Poisons, Toxins, and Venoms…Oh My!

By Mark C Glassy, Ph.D.

Submitted for your approval

[personal note]
Wise words from Universal's, *House of Dracula*
In the film, Dr. Edelman explains the biological basis of the werewolf condition to Larry Talbot. After hearing this Talbot tersely responds, "Explaining doesn't help. What can you do about it?" The curse of the scientist is in wanting to explain and understand everything whereas the patient more or less could care less. "What can you do about it?" is, unfortunately, a way too common question from patients. (Though I digress, but on a personal level, as a cancer immunologist, I have focused my career on 'doing something about it'.) These articles are not meant to inundate with scientific jargon ("explaining doesn't help"). It's a challenge to simplify complicated concepts and procedures and hopefully you gentle readers will learn something new and fun by reading them and appreciate even more the films we all know and love.

Overview
Though all are deadly there are significant differences between poisons, toxins, and venoms. Toxins are poisons made in nature that cause pain when ingested and venoms are toxins that are injected by a bite or a sting. The main difference between venoms and other poisons is the delivery method. All in all poisons, toxins, and venoms work by either interfering with metabolism or neuromuscular responses. For some, even a small quantity ("just a pinpoint"), is enough to kill. With sufficient quantity some substances that are not poisons can become poisonous and cause problems so they are dose dependent, meaning small amounts maybe OK but large amounts are deadly.

Please note that substances that destroy tissue but do not absorb, such as lye, are classified as corrosives rather than poisons. Though these substances are indeed deadly it should be noted that many poisons are used in industry and agriculture for reasons other than toxicity. Substances like ammonia, carbon monoxide, methanol, and sodium cyanide can be poisonously deadly when in high enough a dose. These industrial uses include chemical reagents, solvents, and complexing reagents. Some herbicides (generically called biocides) may be poisonous to plants but not to humans whereas some pesticides, such as rat poison, may be harmful to humans if consumed in enough quantity.

Also, it should be noted that just about all species make some sort of poison or harmful substance so we will only be concerned with those that affect humans,

directlly or indirectly. For example, substances poisonous to bacteria, called antibiotics, are not poisonous to humans. Also, environmental hazards, though maybe a hazard to ecosystems – by consuming oxygen – are not necessarily poisonous to humans. Also for consideration is poisons, toxins, and venoms can vary considerably from species to species.

Misuse of terms

When used non-technically, the term "toxin" is often referred to as any toxic substance, even though the term toxicant would be more appropriate. Toxic substances not directly of biological origin are also called poisons and many non-technical and lifestyle journalists follow this and refer to toxic substances in general. Not to confuse the issue but it should be noted that some poisons are also considered toxins and are often synonymous, common examples being tetanus and botulism. A poisonous organism would normally be harmful to eat whereas a venomous organism would normally be safe to eat.

To add to the nomenclature confusion animals produce two types of toxins: poisons and venoms. Simply stated, poisons cause symptoms (pain, illness) when ingested whereas venoms need to be injected (via bite or sting) to cause symptoms. So an ingested venom may not be effective since the natural digestive processes could inactivate it.

Nature's Weapons of Mass Destruction

The assassins of the natural world consist of the usual suspects: bees, scorpions, snakes, and spiders. Other contenders for that list are anemones, fish (and jellyfish), frogs, and snails. Also included on this list are countless plants.

Hazardous substances/materials (hazmat)

Whether a poison, toxin, or venom, a gas, liquid, or solid, they are all dangerous and therefore considered hazardous materials (hazmat) since they can harm people. Hazmat situations can involve allergens, biohazards, corrosives, explosives, flammables, radioactive compounds, and toxic substances. Also included are normal materials or chemicals (compressed gasses or hot materials) that become hazardous due to circumstances.

Poisons

Human history is filled with intentional uses of poisons for murder, suicide, execution, and pest-control. Poisons can be inhaled, injected, or ingested, such as Socrates who famously ingested hemlock poison.

The word, "poison" has been in use for many centuries and was first used around 1200A.D. to mean a "deadly potion or substance". As an adjective, "poisonous", was first used around 1520. The term "poison ivy" was first used in 1784 and "poison gas" was first used in 1915 during World War I. Currently, poison has

come to mean any harmful substance, including corrosives, carcinogens, mutagens, and pollutants.

Paracelsus (1493-1541), an alchemist and considered the father of toxicology, said, “Everything is poison, there is poison in everything. Only the dose makes a thing not a poison.” Therefore, substances generally not considered a poison can cause medical conditions of poisoning when taken in a large enough dose and, if given in large enough amounts, can cause death. For example, swallowing several kilograms of water could be a lethal dose.

The Food Chain

Many poisons either from the air, water or soil rapidly diffuse into biological tissues. Some poisons accumulate in a particular species which are then in the food chain that affects other species. An example of this are insects that consume a poison (pesticide) which are then eaten by birds thereby also consuming the poison. Also, some poisons, industrial, agricultural, or natural, that enter the food chain may not be toxic to the first animal that ingests it but can become a problem when concentrated and moved up the food chain. This is a problem mostly for carnivores and omnivores. This is especially important for fat soluble toxins that stay in the body’s fat tissues for some time and consumed later by another species.

Since all organisms on Earth all share a common biochemistry then key concerns for poisons are selective toxicity (one animal over another), controlled application, and perhaps controlled biodegradation. However, each organism also has unique biochemical processes that can be exploited in one form or another. How have Earth’s deadliest creatures mastered biochemistry? How are they immune to the effects of their own poisons, toxins, and venoms?

Immunity to poisons

Background: Stating the obvious, brick walls are composed of individual bricks held together. For trains the individual cars are coupled together and the length of the train is determined by several factors. Proteins are like these examples in that they are composed of individual amino acids (the “bricks”) and coupled together like train cars. There are 20 different types of amino acids that make up proteins and depending upon the type of amino acid they will fold in certain predictable ways in a compact structure. You change one of the amino acids (a ‘brick’) and the structure could dramatically change. Over time these single amino acid changes can be significant and is what drives evolution.

At the molecular level poisons are chemical molecules that have certain shapes and structures. Most act in the same way by either inhibiting respiration or causing neuromuscular collapse. Those animals that make poisons must be somehow immune to their effects or otherwise they too would suffer from the poison. So, how are these animals immune? An example is the poison frog.

One particular nasty compound from frog skin, a neurotoxin called epibatidine, is a stronger painkiller than morphine and deadly to rodents.

