venom contains hemotoxic proteins which triggers inflammation and necrosis. Metalloproteinases in the venom cause local hemorrhage. Symptoms of this bite include pain, swelling of the affected area, bruising, necrosis of tissues, coagulopathies, systemic hemorrhage and renal failure.

Be there soon!

Janet
Janet Norton, Ph.D.

thoughts raced through his head as blood raced through his veins. *Was that a venomous snake? Is there an antidote? Can I even get medical help in this storm? What about my family? Where did that snake go? Where are the others? What if I die!? What if no one finds me?!*

After taking several deep breaths, Joseph gained his composure and realized he needed to be efficient and methodical. Unsure if the new bite was from a venomous snake Joseph thought it best to record his current condition and any symptoms as they presented themselves. Although the odds were against him, this exhibit had ten snakes, only two of which were non-venomous, and he had already cataloged one of those. Moreover, the two puncture wounds were a telltale sign of a venomous snake bite. Joseph took another deep breath and wrote in his observation log: *bite, two red puncture sites, bleeding, pain at site, cleaned with antiseptic and Band-Aid applied.* But at the current moment he felt fine. Maybe it was just a boa that bit him; after all, they have teeth and can draw blood. *Man, I hope it was the boa,* he thought. He tried calling Dr. Norton, but his cell phone was not working due to the storm. Joseph continued his work and was able to gather and pack up the remaining eight snakes. Around 2:20 AM Joseph carted the transport boxes to a repurposed, partially underground concrete building on site. It was about that time when he noticed that he had a headache and felt exhausted and achy, he also had the chills. He did not want to believe it was from the snake. *Maybe it's just from stress and lack of sleep,* he thought.

Snake Transport Log		
Exhibit #	*Time*	*Species handled and count*
1	11:45 PM	Bull Snake *(Pituophis catenifer)* – count 4
1	11:58 PM	Calabar Python *(Calabaria reinhardtii)* – count 2
1	12:07 AM	Green anaconda *(Eunectes murinus)* – count 1
1	12:14 AM	Scarlet kingsnake *(Lampropeltis elapsoides)* – count 3
2	12:39 AM	Madagascar tree boa *(Sanzinia madagascariensis)* – count 1
2	12:46 AM	Black Mamba *(Dendroaspis polylepis)* – count 1
2	1:15 AM	Common krait *(Bungarus caeruleus)* – count 1
2	1:30 AM	Madagascar tree boa *(Sanzinia madagascariensis)* – count 1
2	1:38 AM	Fer-de-lance *(Bothrops atrox)* – count 1
2	1:47 AM	Black Mamba *(Dendroaspis polylepis)* – count 1
2	1:55 AM	Green Mamba *(Dendroaspis angusticeps)* – count 1
2	1:59 AM	Boomslang *(Dispholidus typus)* – count 1
2	2:09 AM	Green Mamba *(Dendroaspis angusticeps)* – count 1
2	2:15 AM	Boomslang *(Dispholidus typus)* – count 1

Part I – Signs and Symptoms

Joseph changed his bandage; his leg was still bleeding and he was growing more concerned. He called Dr. Norton again and this time got through. She was still stuck in traffic; several trees had fallen and blocked the road, but she had made progress. She was quite concerned that Joseph had been bitten and told him he needed to act immediately. She instructed Joseph to organize the known information in a chart so that they could narrow down possible serpentine suspects. Dr. Norton said there were various vials of antivenom in the medical refrigerator and freezer, but in order to be useful, the antivenom needed to be for the correct venom. As Joseph was on the phone with Dr. Norton he got a metallic taste in this mouth; his gums had started to bleed.

Questions

1. List the signs and symptoms that Joseph experiences.

2. Which of Joseph's physiological systems appear to be most affected? What evidence supports this?

3. Joseph follows Dr. Norton's advice and organizes the information about the snakes in Exhibit 2 into a table. Using what you know and the information provided above, complete his table.

Snake Venom Table					
Snake	*Venomous?*	*Venom mechanism of action*	*Physiological systems impacted by venom*	*Proposed signs and symptoms from envenomation*	*Symptoms match Joseph's? (Y/N)*
Madagascar tree boa					
Fer-de-lance					
Green mamba					
Boomslang					
Black mamba					
Krait					

4. Based on the information in the snake venom table above, which snake(s) are still likely culprits? Why?

Part II – The Diagnosis

Joseph finished filling out his snake venom table but he was still not totally sure which snake bit him. He was also starting to feel worse. He made sure his symptom observation log was up to date and cross referenced this with his snake venom table.

