Arndt Schultz Law: What effects a poison does in a large dose, a small dose of the poison will have opposite effects.

Figure 2. Dose-response curve showing the quantitative features of hormesis. NOAEL, no observed adverse effect level.
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Lauding low doses

Lawrence Solomon  Jun 4, 2010 – 7:03 PM ET | Last Updated: Jun 5, 2010 2:15 PM ET

A revolutionary field called hormesis shows that dangerous substances can be beneficial at low levels

To the greatest extent possible, remove all carcinogens from our air, food, and drinking water. Because there is no safe dose of radiation, avoid medical X-rays and CT scans whenever you have a practical alternative. Cut back on energy consumption where practical to reduce harmful emissions from smokestacks and tailpipes.

These simple strictures for leading a good and responsible life in a good and responsible society are too obvious to mention. Except that they are wrong — even dangerously so — according to a fast-growing branch of science called hormesis. The conventional wisdom on health and the environment is not only ruinously expensive,
Michael decided to go for a swim. He was on vacation with his family in Guerrero, Mexico, and it was hotter than blazes. He grabbed his swimming trunks from where they’d been drying on a chair, slid them on, and jumped into the pool. Instead of cool relief, a burning pain ripped through the back of his thigh. Tearing off his trunks, he leaped naked from the pool, his leg on fire.

Behind him a small, ugly, yellow creature was treading water. He scooped it into a Tupperware container, and the caretaker of the house rushed him to the local Red Cross facility, where doctors immediately identified his attacker: a bark scorpion, *Centruroides sculpturatus*, one of the most venomous species in North America. The fierce pain from a sting is typically followed by what feels like electric shocks racking the body. Occasionally victims die.

Luckily for Michael (who asked me not to give his full name), the bark scorpion is common in the area, and anti-venom was readily available. He had an injection and was released a few hours later. In about 30 hours the pain was gone.

What happened next could not have been predicted. For eight years Michael had endured a condition called ankylosing spondylitis, a chronic autoimmune disease of the skeleton, a sort of spinal arthritis. No one knows what triggers it. In the worst cases the spine may fuse, leaving the patient forever stooped and in anguish. “My back hurt every morning, and during bad flare-ups it was so horrible I couldn’t even walk,” he says.

But days after the scorpion sting, the pain went away, and now, two years later, he remains essentially pain free and off most of his medications. As a doctor himself, Michael is cautious about overstating the role of the scorpion’s venom in his remission. Still, he says, “if my pain came back, I’d let that scorpion sting me again.”

**Venom—the stuff** that drips from the fangs and stingers of creatures lurking on the hiking trail or hiding in the cellar or under the woodpile—is nature’s most efficient killer. Venom is exquisitely honed to stop a body in its tracks. The complex soup swirls with toxic proteins and peptides—short strings of amino acids similar to proteins. The molecules may have different targets and effects, but
they work synergistically for the mightiest punch. Some go for the nervous system, paralyzing by blocking messages between nerves and muscle. Some eat away at molecules so that cells and tissues collapse. Venom can kill by clotting blood and stopping the heart or by preventing clotting and triggering a killer bleed.

All venom is multifaceted and multitasking. (The difference between venom and poison is that venom is injected, or dibbled, into victims by way of specialized body parts, and poison is ingested.) Dozens, even hundreds, of toxins can be delivered in a single bite, some with redundant jobs and others with unique ones. In the evolutionary arms race between predator and prey, weapons and defenses are constantly tweaked. Drastically potent concoctions can result: Imagine administering poison to an adversary, then jabbing him with a knife, then finishing him off with a bullet to the head. That’s venom at work.

**Ironically, the properties** that make venom deadly are also what make it so valuable for medicine. Many venom toxins target the same molecules that need to be controlled to treat diseases. Venom works fast and is highly specific. Its active components—those peptides and proteins, working as toxins and enzymes—target particular molecules, fitting into them like keys into locks. Most medicines work the same way, fitting into and controlling molecular locks to thwart ill effects. It’s a challenge to find the toxin that hits only a certain target, but already top medicines for heart disease and diabetes have been derived from venom. New treatments for autoimmune diseases, cancer, and pain could be available within a decade.

“We aren’t talking just a few novel drugs but entire classes of drugs,” says National Geographic Society Emerging Explorer Zoltan Takacs, a toxinologist and herpetologist. So far, fewer than a thousand toxins have been scrutinized for medicinal value, and a dozen or so major drugs have made it to market. “There could be upwards of 20 million venom toxins out there waiting to be screened,” Takacs says. “It’s huge. Venom has opened up whole new avenues of pharmacology.”

Toxins from venom and poison sources are also giving us a clearer picture of how proteins that control many of the body’s crucial cellular functions work. Studies of the deadly poison tetrodotoxin (TTX) from puffer fish, for instance, have revealed intricate details about the way nerve cells communicate.

“We’re motivated to look for new compounds to lessen human suffering,” Angel Yanagihara of the University of Hawaii told me. “But while doing that, you may uncover things you don’t expect.”
Driven in part out of revenge for a box jellyfish sting she endured 15 years ago, Yanagihara discovered a potential wound-healing agent within the tubules that contain jellyfish venom. “It had nothing to do with the venom itself,” she said. “By getting intimate with a noxious animal, I’ve been informed way beyond my expectations.”

More than 100,000 animals have evolved to produce venom, along with the glands to house it and the apparatuses to expel it: snakes, scorpions, spiders, a few lizards, bees, sea creatures such as octopuses, numerous species of fish, and cone snails. The male duck-billed platypus, which carries venom inside ankle spurs, is one of the few venomous mammals. Venom and its components emerged independently, again and again, in different animal groups. The composition of the venom of a single snake species varies from place to place and between adults and their young. An individual snake’s venom may even change with its diet.

Although evolution has been fine-tuning these compounds for more than a hundred million years, venom’s molecular architecture has been in place much longer. Nature repurposes key molecules from around the body—the blood, brain, digestive tract, and elsewhere—to serve animals for predation or protection. “It makes sense for nature to steal the scaffolds already in place,” Takacs says. “To make a toxin to wreck the nervous system, it’s most efficient to take a template from the brain that already works in that system, make some tiny changes, and there you have it: Now it’s a toxin.”

Not all venom kills, of course—bees have it as a nonlethal defense, and the male platypus uses it to show rival males who’s boss during mating season. But mostly it’s for killing, or at least immobilizing, an animal’s next meal. Humans are often accidental victims. The World Health Organization estimates that every year some five million bites kill 100,000 people, although the actual number is presumed to be much higher. In rural areas of developing countries, where most bites occur, victims may not be able to get treatment or may instead choose traditional therapies and are therefore not counted.

The 44-year-old Takacs, Hungarian born and with a voice like tires crunching gravel, recently left the University of Chicago to launch World Toxin Bank. When not at the lab bench, he can be found wrangling puff adders in South Sudan, sampling kraits in Vietnam, and milking Gaboon vipers in Congo. His goal is to collect blueprints for “toxin libraries” that could eventually hold the venom toxins of every animal on Earth.
His quest also takes him out to sea. From afar, the tiny tree-lined coral island of Mabualau, about eight miles east of Fiji’s main island, Viti Levu, seems a tropical paradise. Up close, thousands of squawking red-footed boobies, frigates, and gulls clog the trees and sky. Their waste turns the shallow water into a fetid white soup whose stench somehow infiltrates the back of my throat. Before we’ve even anchored our tiny boat, Takacs hops over the side and wades ashore.

Yellow-lipped sea kraits, smooth-scaled silver-blue snakes with zebra stripes, thrive here, essing along the sandy bottom. The land-and-sea-going snakes, which need air to breathe, ascend the island’s rough coral and limestone banks. They coil up under shells and foliage to digest their food and, every few months, shed their skins.

The kraits feed almost exclusively on eels, and their neurotoxic venom has evolved accordingly. The eels are big and strong and have sharp teeth, and it’s hard to pry them out of their burrows. “The snake needs a potent and fast venom aimed at vital body parts,” Takacs says, “so it can get the meal with low risk of injury to itself.” Snake venom and the eel’s defenses have been in an evolutionary one-upmanship for ages, he says.

The reefs also harbor venomous anemones, blue-ring octopuses, and a host of toxin-spewing fish about which little is known. And cone snails. Lovely as jewels, each of the more than 600 Conus species concocts a unique and wicked brew, some strong enough to kill a person with a single shot. (No matter how pretty it looks, never put a cone snail in your pocket.)

After a shallow dive, Takacs strolls along the water’s edge holding treasure: a sea krait wriggling in one glove and a fist-size cone snail in the other. “The best the sea has to offer,” he grins. “I have hundreds of toxins in my hands.” The cone snail’s shell is a gorgeous mosaic of brown paint-daubs on white. After I admire his finds, Takacs drops the snail into a seawater-filled container for later examination. Snakes are his first priority.

Always equipped with a sampling kit, Takacs sets up a basic field lab on the boat: lidded containers, tubes filled with preservatives, syringes and needles, a pair of snippers for tissue sampling, a camera for documenting each animal’s patterns, and a big black glove. Sea kraits are quite passive, so the chances of getting bitten are almost nil. But Takacs wears the glove anyway. He’s allergic to venom, which would cause him anaphylactic shock in addition to its usual paralyzing effects. He’s also allergic to antivenom, made with serum from horses, so it’s extraordinary that he’s survived a total of six snakebites.
I help by holding the snake’s tail, belly scales up. Takacs grips the biting end, stretches the snake to its length, and runs a finger down the body, feeling for the heart. When he locates it, pulsing against the skin about a third of the way down, he carefully inserts a needle and draws blood. He also clips off a fragment of tail tissue and shoots a few photos before setting the snake back in the water and watching it swim away.

Takacs processes numerous snakes this way during our days on the water. And anytime we encounter local fishermen, he motors up to ask about their sea snake sightings, hoping to hear of other species in the area. “If you see the one with the yellow and black bands,” he says, “would you let me know?” Indeed, one day he was summoned to the dock, where a slender-necked sea snake awaited in a bucket. Takacs is known to have engaged entire villages to look for snakes.

In Fiji, and wherever else he collects venomous animals, Takacs is adding to his venom library. Meanwhile, in the lab he teases out variations in the makeup of toxins between species, within species, and even within populations. He also investigates what makes animals resistant to their own venom—information that could help yield better venom-derived therapeutic drugs.

I was surprised that Takacs wasn’t milking the venom of the sea kraits, but he explained that DNA underpins his work. Venom itself can offer important information, but when you have tissue, Takacs says, “you can take it home and extract the blueprint for the entire animal—including most of its toxins.” Each toxin is expressed by a gene, and genes can be copied and manipulated. “We can make bucketloads at a time, and then we have the luxury of being able to modify the toxins any way we want, and screen quickly to see which version has the most promising effects.”

At the University of Chicago, Takacs co-invented Designer Toxins, a system that allows researchers to make variations of nature’s originals by recombining toxins and comparing therapeutic values. Designer Toxins encompasses the millions of years of evolutionary wisdom preserved in venoms. This makes it possible to create vast numbers of variants (more than a million so far), potentially streamlining efforts to develop drugs. “We’re mining the molecular biodiversity in nature,” Takacs says.

**Venom-based cures** aren’t a new idea. They show up, for example, in Sanskrit texts from the second century A.D., and around 67 B.C. Mithradates VI of Pontus, an enemy of Rome who dabbled in toxicology, was supposedly saved twice on the battlefield by shamans who administered steppe viper venom to his wounds. (Crystallized venom from the snakes is now a medical export from
Azerbaijan.) Cobra venom, applied for centuries in traditional Chinese and Indian medicine, was introduced to the West in the 1830s as a homeopathic pain remedy. John Henry Clarke’s *Materia Medica*, published around 1900, describes the venom as alleviating many ills, even those caused by venom. “We should always endeavour to use the same drug to cure as produced the symptoms,” the author wrote. Clinical applications of carefully diluted cobra venom included “Angina pectoris. Asthma. Dysmenia. Hay-fever. Headache. Heart, affections of. Oesophagus, spasmodic stricture of. Ovaries, affections of. Plague ... Throat, sore.” But be careful, it was noted: “The curative dose [is] just within the limit of the pathogenetic dose.” Walking such a fine line, physicians of old likely hastened patients’ deaths as often as—or more often than—they prolonged their lives.

The science of transforming venoms into cures took off in the 1960s, when an English clinician named Hugh Alistair Reid suggested that the venom of the Malayan pit viper might be used against deep-vein thrombosis. He’d discovered that one of the snake’s toxins, a protein called ancrod, saps a fibrous protein from the blood, preventing clotting. Arvin, a clot-busting drug derived from pit viper venom, reached clinics in Europe in 1968. Today Arvin has been replaced by other viper venom anticoagulants.

The Brazilian pit viper’s venom led to the development in the 1970s of a class of drugs called ACE inhibitors, now widely used against hypertension. Researchers began by asking why Brazilian banana plantation workers bitten by these snakes collapsed with crashing blood pressure. The researchers then teased out the key pressure-lowering component in the venom. But drug-company managers needed convincing that what comes from snake fangs would save human lives. And you can’t just put venom in a pill and hand it to patients, so the useful component of the venom had to be modified at the molecular level—resized and tinkered with to survive the harsh effects of the human digestive system. Eventually a synthetic version made it to human trials, and in 1975 the first oral drug for hypertension, captopril, was approved for use. The ACE inhibitor class of drugs pioneered by captopril now treats tens of millions worldwide, with multibillion-dollar sales.

**The molecular gifts** of toxic animals offer hope in the fight against a host of debilitating diseases. Heart patients owe gratitude to the Eastern green mamba, a deadly African tree snake whose venom impairs its victim’s nerves and blood circulation. Researchers at the Mayo Clinic fused a key peptide from the venom with a peptide from cells in the lining of human blood vessels to make cenderitide, the subject of clinical trials. It is intended not only to lower blood pressure and reduce fibrosis (the growth of excess connective tissue) in a failing heart but also to shield the kidneys from an overload
of salt and water. “That’s the beauty of this drug,” says Mayo cardiovascular researcher John Burnett. “It’s designed to cover both things.” The closely related black mamba, a snake whose open mouth resembles a coffin and whose venom can quickly put you in one, holds a toxin with huge potential to be a powerful new painkiller.

Gila monsters, pebbly-skinned lizards found in the deserts of the U.S. Southwest, eat as few as three big meals a year (storing fat in their tails for the long wait), but their blood sugar remains stable. In 1992 an endocrinologist named John Eng at the Bronx/James J. Peters VA Medical Center in New York identified a component in Gila venom that controls blood sugar and even reduces appetite. Exenatide, a drug derived from the venom in their saliva, works like a natural hormone, stimulating cells to deal with sugar overload but remaining inactive when sugar levels are normal. It even helps diabetics produce their own insulin and lose weight. With almost 25 million people suffering from type 2 diabetes in the U.S. alone, the Gila monster is nothing short of a medical superhero.

Venomous mammals, though rare, are in the game. The current drug for ischemic stroke victims works only if administered within three hours. A drug based on an anticoagulant toxin in the saliva of the vampire bat is now in clinical trials and would extend the time to nine hours. Even some arthropods are skittering down the venom-to-medicine track. Recall Michael’s run-in with the scorpion in Mexico. Takacs, in what may be his first Designer Toxins breakthrough, is investigating a novel toxin fused from the venoms of three different scorpion species that selectively blocks immune T cells, implicated in numerous autoimmune diseases. Several drug companies are also pursuing this lead.

Meanwhile, a neurotoxin from the venom of the giant deathstalker scorpion has been found to attach to the surface of brain cancer cells. The overwhelming reason tumors come back is that surgeons can’t reliably distinguish good cells from bad at the growths’ edges. Magnetic resonance imaging—the best available diagnostic tool—doesn’t detect masses smaller than about a billion cells. This means surgeons have to find the boundaries between tumors and healthy tissue “purely by visual and textural cues,” says James Olson of the Fred Hutchinson Cancer Research Center in Seattle, Washington. “It’s a very imperfect science. Glioma cells weave into normal tissue, and pieces sometimes get left behind.”

Doctors who treat glioma, the most common form of brain cancer, created a “molecular flashlight” by marking chlorotoxin with a near-infrared dye. On the very first trial, Olson says, the “tumor paint,”
as he calls the scorpion-derived marker, “lit up the cancer beautifully. We were literally jumping up and down because we knew what incredible potential this had.” The paint reveals masses with as few as 200 tumor cells. “You can truly see the tumor almost cell by cell,” Olson says. “This will let surgeons get more cancer out, maybe even 100 percent.” Human trials on the dyed toxin will start later this year, and if tests go well, the paint could be used for prostate, colorectal, lung, breast, pancreatic, and skin cancers, as well as glioma, potentially saving or prolonging millions of lives every year.

No drugs based on scorpion toxins have yet been approved, but these toxins represent a versatile chemical arsenal. One may be a cancer foe, others the basis of cardiac, painkilling, anti-seizure, and antimalarial drugs. There’s even a possible pesticide among them.

The cone snail lacks the menacing air of a scorpion, but as I’d learned with Takacs in Fiji, there’s a beast in this beauty. Cone snails have no jaws and no claws. “They have only a very precarious tether for grabbing their prey,” says Baldomero Olivera, a Conus expert at the University of Utah. “So they compensate by having 50 or more venom components working on different levels.” The fish-eating species Conus purpurascens, one of Olivera’s favorites, uses its extendable, venom-loaded proboscis to essentially Taser a fish, immobilizing it in an instant. That gives time for multiple toxins in the venom to disperse and destroy muscle activity.