Poison frogs resist their own chemical defenses with amino acid modifications (changing 'bricks' in the wall) in the sequence for a target receptor protein. Epibatidine-bearing frogs have independently evolved amino acid changes in the poison's protein target, the nicotinic acetylecholine receptor. These modifications, a single amino acid change, allow the frogs to avoid self-toxicity while also preserving the receptor's ability to bind the neurotransmitter acetylcholine. In other words, interacting amino acid replacements (changing 'bricks' in the wall) allow poison frogs to evolve epibatidine resistance.

Other animal species, including some insects, newts, and puffer fish, have evolved a similar resistance to toxins—self or otherwise—also by amino acid replacement.

Poisoned possibilities

Poisons are naturally in the environment and one common example is mushroom poisoning in humans. A natural environmental poison is arsenic. In addition to food many poisons enter the body through the skin or lungs. One common example that many have experienced is poison ivy contact that turns the body's natural defenses against itself. Other example is lethal poison injection as used in capital punishment.

In humans, chemical poisons are often passed from mother to baby through the placenta during gestation or through breast milk during nursing. In contrast, radiation poisoning can cause long term genetic mutations that can be passed from mother or father to offspring which—if not fatal in miscarriage or childhood, or a direct cause of infertility—can then be passed along again to a subsequent generation.

Poisons that enter the environment are referred to as pollution. Though most pollution is man made there are also natural pollution events such as toxic red tides. The environmental life cycle of poisons and toxic compounds is complex and far-reaching.

Acute vs Chronic

Acute poisoning is either a single event or something occurring over a short period of time. Chronic poisoning is long-term repeated or continuous exposure. Either way, the poison is absorbed systemically. Eventhough a substance may not be inherently poisonous it can be a poison when enough enters the body in a specific way. In this way, a poison can 'bioaccumulate' in the body with examples being mercury and lead poisoning that can build up over time.

Some poisons act immediately and can cause rapid death. Such poisons act on the nervous system and can paralyze in seconds (or less!). Neurotoxins and nerve gases are examples.

Cyanide poisoning starves the body of energy by inhibiting the metabolic steps in the mitochondria that make ATP. Other poisons, such as potassium chloride, can quickly stop the heart's muscle contraction. Methanol, or 'wood alcohol', is itself not a poison but is metabolically converted to formaldehyde [distant cousin of (ahem) Dr. Jekyll's Mr. Hyde] and formic acid which are poisons. With methanol you pickle your own liver. Which brings up another point. Many substances are made poisonous or toxic by the liver as well as the converse in that one of the chief functions of the liver is to de-toxify some molecules.

Radiation poisoning
When exposed to a high dose of ionizing radiation severe health effects can occur. This radiation causes damage to DNA and other key metabolic processes prohibiting cells from dividing that can lead to morbidity and perhaps even death. The onset and type of symptoms depends upon the amount of radiation exposure. Depending upon the dose symptoms of radiation poisoning can take years to develop or days. Small doses can lead to nausea and vomiting and large doses can result in neurological effects (seizures and tremors) including cancers. Scary indeed was the radiological poison assassination of Alexander Litvinenko in 2006.

Poison management
The initial effects of poisoning involve cardiopulmonary functions, seizures, and shock. For injected poisons like bee stings or spider bites often times a simple pressure bandage (keeps the poison from being pumped throughout the body) and hot water are enough to break down the poison helpling to alleviate some symptoms.

Ingestion of poisons may require what is called gastric decontamination to help decrease absorption. Depending upon the poison such treatment involves activated charcoal, gastric lavage (stomach pump), aspiration, cathartics, or whole body irrigation.

Poison or cure?
A drug as common as acetaminophen, marketed under many names, one being Tylenol, is an accepted and effective painkiller for such things as headaches and muscle cramps. However, when used in large doses it can cause poisonous liver damage and if the overdose is not treated the patient could die. So, depending upon the amount, acetaminophen can either be a cure or a poison.

White Zombie (1932)

Brief film summary: A young man, Belmont, turns to a witch doctor, Murder Legendre (Bela Lugosi), to lure the woman, Madeline, he loves away from her fiancé, but instead turns her into a zombie slave. After the witch doctor is dispatched the woman returns to normal.

The character, Neil Parker asks, “Who are you and what are they?” as he is looking around at Murder Legendre and the zombies. Legendre responds with, “For you, my friend, they are the angels of death.”

Key to the film is the white powder poison Legendre uses and comments, “Only a pinpoint, Monsieur Belmont, in a glass of wine or perhaps a flower.” Madeline sniffs flowers at her wedding containing the poison and then later drinks wine containing the poison. She passes out and is pronounced dead. She then becomes zombie-like with no emotion and appears to be in a trance-like state. Realizing his mistake Belmont says, “Better to see hatred in them (Madeline’s eyes) than that dreadful emptiness.”

Belmont himself drinks poison laced wine with Legendre commenting, “Only a pinpoint, monsieur, the flower or perhaps a glass of wine.” Legendre wants Madeline for himself so he wants to get rid of Belmont. Belmont can hear but not respond once poisoned. Legendre says, “Can you still hear me? It is unfortunate you are no longer able to speak. I should be interested to hear you describe your symptoms.”

Since Madeline eventually regains consciousness at the end of the film suggests the effects of the poison were temporary.

For any drug to work it must get into the body and Legendre thought ingestion or inhalation were the most efficient ways. Perhaps the liquid environment of wine would not only solubilize the powder but the alcohol could also act as a catalyst to strengthen the mode of action (alcohol could enhance the drugs absorption). “Only a pinpoint” suggests the drug acts in a catalytic manner since a small amount is necessary.

Most likely Legendre’s zombie powder contains the neurotoxin, tetrodotoxin (see below), which is obtained from puffer fish. The zombie powder works by inhibiting neuromuscular body movements and the chemical communication between nerve endings and muscle cells is disrupted by the action of tetrodotoxin. In the film, the drug’s effects would have to be long lasting, though apparently temporary, since multiple doses were not seen.

The Creature From the Black Lagoon (1954)

Brief film summary: During an expedition to the Amazon region of South America a strange prehistoric creature from the black lagoon was discovered. Scientists try to capture the animal to bring back to civilization to study.

