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## From the Kiss of a Cobra: A Sidelong View of Snakebite, Antivenin & Serum Sickness

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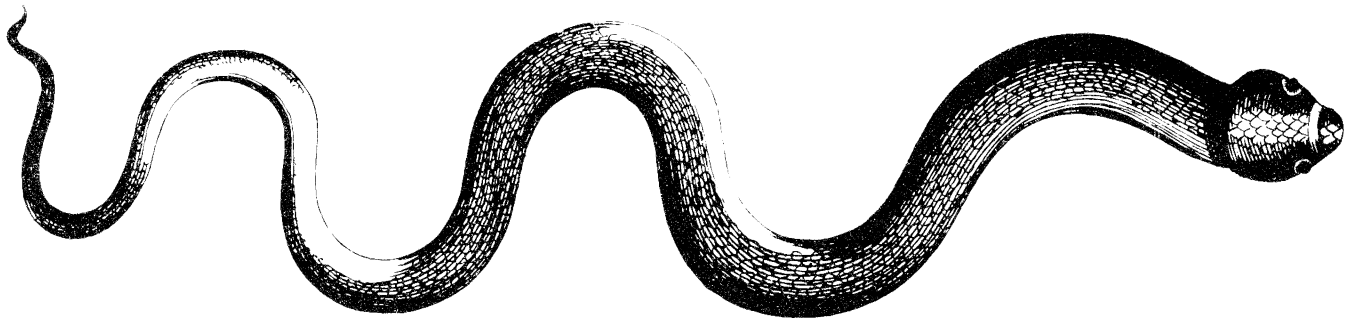


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# From the Kiss of a Cobra: A Sidelong View of Snakebite, Antivenin & Serum Sickness

Douglas H. Graham



*With thy sharp teeth this knot intricate  
Of life at once intie: poor venomous fool,  
Be angry, and despatch.*

So commanded Shakespeare's Cleopatra to the asp which she clutched at her breast moments before her suicide. In an instant, the deed was done and she soon joined her beloved Antony, thus being spared the indignity of surrendering to Rome. Snake venom is rarely employed in such stoic fashion. The circumstances surrounding most poisonous bites are considerably more traumatic, and doctors and toxicologists have long been intrigued by what venom can do to a person. I recently visited several people whose otherwise divergent careers find common ground on the subject of snakebites. Their accounts provide an enlightening, if not unusual introduction to the many peculiar properties of venom, antivenin and serum sickness.

The following narrative is also a brief excursion through an incongruous occupational milieu ranging from biochemistry to smuggling, from serpentariums to private basements, and from the intricacies of immunoglobulins to the sudden need to be rushed to an emergency room. It began with a medical case report titled "A King Cobra Bite in New York City" (Wetzel & Christy 1989), and its description of what seemed a bizarre and grueling odyssey of symptoms suffered by the victim. Several phone calls later, I was walking down a narrow garden path to meet the

nameless "30-year-old male" whose misfortune was documented in the report. He introduced himself as Bob.

## *Incident at JFK International*

For more than half his life, Bob Hughes has been a devoted connoisseur and purveyor of venomous snakes. He has trudged the far reaches of Asia in search of rare serpents, been bitten numerous times, and endured police and television camera crews raiding his home and confiscating his prized collection. Hughes recalls these events with a nostalgic chuckle, but he winces and shakes his head when reminded of the ordeal that befell him in New York City.

It began with a freakish incident at JFK airport. He and several members of the New York Bureau of Fish and Wildlife were in one of KLM's cargo bays, inspecting a wooden crate which had arrived from Thailand. Inside the crate were several large twitching bags containing king cobras, and one of the bags, it seemed, needed tightening.

"Fish and Wildlife had a system where we would check on the snakes by sticking a plastic tube down into the bag and looking through it. Of course," he added sarcastically, "this only works if the snake doesn't use the tube to shimmy up the bag. Before I knew it, bang, I felt teeth clamp down on my thumb. I jerked my hand back and ended up yanking the whole snake clean out of the bag, over my shoulder and onto the floor behind me. You should have seen the customs people scatter."

Hughes recaptured the snake and wrestled it back into the sack. Gently, he sat down on the concrete

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floor of the loading dock, as the gravity of the situation caught up with him.

"At first, it was like a nice mild hallucinogenic, a warm euphoric rush that flowed through my body with mescaline-like trails across my vision. I actually enjoyed it for a few minutes. *La La* land. Then, suddenly I couldn't see in color anymore. Everything became black and white and, whoa, I started to panic. Then came the pain. God, the pain. It honestly felt like there were razors under my skin trying to get out. It was absolutely horrible."

Hughes rapidly weakened. Fifteen minutes after the bite, he couldn't raise his shoulders or speak coherently. His condition deteriorated further as he was transported by helicopter to the Bronx Municipal Hospital where, one hour after the bite, he arrived unconscious.