Being stung by a cone snail, Olivera says, “is like being bitten by a cobra and eating fugu at the same time.” (The fugu’s TTX is more than a thousand times deadlier to humans than cyanide.) Cone snails, Olivera says, “are like little drug companies that have engineered their own compounds to suit their needs.” Conotoxins in snail venom shut down nerve cell processes—which, it turns out, is an effective way to mask pain in people with late-stage cancer. Snail venom peptides called conantokins, which have exceptionally precise molecular targets, are being tested with some success against epileptic seizures. Both conotoxins and conantokins may be protective against Alzheimer’s and Parkinson’s diseases, depression, and even nicotine addiction. So far, five compounds from the snails have made it to human trials, and one morphine-like pain drug, ziconotide, has resulted. Ziconotide is chemically identical to the component the snail makes.

Another sea creature, the sun anemone, has toxic tentacles that stun its prey before wrapping the victim—often a small fish or a shrimp—into its maw for dinner. But the anemone’s stinging cells, called nematocysts, fire off venom that contains peptides useful in treating human autoimmune
diseases. In the 1990s a team led by physiologist George Chandy of the University of California, Irvine revealed that one of the peptides blocks the activity of a protein that promotes inflammation. The researchers reconfigured the peptide into one they called ShK-186. Now Kineta, a biotechnology company based in Seattle, is developing this against autoimmune diseases. What makes it so promising, says Shawn Iadonato, Kineta’s chief scientific officer, is how specifically it binds to diseased cells. “Our drug is very specialized to target the cells at work in these diseases. Other meds are problematic because they have many side effects and leave patients vulnerable to infection and cancer.”

The sun anemone holds promise for treating diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, and lupus. “It will let patients experience a more normal life,” Iadonato says. “It just takes a long time, even when you have a breakthrough discovery. There are so many side avenues to take to make sure there are no unintended effects. There’s a lot of unraveling and putting back together to get it just right.”

**Advances in fields** such as molecular biology continue to give scientists better ways to understand venoms and their targets. While drug companies once relied on luck, screening thousands of compounds for a particular effect, today’s higher tech options, such as Designer Toxins, give sharper detail, making it easier to shape medicinal keys to fit specific molecular locks. This means that a spray to stop bleeding derived from the venom of the brown snake will likely soon be saving lives at accident scenes, and a peptide from mambas will someday be treating heart failure.

The medical potential of venom, Zoltan Takacs never tires of saying, is “mind-blowing.” But we’re at risk of losing the sources of that potential faster than we can identify their toxin gifts. Snakes, in adapting to fill varied niches all over the globe, have evolved a stunning range of venomous compounds. But snakes are in decline, as are so many other animals. The oceans too are under pressure; their changing chemistry could wipe out promising sources of venom, from cone snails to octopuses.

“In conserving biodiversity worldwide,” Takacs says, “we should better appreciate molecular biodiversity.” That would put the molecules in nature’s deadliest potions high on the agenda when conservation decisions are made. And that would be a lifesaver.
Bee venom toxin melittin can destroy human immunodeficiency virus (HIV) while at the same time leaving surrounding cells unharmed, scientists from Washington University School of Medicine reported in the March 2013 issue of *Antiviral Therapy*.

The researchers said that their finding is a major step toward creating a vaginal gel that can prevent HIV spread. HIV is the virus that causes AIDS.

Joshua L. Hood, MD, PhD, a research instructor in medicine, said:

"Our hope is that in places where HIV is running rampant, people could use this gel as a preventive measure to stop the initial infection."

**Melittin destroys some viruses and malignant tumor cells**

Melittin is a powerful toxin found in bee venom. It can poke holes in the protective viral envelope that surrounds the human immunodeficiency virus, as well as other viruses. Free melittin in large-enough quantities can cause considerable damage.

Senior author, Samuel A. Wickline, MD, the J. Russell Hornsby Professor of Biomedical Sciences, has demonstrated that nanoparticles loaded with melittin have anti-cancer properties and have the capacity to kill tumor cells. Linking bee venom with anticancer therapies is not new, in 2004 Croatian scientists reported in the *Journal of the Science of Food and Agriculture* that honey-bee products, including venom, could well have applications in cancer treatment and prevention.

**Normal cells remain intact** - the scientists showed that nanoparticles loaded with melittin do not
harm normal, healthy cells. Protective bumpers were added to the nanoparticles surface, so that when they come into contact with normal cells (which tend to be much larger), the nanoparticles bounce off rather than attach themselves.

Scientists have discovered a powerful toxin in bee venom that could end up playing a crucial role in preventing the spread of HIV.

**HIV is much smaller than the nanoparticles and fits in between the bumpers. When HIV comes across a nanoparticle it goes in between the bumpers and comes into direct contact with its surface, which is coated with the bee toxin, which destroys it.**

Hood explained "Melittin on the nanoparticles fuses with the viral envelope. The melittin forms little pore-like attack complexes and ruptures the envelope, stripping it off the virus."

While most anti-HIV medications work on inhibiting the virus' ability to replicate, this one attacks a vital part of its structure. The problem with attacking a pathogen's ability to replicate is that it does not stop it from starting an infection. Some HIV strains have found ways to circumvent replication-inhibiting drugs, and reproduce regardless.

Hood said: "We are attacking an inherent physical property of HIV. Theoretically, there isn't any way for the virus to adapt to that. The virus has to have a protective coat, a double-layered membrane that covers the virus."

**Melittin nanoparticles may prevent and treat existing HIV infections**

Hood believes that the melittin-loaded nanoparticles have the potential for two types of therapies:
- A vaginal gel to prevent the spread of HIV infection
- Therapy for existing HIV infections, particularly drug-resistant ones
In theory, if the nanoparticles were injected into the patient's bloodstream, they should be able to clear the blood of HIV.

Hood said "The basic particle that we are using in these experiments was developed many years ago as an artificial blood product. It didn't work very well for delivering oxygen, but it circulates safely in the body and gives us a nice platform that we can adapt to fight different kinds of infections."

Melittin attacks double-layered membranes indiscriminately, making it a potential for drug therapies beyond HIV infections. **The hepatitis B and C viruses, among several others, rely on the same type of protective envelope and could be targeted and destroyed by administering melittin-loaded nanoparticles.**

The gel also has the potential to target sperm, the researchers explained, making it a possible contraceptive medication. The study, however, did not look at contraception.

Hood said "We also are looking at this for couples where only one of the partners has HIV, and they want to have a baby. These particles by themselves are actually very safe for sperm, for the same reason they are safe for vaginal cells."

This study was carried out in cells in a laboratory environment. However, the nanoparticles are easy to produce - enough of them could easily be supplied for future human studies.

**Recent research on HIV**

Over the last few years, scientists have made strides in improving HIV/AIDS treatments and prevention strategies.

**Baby "functionally cured" of HIV infection** - researchers from Johns Hopkins Children's Center, the University of Mississippi Medical Center and the University of Massachusetts Medical School reported that a baby who was administered antiretroviral therapy thirty hours after being born was "functionally cured". A functional cure means that there is no detectable viral replication after retroviral therapy has stopped.
SPECIAL NOTE ON LECTINS, NATURAL ANTI-VIRALS, HOMEOPATHICS and NUTRIENTS VALUABLE IN THE TREATMENT OF AIDS

By: W. Nelson, LPCC, M.D.
This article will review a protocol for treating AIDS patients. This protocol has had clinical validation and superlative effects.

Lectins are naturally occurring substances that mostly are found in the plant kingdom. Lectins are proteins or glycoproteins that are not made by the immune system of a human but can influence the immune system of a human. Lectins influence agglutination and precipitate complex carbohydrates. The agglutinizations activity of these highly specific carbohydrate binding molecules is usually inhibited by a simple monosaccharide. For some lectins Di, Tri, or Poly saccharides are required. The plant source often carries the needed molecules for action.

Many Lectins produce stimulation effects on the manufacture of lymphocytes. In fact several of these compounds have mitogenic stimulation of T-cell Lymphocytes. In the last study on the treatment of children with AIDS the use of the miso soups reflect the use of some lectins.

But if we review the Lectin research we can see a more refined type of soup prescription. “The effects of T-cell stimulation can indeed be of the utmost importance to the AIDS patient.”

Biological research has shown several substances to produce this Mitogenic effect. Many of these herbal compounds are in the New Vistas Product Known as HemoA. This product has been tested in cell culture and clinically and proven its ability. But there are many compounds that can provide some dietary effect. We recommend combining the diet of these foods with the HemoA. Many of the best naturally occurring sources of Lectins are herbal controlled substances that are put into the Hemo A. So combining this with the diet has maximum effects.
When taking up the theme of the actions and the use of snake-venoms we pay tribute to that remarkable personality Constantin Hering (1800-1880) who, while in Surinam (1827-1833), collected, prepared and tested the venom of the "bushmaster" Lachesis muta (then called Trigonoccephalus lachesis). After founding, together with Wesselhoeft, the North American Academy of Homeopathic Medicine in Allentown, PA (1835), he published all the data available at that time on Lachesis, Crotalus horridus, Vipera berus (then called V. torva), Vipera Redii and Naja tripudians (Naja naja) in a booklet (1). Though 120 years of extensive use chiefly of Lachesis and Crotalus have passed, Hering's work is still a main source of our knowledge and use of these venoms. His was the first scientific approach to a subject which has roused the imagination of men from times immemorial.

There is no need here to pursue the many myths on serpents from the days of Adam and Eve through the ages. Not all of them are concerned with venomous snakes, witness the classical statue of Laocoon and his two sons strangled by huge serpents. The more primitive ophidians like the Boidae (e.g., Boa constrictor) use sheer muscular force against their victims. The venomous snakes on which pharmacological interest concentrates are more highly specialized, and significantly so in those morphological and biochemical features which have survival value, viz. feeding on sizeable animals (rodents or even other snakes), and defending themselves against enemies.
In view of the but modern medicinal use of snake venoms it is a strange fact that, since Asclepios' times, they have signified the two aspects of the pharmacon as potential poisons or remedies. The snake winding itself around the caduceus and pouring its poison into a recipient vessel has become the symbol for the power of the physician: inimical forces are tamed to heal.

Among the approximately 400 species considered to be venomous, only a few have so far qualified for the inclusion in our materia medica: chiefly *Lachesis muta*, *Crotalus horridus* and *Naja tripudians* (*Naja naja*). Other species of *Crotalus* (the Central American *Cr. durissus terrificus* and the South American *Cr. terrificus terrificus* under the name of *Cr. cascavella*), *Bothrops lanceolatus* (*B. atrox*), three species of the genus *Vipera* *W. berus*, *V. redii* and *V. Russelli*), *Agkistrodon mokeson* under the name of *Cenchrus contortrix*, and lastly *Elaps corallinus* are still of minor importance. These few represent the most poisonous families fairly well.

Though there is no complete conformity with regard to the zoological classification and nomenclature, it is significant that the development of the poison-apparatus has been adopted as a morphological criterion for broad classification, and especially so the development of the formation of teeth or fangs. Those snakes which cannot inoculate venom into their victim by their bite do not come within our scope; they are the Aglyphodonta which have no grooved teeth and the Opistoglyphodonta which possess grooved teeth in the posterior mouth serving as grinders. The two families which concern us as venomous in the stricter sense are the Proteroglyphodonta which have two small grooved fangs firmly implanted in the front of the maxilla, comprising the land-snake family of Elapidae (*Naja trip. and Elaps corral.*) and the Solenoglyphodonta with the families Crotalidae (genera *Crotalus*, *Agkistrodon*, *Bothrops*, *Lachesis*) and Viperidae (genus *Vipera*). The Solenoglyphodonta are the most highly specialized, their two fangs are large, slightly curved and hollow, they inject the poisonous secretion of their supralabial salivary glands, as it were, through a hypodermic needle. In this they are aided by the mobility of the fangs and the jaws, and the synchronized action of several muscles which instantaneously evacuate the salivary glands through the ducts and the tubes of the fangs.

There is no doubt that the counterpart of the morphological evolution is also found on the biochemical level, in the composition of the venoms of the different families and species. The general statement that the venoms of the Elapidae are more neurotoxic, while those of the Crotalidae and Viperidae interfere more strongly with the blood cells and the blood coagulation, is to be considered only as a first approximation. In spite of intense research into the chemical nature of venoms, only some glimpses have as yet been obtained. This is not surprising in view of the fact that dry snake venoms have been found to consist of up to 92 percent of protein. The protein — or at least polypeptide — nature of the active principles is confirmed by a mass of immunological phenomena; they can act as antigens, i.e., they are able to form antibodies when directly injected into the circulating body-fluids of an unrelated species. The immunizing sera thus obtained show a high degree of specificity against that particular venom. From numerous cross-experiments in this field two deductions can be safely made. Firstly, venoms of closely related snakes have similar antigenic composition and, since the antigenic proteins are the active principles, the toxic effects, too, are similar. To some extent such cross-reactions appear even to transcend the class of reptiles altogether, as partial immunization by snake anti-venins against scorpion venoms has been observed. This would indicate that so widely distant types of animals have some active principles of proteinaceous nature in common. A second conclusion to be drawn from pertinent experiments is that each venom is a complex of a number of active principles of antigenic character. At least ten antigens are attributed to the venom of *Naja naja* (*tripudians*), the spectacular cobra of India. Between two species of vipers (*Viper Russelli* and Echis, the saw-scaled viper) at least five cross-reacting antigens have been found. This is, however, not to say that the different antigenic properties are due to so many separate protein-molecules, but rather to distinct active groups on the agglomerate macromolecules. At the present stage of knowledge the various names of these active principles denote merely the kind of effect they have on parts of another organism.

Any foreign protein which gets into the blood-lymph stream by eluding degradation through digestive enzymes constitutes a "poison" and the organism will protect itself against it by a very specific reaction of its globulins, i.e., by the formation of antibodies. In the course of this adaptive process anaphylactic and allergic phenomena are known to occur under certain circumstances. The antigen-antibody reactions represent, in a way, only the spearhead of defensive activities. When in allergic conditions they produce symptoms, these are in the main stereotyped in that they indicate either spasms of involuntary muscles or changes in the permeability of the vessels. According to present theories they are due to the liberation of histamine-like substances from certain cells in the course of the immune-reaction. From our point of view, such syndromes lack distinctiveness, they do not suffice to distinguish the actions of one agent from those of another. For that purpose they have to be
supplemented by methodical provings. On the other hand, such allergic syndromes demonstrate the action of such an "allergens" to be a systemic one. Thus Hering was quite right when he incorporated the symptoms which appeared while he was triturating the venom of Lachesis, into the list of its symptoms. Recently, Stanic (2) has described the allergenic properties of the venom of Vipera ammodytes. When scraping the dry venom from petri dishes he became sensitized by the dust, so that he was seized by sneezing, profuse nasal discharge lasting for hours, and attacks of coughing. He tried to desensitize himself by injecting 0.00001 g. subcut. into the forearm. The dose proved far too strong, since several minutes later urticaria, retrosternal pain and dyspnea appeared; then, through swelling of the tongue, speech became difficult, and finally a heavy asthmatic coughing attack occurred; the forearm gradually got swollen up to the fingers. After a dose of 1:100000 the reaction was milder and after another one of the same strength very mild. Ten days later he experienced only moderate sneezing from the dust, and coughing with retrosternal oppression. Eight months later all the previous symptoms returned! In order to desensitize himself, he injected 0.000004 g. intradermally and had the same reactions as on the first occasion, but to a somewhat milder degree. Another chemist suffered for months from asthma owing to the dust of the venom in the laboratory, so that he could no longer work in the place.

By such experiences the outworn objection that snake venoms, when given orally, are ineffective stands refuted. To be sure, after 130 years of using the potentized venoms in Homeopathy, there is hardly any need for such corroboration. It is true that the venoms in their concentrated state do not pass the intact mucosa and if disintegrated by digestive enzymes become harmless. But when dispersed as minute particles, and the more thoroughly dispersed the better, they enter the lymph-spaces and produce symptoms. To those engaged in the study of enzymes it is familiar that these proteins develop their specific effects only if sufficiently dispersed. The oral administration of potentized venoms would thus appear to be equivalent to the injection of a highly dispersed solution. Although for the snake it is natural to inject its venom into its prey or enemies through the fangs, it is not particularly biological to inject potencies, nor is it necessary. Only when massive doses are used on general diagnoses, such as epilepsy or carcinoma, does parenteral administration seem justified. The use of snake venoms in these types of disease had had its vogue, but nowadays one hears little of it. More recently Sanders, Akin, and Soret (3) have used neurotoxoids (prepared with hydrogen peroxide as detoxifying agent) of Naja and Crotalus species for checking experimental poliomyelitis in rhesus monkeys. The common affinity of virus and venom for the central nervous system appears to have suggested these experiments. It is of interest to note that only when small amounts of toxoid were used, as late as the fifth day after the intracerebral injection of virus, interference with the infection could be achieved.

As constituents of the saliva of the snakes, the venoms have the function of initiating and facilitating the digestion of animal tissues. The proteins of the venoms must therefore, at least partly, be classified as digestive enzymes, and very powerful enzymes at that. For the snakes devour their victims entire, without troubling to break them up first. No wonder that these strong enzymes are highly toxic for the victims. The horrifying consequences of snake bites have, indeed at all times made a profound impression on men.