David Reed (Richard Carlson) says, “I don’t want him creeping up on us while we are sleeping.” Lucas (Nestor Paiva) responds, “I know of a way to bring him up now. Rotenone. It’s a drug the natives make from roots for catching fish in still

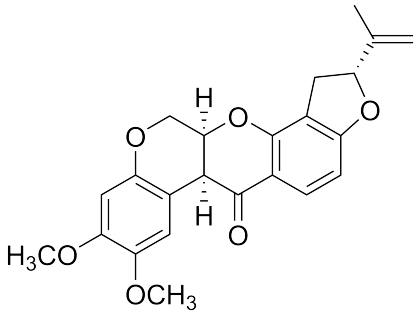
waters. Sometimes I catch fish that way. One taste of the poison water and – poof! – the paralyzed fish float up to the top with a big hangover."

Both Reed and Mark Williams (50's sci-fi stalwart, Richard Denning) put rotenone powder into the still lagoon and soon after many fish are seen floating on the water, but no creature. Reed says, "Maybe the rotenone isn't going deep enough." Lucas says, "Maybe we should fix the rotenone to sink deeper down." Discs of hardened rotenone are put in the lagoon and are seen sinking to the bottom leaving a wake of dissolving poison.

Soon the drugged Creature is seen and Reed asks, "How long does the effect (of rotenone) last?" Lucas replies, "An hour maybe two but for that thing who can tell?" Later, the Creature is seen staggering out from the grotto onto land clearly affected by the rotenone. Apparently the Creature got the 'Goldilocks dose', meaning just enough to drug or anesthetize him but not kill him. An anesthetic depresses nerve functions whereas a poison kills.

The second exposure to rotenone is via the spear gun air bottle while Reed is untangling the blocking tree branches preventing their boat from leaving the lagoon. He has just enough rotenone left to make the Creature "groggy". An air bottle is filled with liquid rotenone and squirted out under pressure while under water. One question to ask is how much residual rotenone was still left in the Creature's body from the first exposure? Based on his movements it is noted that the Creature is still groggy when he climbs onto the boat to capture Kay.

The Creature may have a metabolism that is not overly susceptible to the poisonous effects of rotenone. The Creature could have some respiratory enzyme that is rotenone insensitive or have a completely different way of metabolizing oxygen that is unaffected by the poison. Since the Creature comes from the Amazon and since rotenone is derived from a South American plant perhaps the Creature has a natural defense or immunity against the poison, similar to the above discussed poison frogs that are immune to their own poisons.



Structure of rotenone

Rotenone is an odorless, colorless, crystalline isoflavone used as a broad-spectrum insecticide, piscicide (kills fish), and pesticide. Rotenone occurs naturally in the seeds and stems of several plants, such as the jicama vine plant, and the roots of several members of *Fabaceae* family of legumes. Historically,

rotenone has been used by indigenous South American Indians to catch fish but is now primarily used as an insecticide. Rotenone poisoned fish rise to the surface in an attempt to gulp air so are easily caught. The higher toxicity in fish is because rotenone is lipophilic (fat loving) and easily taken up in gills or trachea but not through the skin or gut.

Rotenone is an inhibitor of what is called “Site I” in the mitochondria respiratory electron transport chain of oxygen breathing animals, which biochemically transfers electrons to molecular oxygen (the end stage of the breathing cycle). Rotenone inhibits the ability to utilize oxygen and in a large enough dose can cause death. [For those gentle readers who are more curious, rotenone inhibits the transfer of electrons from iron-sulfur centers in Site I to ubiquinone. This interferes with NADH during the creation of usable cellular energy in the form of ATP. Site I is unable to pass off its electron to Co-enzyme Q, creating a back-up of electrons within the mitochondrial matrix. Cellular oxygen is reduced to the radical, creating reactive oxygen species, which can damage DNA and other components of the mitochondria, the powerhouse of the cell. The end result is death.]

Rotenone will not anesthetize, as implied by Lucas, but rather kill in a matter of seconds. Also, rotenone is environmentally friendly since only small quantities are needed, it rapidly biodegrades when exposed to sunlight, and its residues are not harmful to mammals so there are only minor to transient side effects.

The Creature Walks Among Us (1956)
Brief film summary: A group of scientists captures the Creature and through surgical intervention turns him into a land-walking, air-breather, only for him to escape and go on a killing rampage.

Dr. Thomas Morgan (Rex Reason) says, “The trick will be to maneuver him to still water. This liquid rotenone compound will anesthetize him in seconds providing, of course, we can give him a concentrated dose.” Yes, for poisons it’s all about the dose. The reason the mechanism of action is important is because rotenone does not “anesthesize in seconds” as the scientists claim but rather kills in seconds. Big difference.

Morgan comments, “There’s enough sleep juice in one of these things (canister) to knock out an elephant…If he comes within a toxic distance…I will discharge the rotenone.” Note: the clearly stenciled word in capital letters, “ROTONONE”, on the canister is misspelled; it should be spelled, ‘rotenone’. Not sure what a ‘toxic distance’ is since the diffusion of rotenone would weaken the concentration over distance plus the fact that the spray gun has limited range, no more than a few feet.

The Four Skulls of Jonathan Drake (1959)

Brief film summary: Jonathan Drake, while attending his brother's funeral, is shocked to find the head of the deceased is missing. Apparently, an ancient curse has been placed upon his grandfather by a tribe of South American Jivaro Indians and that he himself is the next victim. An Indian, whose lips are sewed together with string, similar to a shrunken head, uses a curare-tipped bamboo knife to dispatch his victims.

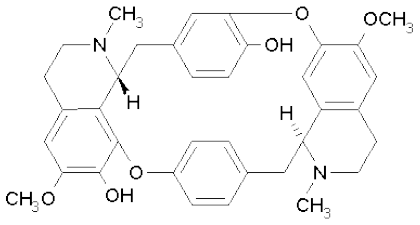
To claim victims they get a small stab, just enough to break the skin, almost like a scratch, at their neck, just below the ear with a curare-tipped bamboo knife. The victim dies almost immediately as judged by, “no sign of a pulse”.

Due to the nature of bamboo one wonders if the bamboo knife is hollow? If so, then there could be fluid inside the bamboo so in addition to the coated tip more curare fluid could enter the wound. From the condition of the victims a physician thought they died of heart issues.

Based on an “ancient curse” of South American Indians the heads from victims were removed and used for making shrunken heads. Jonathan Drake used curare to kill victims and removed their heads to make shrunken heads of them.