Symptoms Observation Log:	
Time	Observation
1:02 AM	Two red, bleeding puncture wounds; left leg; pain at site; washed with antiseptic and covered with Band-Aid
2:20 AM	Headache, exhausted, achy, and have chills; wound is still bleeding
2:25 AM	Gums started bleeding
2:50 AM	Dizzy; bite area darker red and swollen, blood slowly draining from wound
3:52 AM	The site of the bite is still bleeding – it is swollen and pink – no bruising or necrosis. Nausea; nose bleed. Feel feverish

Question

5. Based on the information in both tables, what snake seems to have bitten Joseph? Why?

Joseph was now feeling terrible and was incredibly scared. He called Dr. Norton back but could not get through. He tried to call 9-1-1 but could not get through. The storm was really raging at this point. He figured an ambulance would not be able to get to him anyway. He thought about going to the hospital, but the roads looked too bad. He wanted to call his wife, but he did not want to scare her. He quickly rummaged through the books on the shelf in the break room. He found a basic human physiology book and immediately looked up hemostasis. He also re-read Dr. Norton's email.

Questions

6. Hypothesize how venom from the boomslang could impact hemostasis.

7. What role does factor X play in the clotting cascade?

8. What role does prothrombin play in the clotting cascade?

9. How would increasing both the activity of factor X and the cleavage of prothrombin impact hemostasis? Why?

Part III – Boomslang

In Joseph's frantic struggle looking for information, he came across a news article about Dr. Schmidt at the Chicago Natural History Museum. He read that Dr. Schmidt, the museum herpetologist, had been bitten by what others believed to be a boomslang *(Dispholidus typus)*. At the time of the bite, Dr. Schmidt had not thought that the snake was a boomslang based on his identification and thus he went on with his daily duties. In the article Joseph read that the herpetologist recorded symptoms of nausea, chills, fever, bleeding gums, bloody urine, vomiting, and constant nose bleeds. Along with this article, Joseph noticed a tape. He put the tape into the VCR in the break room and watched it.

[Watch: *Diary of a Snakebite Death*, produced by Science Friday, 2015, **https://youtu.be/jEyjF2bNQOA**.]

Joseph now realized that Dr. Schmidt suffered from severe internal hemorrhaging; nearly all of his vital organs were bleeding. The boomslang venom had caused disseminated intravascular coagulation (DIC), also known as consumption coagulopathy. Joseph also found a video resource on DIC.

[Watch: *Disseminated Intravascular Coagulation,* produced by Osmosis, 2017, **https://youtu.be/Gmh01S0msfY**.]

Questions

10. After watching the videos, describe what happens, physiologically, in DIC and how it led to Dr. Schmidt's death.

11. The boomslang's venom is known to affect the conversion of prothrombin to thrombin, and to increase the activation of factor X. How might a bite from the boomslang induce DIC?

Part IV – Antivenom

Finally, Dr. Norton arrived on site. Joseph was sitting in a chair in the break room, awake but in pain and slightly disoriented. Dr. Norton grabbed his notes from the table and took a quick read through.

Symptoms Observation Log:	
Time	Observation
1:02 AM	Two red, bleeding puncture wounds; left leg; pain at site; washed with antiseptic and covered with Band-Aid
2:20 AM	Headache, exhausted, achy, and have chills; wound is still bleeding
2:25 AM	Gums started bleeding
2:50 AM	Dizzy; bite area darker red and swollen, blood slowly draining from wound
3:52 AM	The site of the bite is still bleeding – it is swollen and pink – no bruising or necrosis. Nausea; nose bleed. Feel feverish
4:40 AM	Decide to eat something. Have chills; found thermometer, temperature is 104° F
5:15 AM	Go to restroom, blood in urine. Eyes look bloodshot.
5:35 AM	Vomit up sandwich and a little bit of blood. Fever is still present.
5:45 AM	Pain on the upper right side of the abdomen; more bloody urine

"Boomslang!" she yelled after reading his notes. She immediately ran to the medical cabinet and grabbed the boomslang antivenom ampule. She grabbed the first-aid kit and inserted an IV in Josephs arm; she immediately started to deliver the antivenom at 6:02 AM. She tried to call 9-1-1 but she could not get through. She hoped that she has reached Joseph in time.

Question

12. Based on what you know about hemostasis and what you learned above, if you were to create an antivenom for Boomslang venom, what protein would your drug target?