If certain proteins of the venoms are distinguished by the epithet "toxin," such as neurotoxin and cardiotoxin, this does not mean that their action is not enzymatic. They may not be digestive enzymes, since their primary function could be to paralyze or kill the prey; but their rapid and strong effects are considered to be due to their interference with vital enzyme-systems of the animal's organism, the proteinaceous "toxins" acting as antienzymes. After all, the names are merely provisional, as long as the structural configuration of the agent is unknown; they indicate no more than the main direction of the actions (e.g., neuro-, cardio-, haemo-) of isolated fractions of the whole biological complex of the venom. The names of enzymes, however, acquire a fuller meaning the more precisely their mode of action is understood.

With the progress of biochemical research such terms as proteolysins, cytolysis (including hemolysins and neurocytolysins), coagulins and anticoagulins are replaced by terms denoting the particular enzymes which catalyze the pertinent actions. So far the following enzymes have been recognized in snake venoms: proteinases, which decompose proteins, a 5- nucleotidase which specifically dephosphorylates adenosin-5-phosphate and a L-aminoacid-oxidase; phospholipase A which splits off an unsaturated fatty acid from lecithin and cephalin; hyaluronidase which hydrolyzes the polysaccharide hyaluronic acid; and acetylcholinesterase which hydrolyzes acetylcholine into choline and acetic acid. Of these, the L-aminoacid-oxidase need not be considered here, because no toxic effects are known of this enzyme, nor are they to be expected. Its action seems to be correlated to riboflavin which appears to be present in many snake venoms and to be responsible for their yellow color (4). The 5-nucleotidase may well be responsible for the powerful inhibition of cell-respiration seen from snake venoms.
through decomposing the enzyme-apparatus (mitochondria!) of the cells; but nothing definite is known. The acetylcholinesterase may play a part, though probably not a decisive one, in the action of some venoms on the neuromuscular system; it is in this respect suggestive that the enzyme has been found only in venoms of the neurotoxic Elapidae and not in those of the Viperidae.

More than one proteinase is assumed in snake venoms. The principal one appears to be similar to trypsin, but is not identical with it. The decomposition of proteins by these powerful enzymes is apparently the first step in the poisoning process of snake bites. The signs and symptoms at the site of the bite—pain, swelling, blood extravasation and necrosis—are due to this parenteral digestion. Not all the snake venoms cause this local inflammation and necrosis, the Crotalidae and Viperidae more so than the Elapidae (though the bite of Naja causes some pain and swelling). Further the proteinases interfere with the globulins and the fibrinogen of the plasma. From the globulins a hypotensive substance, bradykinin, appears to be set free. The extreme prostration with cold perspiration soon after the bite of Lachesis and Crotalus horridus may be attributed to the sudden lowering of the blood pressure. The action of proteinases on fibrinogen manifests itself in the final stage of blood coagulation, the transformation of fibrinogen into fibrin. This process is generally recognized as proteolytic. Like thrombin, the proteinases of snake venoms activate fibrinogen by splitting off a part of the molecule and, in the presence of calcium ions, a rapid polymerization to fibrin then takes place. The structure of the fibrin clot seems, however, not the same as that from thrombin. Most, but not all, of the venoms of Crotalidae and Viperidae promote blood clotting. In some instances the venom proteinase appears to act so rapidly on the fibrinogen that it is decomposed and cannot form a fibrin clot. The venom is then an anti-coagulant. Furthermore, these venoms interfere also with the preceding stage of blood coagulation, the formation of prothrombin and its conversion to thrombin. This action is, however, probably due mainly to another enzyme of the venoms, viz. the phospholipase A. This will be discussed later. From the quantitative point of view, experimental results with the venom of Vipera aspis are of interest (5). The addition of 1:1000 to 1:5000 concentrations of venom shortened the time of coagulation of recalcified plasma. With concentrations between 1:10000 and 1:50000 the time of coagulation dropped to a minimum level. Further dilutions of the same venom resulted in a new increase of the coagulation time, finally reaching a plateau value which corresponded to the coagulation time observed in the absence of venom. There was thus an optimal effect as to acceleration of plasma-clottin in the range of 10^-5, 10^-6.

The hyaluronidase enzymes found in snake venoms, as in venomous secretions and tissue extracts of many other animals, are not particularly toxic by themselves, but they facilitate the penetration of other toxic substances into the system. They are what used to be called the “spreading factor”. By splitting the mucopolysaccharide hyaluronic acid (similar to heparin and chondroitin-sulfuric acid) apparently a normal tissue-protection is removed. The hyaluronidases are antigenic. As the anti-viper sera do not neutralize the spreading effect of the venom of Elapidae, the hyaluronidases of those two series appear to be different.

Phospholipase seems to be the enzyme in snake venoms which has the most deleterious systemic effect. It was first called lecithinase A because it splits a fatty acid off lecithin A, but as it does the same with another phospholipid, cephalin, the name phospholipase A is now preferred. For a better understanding of its action, the formulae of lecithin and cephalin may be recalled:

![Diagram of lecithin and cephalin](image)

It will be seen that lecithin is glycerol of which 2 OH-groups are esterified by fatty acids (the second one being unsaturated). The third OH-group is esterified with phosphoric acid and this in turn with choline. Cephalin differs from lecithin only by having colamine in the place of choline. Phospholipase A does not catalyze other phospholipids, but only the two derived from glycerol, lecithin and cephalin. It splits off the unsaturated fatty acid and thereby produces lysolecithin and lysocephalin respectively. It is conceivable that the selective permeability of
cell membranes will be thoroughly altered by this. Indeed, the lysophosphatides produced by the enzyme have a strong lytic effect not only on the red blood corpuscles, but also on other cells. The terms of hemolysin and cytolysis can, at the present stage of knowledge and in respect of snake venoms, be replaced by phospholipase A. The enzyme shows antigenic properties and is inhibited by snake venom sera.

Not only erythrocytes but also leukocytes are broken up by phospholipases, and leukopenia and even agranulocytosis may ensue. The phospholipid content of leukocytes on the whole runs parallel to their phagocytic activities. This makes such features of the effects of Crotalidae venoms, especially of Lachesis and Crotalus, as the lack of "pus bonum" and the poor healing tendency of necrotic-hemorrhagic ulcers more easily understood.

Since the cephalin constituent of the blood platelets appears to be the carrier of the enzyme thrombokinase which activates prothrombin to form thrombin, the phospholipases may also interfere with this first stage of blood coagulation. Destruction of thrombokinase would lead to retarded coagulation and a tendency to bleeding, features well-known in the syndrome, especially of Crotalus horridus. The phospholipase content of the venom of Crotalus terrificus terrificus (Cascavella) has been found to be very high (6). In Bothrops species, on the other hand, the phospholipase content was low, their venom is strongly coagulant. This action is generally attributed to proteolytic enzymes, not only on fibrinogen, as mentioned above, but also on prothrombin. According to H. Eagle (7), the Bothrops venoms in extremely low concentrations, convert prothrombin to thrombin and thus set going the coagulation mechanism. The varying proportions of proteinases (acting on fibrinogen and/or on prothrombin) and phospholipases obviously have a profound influence on the syndromes of the different species, especially of Crotalidae and Viperidae. In the Elapidae interference with blood coagulation is much less prominent.

It should be mentioned that lately a useful test for snake (and bee's) venoms has been developed from the action of their phospholipases on egg yolk emulsions, the heat coagulability of which is inhibited. The retardation of the coagulation is measured.

The phospholipases (in collaboration with the 5'-nucleotidase, as mentioned above, inactivate further physiological enzymes in the tricarbon (or "citric acid") cycle of intermediary cell metabolism, thus interfering with end-oxidation. Particularly the succinodehydrase is known to be inhibited. Such inhibition of dehydrases has been seen from concentrations of snake venom of 1:50 billion (i.e. 10^{-13} to 10^{-14}), while with a concentration of 1:1 million (10^{-6}) inhibition was complete. Crystallized lecithinase A has been allowed to act on mitochondria of liver cells which are known to have a high turnover in phospholipids, and inhibition of the oxidation of succinic acid was then seen. The dehydrases of the so-called cyclophorase system are attached to the mitochondria; the lecithin probably binds the enzymes to the mitochondria. In view of the discussion to follow, it may be recalled that succinodehydrase has a thiol-(SH-) group on which its enzymatic activity apparently depends.

Of special importance are the phospholipases for the action of venoms on the nerve system, the neuraxis as well as the medullary sheaths of the peripheral nerves. There the cephalins are known to prevail over the lecithins. When peripheral nerves degenerate, the cephalins are the first to decompose. The neurotoxic principles of snake venoms have generally been termed neurotoxins, but may now be described more precisely as phospholipases, especially cephalinases, decomposing cephalins to lysocephalins. Since Slotta and Fraenkel-Conrat (8) obtained from the venom of Crotalus terrificus terrificus a uniform protein in quadratic, thin, tabular crystals, which they called "crotoxin," it seems established that the neurotoxic activity, too, is due to phospholipases. The neurotoxic and the (in Crotalus venoms prevailing) hemotoxic actions were found to have the same proportions in the crystalline "crotoxin" as in the crude venom. The fact that crotoxin was free of coagulating principles appears significant. The proportion to which proteolytic enzymes are present in a particular venom may well have a bearing on whether the hemotoxic or the neurotoxic actions of the proteic enzyme phospholipase predominates; but other directive conditions, as yet unknown, also may play their part. In the Naja naja (tripudians) venom, long recognized as chiefly neurotoxic, Slotta and Fraenkel-Conrat (9) significantly found practically no coagulant nor proteolytic action.

Surprisingly, Slotta and Fraenkel-Conrat did not find in their crotoxin any zinc which, since 1919, has repeatedly been ascertained in snake venoms and was thought to be a constituent of the neurotoxic principle. In view of the affinity of zincum to the nerve system, the presence of this co-catalyst might have presented a clue to the neurotoxic action of the enzyme. It has to be seen whether the more neurotoxic venoms of Naja and the Elapidae generally contain zincum. They were reputed to be particularly rich in the metal.
There is general agreement on the cardinal role which sulfur has in the venom actions, and as a constituent of active atom groupings of the neurotoxic principle in particular. About the configuration of this active group, however, Slotta et al (9) and Micheel et al (10) held opposite opinions twenty years ago, and up to now the question appears to have remained unsolved. Slotta asserted that all the sulphur of his "crotoxin" as well as of the Naja neurotoxin was present as a cystin-like S-S-bridge, while Micheel interpreted his own tests with Naja venom as showing that the sulfur could not be present in the cystin-like S-S-form, nor a thiolactone or a thiazolidine grouping, both of which had been considered possible. Micheel did not, however, give an alternative solution. In the absence of a better working hypothesis, the present author ventures the following which is amenable to tests: the action group may be a structural analogue of either ax-lipoic acid (a cyclic disulphide of a low fatty acid, thus containing the S-S-bond) or of the thiazol grouping of thiamine (vitamin B1). Both these compounds are essentially active in the enzymatic process which reduces pyruvate to acetate (by oxidative decarboxylation). Inhibition of this process would then produce syndromes similar to B1-hypovitaminosis or even avitaminosis (Beriberi). That is to say, the neurotoxic and the cardiotoxic actions of venoms could be traced to the same faulty metabolic process. Furthermore, as a diminished difference in the oxygen contents of arterial and venous blood is a characteristic sign of B1-hypovitaminosis, the familiar "venosity" of Lachesis and other snake venoms could be better understood. In Beriberi the right auricle and ventricle are known to suffer more than the left ones.

Sarkar (11) has separated an active principle from Naja naja venom which has an affinity to muscle and particularly that of the heart; he has called it "cardiotoxin." Injected intravenously into cats this "cardiotoxin" caused a sharp fall in blood pressure. Anima, Devi and Sarkar (12) observed an increased systole and diastole of the heart when it was per-fused with a solution of Naja venom of a concentration 1:50000 to 1:10000, while with a concentration of 1:400 to 1:300 the heart went into final systolic contracture. In view of the — to us — familiar cardiac syndrome of Naja these finds are noteworthy. The relation of this fraction to the other toxic proteins, though, remains to be clarified.

From the venom of the South Brazilian Crotalus terrificus terrificus another protein has been separated and, on account of its basic properties, has been called "crotamine." Other Crotalus species do not appear to contain crotamine. If that should be confirmed, one would have to make a greater distinction between Crot. horridus and Crot. cascavella than is usually done. The characteristic effect of crotamine is said to be a paralysis of the posterior extremities in mice. As the crotamine has been separated from crotoxin by electrophoresis, it may well be that, in the natural protein complex, the two neurotropic polypeptides are combined.

By and large, these are the relevant facts so far revealed by biochemical analysis of the various venoms. Obviously the relative amounts of the different enzymes in the complex venom of each species will determine the trend of the toxic effects. Though by their nature the snake venoms manifest certain common features when acting on the human organism, contrasts between families are evident, as between Elapidae on the one hand and Crotalidae and Viperidae on the other. With species of the Elapidae, neuro-muscular and cardiac affinities predominate, and the inflammatory, necrotic, hemorrhagic and coagulant signs are practically absent, while with the Crotalidae the latter are pronounced and even more so with the Viperidae. Nor must the time factor in the development of the syndromes be overlooked. Though Naja, for instance, may have hemolytic actions, they are overtaken by those on nerve centers and the heart. Closer examination reveals toxicological differences between genera of the same family and even between species of the same genus. At this point the need for distinctive symptoms and modalities arises, as they are ascertained by systematic provings and then sifted, confirmed and emphasized by experience. These pointers to the "simile" in an individual case have to be elaborated as specifically as possible, they should permit discrimination not only between drugs from different species of snakes, but also from others that may have more or less features in common with snake venoms. For the symptomatology of a patient does not generally lead to the conclusion that the appropriate remedy has to be found among the snake venoms, but the last choice may be, for instance, between Lachesis and Arsenicum album or between Naja and Spigelia.

**LACHESIS MUTA**

It is fortunate that Hering gave his searching mind first and foremost to the venom of the much dreaded "bushmaster" of the South American and Central American tropics. This very aggressive monster excels among the
highly specialized family of the vipers by its length (up to 3.60 m.) and its large fangs. To judge from the mostly fatal consequences of its bite, Lachesis possesses a full range of strong enzymes; the proteolytic, cytolytic and coagulant ones appear, however, to preponderate over the neurotoxins. The sudden stabbing pain at the site of the bite may extend from the limb to the trunk and become intense, even intolerable, the bitten region becomes edematous and discolored from ecchymoses, and may be covered with blisters; necrosis and even gangrene may set in. A dark oozing hemorrhage is often striking. The lack of purulent discharge shows the low level of defensive reactions in the tissues. The venom spreads so rapidly that general symptoms appear almost immediately.

Such a rapid sequence of events after the bit of Lachesis can manifest only the general trends of the toxic action. The organism has little opportunity to develop its defensive reactivity, the lesions are irreversible. In order to obtain detailed distinctive symptoms, the more transient reactions elicited by suitable preparations and doses of the venom have to be detected and integrated into the picture of drug actions. The gross toxicological effects serve, however, as firm outlines of the picture into which the subtler details have to be fitted. Such a synopsis must depend on present-day physiological knowledge and to some extent the interpretation will be provisional.

Even the gross signs near the point of entry of the venom supply valuable clues for Lachesis. Wounds and ulcers are characterized by poor healing tendency, no proper suppuration develops, the damaged tissues are not well demarcated, and the margins are discolored, blue-red. In a Lachesis case the inflamed regions of skin or mucosa are often dark blue or purple and somewhat swollen by edema. Thin fetid discharges indicate the necrotic and even gangrenous tendency. Ulcers are sensitive to touch; the often considerable pains are relieved by warmth. (The frequently asserted aggravation of all Lachesis symptoms by warmth is not supported in this and other respects, neither by provings nor by clinical experience.) The more severe cases of varicose ulcers do not seldom show these features and, considering the strong tendency of Lachesis for thrombosis, it is not surprising to find the choice of Lachesis vindicated by such gross local signs and symptoms alone. The same may apply in cases of thrombophlebitis, though Crotalus may prove superior there.

The mucous membranes of the throat, and in particular the tonsils, are a favorite site for necrotic inflammation which exhibits the characteristics of Lachesis. The dark blue-red discoloration, the offensive breath distinguish Lachesis well from Apis with its pale red acute edema. Sensations of constriction, difficulties in swallowing and a feeling of suffocation are only what one would expect in such a case; common to several snake venoms also in non-infectious conditions, they appear accentuated with Lachesis. The high sensitivity to superficial touch, but not so much to pressure, is a characteristic of Lachesis and may lie behind the symptom: swallowing of liquids is more difficult than of solids.

The malignant, "septic" character of infectious Lachesis cases is underlined by a number of signs and symptoms which are not so much derived from provings as from clinical cases cured by Lachesis. The tongue is dry and a shiny red, cracked at the tip, in more severe cases black at the center and red at the tip, swollen, "heavy" and stiff. It is protruded only with difficulty, remains attached to the teeth and trembles. The fever is of the adynamic type. The discharges are offensive, the stools in particular are fetid. Skin and sclerae may take on a yellowish tint, but this has to be attributed to increased destruction of the red blood cells rather than to disorders of the liver. It is also due to the hemolytic component if hemorrhages are dark, fluid and do not coagulate easily. On the skin blood extravasations may occur in the form of ecchymoses, purpura or petechiae. In the low fevers of Lachesis cold shivers alternate with spells of dry heat; skin and mouth are dry; when sweating does occur, it is felt to be a great relief. This relief from the onset of secretions and discharges, especially from the onset of the menses, has clinically proved to be a valuable modality, though Lachesis shares it with several other remedies.