Blood from one of the victims was analyzed and found to contain curare. A scientist comments, “The only people I know that use curare as a poison are some Indians from South America.” A cop asks a doctor, “Did you get the antidote?” The doctor replies, “It wasn’t difficult. Curare is one of the phenolic alkaloids (see below). I only hope I was able to administer it in time.” It should be noted that curare-induced muscle paralysis can be reversed by administration of a cholinesterase inhibitor such as pyridostigmine so this is what the doctor probably administered. However, the victim, Jonathan Drake, does have hallucinations as a result, usually not a side-effect with such antidotes so they most likely are psychosomatic.

(Note: phenolic alkaloids are known for their antioxidant activity (scavenge free radicals), primarily inhibiting hydrogen peroxide formation and are used in phytotherapy research. Though curare is an alkaloid (see below) referring to it as a “phenolic alkaloid” is quaint and outdated.)



Structure of curare

Curare is a common name for various plant extracts (most frequently from the bark of *Strychnos toxifera*) originating in Central and South America that contain tubocurarine, curarine, quinine, and protocurarine and related alkaloids. Curare belongs to the alkaloid family which are a group of naturally occurring compounds that mostly contain nitrogen. Some common examples of alkaloids are anti-malarials (quinine), anti-asthma (ephedrine), vasodilators, and even morphine. Other examples of alkaloids are caffeine, nicotine, and cocaine. Almost all alkaloids have a bitter taste.

The curare poison inhibits the nicotinic acetylcholine receptor at the neuromuscular junction causing a weakness of skeletal muscles and in sufficient enough dose can cause death by asphyxiation due to paralysis of the diaphragm. And that is the key here: sufficient enough dose. The small amount of curare on the end of a bamboo knife may be enough to temporarily weaken, even presenting a weak pulse, but maybe not enough to cause eventual death.

It should be noted that both curare and rotenone have a South American connection.

The Diabolical Dr. Z (1966)

Brief film synopsis: A woman seeks to avenge her father's death by using a local dancer, with long curare-tipped fingernails, to do her bidding as an unconscious killer.

A woman with very long fingernails is placed under mind control by Doctor Zimmer. The woman's fingernails are tipped with curare and she scrapes them against the cheeks of those she is ordered to kill. The victims die almost immediately.

An interesting POV scene is when a scientist (who is actually director Jess Franco in a 'Hitchcock cameo') is looking at a victim's sample under a microscope and we see what appears to be marked cross hatches of…something, maybe crystals. After seeing these the scientist immediately pronounces, "curare", which is a challenge to surmise from just seeing this (drawn) sample under the microscope. Quite frankly an actual delivered dose of curare would have dissolved and dissipated within the victim's body so no such POV sample as seen in this film could exist.

Toxins

A toxin (from Ancient Greek: τοξικόν, *toxikon*) is a biologically poisonous substance produced within living cells or organisms. According to an International Committee of the Red Cross report, "Toxins are poisonous products of organisms; unlike biological agents, they are inanimate and not capable of reproducing themselves." Furthermore, According to Title 18 of the United States Code, "... the term "toxin" means the toxic material or product of plants, animals, microorganisms (including but not limited to bacteria, viruses,

fungi, rickettsiae or protozoa), or infections substances, or a recombinant or synthesizes molecule, whatever their origin and method of production."

Toxins can vary considerably in type and size from small molecules to peptides and proteins. Toxin toxicity also varies considerably from minor bee stings to something much more deadly such as botulinum toxin. Toxins can simply be absorbed by the skin or ingested.

In the context of quackery and alternative medicine, the term "toxin" is used to refer to any substance alleged to cause ill health. This could range from trace amounts of potentially dangerous pesticides, to supposedly harmful substances produced in the body by intestinal fermentation (auto-intoxication), to food ingredients such as table sugar, monosodium glutamate (MSG), and aspartame.

Animal analgesics

Analgesic drugs act on the peripheral and central nervous systems by relieving pain. In the news lately are opioid drugs that are analgesics. Simply stated, analgesics are synthetic drugs used as painkillers. The only toxin-derived analgesic approved by the FDA is ziconotide (tradename: Prialt), a compound 1000 times more potent than morphine (also an opioid), originating from a component of the venom of the cone snail, *Conus magus*, that is used for intractable pain. Ziconotide works by blocking voltage-gated calcium channels (see below) that inhibits the release of pain-transmitting chemical messengers.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is caused by the release of bacteria toxins resulting in fever, rash, skin peeling, and low blood pressure symptoms. The bacteria toxins, called super antigens, come from *Streptococcus pyogenes* or *Staphylococcus aureus*.

Botox

Botulinum toxin or botox is a neurotoxic protein made by the bacterium, *Clostridium botulinum* and one of the most lethal toxins known. Botox prevents the release of acetylcholine, a neurotransmitter involved in muscle movement, and this causes muscle paralysis. Infection by the bacterium *C. botulinum*, either by contact or inhalation, causes botulism, a potentially fatal illness. There are eight types of botulinum toxin. Types A and B are used in medicine to treat muscle spasms (Botox) while type H is considered the deadliest substance in the world since only two-billionths of a gram (2ng) can kill an adult.

Toxin types

Toxins are typically referred to the anatomical areas where their effects are most prominent. For example, a hemotoxin causes destruction of red blood cells (RBC) and phototoxins cause photosensitivity. Endotoxins are released by bacteria.

Biotoxins are of biological origin (animal, fungal, microbial, or plant) and have two main functions: predation (jellyfish, scorpion, snake, spiders, and wasps) and defense (ants, bees, poison dart frog, and termites).

Neurotoxins affect the nervous system and typically consist of ion channel toxins. Common examples of biotoxins include those from the black widow spider, scorpions, box jellyfish, elapid snakes, cone snail, blue-ringed octopus, frogs, and some venomous fish. Some myotoxins found in snake and lizard venom are small basic peptides that cause muscle tissue damage. Cytotoxins include ricin from castor beans, apitoxin from honey bees, and T-2 mycotoxin from some mushrooms.

Also in scorpion and snake venom is domoic acid, a toxin, which affects reproduction and fetal development, stimulation of uterine contractions, and may even induce fetal malformations.
In some individuals bee venom can cause a strong anaphylaxis response often resulting in massive inflammation, an allergic response that involves immunoglobulin E (IgE) that could be life-threatening.

Synthetic toxins

Environmental or synthetic toxins are usually considered industrial pollutants and chronic exposure to high enough levels often cause toxic effects, especially when these toxins enter the food chain. For example, shellfish consume toxins that are consumed by others higher in the food chain, including man.