### **Venom, Toxins & Vital Signs**

Snake venom is a complex and highly potent blend of chemicals. In contrast with most inorganic poisons, which take effect comparatively slowly, snake venom is biologically active: Its myriad components have evolved to spread rapidly within, and degrade, living tissue. Rupturing cell membranes, blocking the transmission of nerve impulses, often acting synergistically with the victim's own cell secretions, snake venom is designed to wreak metabolic havoc on biological systems. People the world over are quite justified in their fear and awe of the speed with which the bite of a relatively small creature can cause such an excruciating breakdown of bodily functions.

It is estimated that close to 100,000 people die from venomous snakebites worldwide each year. Although this figure is much lower in the United States (10 to 15 deaths per annum), in any given year as many as 8,000 Americans are bitten and treated in hospitals.

I visited the Bronx Municipal Hospital's department of surgery where I sat beneath a large rubber cobra hanging from a tree in a conference room. Warren Wetzel, an ebullient trauma surgeon with a thick goatee and strong baritone voice, remembered Bob Hughes.

"I had only recently been designated as the new snakebite consultant for the region, and he was my first patient," recalled Wetzel. "Talk about starting with a bang. They brought him in and we immediately put him on a respirator because the neurotoxin had obviously taken effect." Hughes' symptoms were the direct result of certain properties peculiar to cobra venom.

There is considerable variation in snake venoms, especially between snakes of different families. This difference will often manifest itself in the clinical

effects produced in the victim. Two of these effects, hemotoxicity and cytotoxicity (affecting, respectively, blood and tissue), are common components of viper venom. With scant regard for translation, Dr. Wetzel launched into a clinical description of the symptoms.

"The hemotoxic component initiates a coagulation cascade in the pulmonary bed where the digestion of all the clotting factors occurs," he said. "The patient then dies of a consumptive coagulopathy."

"I see. Could you maybe rephrase that?" I asked.

"Sure," he replied. "It's not a true D.I.C. type picture, but they consume their platelets and clotting factors, and exsanguinate."

"I see."

"They bleed to death."

By contrast, cytotoxicity involves the destruction of tissue cells. "Some of the breakdown products of cellular destruction, such as kinins and plasminogens, will have a systemic effect as well as the venom itself. And if these patients aren't treated," Wetzel continued, "ultimately, from all the outpouring of fluid, from the breakdown of all the cells and their digestive products getting into the system, patients develop a vascular collapse and suffer a cardiac arrest."

Bob Hughes presented Wetzel and his staff with a different clinical challenge. The hallmark of a cobra bite (and others in the elapid family such as coral snakes and mambas) lies in the neurotoxicity of its venom and the disabling effect it has on the nervous system. Again, Wetzel expounded: "It's a large molecule that doesn't cross the blood-brain barrier. It latches onto the motor endplates and causes peripheral paralysis, so the patient stops breathing. Within an hour or so, if you don't breathe for the patient—put him on a respirator—he dies."

To make matters worse, many venomous snakes, including cobras, possess some combination of all three components. Hughes' life was temporarily supported by a respirator while the critical task of neutralizing the venom was carried out with massive infusions of antivenin. Four hours after the bite, his vital signs continued to drop and, with his wife Diane at his side, he was read his last rites.

### **The Battle of Self vs. Nonsell**

Antivenin is produced commercially by immunizing horses with sublethal doses of venom. These horses essentially become hooved antibody factories whose products are harvested from the roughly two gallons of blood that are siphoned from their necks twice a month or so. Antivenin consists largely of these antibody molecules, the bulk of which, once injected into the patient, bind to the circulating venom proteins before they do damage to the body's tissues.

Antibodies to related venoms are often blended to produce a polyvalent serum, one that will provide coverage from a variety of species. Crotalid antivenin, manufactured by Wyeth-Ayerst Laboratories in Philadelphia, is produced from the venoms of four different snakes. The efficacy of such a product becomes immediately apparent in those situations when the identity of the snake is in question. "If someone is wheeled in here unconscious and I have nothing to go on but the fact that they were bitten in the wild in the Northeastern U.S., it's either going to be a timber rattler or a copperhead," stated Wetzel, "and the crotalid antivenin covers both types."

Bob Hughes was treated with Thai king cobra antivenin. Over the course of 10 hours he received 500 ml (50 vials) intravenously, a massive dose by any standard, and at \$300 per vial, an expensive one. He eventually recovered. Four days later he was discharged from the hospital becoming only the second person in medical history to survive the bite of a king cobra.

But Hughes' troubles were far from over. His new problem actually had less to do with snakes than it did with horses. And by his account, it was an ordeal far more prolonged and excruciating than what he experienced from the snakebite.