In the broad field of cardiovascular disturbances, with their repercussions on respiration and on the sensorium, it appears futile to trace one part to peripheral, another to central origins. For they are interlocked in one functional cycle. What we call "venosity" in the syndrome of Lachesis, as indeed of several other remedies, may be partly due to damaged red blood cells, to a relaxation of the veins from lesions of the intima, venous stasis and thrombotic occurrences, partly to impaired metabolic functions with incomplete end-oxidation, partly to the involvement of the right auricle and ventricle; but either indirectly or primarily the autonomous nerve centers, cardiovascular, respiratory, parasympathetic and sympathetic, will be implicated. That is why we may frequently find muscular spasms and sensations of constriction associated with the vasomotor disorders of Lachesis. It should be recalled
that the snake venoms tend to lower the blood pressure. A tendency to faint from sudden change of position, pallor of the face, some nausea and precordial pain point in this direction. These is also a hypotensive kind ofolinginess with a pale face alleged to be worse after walking in open air, which contrasts with the modality more frequently encountered in Lachesis cases, especially with the congestive headaches of the climacteric: relief in the open air. Again this modality is shared by other remedies favored in climacteric troubles, e.g., Pulsatilla and Sepia. The congestive headaches, often in the form of heat and pulsating on the crown of the head, are aggravated in the sun, similarly as withGlonoin from which the case for Lachesis then has to be distinguished by other symptoms and modalities. Alternating shivers and heat flushes are frequent vasomotor symptoms of Lachesis without connection with feverish states; another indication for its use in the climacteric. Palpitations and pulsations, a restless anxiety, oppression around the heart, a feeling of constriction in the throat and even suffocation may further mark the spells due to vasomotor imbalance.

The changes from the waking to the sleeping state and from sleep to wakening tend to bring about a marked aggravation of Lachesis symptoms, very likely via the autonomic centers of the midbrain. On falling asleep, breathing stops and this causes a sudden start with feeling of suffocation; or an oppression in the precordial region with a fast, weak and arrhythmic pulse may hinder the smooth transition into sleep. The peculiar constriction in the throat, the feeling of a tight collar around the throat, too, may come in. Even more marked is the aggravation of most symptoms on awakening from sleep; "the patient sleeps into aggravation" is the usual term for this modality of Lachesis. The same modality is, however, found not only with the venoms of other snakes, but also with those of other animals, such as Apis and Bufo. In some cases the starts when falling asleep (even more characteristic for Digitalis than Lachesis) may be early signs of insufficiency from anoxemia or even structural lesions of the heart muscle. (In true angina pectoris Latrodectus mactans has proved superior, when the icy coldness of the extremities during the attacks indicated the spider venom.)

The heightened surface-sensitivity to touch and the spasmodic tendencies, already alluded to above, are of general significance in the Lachesis syndrome. They manifest the lowered threshold in the sensory motor reflex mechanism. The region of the throat and larynx appear to be peculiarly sensitive and prone to respond with sensations of constriction. (The snake does not seem to suffer from it when it swallows a rabbit entire!) The feeling of constriction is also noted in the stomach region and around the abdomen which may be distended from portal stagnation. In the lower abdomen the sensation is supposed to occur frequently in connection with inflammations and cysts of the ovary, with preference to the left one. The latter detail, though derived merely from clinical observations, has proved useful for discriminating against Apis which appears to affect rather the right ovary. It would be futile to look for an explanation. The assertion that the throat syndrome of Lachesis is left-sided or starts on the left and goes to the right, cannot be supported in the experience of the author. To some extent the predilection for the left side is accounted for by the heart symptoms of Lachesis. Judging from the provings, the left-sided symptoms surpass the right-sided ones chiefly in the neuromuscular sphere. Paretic conditions, numbness and other parasthesias are recorded almost exclusively for the left side. Thus on the whole the old assertion that Lachesis is one of the left-sided remedies can be upheld.

The sensitivity io touch may go to such extremes that even the contact of tight clothes and that of the bed-clothes on the abdomen is ill tolerated and avoided. Though pressure is generally not so unpleasant as slight touch, a tight collar or waist-band are aggravating. In the motor sphere, symptoms such as tremulous weakness and a certain lameness of the left side are not particularly characteristic. If in paralyses from apoplectic insults Lachesis be called for, it is on the strength of peculiar symptoms and modalities. The use of Lachesis in epileptic conditions seems, however, to have been unduly neglected of late. In the early days already Hering and Gross reported good results in clear cases of epilepsy, and the present writer remembers having seen benefit from Lachesis in a few cases, especially of "petit mal". Indeed, a number of the symptoms of Lachesis point strongly in this direction. The fits of vertigo show epileptoid traits: viz. staggering, threatening to fall to the floor and as if to lose consciousness; marked failure of memory, does not remember what he has been told just before, loses the connection in speaking, makes mistakes in writing, sense of time is deranged. It is not surprising that the indiscriminate use of snake venoms merely on the diagnostic indication "epilepsy" has been abandoned, but there are good grounds for a selective use of Lachesis in individual cases. It is in these cerebral disorders that the often repeated, but scarcely verified modality "complaints recur in spring" may find some justification; it might be related to the better substantiated modality, mainly for congestive symptoms of the head, "aggravation from exposure to sun". A similar recurrence and increase of fits is known in the brain-injured, and there, too, the first piercing rays of the sun may be held responsible for the aggravation.
Finally, the actions of *Lachesis* on men culminate in a wealth of diverse psychic symptoms. They are well brought out by Hering in the booklet mentioned above. In his annotations he even expresses some surprisingly modern views on the emotional determination of psychic disorders. The two main constitutional trends, the cyclothymic and the schizothymic, are well represented in the symptomatology of *Lachesis*. A submanic state was experienced by Hering himself while triturating the venom. The mental activities, particularly the imagination, were stirred up to a kind of ecstasy. *Loquacity*, a good characteristic of *Lachesis*, goes to the brink of incoherence and “flight of ideas”. The contrasting depressive phase of sadness, anxiety, and fears is also brought out, but apart from the general modality that it is worse after sleep and in the morning, it has no distinctive features. In the schizothymic sphere, two phases are also apparent: an emotional indifference and a paranoid state. The symptoms of the latter, *suspicion, jealousy* and a certain supercilious and quarrelsome behavior, have proved the more characteristic and useful clues to *Lachesis*. It is said that grief, disappointment and mental anguish are at the root of the psychic symptoms of *Lachesis*, but that is too common to be of distinctive value. If the psychic abnormalities develop in the climacteric, it is one more reason to consider *Lachesis* as the remedy.

To sum up:

**LACHESIS MUTA**  
(Reptilia; Ophidia; Solenoglyphodonta; Crotalidae)

1. **ACTION ON BLOOD PLASMA, BLOOD CORPUSCLES, CAPILLARIES, VEINS**
   
   Inflammations and ulcers on skin or mucosa discolored dark blue and purple; wounds and ulcers with blue-red margins.

   Impaired reactivity and demarcation (Leukopenia and agranulocytosis).

   Affected parts highly sensitive to touch.

   Thrombosis, embolism, thrombophlebitis.

   Necrotic-gangrenous tendency.

   Blood disintegrates easily, is fluid, dark, does not coagulate properly.

   Yellowish skin and sclerae, hematogenic icterus.

   Ecchymoses, purpura, petechiae.

   In infectious conditions: adynamic fever, tongue dry, shiny red, trembling, protruded only with difficulty; dry skin, perspiration relieving.

   Secretions offensive; decomposed, fetid stools.

   Anoxemia of parts and venous stasis, “venosity”.

   Better from onset of discharges and hemorrhages, e.g., menses.

2. **CARDIOVASCULAR AND VASOMOTOR EFFECTS**

   Hypotension, dizziness with pale face, tendency to faint.

   Congestive headaches, relieved in open air, aggravated in the sun, cold extremities with head hot, cold shivers alternate with flushes of heat (climacteric!). Palpitations with anxiety and oppression.
Heat, pulsating, pressure especially on top of head, worse from sun. Spasmodic oppression in precordial region, pulse fast, weak, sometimes irregular.

On going to sleep, breathing stops, sudden start, with feeling of suffocation.

sleeps into aggravation.

Dry throat, feeling of suffocation especially if throat is touched externally.

Swallowing of liquids more difficult than of solid food; constraint to empty swallowing.

Strong feeling of constriction in the throat; collar-sensation.

Very sensitive to the touch of clothes, especially neck and abdomen; tight band also ill tolerated. Distended abdomen.

Left side more susceptible, e.g., left ovary.

3. ACTIONS ON NERVE SYSTEM (NEUROMUSCULAR, SENSORIUM, PSYCHE)

Hyperesthesia and hyperreflexia, see above: slight touch provokes spasms.

Trembling weakness bordering on paresis (left side preferably affected).

Epileptoid: vertigo, cannot recall recent happenings, loses connection when talking, makes mistakes in writing, deranged sense of time.

Submanic state: ecstasy, loquacity, "flight of ideas".

Depressive phase: sadness, anxiety, fears worse after sleep, in the morning.

Paranoid state: suspicious, jealous, supercilious, quarrelsome.

Emotional indifference (in another phase).

MODALITIES

Worse after sleep.

Surface-sensitivity to touch, provoking spasm and constriction (especially throat, stomach, abdominal region); cannot bear anything tight there.

Congestive symptoms worse from sun, better in fresh, cool air.

Relief from onset of discharges.

Predominantly left-sided.

DOSAGE (Author's)

12x twice a day, 30x and 30, single doses at varying intervals.
The two species of the genus Crotalus which have been introduced into our materia medica, Crotalus horridus by Hering and Crotalus cascavella by Mure, should be well distinguished from each other. Unfortunately, we cannot be sure whether the extensive symptomatology of Crotalus horridus has been obtained solely from that species, the "timber rattler" of the eastern and central states of the USA, for in other parts of North America different, though closely related species are encountered. Moreover, it seems that Crotalus durissus terrificus of Central America has not always been distinguished from Crotalus horridus. Mure's Crotalus cascavella (from the Latin-American name "cascabel" or "cascavel") was almost certainly what nowadays is known as Crotalus terrificus terrificus, found in Brazil and Argentina. (As Crotalus durissus terrificus in Central America is also called cascabel, further confusion may arise; but the latter species need not concern us here.)

As mentioned before, the venoms of Crotalus horridus and Crotalus terrificus terrificus show marked differences in their composition. The "crotamine" separated from the proteins of Crotalus terrificus terrificus (Cascavella) is not found in the venom of Crotalus horridus. This may explain why the bite of Crotalus terrificus terrificus has less localized effects, less pain, inflammation and necrosis, but is more lethal through protracted action on cell respiration and nerve centers than that of Crotalus horridus. The latter acts more rapidly and appears to deploy foremost proteolytic and hemolytic properties. Among the numerous cases reported of bites by the North American rattlesnakes remarkably many have recovered, though the condition appeared most alarming. Whether this was due to the much advocated and liberally dispensed whisky is another matter.

To judge from the sequelae of the bite, the venom of Crotalus horridus acts foremost on the walls of the blood and lymph vessels. Intense edema spreads rapidly and, in the wake of it, bleeding into the tissues occurs, so that the whole spectrum of discoloration from black, purple, blue to yellow may show itself. Apparently from the massive destruction of red blood cells, skin and sclerae become icteric. Bleeding from any orifice of the body, even from ears and eyes, has been seen. The blood is dark and remains fluid. The venom inhibits coagulation, whether in the fibrinogen-fibrin or in the prothrombin-thrombin phase or in both, cannot yet be said. It has further to be considered that the proteolytic and hemolytic enzymes of the venom cannot be termed simply as "anticoagulants," but in different proportions, especially in low concentrations of the proteolysins, they could act as "coagulants" as well. The immediate lesion of capillary walls by the venom of Crotalus was well demonstrated by the experiments of Hayward (Mat. Med. Physiol. and Applied, I, cited from Cyclop. of Drug. Pathogen., II pp. 418 and 420). He applied the venom, dissolved in glycerine, to a small spot, from which the cuticle had been scraped off; immediately blood began to flow excessively. The consequent symptoms of his inoculation experiments, too, are noteworthy, as they supplement those observed from bites on the one hand, and in provings with potencies on the other.

The tendency to hemorrhages is an outstanding feature of Crotalus horridus. In this respect it exceeds Lachesis significantly, and from the practical point of view it has proved useful in differentiating between the two remedies, otherwise so closely related. A hundred years ago, inoculations with Crotalus venom had been used extensively as prophylactic for yellow fever, the hemorrhagic signs, black vomits (like "coffee grounds"), black fetid stools and the jaundice apparently pointing to a similarity in the morbid processes. It is difficult enough anyhow to assess the prophylactic value of a remedy, but even more so in respect of diseases of which one has only knowledge from books. There is, fortunately, hardly any opportunity left for testing the curative value of Crotalus in yellow fever. All kinds of hemorrhagic diatheses may, however, come into the orbit of Crotalus, though the evidence in a particular case must decide whether or not other remedies, e.g., Phosphorus, are more suitable. In purpura haemorrhagica and in haemophilic extravasations Crotalus is among those remedies which have to be considered foremost. Intra-ocular bleeding in particular is adduced for Crotalus. Clinically some good results have been seen even in bleeding carcinomata of the tongue and of the stomach with "coffee ground" vomits and thin, black, fetid stools, though no more than palliation is to be expected in such cases; further, in infectious conditions which, by severe disorganization of the blood, extravasations, adynamic remittent fever with muttering delirium show a "septic" character. As with Lachesis, the site of origin is frequently found in the fauces, but carbuncles with blue-black and yellow discoloration are also cited. The ulcers with their unhealthy granulations and discolored margins are similar to those described for Lachesis.
In thrombotic processes Crotalus, in contrast to Lachesis, is hardly ever mentioned, but unjustly so, it seems. At first sight the strong anticoagulant action of the Crotalus venom may be taken to vindicate a heparin-like use of the venom rather than a homeopathic one. It has, however, to be kept in mind that the formation of thrombi, and thrombophlebitis in particular, constitute processes very different from extravasal coagulation. They involve a lesion of the intima of the vessel first and subsequently an agglutination of platelets. Both are well within the potential actions of Crotalus. It is true that the provings in this direction have not brought out much more than cramp-like pains, especially in the legs. The appended case-reports of O. E. Manasse are all the more welcome to show that in thrombophlebitis Crotalus can be just as effective as Lachesis. The cramp-like pains in the legs in such cases are so as to make standing almost impossible and become worse on stretching.

In the cardiovascular and vasomotor sphere Crotalus horridus has so much in common with Lachesis that only certain differences need to be pointed out here. Heart symptoms are less prominent with Crotalus horridus, in particular the spasmotic, oppressive pains have not been recorded. Hence there is no indication for its use in angina pectoris. Anxious oppression, shaky feeling about the heart, sudden giddiness and prostration even to a kind of somnolence are, as with Lachesis, indicative of a hypotensive state. Congestion to the head and cold extremities are likewise a feature of Crotalus horridus, but the alternative shiverings and hot flushes are less marked. In the climacteric Crotalus cannot compare with Lachesis. The headaches of Crotalus are often severe and one-sided, mostly frontal, and as they are frequently accompanied by nausea and even vomiting, Crotalus may have equal claim with Lachesis in migraine, though the latter is usually preferred. The assertion that Crotalus has a predilection for the right side has, since Hering, been copied faithfully again and again, but it is not borne out by the provings where the headaches appear at least as much on the left as on the right side. In the author’s experience this modality has no selective value. The headaches of Crotalus are relieved in the open air, like those of Lachesis: but the aggravation in the sun is not mentioned for Crotalus. The aggravation from sleep should be less emphasized for Crotalus as the provings offer some evidence to the contrary, i.e., disappearance of symptoms after a good night’s sleep. "Drowsiness, but cannot sleep" is more characteristic for Crotalus, not so much the "starts with suffocation" found with Lachesis.

A feeling of constriction in the throat has been noted with Crotalus too, and that without signs of the mucosa being affected. Difficulties in swallowing are said to arise from solids rather than from liquids, in contrast to Lachesis. The sensitivity to touch is less emphasized with Crotalus than it is with Lachesis tight pressure around the neck and the hypochondria are ill tolerated in the case of Crotalus like in that of Lachesis.

Hyperreflexia is less marked than with Lachesis. There is also nothing known of Crotalus being used in epileptoid conditions, though clouded perception, forgetful behavior, mistakes in writing, incoherence in conversation have been recorded with Crotalus as well. As there is no evidence of Crotalus acting directly on nerve centers, it may be thought that these symptoms of mental confusion are due to congestion of the brain. Post mortem findings in lethal cases of Crotalus bite tend to support such a view.

In such grave derangements of the organism as Crotalus can bring about it is no wonder that depressive symptoms, anxiety and fear of death are observed, but they are not distinctive. A certain sentimentality has been recorded in the provings of Crotalus, but this, too, does not seem to have any peculiar significance in determining the choice of Crotalus as a remedy. The paranoid symptoms described for Lachesis are absent from the syndrome of Crotalus horridus.