The Mad Ghoul (1943)

Brief film synopsis: A university chemistry professor, Dr. Alfred Morris (George Zucco) experiments with an ancient Mesoamerican Mayan gas on a medical student, Ted Allison (David Bruce), turning the would-be surgeon into a murdering ghoul.

Not all toxins need be solid or liquid and in this film a toxic gas is used so what constitutes a toxic gas? For gases the term, LD_{50}, refers to the mean lethal dose (expressed in terms of mass fraction (e.g., milligrams of toxin per kilogram of body mass) that will kill 50% of a laboratory mouse population) of a gas in air and is a measure of amounts that can kill, typically within the range of more than 20 parts per million (ppm) but not more than 2,000ppm.

In addition to gas, toxic inhalents can be dust, fume, mist, or vapors. Many toxic gases can be detected by odor but some cannot. Some of the better known toxic gases are carbon monoxide, chlorine, nitrogen dioxide, and phosgene.

In the film, Morris comments on the effect of the Mayan gas he is studying by saying, “Brought death in life or if you prefer, life in death.”

Morris wants to recreate the native Mayan poison gas and needs specialized glassware to achieve this. His lab seems appropriate for the chemical work necessary and seen are a shelf on a benchtop, plenty of appropriate glassware, the proverbial Bunsen burner (used to activate the gas), books, monkeys in

cages, chemicals and reagents. Morris comments on the well-equipped nature of his lab by saying, “The world in a test tube”, meaning he has everything he needs.

The gas crystals are kept in a stoppered erlenmeyer flask kept inside a beaker. Morris says, “These crystals and the gas they give off are colorless and odorless therefore the more deadly.” When the crystals are placed in a metal bowl and heated over a Bunsen burner the deadly gas is easily seen which is at odds with “colorless”.

Morris continues, “The effects of the gas are almost instantaneous. Physical changes took place within a few minutes…emaciation, then more marked physical changes, and a paralysis of the will.”

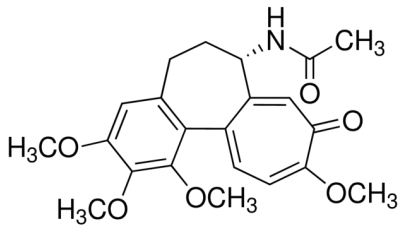
Morris’s assistant, Ted, inhales fumes from the gas and has rapid facial changes such as dark eyes, wrinkled skin, hair in disarray, and is lethargic with no will.

The antidote for the gas is a heart extract mixed with certain herbs so each time Ted transforms Morris has him locate a newly deceased body, perform a “cardiectomy”, and use the heart to return him to normal. Unfortunately, the antidote is temporary so Ted reverts (relapse?) back to the ghoul suggesting the effects of the gas are permanent. An emotional outburst is enough to cause Ted to revert to the ghoul. Ted may have a “split personality”, aka, schizophrenic as a result of the gas.

Curucu, Beast of the Amazon (1956)

Brief film synopsis: Rock Dean (John Bromfield) and Dr. Andrea Romar (Beverly Garland) travel up the Amazon River to not only find out why the plantation workers have left their work in panic, allegedly because of attacks from Curucu, a monster who is said to live up the river where no white man has ever been before but also in search of a new medicine, the toxin colchicine. This film is an example of a toxin used for non-lethal purposes in biomedical research.

Romar explains her work to Dean, “Cancer research that I carry on with doctor Vale. We discovered that single sub-cutaneous injections of purified penicillin have no regressional effects at all…the headhunters have a drug that we want…the headhunters prepared an extract from a certain plant to shrink live tissues (i.e., shrunken heads)…if I can find that preparation medicine will have taken a giant step…it’s a drug called colchicine. The headhunters know about this preparation in non-lethal concentration. We don’t.”



Structure of colchicine

Colchicine is a natural product extracted from the plant, *Colchicum autumnale*, also known as “meadow saffron”. Currently, colchicine is used to treat gout, some forms of fever, pericarditis, and Bechet’s disease. In large enough doses colchicine can be toxic if ingested, inhaled, or absorbed in the eyes. Within 2 to 24 hours of ingestion symptoms can include, abdominal pain, diarrhea, fever, and vomiting. In extreme cases this can cause hypovolemic shock due to fluid loss through the gut. In addition to systemic issues colchicine also affects the nervous system and includes confusion, delirium, hallucinations, and seizures. Long term exposure can cause bone marrow, kidney, and nerve damage. Currently, no specific antidote for colchicine is known.

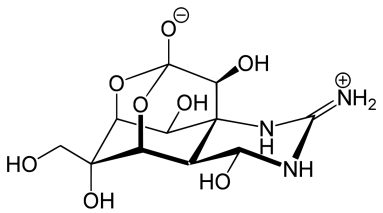
Specifically, colchicine inhibits microtubule polymerization within cells thereby acting as a toxic “mitotic poison” and preventing cell growth.

The Serpent and the Rainbow (1988)

Brief film synopsis: An anthropologist goes to Haiti after hearing rumors about a drug used by black magic practitioners to turn people into zombies.

The driving factor in this film is the desire to find a new anesthetic that would not be harmful to surgery patients and the properties of zombie powder are investigated.

Anthropologist, Dr. Allen, says, “The ingredients of the powder are terrifically varied. There is the poisonous sea toad, *Bufo marinis*, the same animal Lucretia Borgia used. Made even more toxic by frightening it with a stinging sea worm. And the puffer fish, which produces one of nature’s most powerful poisons, tetrodotoxin. Plus a whole pharmacy of herbs, minerals, charred, then ground and mixed with a skill that’s astonishing…the process takes three days and nights.” Since this powder is prepared in advance then it must have some sort of ‘shelf life’ since it may not be stable for very long. The powder is applied on the skin and/or inhaled so it must be absorbed and enter the blood supply to be effective. As stated in the film, “you cannot eat the powder in food. That would kill completely.” The natural digestive processes in the stomach and intestines would de-toxify the compounds.



Structure of tetrodotoxin

Tetrodotoxin is a potent neurotoxin from the Tetraodontidae family of puffer fish. Just a few milligrams of tetrodotoxin is enough to kill a man. Tetrodotoxin blocks the passage of sodium ions in voltage-gated sodium channels on the surface of neurons effectively stopping their electrical transmission or action potential (see below). This prevents the nervous system from carrying messages and prevents muscles from flexing. Your diaphragm stops working and your heart stops beating. Death will quickly follow.