Sitting around the kitchen table at their Long Island home, Bob and Diane recounted what life was like upon his return from the hospital. "When I got home, the reaction I had to the antivenin . . ." Hughes took a deep breath. "Oh God, let me tell you, it was by far worse than any bite I've ever had in my life. None of the medications Dr. Wetzel gave me worked. I'm telling you, pints of gin a day didn't help. I smoked pot 'til I was blue in the face. Nothing helped. I would just lay there and watch these giant welts or hives or whatever they were, these huge massive things, just appear on my body, and a few minutes later they would just go away."

"The most disgusting thing was his rash," volunteered Diane. "You know what a blood blister looks like? Well he had that all over his body. He couldn't relax, he couldn't sleep, he couldn't sit down, he couldn't wear clothes. He was impossible to live with, I should have sued for lack of services."

Hughes was in the throes of serum sickness. The medical dilemma surrounding the use of horse-derived antivenins is that, while it may ultimately save a person's life, it contains a sizeable quantity of extraneous horse proteins. Upon contact with these foreign proteins, the human immune system will often launch a powerful systemic attack. A

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*. . . unlike insulin and other hormones, snake venom consists of not one, but several hundred disparate molecules. To date nothing less than a fully-functioning immune system . . . can effectively generate the array of antibodies needed to produce antivenin.*

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few hypersensitive individuals will lapse into anaphylactic shock, a life-threatening condition characterized by a drastic drop in blood pressure, intense itching, flushing and inability to breathe. Furthermore, if a person has been bitten and received antivenin once before, his immune system already has the horse protein signature in its memory banks and will respond the second time around with a blitzkrieg so severe as to give pause to using antivenin at all.

I brought this matter up with Sean Carroll, a developmental biologist at the University of Wisconsin-Madison's Howard Hughes Medical Institute. "Let's just say I'm bitten and receive a horse-derived antivenin," I posited. "Then I'm bitten a year later and facing the prospect of a second injection of antivenin."

"You could be in big trouble," Carroll replied. "If you've already been sensitized to horse protein or (especially) if you're allergic to horses, the physician is going to have to make a judgment as to whether the side effects of the antivenin are more damaging than

those of the venom."

"In other words," I continued, "the second time around I could be in a catch-22, even if I have full and immediate medical support, and I've got the antivenin right there in my hand?"

"Yes, in certain situations you would be," he explained. "You might lose a foot or a hand, or even an arm or a leg, to the effects of the venom. Or you may need life support to get you through the antivenin treatment."

Doctors can eliminate some of this guesswork by first administering a tiny bit of horse serum under the patient's skin and noting the immune response. If the reaction is within tolerable limits, antivenin is prescribed. If the reaction is severe, and the bite happens to be a serious one, the doctor, again, is compelled to make a critical bedside judgment call. In those instances when the choice is to use antivenin, a battery of immune suppressant drugs is administered along with it, while still others are loaded into syringes, on standby.

In short, antivenin in its present state of development is not without its downside. The complications surrounding its use are somewhat akin to those that plagued cow- and pig-derived insulin until 1982. However, the more than 2 million diabetics in the U.S. were a strong lobby and provided the impetus to harness the costly methods of recombinant DNA technology. As a result, genetically engineered "humulin" was developed and FDA-approved almost a decade ago.

Compared with insulin, however, antivenin enjoys far less demand. Furthermore, unlike insulin and other hormones, snake venom consists of not one, but several hundred disparate molecules. Although many of these are harmless, the task of isolating, purifying and genetically replicating the antibodies to those that comprise the "lethal component" would nonetheless be a herculean endeavor. To date nothing less than a fully-functioning immune system, with its T cells, immunoglobulins and cloning capacity, can effectively generate the array of antibodies needed to produce antivenin.

Not surprisingly then, even those in the vanguard of snake venom immunotherapy are still reliant upon inducing a surrogate immune system to produce the desired antibodies, an approach that has changed very little since it was first developed at the Pasteur Institute in Paris close to a century ago.

Within this ancient protocol, there have nonetheless been some promising advances. Among the innovators are Sean Carroll and his colleagues who have forsaken the horse altogether. Their approach to the antivenin problem, although it may appear comical or peculiar to the casual observer, is actually elegantly simple and fraught with possibility. It hinges on the cooperation of a much smaller animal, the chicken. More precisely, chicken eggs.

"A laying hen that has been immunized will transport her antibodies to her egg yolk in the same concentration as in her body's serum," said Carroll.

Instead of bleeding horses, this group collects eggs. Lots of eggs, to be sure, but Carroll defended his procedure. "A good laying hen produces roughly two dozen eggs a month. The serum volume which that represents, in those 24 yolks, is much more efficient than any mammal. A small number of birds can match the antibody output of a half ton horse and they cost far less to maintain."