In cases of snake bite, particularly of Crotalus and Vipera, it has been noted that local signs reappear for years at periodic intervals. Old records have it that this happens annually at the time of the accident, but in a well-authenticated case of rattlesnake bite (Piffard, Amer. Med. Recorder, Jan. 1875, cited Cycl. of Drug Pathog., II, 429) local signs of inflammation with eruption of small vesicles recurred at regular three-monthly intervals over at least six years. This and other instances of chronic ailing after recovery from the acute poisoning go to show that the venom can have a long-lasting effect with periodical exacerbations. For the often repeated assertion "aggravation in spring" there is, however, hardly any support. Even the modality "aggravation of complaints at the onset of warm weather" is not supported by the provings and needs confirmation before it can be accepted as characteristic for Crotalus. Whether the alleged indication for Crotalus, "old wounds and ulcers reopen," is merely an inference from the just mentioned periodical recurrence of symptoms or is of clinical significance remains to be seen.
CROTALUS CASCAVELLA

Crotalus cascavella has more neurotoxic properties than Crotalus horridus. Local symptoms and signs from the bite of Crotalus terrificus terrificus (Cascavella) are less apparent. The sequelae do not develop so rapidly as with Crotalus horridus, but are rather more insidious. This is shown, for instance, by an impairment of the visual function, even blindness, lasting from minutes to several days, which may persist after the patient has recovered. In Mure's proving this is reflected by "the sight is affected" and "a dazzling blue light before the eyes." The auditory system, too, appears to be affected, for the prover experienced deafness (on the second day) and recorded "very deaf (after a month)." In the later stages of poisoning by the venom of Crotalus terrificus terrificus, muscular pareses and paralyses appear and impair locomotion. Of this action the provings revealed only "weariness of the arms and legs," "muscular prostration, trembling of all the limbs" and some other, even less definite, symptoms. Mure's provings are, however, no more than a good beginning, as they are obtained from too few provers. Like all other neurotoxic venoms, that of the Crotalus cascavella increasingly impedes the respiration up to the fatal end; whether through action on the medullary centers or on the respiratory muscles, or both, is not yet clear. Impeded respiration, oppression of breathing, suffocative feeling are noted in the provings, but such symptoms could arise from blood disorganization or interference with cell metabolism as well. From what we know so far of Crotalus cascavella, it appears closer to Lachesis than to Crotalus horridus, and possibly even exceeds Lachesis in neurotoxic properties.

DOSAGE

Author's experience of Crotalus horridus almost exclusively with the 6th (12x) potency.

BOTHROPS LANCEOLATUS

The genus Bothrops is represented by some forty species in tropical America. The name Bothrops lanceolatus refers to the 'fer-de-lance' of the isle of Martinique, but it is doubtful whether this species differs from Bothrops atrox. There are no provings of the venom. What little use has been made of Bothrops in homeopathy can therefore not have been very discriminative. C. H. Ozanam (L'art med. 19, 116, cited F. T. Allen's Encyclop., II, 210) has, however, reported on a number of cases of Bothrops bite which fill in many details in the literature available on this special subject.

The effects of Bothrops venom, chiefly on the blood and blood-vessels, are formidable. The first stages remind strongly of Crotalus horridus. Under intense pain immediate edema spreads rapidly, followed by serosanguinous infiltration of the subcutaneous tissue, ecchymoses and hemorrhage. Bleeding occurs from the engorged mucous membranes and skin, the throat is parched, thirst intense. Complete exhaustion may lead to the fatal end. Where death does not supervene, suppuration, necrosis, gangrene and sloughing of tissues to the bones may lead to gross mutilation. In this the course of events appears to differ from that of Crotalus; possibly the much higher coagulating power of Bothrops venom, thus its tendency to thrombotic and embolic processes, has something to do with it.

While some of the paretic conditions described as consequences of Bothrops bite are undoubtedly due to thromboembolic processes, for instance a hemiplegia of the right side and inability to articulate without there being any affection of the tongue, it is not sure whether the same is true for other lesions within the neuraxis. From experiments there is less evidence of a neurotoxic action from Bothrops than from Crotalus terrificus terrificus, but this assertion may not be final. Blindness both immediately after the bite of Bothrops and a more persistent one have been noted, and in particular a "blindness" during daytime only; the latter may well have been due to bleeding in the fovea centralis retinae and the other amaurotic occurrences to embolism at other sites in the optical apparatus. The same may apply to the observed paralysis of one arm or one leg; a direct action of Bothrops venom on nerve cells cannot, however, be excluded.

In the absence of provings, Bothrops has to be chosen on the indication of gross pathological signs which are, however, insufficient to distinguish it from other Crotalidae. The author has tried Bothrops 12x in several cases of
persistent aphasia after cerebral apoplexia. Though some improvement was seen in one or two patients, the results were not conclusive.

**CENCHRIS CONTORTRIX (Ancistrodon Mokeson)**

Agkistrodon (or Ancistrodon) is another genus of the Crotalidae. The species introduced into homeopathic materia medica is Ancistrodon Mokeson whose habitat is almost the same as that of Crotalus horridus, namely the eastern and central parts of the USA. There the common name of this mocsain snake is "copperhead" and, as it has a bad reputation for its vicious nature, "copperhead" had become a personal invective.

There are so far hardly any grounds for the homeopathic use of Cenchris; the author has no experience of it. Cases of persons bitten by the copperhead are not of sufficiently precise and detailed description to permit the syndrome to be distinguished from that of Crotalus horridus or Lachesis. Experimental analysis has shown the venom to be highly proteolytic. It retards or inhibits blood coagulation, is, at least in massive doses, hemolytic and causes hemorrhages; a rapid fall in blood pressure accounts for the extreme prostration, fainting and collapse.

A proving of Cenchris is found in Kent, *New Remedies* (Chicago, 1926, p.88). Unfortunately the long list of symptoms from five provers, three female and two male, is open to severe criticisms. It is hardly feasible to attribute all the symptoms noted by the provers within three weeks to the one dose of the 6th or 30th or 10m potency. Furthermore, it looks as if the provers knew what they had been given and were even acquainted with the *Lachesis* syndrome. There are too many symptoms phrased in almost identical terms as they are found in any essay on *Lachesis*: sensitive to clothing about the body and neck, tight clothing unbearable, suspicious of everybody, stops breathing on going to sleep, etc. It would be premature to emphasize the few differences from Lachesis in this proving of Cenchris, such as "most symptoms are better in the morning." More systematic provings and confirmation by clinical use are needed before a dependable drug picture of Cenchris can be drawn.

**VIPERA**

In the older classification the name "Viperidae" applies to all Solenoglyphodonta, comprising all the "vipers." The pitless vipers of Europe, Africa and Asia would then have to be separated from the American pit vipers or Crotalidae as "Viperinae." (The "pit" present in the Crotalidae and absent in the Viperinae is a cavity on each side of the head of the snake, between the eye and the nostril.) The genus Vipera is represented by Vipera berus (the common adder or German "Kreuzotter") and the similar Southern species Vipera reidi. The use of the Indian "daboia," Vipera Russellii, has been advocated by Le Hunte Cooper on the ground that its venom interferes most strongly with blood coagulation. Of all these species numerous cases of the severe consequences of their bite have been recorded, but no provings on healthy persons. There are thus only a few clinical features indicating Viperina in preference to one of the Crotalidae.

The signs and symptoms of persons bitten by a species of Vipera accord with the analytic finding that proteolytic enzymes predominate in the venom. Interference with the process of coagulation is marked, but it cannot be stated in terms of either promoting or inhibiting the clotting of blood, since that depends on the concentration of the enzyme and possibly other circumstances, and furthermore, the clots formed by the venom are not of the same structure and consistency as normal ones. A tendency to bleeding into the tissues is conspicuous and indicates an enhanced permeability of the vessels, especially the veins, through lesions of their walls. The extensive extravasations could account for the jaundiced hue of skin and sclerae mentioned in some instances. Hemolysis does not appear to play a prominent part, certainly there is no evidence of the liver being particularly involved. Some paretic and paralytic signs are reported in cases of Vipera bite, suggesting the presence of a neurotoxic component in the venom, but this can be only of minor significance in view of the overwhelming hemotoxic actions.

Very rapid and strong reactions of the tissues around the site of the bite are to be expected from this kind of venom. With Vipera the hardness of the intense and fast-spreading swelling has been noted, pressure by a finger makes hardly any "pitting" impression. The swelling is painful to touch. Discolored stripes follow the course of the
cutaneous veins, a tense bluish-red swelling causes pain as if it would burst. Besides extensive ecchymoses, spots of purpura hemorrhagica may be seen. The systemic syndrome follows the pattern known from other hemotoxic venoms: fall of blood pressure, fainting, rapid and thread-like pulse, nausea, vomiting and frequent, sometimes bloody and involuntary stools, collapse, and in fatal cases, coma. Albuminuria and hematuria, too, frequently seem to contribute to grave exhaustion through the depletion of water and proteins in the circulating fluids.

In the absence of provings the homeopathic use of Vipera is restricted mainly to a venous syndrome confirmed by clinical experience: *unbearable pains in the extremities when they are hanging down, as though they were going to burst*; the patient must keep the affected extremity in a raised position. In the cases where the author used Vipera berus 12x with success the leg swelled instantly and grew purple on hanging down, relief being felt in horizontal position of the leg and in walking. One patient who showed the syndrome and the result of the medication strikingly was a diabetic.

Chronic cachexia after the bite of Vipera has been recorded and an annual recurrence of local and systemic symptoms at the onset of hot weather and at the time of the year when the bite occurred has been reported in too many instances to be wholly overlooked. It has to be seen whether this periodicity can serve as a clue to the use of Vipera in chronic ailments.

**NAJA**

The spectacled cobra of India, *Naja naja* (tripudians) is to us the main representative of the Elapidae, a family of the Proteroglyphodonta with small longitudinally grooved fangs. As accidents from the bite of the cobra go into many thousands a year, there is an abundance of records, more or less reliable, from which to abstract the characteristic features. The recently improved knowledge of the components of the venom serves as a helpful criterion. The provings done a hundred years ago with very low potencies have supplemented some useful details (Stokes, Br. Jour. of Hom. 11, 95, 1853; Russell, ibid., 593 and 12, 244; Stokes, Monthl. Hom. Review, 3, 162, 1859, cited Cycl. of Drug Pathog., Vol. III, 328). Further, more methodical provings, using a wider range of potencies, seem highly desirable, however. For, judging from the homeopathic literature, this potent drug has been used comparatively seldom so far, apparently through lack of precise distinctive modalities.

It has long been recognized that the venom of Naja (as of other Elapidae) contains a very potent neurotoxic principle acting on the autonomic centers of the medulla. It is not yet certain whether its hemolytic principle is altogether separable from the neurotoxic. The acetyl-cholinesterase present in the venom of Elapidae may well be a co-factor in their action on muscles. The “cardiotoxin” recently isolated from Naja venom lends new weight to the well-established homeopathic use of Naja in heart disorders. Failing of heart and respiratory functions complement each other in the main syndrome. In some cases of cobra bite local symptoms—swelling, mottled appearance, necrotic ulceration and even gangrene—have been reported, such as is usually associated with proteolytic actions of venoms. Generally these local effects on tissues and on blood coagulation are, however, much less in evidence than from the venoms of Crotalidae and Viperidae.

The bite of the cobra causes a sharp pain. The extent of swelling varies considerably. A peculiar numbness of the limb indicates an early involvement of sensory nerves. Soon lassitude, drowsiness and confusion set in, sometimes swooning fits; receding consciousness may lead to outright coma. Difficulties in breathing are pronounced. Paralysis of the tongue and of laryngeal muscles may complicate the dyspnea. The heart action is accelerated, may be irregular in rhythm and unequal in force, the pulse becomes threadlike. In some cases dribbling of saliva and mucus and foaming at the mouth is seen; in others various signs of paresis develop, the eyelids droop, deglutition is impeded, speech becomes labored, limbs are paralyzed and control of sphincters is lost. In the later stages even trismus, locked jaws and convulsions may occur. Death is then due to respiratory paralysis.

The cardiac syndrome is in the center of the picture of Naja, but almost invariably it is associated with symptoms from the respiratory tract and in particular the larynx. It might be inferred that the right heart is more and earlier affected than the left ventricle. In the circulatory sphere coldness of the body and extremities prevail with a desire for warmth; the severe headaches, often of the migraine type, appear to be congestive, they are relieved in open air. The pain is mainly in the forehead or temples, more often left-sided, and as a proven recorded, attended by
fluttering of the heart. The provings have added some details to the heart syndrome as described in cases of poisoning: unusual beating of the heart, audible to himself; feeling of "lowness" about the heart, as of something wanting about the precordia; pressing pains in the left pectoral region; pain at the heart, extending through to the left scapula, and pain between the shoulders; sudden sense of choking, a sort of grasping at throat; gasping for breath, with several deep-drawn inspirations; constriction of chest, ending in mucous expectoration; uneasy dryness in fauces, constriction and irritation of larynx, sharpish prick in larynx causing cough; hoarseness; tightness of larynx; constriction, pressure and gagging in throat; great dryness of mouth and throat. Cases of failing heart, at various stages and of different etiology, somewhere the bundle of His seemed specially affected, appear to have been benefitted by Naja, in the experience of the author (12x), particularly in post-infectious cases of children. A tendency to collapse would strengthen the call of Naja. Aggravation from movement and exercise is only what one would expect in these mycarditic conditions. The modality "cannot lie on the left side" is found in most drugs affecting the heart, but for Naja its significance has to be reconsidered in view of the observation of a prover that pain and breathing were much relieved by lying on the affected side (in this instance the right side).

It has been claimed for Naja that it has a place in angina pectoris and coronary thrombosis similar to that of Lachesis. The claim has been based on the syndrome: cardiac pains go to the nape, or into the left shoulder and left arm; they are accompanied by anxiety and fear of death. This syndrome cannot be traced, however, in the provings, and so far seems insufficiently corroborated by experience.

The association of heart symptoms with left-sided headaches of migraine type suggests that Naja disturbs the vagus-sympathetic balance, before it affects the heart muscle itself. The symptoms then are so similar to those of Spigelia anthelmia that the choice may become difficult. With both, the left frontal eminence and temple are seats of predilection and the eye is frequently involved; the pains are violent and throbbing, often accompanied by nausea, sometimes by vomiting, they may extend to the back of the head and are worse from movement. For Naja a shooting pain from one temple to the other is mentioned and it is perhaps significant that the headaches come on during the night and disturb sleeping, and that they are particularly bad on awaking; they are aggravated by motion and exertion, relieved in open air.

The psychic background of the Naja syndrome is well brought out by the provings: sadness and irresolution, the mind broods over imaginary troubles, dull spirits, head heavy, with dull, confused mental state, a feeling of depression; feeling prostrate and miserable.

In view of the recent animal experiments with Naja venom on poliomyelitis it may be mentioned that another species of the Elapidae, Bungarus (coeruleus?), has been recommended for this viral infection.

**ELAPS CORALLINUS**

We are not yet in a position to give a concise and reliable account of the actions of the Brazilian coral snake, Elaps corallinus. In the first place no detailed descriptions of the sequel of its bite are available. Nor has an analysis of the venom been made known which would permit us to ascertain the characteristic trends from the nature of the active components. Being a species of the Elapidae, Elaps is supposed to contain in its venom mainly neurotoxic and hemolytic principles. The provings of Mure (Pathog. bresil, loc.cit.) on two persons, and Lippe’s (Allg. Hom. Ztg., 61, 28, 1860) on one lady only are too scanty for drawing a consistent picture of Elaps. The expectation of Lippe that Elaps would be helpful in various heart disorders is hardly substantiated by conspicuous symptoms in the provings, nor is it confirmed by experience.

So far as the meager evidence goes, the vasomotor syndrome is similar to that of Naja: severe headache mainly in the forehead (aggravation during the night and on awakening is mentioned only once). All the blood seems to be congested in the head, the feet are ice-cold and the (right) hand blue and as if paralyzed, benumbed and unsteady. Ears and eyes appear particularly involved: deafness, buzzing and crackling in the ear and vertigo with tendency to fall forward; a grey veil or a cloud, or fiery and colored spots before the eyes, unsteady vision (letters run together when reading), strong aversion to light and even transient blindness. Of the mental symptoms "excessive horror of rain" and "hears what is said without understanding it" may be mentioned with all due reservation. The solitary symptom of one prover "fruits and cold drinks lie on the stomach like ice" seems to have been over-emphasized.
Constrictive sensations, familiar from many other snake venoms, are reported from the esophagus and the sphincter ani and vesicae in the provings of *Elaps*.

To judge from the provings, *Elaps* has a greater tendency to hemorrhages than *Naja*. The black color of the blood, from the respiratory tract on coughing, from the rectum and from the uterus between the menstrual periods, is peculiar; bright (“arterial”) blood from the nose and ears is, however, also recorded. Much more information is wanted before the significance of these observations can be assessed. Likewise some data in the provings, hinting at chronic inflammation of mucous membranes of nose and ear, should be regarded with caution: bad smell from the nose and stoppage of both nostrils; discharge of a yellowish-green liquid from the ear. It would be rash to assert the usefulness of *Elaps* in ozena from the former and in otitis media from the latter date in the provings.