Venoms

Venoms are a form of toxin, mainly as peptides and proteins, that are secreted by animals which interfere with one or more metabolic or neurological steps to capture prey or for defense. In 2013, 57,000 humans died of venom bites. Venomous invertebrates include spiders (fangs), centipedes (modified legs), scorpions and other stinging insects with the best known being bee stings (stinger). Other invertebrate venoms include jellyfish (box jellyfish is the most venomous jellyfish in the world), sea anemones, cone snails, and coleoids (cephalopods). Venomous animals are usually keystone species that play crucial roles in their ecosystems.

The best known example of venoms we are all unfortunately familiar with comes from the stingers of bees and wasps. Bee venom, an acidic version called apitoxin, can serve many functions from an alarm pheromone, enhance immunity, inhibit chemotaxis (a form of cell movement), and cause hemolysis (disrupting red blood cells) that can lead to organ failure. Wasp venom is different and consists of an alkaline venom made to paralyze prey for storage in food chambers. (There are many to choose from so what is your favorite bee movie?)

The best known reptile venom comes from snakes who inject their venom into prey via fangs, though some are known to spit their venom. Snake venom is produced by salivary mandibular glands below the eye and channeled to the fangs. Snake venom is complex and composed of peptide toxins, proteases (enzymes that break down proteins), nucleases (enzymes that breakdown DNA), and neurotoxins that disrupt the nervous system.

Complex venoms

Many venoms are complex and can contain up to 20 different compounds, though mostly proteins, enzymes, and polypeptides. Snake venom can vary significantly in their function and is composed of peptide toxins, proteases (enzymes that break down proteins), hemotoxins (coagulate blood and deregulate blood pressure), nucleases (enzymes that breakdown DNA), and neurotoxins that disrupt the nervous system. The pharmaceutical industry has taken note of all this and have vigorously pursued many drug development programs based on venom biology. Most rattlesnakes and vipers produce a

phospholipase and serine proteases in their venom, both which break down cells and tissues.

Some venoms can disrupt the electrical activity of the heart which in turn affects the heart's impulse conduction. Also, some venoms have a direct cardiotoxic effect by acting on cardiac myocytes that affects the pumping capacity of the heart possibly causing myocardial ischemia (heart attack).

Snail cone venom works by restricting the diaphragm preventing the victim from breathing often resulting in death by heart attack. A lot of insect and snake venoms have acetylcholine in them which reacts with pain receptors causing throbbing pain.

Venomous animals with bites and stings

Bees, centipedes, frogs, scorpions, snakes, and wasps are just a few of the animals that use venoms. Some fish produce venom such as stingrays, scorpionfishes, and lionfishes among others. A few salamanders secrete toxic fluids via specialized glands. The gila monster (*Heloderma suspectum*), a lizard, has venom as well as the Komodo dragon (*Varanus komodoensis*). Interestingly, the duck-billed platypus (*Ornithorhynchus anatinus*) and some bats are also venomous.

Centipede venom from the Chinese red-headed centipede (*Scolopendra subspinipes mutilans*) has been used in Chinese medicine for hundreds of years as a painkiller. These centipede toxins also interfere with voltage-gated sodium channels (ion channel modulators) involved in pain sensing (see below).

In general, venomous mammals are rare, mostly due to their efficiency in using claws and teeth for killing, a much faster procedure than slower acting venoms.

Scorpion venom

Scorpions have developed an extensive venom arsenal composed of extremely diverse active components that are analgesic peptides that target voltage-gated sodium channels. Note: the southern grasshopper mouse (*Onychomys torridus*) is unaffected by scorpion venom. This mouse has evolved amino acid changes in the ion channel protein that prevents the channel's activation by the scorpion sting so no pain signal is transmitted to the central nervous system. (What is your favorite scary scorpion movie?)

Antidotes and antivenoms

Various antivenoms are made of antibodies, natural proteins of immune systems, and are typically given by injection. Antivenoms are specific depending upon the species of venom involved and are only given in cases of significant toxicity since some side effects can be severe, such as serum sickness, shortness of breath,

and allergic reactions including anaphylaxis. Also, some antivenom treatments are effective for only a limited number of times so care must be used in their use. Included in some antivenoms is plant-derived aristolochic acid which inhibits the activity of snake venom phospholipase and therefore inflammation and pain at the bite site.

Tarantula (1955)

Brief film synopsis: A spider escapes from an isolated desert laboratory experimenting in giantism and grows to tremendous size as it wreaks havoc on the local inhabitants.

The tarantula invaded a cattle ranch and near some picked clean cattle bones is a large pool, approximately 5'x5', of a white creamy gooey substance. Later, near a truck wrecked by the tarantula, are three large pools of the same white creamy substance, again each about 5'x5'. Dr. Matt Hastings (John Agar) gets a small sample on his finger and smells it commenting, "There doesn't seem to be any distinctive odor." Hastings then places a small amount on his tongue (?!?!) and after some 'bad taste' facial grimacing he comments, "Hmmm…wow", suggesting a strong taste (acidic? basic?). Hastings shows his total lack of personal safety by tasting the goo which no respecting scientist would do! Hastings loses points for this. Sheriff Jack Andrews says, "Same stuff you found at (cattle rancher) Andy's?...A couple gallons of this liquid beside him".

Later Hastings looks at a sample of the liquid under a microscope commenting, "I'm not sure. It's impossible at this stage to give you a positive answer but it is related to insect venom (Note: spiders are not insects). A reporter incredulously says, "There's not an insect in the world with that much venom." Then, "Insect venom in the large economy size. I've heard everything."

At the Arizona Agricultural Institute, Zoology Department, Entomology Laboratory, a professor Townsend says to Hastings, while holding a sample of the tarantula venom, "That was a pretty accurate analysis you made, doctor…from a species called arachnida…a tarantula to be exact but I've never seen venom is such quantity before. There is more venom in this test tube than you will find in a hundred tarantulas." Hastings says, "You mean a tarantula that can secrete that much venom would be a hundred times larger than normal?" Professor responds, "At least that." Hastings asks, "How deadly is the venom?" Professor responds, "Not deadly at all. About as poisonous as a hornet. No fun, mind you but harmless. The few deaths that have been reported have been the result of germs entering the wound at the time of the bite."