But practicality aside, the far more salient reason to experiment with chicken antibodies has to do with their molecular structure. An antibody molecule is shaped like the letter Y. The upper arms of the antibody perform the task of neutralizing the venom. The lower leg of the antibody, termed the constant region, bears the biochemical signature of the species that created it. It is this section of a horse-derived antibody that triggers in humans the notorious cascade of reactions that survivors of anaphylaxis and serum sickness know only too well.

Carroll's research is contributing to a growing body of evidence which suggests that the constant region of a chicken antibody may cause only negligible adverse reactions in humans. This development, when coupled with certain novel purification techniques, holds such commercial promise that Carroll politely abstained from going into detail with me. He has applied for a patent on the procedure.

## **A Maverick Solution**

If one follows a certain line of thinking, one that reduces the problem of serum sickness to the simple issue of self versus nonself, it stands to reason that the most logical species to immunize is none other than the very one receiving the serum. Proteins from donor and recipient could mix freely without complication; serum sickness would become a thing of the past. Admittedly, the notion of injecting groups of humans with doses of snake venom seems far-fetched, to say the least. However, one pioneering individual has been putting this idea into practice for more than 40 years, on himself.

At his Punta Gorda, Florida, serpentarium and venom laboratory, I spent an afternoon watching Bill Haast extract venom from a batch of copperheads. Coaxing them to bare their fangs and bite through the rubber seal on a collecting flask, he handled each writhing snake with an adroitness that belied his 80 years.

"I started injecting myself with cape cobra venom in 1948," he said. A stream of amber fluid slowly trickled down the glass neck of the flask. "I saw it as a challenge. I wanted to see if it could be done. Of course, it was highly diluted at first, but I gradually increased the concentration and added other venoms."

He paused briefly while his assistant, Nancy Harrell, administered his weekly injection, which now contains more than 30 different venoms. As I watched the syringe empty into his right shoulder, I asked him what would happen if I were to receive the same dose.

"Without treatment, you would quickly die," he replied as a matter of course.

To date, Haast has survived 151 poisonous bites. "Most of those were like booster shots to him," Harrell said proudly, "and he didn't need antivenin."

With such a formidable array of antibodies in his blood, Haast has occasionally been called upon to donate a portion of them. Before 1968, for example, antivenin for snakes in the elapid family did not exist. During this time Haast saved the lives of 21 people by donating his own blood. (Potential complications arising from blood type incompatibility were averted by filtering out Haast's red blood cells. The all-important antibodies established themselves in their hosts' systems without incident.)

Despite his resilience to most bites, Haast has been close to death no fewer than 17 times, and he is no stranger to antivenin and serum sickness. The king cobra, capable of delivering a venom payload equivalent to 120 lethal doses, has been responsible for many of his trips to the hospital. (Haast, not surprisingly, was the first person in medical history to survive the bite of a king cobra.)

Through it all, however, Haast has persevered with his vision of venom's potential role in today's pharmacopoeia. The philosophy behind his lifelong commitment to working with snake venom, and promoting its use in research, is effectively summarized by the Middle Eastern adage: "From the most potent poisons, the most successful remedies come." For more than half his life, in addition to supplying antivenin manufacturers with venom, he has tirelessly championed its medicinal value in treating polio, multiple sclerosis, arthritis, and more recently, AIDS. A number of experiments that have targeted cancer cells with venom enzymes have met with compelling success. And it is from Bill Haast that all these research labs and pharmaceutical companies requisition their venom.

### Contemplating the Kiss

On a recent hike near my New England home, I came across a timber rattlesnake languidly half-coiled on a slab of granite—not an uncommon sight in these parts. It was a large, robust-looking specimen and had been warming itself in a patch of sunlight. With a long stick that had a nice safe feel to it, I gave it a cautious nudge. The swiftness of its reaction was impressive as it reared up to face me. The rattling was immediate and vigorous, echoing off the surrounding rock.

I have never been bitten by a poisonous snake. Yet, with morbid curiosity, I found myself contemplating the prospect. Staring, mesmerized, at the reptile before me, I fantasized about what it would feel like to suddenly have a tiny quantity of its venom coursing through my system. The "joy of the worm," as Cleopatra's attendant had described it. How would this enigmatic fluid affect my thinking, my coordination? On this point, all the snake handlers that I have queried have responded unanimously, often with a hint of disdain, to the effect that I can't even begin to comprehend the feeling until it actually happens to me. Maybe, I thought to myself, if I'm careless for a few moments, I'll have my answer.

This reverie was dashed by an image of Bob Hughes covered with festering, gangrenous blood blisters. Suddenly my respect for the efforts of people like Warren Wetzel and Sean Carroll seemed heightened. Bill Haast's work also took on a renewed legitimacy in my mind. He seems like a perfectly normal guy.

I dropped the stick and moved on.

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