From the foregoing survey it will be obvious to what different degrees the drug pictures of the snake venoms have been elaborated up to the present juncture. Any survey of this kind is bound to be pro tempore and to expose the gaps of our knowledge and experience. On the other hand, this chapter of our materia medics stands to gain in perspicuity, when seen in the broader context with the venoms of other classes of animals, such as spiders, scorpions and insects.


**REFERENCES**


Tarantulas harbor proteins and toxins that are used as painkillers. CC BY-NC-ND 2.0

Evolutionarily, humans are scared of creepy-crawlers and poisonous things. Our fight-or-flight kicks in whenever we’re confronted with something that has more than 4 legs, stares at us with 8 glistening eyes, or exhibits protruding fangs or a stinger. Either you kill that spider or you run away from it, as shudders contort your body and squeals escape your lips.

However, science shows that the venoms of the natural world can actually be harvested as potential medicinal treatments and cures. From using scorpion, bee, and snake venom for cancer treatments to employing venom immunotherapy to treat insect sting allergies, researchers have investigated the therapeutic effects of a wide variety of animal and insect poisons. And it turns out that when used the right way, the poisons that would typically kill us can actually save our lives, too.
“Ironically, the properties that make venom deadly are also what make it so valuable for medicine,” Jennifer Holland writes for National Geographic. “Many venom toxins target the same molecules that need to be controlled to treat disease. Venom works fast and is highly specific. Its active components — those peptides and proteins, working as toxins and enzymes – target particular molecules, fitting into them like keys into locks.”

Thousands of animals are venomous — from snakes, scorpions, spiders, and bees to lizards, octopuses, fish, and snails. Researchers still haven’t studied or unleashed all the medicinal properties of these thousands of different venoms, all of which are seething with various toxins, proteins, molecules, and enzymes that could potentially be used to treat diseases. But below are the current ways that scientists have used venoms in medicine.

Tarantulas produce toxins that are used in painkiller drugs. Photo courtesy of Shutterstock

**Spiders**

According to a 2012 study out of the University of Buffalo, a particular protein found in spider venom could work as a treatment for muscular dystrophy — an umbrella term for a number of diseases that cause loss of muscle mass and eventual inability to walk, move, or swallow. The study found that the protein helped stop
muscle cells from deteriorating, and though it wasn’t a cure, it assisted in slowing down the progression of the disease.

Tarantulas, in particular, have been shown to harbor healing properties in their venom. One 2014 study out of Yale University described a new screening process known as “toxineering” that could sift through millions of spider toxins and find which ones were most compatible in painkiller drugs. They found that one toxin in the Peruvian green velvet tarantula could block chronic pain. Another recent study found that 7 different compounds in spider venom could potentially be used to help people with chronic pain too. Researchers analyzed 206 different spider species, and found that 40 percent of the venoms had compounds that blocked nerve activity linked to chronic pain.

The creepy crawlers that hang out in niches and in your basement may provide scientists with certain therapeutic properties. Photo courtesy of Shutterstock

**Centipedes**

It turns out that centipedes may be used as painkillers, too. In one study, researchers examined the effects of the Chinese redheaded centipede which injects its prey with venom that blocks a sodium channel protein and ultimately paralyzes its victims. They then tested mice with a peptide taken from the venom, and found that it was comparable to the effects of morphine — the mice were able to tolerate thermal, chemical, and acid pain tests.
Scorpions may be some of the freakiest creepy-crawlers on this planet, but their venom has medicinal properties. Photo courtesy of Shutterstock

Scorpions

Similarly to the centipede and spider peptides that are able to interact with sodium channels, researchers found in a 2010 study that scorpion venom too could have painkiller properties. But this isn’t all: researchers also found that scorpion venom could assist in fighting cancer.

Seattle researchers developed something called “tumor paint” out of scorpion venom, which was successful in identifying brain cancer and lighting it up for doctors to see. They re-engineered a specific protein from the Israeli deathstalker scorpion to make it bind to cancer cells, then tied it to a fluorescent molecule that acts as a sort of flashlight or glow to assist in surgeries or identifying cells within the body. “The scorpion toxin finds the cancer cells and drags the flashlight into them and makes them glow brilliantly,” Dr. Jim Olson, a brain cancer specialist at Seattle Children’s Hospital, said, according to ABC News.
Snake venom is already used by doctors in various drugs to treat heart problems and even disorders like Alzheimer's and Parkinson's.

**Snakes**

Scientists have been studying the medicinal properties of various snake venoms for decades. For example, certain Tunisian vipers have been shown to have anti-tumor properties. Others have antibacterial and painkiller features.

Hemotoxins in *snake venom* target the circulatory system, and typically attack the body’s clotting ability and muscles. But scientists have also found ways to use hemotoxins for medicine — such as treating heart attacks and blood disorders. Other drugs have been developed from neurotoxins in snake venom, which are used to treat Alzheimer’s and Parkinson’s, as well as stroke and brain injuries; more research will need to be done to better understand the medicinal properties of these toxins.
Sea creatures like anemones that contain poison have also been shown to have medicinal properties. Photo courtesy of Shutterstock

Sea Creatures

Deep in the ocean, thousands and even millions of critters lurk way out of our sight. But many of them may harbor potential cures and treatments for diseases in their venom. One study found that sea anemones and core snails produce toxins that could treat autoimmune diseases like arthritis, multiple sclerosis, and lupus.

Great Results

Homeopathic Octopus Venom — 6x
Arsenicum Alb — 7x
Lud — 3x
Myrrh — 4x
Aconite — 6x
Echinacea — 3x
Chrysoplatinum — 6x
Diluted Poisonous Venoms have the Reverse Effect

Great Results

Sweet Potato Greens Inhibit Cancer Cell Growth by 69%

Yams Very Very Rich in Vitamin A Retanoic Acid

Beta - Carotene

Homeopathic Octopus Venom – 6x
Arsenicum Alb – 7x
Lein – 3x
Myrrha – 4x
Aconite – 6x
Echinacea – 3x
Chyroplegium – 6x
Diluted Poisonous Venoms have the Reverse Effect

HORMESIS

That which does not kill us makes us stronger.

YOU
Push YOURself to the Limit

everybody wants happiness
nobody wants pain
but you can't have a rainbow
without a little rain
Hormesis (from Greek hórmēsis "rapid motion, eagerness," from ancient Greek hormáein "to set in motion, impel, urge on") is the term for generally favorable biological responses to low exposures to toxins and other stressors. A pollutant or toxin showing hormesis thus has the opposite effect in small doses as in large doses. A related concept is Mithridatism, which refers to the willful exposure to toxins in an attempt to develop immunity against them. Hormetics is the term proposed for the study and science of hormesis.

In toxicology, hormesis is a dose response phenomenon characterized by low dose stimulation, high dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose response. Such environmental factors that would seem to produce positive responses have also been termed "eustress."

Diluted Poisonous Venoms have the Reverse Effect

Examples of Hormesis - Low Dose Stimulation and High-Dose Inhibition

Diluted Poisonous Venoms have the Reverse Effect

A small amount is a Stimulant

Arndt Schultz Law: What effects a poison does in a large dose, a small dose of the poison will have opposite effects
Health beneficial effects of repeated mild stress of choice….

HORMETICS – is the science and the study of hormesis

The consequences of stress can be both harmful and beneficial depending on the intensity, duration and frequency of the stress, and on the price paid in terms of energy utilisation and other metabolic disturbances. But the most important aspect of stress response (SR) is that it is not monotonic with respect to the dose of the stressor. Rather it is almost always characterized by a nonlinear biphasic relationship. Several meta-analyses performed on a large number of papers published in the fields of toxicology, pharmacology, medicine, and radiation biology have led to the conclusion that the most fundamental shape of the dose response is neither threshold nor linear, but is U- or inverted U-shaped, depending on the endpoint being measured. This phenomenon of biphasic dose response is termed as hormesis, and I suggest HORMETICS as the term to refer to the science and the study of hormesis.

The homeodynamic ability of a biological system is affected by stress in a biphasic dose response manner, termed physiological hormesis. Lower levels of stress result in the strengthening of homeodynamics in a hormetic zone (H), and a chronic and severe stress results in the weakening and disruption (D) of the homeodynamics leading to functional impairments, diseases and eventual death. The key conceptual features of hormesis are the disruption of homeodynamics, the modest overcompensation, and the reestablishment of homeodynamics.
Hormesis — an introduction (a 45-minute my webinar on Hormesis and Ageing can be seen by going to the university’s podcast archives at: http://podcast.au.dk)

HORMETINS AS MODULATORS OF AGEING, DIFFERENTIATION AND WOUND HEALING

Various natural or synthetic compounds which can bring about biologically beneficial hormetic effects by activating one or more pathways of stress response, are termed as hormetins. Actually, hormetin can be any condition which challenges one or more stress response pathways in the cells, and is potentially hormetic in strenghtening the homeodynamic space. Three main categories of hormetins can be:

– Physical hormetins – exercise (running, walking, weight lifting etc), temperature (hot sauna or cold baths), irradiation (sunlight, solar-treatments), needle-pressure (acupuncture?)

– Nutritional hormetins – food restriction (fasting, low calorie diet), spices (turmeric, clove), zinger, garlic, onion, and micronutrients (zinc). There are many more nutritional hormetins yet to be identified, and synthetic hormetins yet to be synthesized.

– Mental hormetins – mental activity (reading, puzzle solving, chess), public speaking/performance, focussed attention (meditation), “falling” in love….

Multifactorial HORMESIS – the theory and practice of maintaining health and longevity

Posted on 11. December 2012 by Vince Giuliano

By Vince Giuliano and James P Watson

This blog entry generalizes on the concept of hormesis, discusses the multiple pathways through which hormesis takes place, and suggests a myriad of ways that ordinary people can take advantage of hormesis to maintain their health and possibly extend their lifespans. Some of the ideas laid out here emerged from a series of e-mail and phone exchanges between Jim Watson and myself although I (Vince) am the primary writer of this blog. We believe that hormesis is a fundamental process of human biology widely applicable in both a theoretical and practical sense across a very wide variety of health and aging issues. It is time that this concept, so long in the closet, be accorded front-stage status.

Background

Hormesis is a process through which moderate stress induces a body response that is protective against insults, confers health and possibly even longevity benefits. It is a
process much mentioned in previous entries in this blog. I introduced the concept of hormesis without naming it in a July 2009 entry *Stress and longevity*. “Longevity is correlated with having and meeting a healthy level of challenge – not too little and not too much stress.” A later 2009 blog entry *Hormesis and age retardation* started out by saying “An important approach to retarding aging that I have not discussed explicitly so far is *hormesis*, challenging cells and body systems by mild stress resulting in them becoming stronger and resistant to aging(*ref*). The stress can be physical, chemical and even possibly psychological.” The definition applies to the maintenance of health as well as to slowing aging. That entry was the first to discuss the roles of heat shock and chaperone proteins in hormesis. One important heat shock protein is discussed further in the blog entry *HSP70 to the rescue*. The relatively recent blog entries *Mitohormesis* and *Radiation hormesis* define hormesis in more detail and discuss it as it relates to mitochondrial oxidative stress and stress induced by radiation. Unlike the conventional wisdom, there is much evidence that small doses of X or gamma rays are health producing. Jim Watson’s recent post *The Hormetic Wild Animal “Zoo” and Their “Zookeepers”* discusses some familiar gasses like CO, NO, H2S and non- gases like HCN, O2-, and H2O2. These are Dr. Jekyll and Mr. Hyde substances. They serve as signaling molecules that act as 2nd messengers at very low doses triggering healthful body reactions in animals. Yet, at higher doses they are very toxic and even deadly.

Two sides of a familiar hormetic character

**On hormesis and homeostasis**
The basic purpose of hormesis is maintaining a health condition of homeostasis or better in a cell, organ or entire organism. That is, it is to keep conditions within a normal functioning range and also improve that functioning. “All organisms live in a world of changing conditions. But, to remain alive, the conditions inside of every organism need to remain fairly constant. An organism must have ways to keep the conditions inside of itself from changing (too much, that is) as its external environment changes. One of the most important characteristics of all living things is the ability to maintain a (reasonably) constant internal environment. This ability is known as homeostasis(ref).” Homeostasis is not a static state; rather it is a dynamic process of constant changes and adjustments. A hormetic response to a stress not only maintains a functional internal environment but also improves it. It can be thought of as a tune-up on homeostasis.

**The basic hormesis response curve**

Fundamental to understanding hormesis is a dose response-curve which I have discussed in previous blog entries and included yet-again here. Forgive me, I would rather err here by redundancy rather than by incompleteness.

Understanding the typical dose-response curve associated with hormesis is critical for interpreting seemingly contradictory research. I explain the curve somewhat more generally here than in previous blog entries. In my interpretation, the horizontal axis depicts level of applied stress, say as driven by ROS load in a cell. On a more macroscopic level it could represent the amount of whole-body radiation received due to an exposure event or to the amount of exposure to carbon monoxide or to stress due to
being at high altitude (hypoxia). The vertical axis represents relative risk, level of probable pathological organism response where normal level is 1. Below 1, there is a “health reserve,” such as an enhanced ability to do exercise or enhanced resistance to disease. Above 1 there is a less than normal “health reserve,” such as a lessened ability to resist disease or to do additional exercise. To the left of the first axis crossing in the diagram (point b), positive body reactions to the stress situation is progressively kicking but not sufficiently so as to overcome the direct negative effects of the stress. In the case discussed in other blog entries of ROS stress in cells, the Keap1-Nrf2 pathway is progressively becoming activated but in Transition zone A to the left of point b there is under-expression of the ARE genes and a negative health reserve. Between stress levels b and D*** there is hormetic protection compared to what would be expected given a linear model of negative response to stress. In the case of oxidative stress in cells, this is due at least in part to activation of Nrf2 and the ARE genes. The zone of maximum protection is between D* and D**. Starting at D** to D*** the stress load begins to overwhelm the hormetic defensive activities and the hormetic protection becomes less and less until at point D*** it vanishes. In the case of oxidative stress in cells, at that point the hormetic response associated with ARE gene activation becomes negligible. In the case of radiation damage at least, beyond point D*** the damage according to conventional wisdom is in linear proportion to the stressor, the amount of radiation. Phantom risk is theoretical risk for low stress levels that would apply if the linear model were extrapolated for low stress dosages.

We conjecture that the hormesis curve applies to all forms of stress, physical or psychological. However the scaling will vary widely from individual to individual and from one stress event to another for a given individual. We explore how some of those variances work in this blog entry.

**History of hormesis – The establishment of hormesis as a sound biological principle has been a slow process and until recently many scientists did not recognize its legitimacy.**

From the 2010 publication *Cellular Stress Responses, The Hormesis Paradigm, and Vitagenes: Novel Targets for Therapeutic Intervention in Neurodegenerative Disorders:* “Hormesis is a dose–response phenomenon characterized by a low-dose stimulation and a high-dose inhibition (Fig. 1). It may be graphically represented by either an inverted U-shaped dose response or by a J- or U-shaped dose response. The term hormesis was first presented in the published literature in 1943 by Southam and Ehrlich, who reported that low doses of extracts from the red cider tree enhanced the
proliferation of fungi with the overall shape of the dose response being biphasic. However, credit for experimentally demonstrating the occurrence of hormesis goes to Hugo Schulz (396), who reported biphasic dose responses in yeast after exposure to a large number of toxic agents. The work of Schulz inspired a large number of investigators in diverse fields to assess whether such low-dose effects may be a general feature of biological systems. In fact, similar types of dose–response observations were subsequently reported by numerous researchers assessing chemicals (49) and radiation (41, 50–53, 246, 307, 313, 367, 381, 397, 431, 432) with investigators adopting different names such as the Arndt-Schulz Law, Huppe’s Rule, and other terms to describe these similar dose–response phenomena (368). Despite the rather substantial historical literature concerning hormetic dose responses, this concept had a difficult time being incorporated into routine safety assessment and pharmacological investigations, principally because it (a) required more rigorous evaluation in the low-dose zone, (b) failure of investigators to understand its clinical significance, (c) failure to appreciate the quantitative features of the hormetic dose response, (d) failure to understand the limitations of its implications for commercial applications in agriculture as well as medicine, (e) because of the predominant interest in responses at relatively high doses during most of the 20th century, and (f) the continuing, yet inappropriate, tendency to associate the concept of hormesis with the medical practice of homeopathy (64, 89, 91). However, from the late 1970s (423, 433) there has been a growing interest in hormetic-like biphasic dose responses across the broad spectrum of biomedical sciences. This resurgence of interest resulted from a variety of factors, including the capacity to measure progressively lower doses of drugs and chemicals, the adoption of cell culture methods, which has permitted more efficient testing of numerous doses and the need to reexamine the validity of linearity at low-dose modeling of cancer risks due to their enormous cost implications for regulations (379), as well the astute observations of independent investigators and their capacity to generalize their findings across biological systems (267, 423).