Tarantulas belong to the Theraphosidae family of spiders and about 900 species have been identified so far. Due to their size tarantulas are more fearful looking than they are venomous. Though their bites can cause serious issues and discomfort that could last for days no bite has caused a human fatality. Some equate the bite of a tarantula to that of a wasp sting. Also, the bites of some African tarantulas induce hallucinations. Most tarantula bites result in muscle

cramps that do resolve over several days. Since tarantula venom does contain some proteins then some people may suffer allergic reactions in addition to the actions of the venom. These allergic effects, such as anaphylaxis, can be life-threatening. It should be noted that the tarantula should be immune to its own venom.

Spider bites

There are about 40,000 species of spiders and just about all of them produce venom. Though not all spider bites inject venom those that do can be a serious concern for humans. The amount of venom injected can vary considerably depending upon the spider and the circumstances. It is the toxicity of the spider bite that can cause injury. Fortunately, most spider bites do not contain enough venom to cause serious or life-threatening problems.

Spider bites are either neurotoxic (affects nervous system) or necrotic (destroys tissues). Spider venoms are known to cause heart muscle damage, pulmonary edema (fluid in lungs), and hemolysis (destruction of red blood cells).

Neurotoxic spider venom paralyzes with muscle spasms, cramps, and twitching. Other effects include sweating, drooling, and gooseflesh and in extreme cases both blood pressure and heart rate are destabilized. Some spider venoms contain latrotoxins which cause a massive release of neurotransmitters causing muscle contractions often resulting in painful abdominal cramps.

Other spider venoms work by opening sodium channels causing muscle contractions and hypertension. Just about all target ion channels (see below) in the membranes of pain-sensing neurons. Some inhibit channels whereas others activate channels.

Necrotic venom contains enzymes, such as sphingomyelinase D, that destroys tissues, much like tissue eating bacteria. Necrotic spider venom can range in symptoms from minor localized effects to severe skin lesions, renal failure, and even death. Often times it takes years for such destroyed tissues to heal leaving deep scars. At first such bites are itchy and quickly worsen within 12 to 36 hours and necrosis can develop over the next few days.

The Killer Shrews (1959)Brief film synopsis: On an isolated island, a small group of scientists perform genetic experiments on shrews which grow to giant size. Due to a hurricane a group of people are stranded on the island and are terrorized by the giant voracious shrews before escaping.

Shrew (*Sorex soricidie*) saliva contains a kallikrein-like protease that paralyzes and subdues its prey. This toxin is strong enough to kill small animals and results in painful bites to humans. The shrew saliva comes from submaxillary glands through a duct that opens at the incisor teeth and into prey. Not sure how much, if any, this endogenous toxin poison is involved in human morbidity in the film since it was made clear that the giant shrews harbored a different poison. As explained by chief scientist, Craigis, “I concocted the most virulent poison I could with the materials I had at hand…put it out as bait…to destroy the giant shrews.”

Colleague Bradford adds, “Extremely high poison content in the shrew’s saliva. The system of the Sorex enabled them to assimilate that poison. It remained in the salivary glands of their jaws.” So when the shrews bit a human it was this poison that killed them and not necessarily endogenous shrew toxin poison, though both no doubt contributed.

Sherman responds, “Don’t you have something to counteract that poison?” Once bitten nothing can be done. As Craigis says, “This indicates you cannot afford to get even as much as a scratch from these animals. They are more poisonous than snakes.” So, the shrews consumed the Craigis poison and are apparently immune to its effects whereas humans bit by the Craigis poison-laden shrews quickly died, within one minute.

The Undying Monster (1942)

Brief film synopsis: A werewolf prowls around at night but only kills certain members of one family, the Hammonds. It seems like just a coincidence but the investigating Inspector soon finds out that this tradition has gone on for generations and tries to find a link between the werewolf and the family. One of the werewolf’s victims has cobra venom extract in her blood. A Hammond family doctor is using cobra venom in an attempt to cure Hammond of the werewolf curse.

In the film Kate O’Malley is attacked and ultimately dies. An inspector, Curtis, examines the victim’s blood and shows that it contains cobra venom. The inspector surmises that the cobra venom got into O’Malley from the scratches of whatever clawed her. Based on a careful examination of a hair sample taken from the victim the Inspector showed that a wolf was involved.

After the werewolf, Oliver Hammond, was dispatched at the end of the film, Dr. Jeff Colbert (Bramwell Fletcher) says, “From a medical point of view it was a rare case.” Curtis responds, “You hoped to cure him (Oliver)?” Colbert says, “I’ve been working on the theory that the shock of the cobra venom would eventually straighten out the dreadful kink in his brain.” Curtis responds, “Didn’t he suspect he was a victim of lycanthropy?” The assumption here is that cobra venom will only go to the brain in the concentrations necessary (and be able to bypass the blood brain barrier) which could potentially cure a complex psychiatric disorder. Based on this information Colbert should lose his license to practice medicine.

In general, snakes use venom primarily for hunting though if threatened will also use their venom for defense. Snake venom can cause a variety of symptoms such as coma, convulsions, hemorrhage (varies by snake), kidney failure, low blood pressure, pain, respiratory paralysis, swelling, tissue necrosis, and in severe cases, death. Some have referred to snake venom as a modified form of saliva. To further attest to the complexity of snake venom the various

components can vary even within a species due to diet differences brought about by different geologic locations.

Though cobra venom is complex there is one protein in particular that is especially nasty called, cobra venom factor (CVF). CVF is from, *Naja naja kaouthia,* and is a glycoprotein that is structurally and functionally similar to a natural enzyme of the immune system called Complement 3 or C3. The primary role of C3 is to activate the natural Complement enzyme cascade system that disrupts cell membranes by forming holes that causes cell death. C3 acts in a similar way as a stack of dominoes in that you knock down the first one and all the rest follow; same with C3 in that activate this one and all the rest of the Complement cascade enzymes will follow. Massive activation of the Complement system, such as what happens with evenomation from a cobra, also causes acute inflammatory injury to the lungs. Therefore, since CVF mimics C3 then CVF can also activate the natural Complement enzyme cascade that brings about cell death that can ultimately lead to body death if not properly treated.

In the biomedical world CVF has been used to study the Complement pathways and to better understand disease pathology. Another application is using Complement to help prevent organ rejection in transplant patients.

Pain in the toxin

No matter what you want to call it poisons, toxins, and venoms cause pain. So, why do they hurt and what is pain? According to the *International Association for the Study of Pain*, they define pain as, “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.” Nevertheless, defining pain is a challenge.