**Hormesis is a remarkably general phenomenon, producing the same results across a wide variety of stimuli. Yet, it has taken a long time for its importance to be recognized.**

“What has emerged from these research initiatives from highly diverse biomedical areas is the recognition that hormetic dose responses were common and highly generalizable, being independent of biological model, endpoints measured, and chemical class and/or physical agent studied (50–54, 68, 306, 448). This was an unexpected finding as hormetic responses were often considered by many in the so-called mainstream
branches of toxicology and pharmacology to be paradoxical, not commonly expected and being of questionable reliability with a lack of capacity for replication. The casual dismissal of the hormesis concept during the mid decades of the last century is reflected in the general absence of the hormesis concept from the leading toxicological and biomedical textbooks. This situation has radically changed such that hormesis is now incorporated into all leading textbooks of toxicology (e.g., ref. 167) encyclopedias (89, 94) and other leading monographs. In fact, while the terms hormetric and hormesis were cited only about 160 times during the entire decade of the 1980s within the Web of Science database, in 2008 alone these terms were cited nearly 2300 times(ref).”

“Analysis of nearly 8,000 dose responses within the hormesis database indicates that quantitative features of phenotypic plasticity are highly generalizable, being independent of biological model, endpoint measured and chemical/physical stress inducing agent(ref).”

Hormesis played a key role in evolution.
The 2010 book The Fundamental Role of Hormesis in Evolution relates: “Hormesis can be considered a major mechanism underlying Darwin’s and Wallace’s theory of evolution by natural selection. The ability of organisms to respond adaptively to low levels of exposure to environmental hazards in a manner that increases their resistance to more severe similar or different hazards is fundamental to the evolutionary process. The organisms that survive and reproduce are those best able to tolerate or avoid environmental hazards while competing successfully for limited energy (food) resources. Therefore many of the genes selected for their survival value encode proteins that protect cells against stress (heat-shock proteins, antioxidant enzymes, antiapoptotic proteins, etc.) or that mediate behavioral responses to environmental stressors (neurotransmitters, hormones, muscle cell growth factors, etc.). Examples of environmental conditions that can, at subtoxic levels, activate hormetric responses and examples of the genes and cellular and molecular pathways that mediate such adaptive stress responses are provided to illustrate how hormesis mediates natural selection.”
So, from the viewpoint of evolution, we would expect that adaptive mechanisms would have evolved for all the important forms of stress that might be encountered by an organism. This appears to be the case. As organisms become more sophisticated the exact pathways used to produce a given stress response also evolve. For example, this
A diagram summarizes the hormetric effects of calorie restriction for yeast, nematodes, mice and us.

**Calorie Restriction Pathways in Different Species**  Image source: Leonard Guarante, *Mitochondria- A Nexus for Aging, Calorie Restriction, and Sirtuins?*. “In yeast, SIR2 has been implicated downstream of mitochondrial changes in response to calorie restriction (CR), whereas in mammals the SIR2 ortholog SIRT1 has been implicated upstream of mitochondrial changes. In C. elegans, sirtuins have not been implicated in dietary restriction to date. The pathway in mice shows that the increase in mitochondrial number and activity may work via the mitochondrial sirtuins SIRT3, 4, and 5 or by reducing reactive oxygen species (ROS). The drug Resveratrol and CR may increase SIRT1 activity, which is part of an autoregulatory feedback loop that includes the enzyme endothelial nitric oxide synthase (eNOS).” SIRT1 is the epicenter for linking the CR Mechanisms found in lower life forms to human CR.

A. The personal practice of hormesis
This short section of this blog entry relates to the personal practice of hormesis, Section B below will further discuss the science of hormesis.

What do you mean, “take it easy?”
Well-meaning friends often tell me that at my age I should take it easy and avoid stress. I tell them that they are 100% wrong. I thrive on stress because that is what keeps me young and going. I tell them that some stress is not only a good thing. It is absolutely necessary for health and longevity.
Hormesis is a commonly-occurring every-day phenomenon. Hormesis is also multi-factorial because multiple stimuli can activate multiple pathways producing multiple results with multiple time and response characteristics. Let me illustrate these points with a down-home highly personal example, based on yesterday which is like most days:

A day of hormesis and me
- When I got out of bed, I woke up in a cold (60 degree F) bedroom and immediately experienced feeling cold. Though I turned up the heat, with no clothes on I was cold for 10-20 minutes while washing up and shaving until I warmly dressed. I was not cold enough to shiver or suffer but definitely cold enough to experience a body reaction. In doing this I triggered the cold shock hormetic pathway to start the morning.
- Before breakfast, I took some phytosubstance supplement pills including curcumin and ashwagandha which triggering the Nrf2 hormesis pathway. Breakfast included blueberries and walnuts, also substances triggering this pathway. The Nrf2 activation happens very quickly. It not only promotes the immediate activation of my ARE genes but also, in ways not completely known, creates a permanent recoding of parts of my epigenome.
- After breakfast coming up to the computer I found some critical software was crashed. I experienced a frustrating time wading through endless phone menus and trying to reason with a customer care representative in India whose mastery of US English was poor. Finally the problem was resolved. There was an amount of emotional/neurological stress. Heart pounding a bit, I probably triggered several hormetic stress pathways.
- Other events producing emotional/neurological stress during the day was learning that an uncle of my wife had died, a small fight with my wife about not emptying the dishwasher, and, especially, trying to get my mind around all the research involved in this hormesis issue (a repeated event). I like to think that each such event was a hormetic one.
- My daily 45 minutes on the treadmill produced exercise-related hormesis, probably via a combination of the Nrf2, heat shock and HIF pathways. I end up breathing hard and sweating. The exercise effect is not only short-term. It affects my daily circadian rhythm clock, my weight, metabolism, muscles, hunger response and critical components of epigenetic encoding.
Chain-sawing some trees fallen by our last hurricane, I spilled a couple of drops of gasoline on my hand and breathed chainsaw fumes for a short time. This no-doubt activated the ARE detoxifying enzymes. Hopefully the toxic stresses where in the hormeric range.

During the day I take additional phytosubstance supplement pills and drink a little green tea, again all Nrf2 hormesis activators.

For lunch I opened a can of Italian tuna fish, a favorite of mine. This exposed me to both mercury and BHP, both toxins. Hopefully the Phase 2 detoxifying enzymes kicked in and the total effect was hormetic. To prevent chronic mercury exposure, I take some dietary supplements in my daily regimen which are heavy-metal chelators.

I ate a couple of small packaged snacks during the day, ones probably containing traces of cancer-producing chemicals and pesticides. These may help too. Yes, at very low doses they too induce hormesis.

Supper included salmon seasoned with olive oil, garlic, ginger, oregano and a touch of pepper sauce, broccoli and mixed greens – After supper, for desert I munched on 80% coco chocolate. All these are Nrf2 hormesis-promoting phytosubstances. I am also working on low-density lipoprotein-induced hormesis. No steak for several weeks now.

In the process of going to bed I again exposed myself to a cold bedroom with no clothes on, like in the morning. Again, in doing this, I triggered the cold shock hormetic pathway.

These are events that I suspect produced hormeric results in me. There probably were many other hormetic events in me in the course of the day that I don’t know about.

Once hormesis was mainly regarded as a curious laboratory phenomenon that happened when you exposed pseudomonas aeruginosa to a polychlorinated dibenzodioxin in a Petri dish. Not just so! It can go off in us multiple times every day.

B. More on the science of hormesis

Mechanisms of hormesis

There are several different pathways through which hormesis can take place, including:

1. The keap1/Nrf2 pathway. In simplistic terms, ROS stress in cells causes the protein keap1 to release Nrf2 which is resident in the cytoplasm whereupon Nrf2 translocates into the nucleus and activates at least 242 health-producing genes called antioxidant response elements (AREs)(ref). The same holds in the case of
electrophilic stress. The basic operation and utility of this pathway is detailed in a trio of blog entries: *The pivotal role of Nrf2. Part 1 – a new view on the control of oxidative damage and generation of hormetic effects*, *The pivotal role of Nrf2. Part 2 – foods, phyto-substances and other substances that turn on Nrf2* and *The pivotal role of Nrf2. Part 3 – Is promotion of Nrf2 expression a viable strategy for human healthspan and lifespan extension?*. This pathway is also discussed in the *Mitohormesis* blog entry. There is much more to what Nrf2 does than I have been able to cover so far. It appears for example that Nrf2 impacts on the Notch1 pathway.

2. **The heat shock response pathway**, involving the actions of heat shock and chaperone proteins. The cellular response to heat shock includes the transcriptional up-regulation of genes encoding heat shock proteins (HSPs) as part of the cell’s internal repair mechanism. They are also called stress-proteins and respond to heat, cold and oxygen deprivation by activating several cascade pathways. HSPs are also present in cells under perfectly normal conditions. Some HSPs, called chaperones, ensure that the cell’s proteins are in the right shape and in the right place at the right time. For example, HSPs help new or misfolded proteins to fold into their correct three-dimensional conformations, which is essential for their function. They also shuttle proteins from one compartment to another inside the cell, and target old or terminally misfolded proteins to proteases for degradation. Heat shock proteins are also believed to play a role in the presentation of pieces of proteins (or peptides) on the cell surface to help the immune system recognize diseased cells. — The up-regulation of HSPs during heat shock is generally controlled by a single transcription factor: in eukaryotes this regulation is performed by *heat shock factor* (HSF) — (ref). The blog entry *HSP70 to the rescue* offers an introductory discussion of HSPs, their role in the unfolded protein response (UPR), how HSPs play their roles in multiple species, and how HSP70 plays a role in the hormesis process. Induction of hormesis by small doses of SIRT1 acting through activation of HSP70 which keeps HSF1 active via deacetylation is also discussed in the blog entry *SIRT1, the hypoxic response, autophagy and hormesis*.

3. **The cold shock response pathway.** Yes, cold shock such as from taking a cold shower can also induce a hormetic response. *This pathway involves the cold-inducible RNA binding proteins: CIRP & RBM3.* Although the molecular dynamics of the cold shock response has been less-understood than the heat shock response, the cold shock hormetic response has been recognized as something going on in lower organisms for some time (ref). It is now known to be evolutionarily conserved.
in humans and a considerable number of publications have been devoted to this subject.\(^\text{ref}\) From *Cold-shock response and cold-shock proteins* (1999) “Both prokaryotes and eukaryotes exhibit a cold-shock response upon an abrupt temperature downshift. Cold-shock proteins are synthesized to overcome the deleterious effects of cold shock. CspA, the major cold-shock protein of Escherichia coli, has recently been studied with respect to its structure, function and regulation at the level of transcription, translation and mRNA stability. Homologues of CspA are present in a number of bacteria. Widespread distribution, ancient origin, involvement in the protein translational machinery of the cell and the existence of multiple families in many organisms suggest that these proteins are indispensable for survival during cold-shock acclimation and that they are probably also important for growth under optimal conditions.”

4. **The hypoxic stress response training pathway.** This is the pathway activated when there is insufficient oxygen, such as at high altitudes. I briefly discussed the hypoxic response and its relationship to hormesis in the 2010 blog entry *SIRT1, the hypoxic response, autophagy and hormesis.* The key stress-responsive transcription factor involved in the hypoxic stress response is HIF-1. From Wikipedia: “Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen in the cellular environment, specifically, to decreases in oxygen, or hypoxia. The HIF signaling cascade mediates the effects of hypoxia, the state of low oxygen concentration, on the cell. Hypoxia often keeps cells from differentiating. However, hypoxia promotes the formation of blood vessels, and is important for the formation of a vascular system in embryos, and cancer tumors. The hypoxia in wounds also promotes the migration of keratinocytes and the restoration of the epithelium. In general, HIFs are vital to development. In mammals, deletion of the HIF-1 genes results in perinatal death. HIF-1 has been shown to be vital to chondrocyte survival, allowing the cells to adapt to low-oxygen conditions within the growth plates of bones. HIF plays a central role in the regulation of human metabolism. (Wiki – HIF-1).”

5. **UPR hormesis pathways.** Heat, ROS, RNS, RSS, XRT, UV, and aging alter proteostasis resulting in the accumulation of unfolded or misfolded proteins. These stressors can up-regulate stress coping mechanisms or induce cellular damage and apoptosis. *Unfolded Protein Responses (UPRs)* sense and deal with accumulation of unfolded proteins, protecting the cell and blocking apoptosis. *One of the UPR pathways involved in hormesis is the heat shock response pathway mentioned above. There are two other UPR pathways to be considered: the mitochondrial...*
UPR and the endoplasmic reticulum UPR. Diagrams of how these three UPR pathways work are thought to work can be found below. The UPR plays a role in a number of diseases of aging including cancer, heart disease, cerebrovascular disease, arthritis, osteoporosis, neurodegenerative disease like Alzheimer’s and Parkinson’s and Type II diabetes.

6. **Cell-membrane mediated hormesis.** From the 2010 publication *Cellular Stress Responses, The Hormesis Paradigm, and Vitagenes: Novel Targets for Therapeutic Intervention in Neurodegenerative Disorders* “Evidence is emerging to support hormetic roles for low and transient increases in membrane oxidative stress. Levels of membrane lipid peroxidation are relatively low under most normal conditions. However, in some types of cells, lipid peroxidation increases considerably during periods of increased energy demand. For example, during vigorous physical exercise there is a marked increase in production of superoxide and hydrogen peroxide, hydroxyl radical, peroxynitrite, and lipid peroxidation (377). Evidence suggests that free radicals and products of lipid peroxidation generated during moderate exercise play important roles in hormetic effects of exercise on muscles, including changes in energy metabolism pathways, mitochondrial biogenesis, and up-regulation of protein chaperones and antioxidant systems (377). Benefits of exercise on the cardiovascular system may also involve membrane oxidative stress-related mechanisms. Thus, it was reported that HNE activates nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant gene expression in vascular cells (412). HNE may also activate other adaptive stress response pathways that promote the survival and plasticity of cells (349). Ceramide is also believed to mediate hormetic effects of moderate/transient increases in membrane-associated oxidative stress. For example, pretreatment of neurons with subtoxic concentrations of ceramide results in increased resistance of the neurons to subsequent high levels of oxidative stress (191). Other studies have provided evidence for a pivotal role for ceramide in the cardio-protective effect of preconditioning ischemia in animal models of myocardial infarction (16, 149). Preconditioning ischemia is a classic example of hormesis, wherein exposure of cells to a moderate transient stress protects them against more severe stresses. Changes in the PMRS in response to stress may also allow cells to adapt to potentially damaging conditions. A dramatic example comes from a study in which the mitochondria of cells were rendered dysfunctional, and the cells were able to survive because of a compensatory upregulation of PMRS enzyme activities (212).”
Hormesis operates through multiple channels for cell survival, dependent on the stimulation.
Illustrating a few of many possible situations, the following diagram illustrates the signaling operations for hormesis originated by three toxic gasses, hydrogen sulfide, carbon monoxide and nitric oxide:

![Diagram of hormetic signaling operations](image-source)

Image source

Regarding these noxious gasses and hormesis, see Jim Watson’s recent blog entry *The Hormetic Wild Animal “Zoo” and Their “Zookeepers.”*

Hormesis, specifically the scaling of the hormesis curve, depends on several critical factors:

1. **Hormetic dose response is a critical consideration encountered in every situation of hormesis.** The hormetic dose response curve is central to the process. Not enough or too much of a given stress can be harmful. A tiny whiff of carbon monoxide may be good for you but too much will kill you. Avoiding all stress in your life could be a good approach to early death.

2. **The time duration of the hormesis-generating stress is critical.** If a hormetic level of stress is maintained too long, the result could be non-hormetic and dangerous. An example could be exercising to utter exhaustion; another would be breathing a very low level of carbon monoxide for too long.

3. **To be effective, the stress must be pulsed; it cannot be chronic.** Chronic exposure to even very low levels of carcinogens, like second-hand tobacco smoke, could result in negative effects outside the hormesis zone. Another example is that radiation hormesis cannot be expected from a chronic stress source like radiation from Strontium70 absorbed in bones. You might be able to experience hormesis
from cold shock by taking a cold shower, but if you stay in the shower too long your immune system might not be able to protect you from viral infections like common colds.

4. **Multiple stressors that address a certain pathway response may produce no better hormetic benefits than single ones.** From *Hormesis provides a generalized quantitative estimate of biological plasticity*: “These quantitative features of the hormetic dose response have important medical implications. Most significantly, the hormetic dose response imposes constraints upon the magnitude of a drug to induce a desired effect. For example, if a drug increased cognitive performance in an elderly patient by approximately 25%–30%, the hormetic model suggests that this level of performance could not be further increased using a new drug combination. This concept has been supported in a variety of studies on hormesis and drug interaction. Flood (173–176) has demonstrated that the hormetic response for memory was bounded by the 30%–60% increase even when several drugs were used in combination that were designed to maximize memory outcome. This response magnitude constraint has been reported for immune stimulation, bacterial growth, increases in hair growth, plant growth, decrease in anxiety, decreases in tumor incidence, and numerous other endpoints (73).” The limits of hormetic responses are set by the nature of the hormetic response machinery that is involved. For example, consuming a phytosubstance like green tea may cause release of Nrf2 into the nucleus of cells activating ARE genes and creating a healthful hormetic response. But there is only so much Nrf2 sitting around in the cytoplasm of cells at any given time. So consuming green tea, curcumin, resveratrol, and ginger pills in the same gulp of pills may release no more Nrf2 or produce no better results – and might even exceed the hormetic dose.

5. **Periods of rest are required between stress impulses.** For example, we all know that periods of rest are required between bouts of exercise. We conjecture that the cells require time to replenish stocks of Nrf2 in the cytoplasm after it is suddenly released into the nucleus. After oxidative stress the body requires time to clear out oxidation byproducts and otherwise re-establish homeostasis.