In medicine, pain is regarded as a symptom of an underlying condition. Pain has specific characteristics such as the region of the body involved (gut, limbs), body system involved (nervous, gastrointestinal), duration and pattern of occurrence, intensity and time of onset, and cause. To further detail this there is inflammatory pain associated with tissue damage and pathological pain such as fibromyalgia (muscle skeletal pain) and tension headaches. With pain comes inflammation so if you can reduce inflammation you can also reduce pain.

We all know what pain is like but, unfortunately, much of it is subjective since not all of us experience pain in the same way. We all know that pain is a distressing feeling caused by something. Pain’s intensity, duration, and unpleasantness can vary greatly. Pain is a strong motivator to withdraw from whatever is causing it and to avoid it in the future. Once the stimulus is removed or resolved then the pain, though it may persist for a while, does go away. Pain can arise even in the absence of any stimulus, damage, or disease, and may be emotionally based.

Chronic versus acute

Most pain is transitory and, though it may seem like the proverbial “forever”, it does not last long primarily because the first response of the one experiencing the pain is to remove the stimulus causing it. However, some chronic pain such as that with arthritis and cancer may persist for years. Chronic pain is usually that which goes beyond the normal duration of healing.

Sources of pain

Thermal (heat, cold), mechanical (crushing, shearing, tearing), and chemical (inflammation) pain are caused by overstimulation of sensory nerve fibers. Visceral or deep pain, such as sprains and broken bones, is diffuse and difficult to locate. Superficial pain, such as minor wounds and some burns, is sharp, well-defined, and clearly located. Depending upon the poison, toxin, or venom, various parts of the body could experience pain, both visceral and superficial.

Ion channels

[No, you cannot get these on your TV!]

The cells in our bodies have pore-forming proteins, called ion channels, embedded in cell membranes that allow ions, mostly sodium, potassium, or calcium, to pass through. These pore-forming proteins, or channels, are multi-subunit assemblies. Though the flow of ions is gated or controlled through these channels the rate of ion transport can be as high as 10^6 per second! The flow of ions also causes an electrochemical gradient to occur that affects membrane potential in cells, especially neuromuscular cells. Ion channels are involved in cardiac, skeletal, and smooth muscle contractions so as you can imagine ion channels are popular targets for drug development.

These protein ion channels are narrow tubes that allow only ions of a certain size and/or charge to pass through, called selective permeability (for example, you cannot push a golf ball through a straw but you can a pea). The channel tube is about one or two atoms wide at the narrowest point so quite selective indeed! There are two types of ions, cations (positive) and anions (negative) that move through these channels, often in single file. Ion passage through the channel is regulated by a “gate” that opens or closes depending upon a response to chemical or electrical signals, mechanical force, or temperature changes. Think of these gates as a ‘plug’ that opens and closes.

These ion channels are the basis of underlying nerve impulses since they mediate nerve synapses and are therefore a key component of the nervous system and muscle movement. When poisons, toxins, and venoms shut down the nervous system they work by modulating these ion channels. Pain comes from overstimulating these ion channels on neurons.

Sodium ion channels

Sodium channels consist of subunits organized in a cluster that span cell membranes and are prominent in neurons. These channels move sodium ions through a cell’s plasma membrane in either one of two ways and are responsible

for neuromuscular movement. Sodium ions cause a voltage change that exploits the positive charge of sodium ions or the binding of a ligand to the channel. Sodium channels exist in different states: closed, open, and inactivated. In response to an electrical or mechanical stimulation the channel gates open allowing positively charged sodium ions (Na^+) to flow into the neuron causing the voltage across the neuronal membrane to increase. Once the voltage increase is high enough the sodium channels inactivate themselves by closing the gate. This then starts over again and continues in a constant cycle. Some diseases, such as cardiovascular disease or epilepsy, have mutated ion channels that cause muscle and/or nerve cells to become over excited (Note: the jerky muscle movements as the Bela Lugosi (*Frankenstein Meets the Wolf Man*) and Glenn Strange (especially from *Abbott & Costello Meet Frankenstein*) Frankensteins walked could be due to muted ion channels that caused spastic neuromuscular responses).

Neurotoxins work on the various subunits of the sodium ion channel complex. Specific receptor sites on the sodium ion channel complex have been identified for tetrodotoxin (from puffer fish), saxitoxin (dinoflagellates, the cause of red tides), and conotoxin. Also specific sites have been identified for scorpion and sea anemone toxins.

Ion channel blockers (a partial list)
Tetrodotoxin – from puffer fish; blocks sodium ion channels
Saxitoxin – dinoflagellates (red tide); blocks voltage-dependent sodium ion channels
Conotoxin – used by cone snails to hunt prey
Lidocaine and Novocaine – local anesthetics (such as at the Dentist's office) that block sodium ion channels
Dendrotoxin – from mamba snakes; block potassium ion channels
Iberiotoxin – from *Buthus tamulus* (scorpion); blocks potassium ion channels
Heteropodatoxin – from *Heteropoda venatoria* (brown huntsman spider); blocks potassium ion channels

Summary
What would a toxic poisonous venom or a venomous toxic poison look like? It would stop the heart from beating, stop you from breathing, stop muscles from moving, and destroy tissues, probably at very small doses. What do these compounds do to the human body? For poisons, toxins, and venoms, where given, how given, and dose determine morbidity and mortality. We can drink, inhale, get stung, get bit, a 'pinpoint', or get scratched and it all comes down to just a couple proteins and enzymes that cause all the problems. These events are at the core of many of our favorite scary films and there are way too many movies to list in one article. Those chosen are just a few of the many examples of the roles that natural and man-made poisons, toxins, and venoms have played in cinema. No matter what, who, or how they can certainly ruin your day.

To quote, again, from Larry Talbot from *House of Dracula*, “explaining doesn’t help”, so ion channels may explain a lot of pain but it certainly does not take the pain away! From my wonderful grandfather, whenever I hurt myself in his presence, he ALWAYS said, “Does it tickle?”, and, though I hated to hear it and knew it was coming whenever the painful event happened (more frequently than you would think), the phrase seemingly and inexplicably did indeed help to salve the pain and make it go away. Thanks, Gramps! So, yes, indeed, pain is subjective and it really does not matter if the cause is a poison, a toxin, or a venom (or finding out your favorite UCR class is overbooked).

Thank you for reading. It’s back to the lab for me. Stay healthy and eat right.