6. **Hormesis is most effective when synchronized with circadian time frame windows.** For example, getting up from sleep and exercising at 3AM is not a good idea. There are likely to be a number of other windows-of-best-opportunity for other circadian clocks. This is an area requiring further research.
7. **The body can increase its stress tolerance and affect the height and breadth of the hormetic response curve to a stressor by repeated hormetic exposures to the stressor.**

8. A familiar example is exercise endurance training, where a runner may gradually increase his running time and speed to levels unthinkable for an ordinary individual. Another example relates to pot, yes, marijuana. THC, the active ingredient in marijuana, appears to be a hormetic molecule capable of promoting neurogenesis at low doses (probably smaller doses than ones from puffing on a marijuana cigarette) ([ref](#)). I know a couple of individuals who are regular marijuana smokers and appear consistently to be functional and mentally present. They tell me they smoke the substance ever day or so and that it leads them to clearer thinking. I conjecture that they have increased their stress tolerance to THC. I also know, based on personal experimentation during my hippy days 45 years ago or so, that just a few puffs of the same weed these friends are smoking would stop me from thinking clearly for a week or more. Another good example of increasing stress tolerance through repetition discussed below is myocardial ischemic preconditioning.

Jim Watson summarized these hormesis factors to me in a phone conversation. Though they are “of course” common sense observations, I have never seen them written down in one place.

**The impacts of simple hormetic events on health and longevity might be profound and long-lasting.**

Take for example, simple everyday events which activate Nrf2. I am talking about eating some broccoli, drinking some green tea, swallowing a curcumin or resveratrol capsule, and many other such everyday actions. We know Nrf2 activates the body’s endogenous antioxidant defense system. But there is solid research that says it does much more including:

1. Affecting the differentiation and apoptosis of stem cell populations so as to affect organ regeneration and lifespan.
2. Affecting the repair of damaged DNA and tissues. Many believe accumulated DNA damage is a fundamental driver of aging.
3. Responding to electrophilic stress. It is possible that electrophilic stress is a more important cause of cellular aging than oxidative stress.
4. Creating permanent changes to one’s epigenome.
Although we do not know the magnitude or relative importance of these responses, I briefly cite evidence for each one.

**Hormetic expression of Nrf2 can affect the differentiation and apoptosis of stem cell populations so as to affect organ regeneration and lifespan.**

The 2010 publication *Regulation of Notch1 Signaling by Nrf2: Implications for Tissue Regeneration* makes the case in point. “–Through transcriptional analyses in Keap1- or Nrf2-disrupted mice, we identified interactions with the Notch1 signaling pathway. We found a functional antioxidant response element (ARE) recognized by Nrf2 in the promoter of *Notch1*. Notch1 regulates processes such as proliferation and cell fate decisions. We report a functional role for this cross talk between the two pathways and show that disruption of Nrf2 impeded liver regeneration following partial hepatectomy and was rescued by re-establishment of Notch1 signaling. — The Notch family of transmembrane receptors participates in a signaling pathway controlling a broad spectrum of metazoan cell fates and developmental processes through local cell-cell interactions (21). Alteration of signaling through the Notch family of receptors can markedly affect differentiation, proliferation, and apoptotic events. Genetic ablation studies indicate that Notch1 is crucial for early development and re-growth of several tissues (22, 23). Activation of the Notch pathway inhibits differentiation in different developmental contexts and has been associated with the amplification of some somatic stem cells— not only the neural (24) and hematopoietic stem cells (25), but also hepatocyte (26, 27) and intestinal epithelial stem cells (28, 29). Considering the importance of the Notch1 signal cascade in developmental biology, the microarray observations indicated the possibility that Nrf2 could be a key molecule affecting both embryonic and adult tissue stem cell renewal as well as cell fates. This study characterizes the effects of Nrf2 genotype on the expression of *Notch1* and its effector genes and the importance of Nrf2-Notch1 crosstalk in liver regeneration.”

**Hormetic expression of Nrf2, among other impacts, can affect the repair of damaged DNA and tissues.**

This point is illustrated in the following graphic from the publication *When NRF2 Talks, Who’s Listening?*
Possible means for regulation of cell survival and other cell-fate responses through interactions of NRF2 with additional cell-signaling pathways, including AhR, NF-κB, p53, and Notch1.

“Nonetheless, it is clear that the protective effects of upregulation of NRF2 signaling can take several forms. Protection can be immediate, reflecting induction of genes directly regulated through NRF2 binding to AREs in target genes (e.g., the innate immune response and elevated cytoprotective responses to blunt cytokine surges or detoxify reactive intermediates, respectively) (73). The protective effects can be secondary through induction of macromolecular damage repair/removal systems (proteasome, DNA repair) (84, 106). Last, the protective effects can be tertiary through activation of tissue repair/regeneration pathways. In these latter cases, involvement in cross talk with additional pathways affecting cell survival and other aspects of cell fate most certainly play important collaborating roles.”

Like oxidative stress, Nrf2 hormetically responds to electrophilic stress via the Keap1 pathway. This phenomenon may be highly relevant to aging.

Electrophilic stress is stress induced by the stealing of pairs of electrons from compounds in cells by electrophiles, creating new and sometimes radical molecular structures. “In general, electrophiles are positively charged species that are attracted to an electron rich centre. In chemistry, an electrophile (literally electron-lover) is a reagent attracted to electrons that participates in a chemical reaction by accepting
an electron pair in order to bond to a nucleophile. (ref) Electrophilic stress is often discussed along with oxidative stress for both appear to activate Nrf2 via a common process.

As stated in *Relationship of electrophilic stress to aging*: “In the present review, I will discuss the nature of electrophilic stress and its role in aging. I hope to present compelling evidence that electrophiles are, in fact, a long-neglected causal contributor to aging, and that electrophilic stress, while initiated by an oxidative event, is distinct, and can be functionally decoupled, from oxidative stress. — “This review begins with the premise that an organism’s life span is determined by the balance between two countervailing forces: (i) the sum of destabilizing effects and (ii) the sum of protective longevity-assurance processes. Against this backdrop, the role of electrophiles is discussed, both as destabilizing factors and as signals that induce protective responses. Because most biological macromolecules contain nucleophilic centers, electrophiles are particularly reactive and toxic in a biological context. The majority of cellular electrophiles are generated from polyunsaturated fatty acids by a peroxidation chain reaction that is readily triggered by oxygen-centered radicals, but propagates without further input of reactive oxygen species (ROS). Thus, the formation of lipid-derived electrophiles such as 4-hydroxynon-2-enal (4-HNE) is proposed to be relatively insensitive to the level of initiating ROS, but to depend mainly on the availability of peroxidation-susceptible fatty acids. This is consistent with numerous observations that life span is inversely correlated to membrane peroxidizability, and with the hypothesis that 4-HNE may constitute the mechanistic link between high susceptibility of membrane lipids to peroxidation and shortened life span.” — “Where do biologically relevant electrophiles come from? There are two major sources of such compounds. The first is external. Xenobiotics can be present in food, especially of plant origin, can be inhaled, or can be administered on purpose, e.g., as pharmacological agents. Many xenobiotics are directly electrophilic or can be metabolically converted to electrophiles [activation of toxins or drugs; see ref. 8 for a review]. The other source of electrophiles is the cell’s own metabolism. Certain intermediary metabolites are electrophilic.” “The paradigm I am proposing, (is) namely that electrophiles such as 4-HNE are relevant to aging, and that the formation of 4-HNE is largely decoupled from the initiating oxidative stress but is a function of membrane peroxidizability.”

**Electrophile Response System for Cellular Stress Tolerance**
“Normally, INrf2 directs the degradation of Nrf2 by recruiting Cul3/Rbx1. After cells are exposed to stressors such as reactive oxygen species, INrf2 undergoes cysteine modification and Nrf2 is phosphorylated by PKC, resulting in dissociation of the INrf2:Nrf2 heterodimers. Phosphorylated Nrf2 translocates to the nucleus and binds the Antioxidant Response Element (ARE) with either small MAF or Jun. This leads to antioxidant gene expression that protects the cell, (A). The pathway is subsequently inactivated by two separate mechanisms. First, Maf homodimers and Bach1:Maf heterodimers compete with Nrf2 for ARE binding, resulting in diminished antioxidant gene expression. Second, GSK3b phosphorylates Fyn which leads to the Fyn translocating to the nucleus. Fyn subsequently phosphorylates Nrf2 at Tyr568. Nrf2 then is exported from the nucleus, binds to INrf2 and is subsequently degraded, (B).”

**Hormetic expression of Nrf2 may create permanent health-inducing modifications to one’s epigenome.**

The idea of permanently changing one’s epigenome in a positive manner by eating a bit of broccoli or kale or exercising a little may not be completely preposterous. Consider the following three graphics from the publication *Epigenetic impact of dietary polyphenols in cancer chemoprevention: Lifelong remodeling of our epigenomes*
“Dietary modulation of transcription factor pathways which regulate chromatin “oscillation” dynamics between euchromatic and heterochromatic states at oncogenes and tumor suppressor genes.”

You can control your level of cellular stress and remodel your epigenome for health and longevity at the Dinner Table
Epigenetic actions of common foods

“Development of functional foods or dietary supplements as nutrition based epigenetic modulators of chromatin writers, readers and erasers in cancer chemoprevention. HAT, histone acetyltransferase; HDAC, histone deacetylase; DNMT, DNA methyltransferase; KMT, lysine methyltransferase; KDM, lysine demethylase; Me-CpG, Methylcytosine; R, transcription repressor; A, Transcription activator; Ac, acetyl; Me, methyl.”

There appears to be no end to the list of toxic and carcinogenic substances that induce hormesis at very low doses. It is tempting to say that all toxic substances administered in pulsed intermittent doses qualify for hormesis. The blog entry *The Hormetic Wild Animal “Zoo” and Their “Zookeepers”* describes some of these substances. Another of many examples is described in the 2006 publication *Alpha-benzene hexachloride exerts hormesis in preneoplastic lesion formation of rat hepatocarcinogenesis with the possible role for hepatic detoxifying enzymes.* “Recently there has been a shift in the prevailing paradigm regarding the dose dependence of carcinogen action with increasing acceptance of hormesis phenomenon, although underlying mechanisms remain to be established. To ascertain whether alpha-benzene hexachloride (alpha-BHC) might act by hormesis, rats were initiated with diethylnitrosamine and then alpha-BHC ranging from 0.01 to 500 ppm was administered in the diet for 10 weeks. The highest concentration of alpha-BHC significantly increased the number and area of glutathione S-transferase placental form
(GST-P) positive foci, preneoplastic lesions in the liver, but its low dose, 0.05 ppm, caused significant reduction, showing a J-shape dose-response curve. The proliferating cell nuclear antigen positive index for GST-P positive foci in the low dose-treated group was significantly reduced. The dose response curves of CYP450 content, NADPH-P450 reductase activity and 8-hydroxydeoxyguanosine formation revealed the same pattern as GST-P positive foci data. The response curves of CYP2B1 and 3A2 in their activities, protein and mRNA expression showed a threshold but CYP2C11 activity exhibited an inverted J-shape. These results might suggest the possibility of hormesis of alpha-BHC at early stages of rat hepatocarcinogenesis. The possible mechanism involves induction of detoxifying enzymes at low dose, influencing free radical production and oxidative stress, and consequently pathological change in the liver.”

Of course, multiple other stresses besides substances can induce hormetic responses: too much cold or heat, radiation, surgery, emotional stresses of many kinds, too bright lights, UV exposure, lack of sleep, lack of oxygen, physical injury, pain, many diseases, etc. etc. I conjecture that evolution has prepared a hormetic response for just about every kind of stress we commonly encounter.

The unfolded protein responses (UPRs) are important stress-response pathways subject to hormesis
As already mentioned, there are three Unfolded Protein Responses. All three of the UPR pathways are activated in response to protein stress.

Mitochondrial UPR

mtUPR in C. elegans
“A model for mitochondrial UPR signaling in C. elegans. It is assumed that signaling within the UPR initiates when the unfolded protein load in the matrix exceeds the capacity of the mitochondrial chaperones. The AAA+ protease ClpXP degrades unfolded or unassembled proteins to peptides, which are pumped across the inner membrane by the ABC-transporter HAF-1 and then cross the more porous outer membrane to the cytosol. The presence of peptides in the cytosol, the process of peptide efflux or some linked activity of HAF-1 leads to the activation and nuclear translocation of the bZip transcription factor ZC376.7; however, the underlying mechanism(s) have yet to be identified. Additionally, the homeobox protein DVE-1 and UBL-5 form a complex and bind to the hsp-60 promoter potentially remodeling chromatin structure to promote ZC376.7 binding and transcriptional activation. Transcriptional upregulation of mitochondrial chaperone genes leads to their subsequent import into mitochondria, thus relieving stress and re-establishing homeostasis.”

Cytoplasmic UPR (AKA Heat Shock response)

Endoplasmic reticulum UPR

The relationship between duration and amplitude of stress to cell response in the endoplasmic reticulum UPR response is illustrated in the following graphic. *If the stress is too great or lasts too long, the cell commits apoptosis.*
Image source – “Figure 1. Kinetics of UPR signaling and cell fate decisions. The accumulation of abnormally folded proteins in the ER engages an adaptive stress response known as the UPR. Temporally distinct UPR-related events are observed in cells undergoing ER stress as a means to determine cell fate decisions. Two major ER stress sensors, IRE1α and PERK, transduce information about the folding status of the ER to the cytosol and nucleus to recover folding capacity. Whereas IRE1α is downregulated under conditions of chronic ER stress, PERK signaling is sustained, possibly sensitizing cells to apoptosis (blue and red lines, respectively). In a first, acute signaling response, IRE1α and PERK activity attenuates protein synthesis at the ER by decreasing protein translation and controlling the decay of mRNAs encoding ER proteins. Autophagy is also activated to remove aggregated proteins and damaged organelles. Then, downstream of PERK and IRE1α, the transcription factors XBP1s and ATF4 are expressed, leading to the upregulation of many genes related to folding, quality control, ERAD and redox metabolism. After prolonged ER stress, IRE1α is turned off, thereby downregulating XBP1s. Downstream of ATF4, expression of the transcription factor CHOP, and other related events, can regulate the transition from adaptation/survival events to a pro-apoptotic phase. This late fourth wave of signaling events is associated with the upregulation of many genes related to the BCL2 protein family including BIM, PUMA and NOXA, thereby activating the canonical mitochondrial apoptosis pathway. During the course of ER stress, a dynamic modulation of IRE1α signaling occurs. Several regulators assemble into the IRE1α scaffold to regulate its activity in terms of kinetic, amplitude and tissue specificity. This signaling platform is termed the UPRosome, and several interacting factors, including PTP1B, AIP1, HSP72, BAX and BAK, increase the amplitude of IRE1α signaling.
Following prolonged ER stress, IRE1α returns to a latent state, a process modulated by an interaction with Bi-1 and possibly the phosphatase PP2A in complex with RACK1. **The heat shock response is relevant to aging and to possible life extension in humans.**

UPR-regulated Heat Shock Proteins decline with age. Cells in young animals rapidly alter levels of HSPs. Older animals lose the ability to induce HSPs and other stress response proteins. This has been observed in yeast, worms, flies, and mouse and human cell lines.

Further, over-expression of Heat Shock Proteins extends lifespan at least in some lower species. This has been observed in *Drosophila*. The lifespan extension seems to be due to impacts on mitochondrial OXPHOS processes. See [Gene expression profiling implicates OXPHOS complexes in lifespan extension of flies over-expressing a small mitochondrial chaperone, Hsp22.](#) “Aging is a complex process accompanied by a decreased capacity to tolerate and respond to various stresses. Heat shock proteins as part of cell defense mechanisms are up-regulated following stress. In *Drosophila*, the mitochondrial Hsp22 is preferentially up-regulated in aged flies. Its over-expression results in an extension of lifespan and an increased resistance to stress. Hsp22 has chaperone-like activity in vitro, but the mechanism(s) by which it increases lifespan in flies are unknown. Genome-wide analysis was performed on long-lived Hsp22+ and control flies to unveil transcriptional changes brought by Hsp22. Transcriptomes obtained at 45 days, 90% and 50% survival were then compared between them to focus more on genes up- or down-regulated in presence of higher levels of hsp22 mRNA. Hsp22+ flies display an upregulation of genes mainly related to mitochondrial energy production and protein biosynthesis, two functions normally down-regulated during aging. Interestingly, among the 26 genes up-regulated in Hsp22+ flies, 7 genes encode for mitochondrial proteins, 5 of which being involved in OXPHOS complexes. Other genes that could influence aging such as CG5002, dGCC185 and GstS1 also displayed a regulation linked to Hsp22 expression. The up-regulation of genes of the OXPHOS system in Hsp22+ flies suggest that mitochondrial homeostasis is at the center of Hsp22 beneficial effects on lifespan.” Some of the stressors that induce the HSP hormetric response are illustrated in this graphic:
Image source: Heat-shock proteins induce T-cell regulation of chronic inflammation

The key transcription factor protein involved in the hypoxic stress response, HIF-1, modulates lifespan in lower species.

The 2009 publication *The HIF-1 Hypoxia-Inducible Factor Modulates Lifespan in C. elegans* relates: “During normal development or during disease, animal cells experience hypoxic (low oxygen) conditions, and the hypoxia-inducible factor (HIF) transcription factors implement most of the critical changes in gene expression that enable animals to adapt to this stress. Here, we examine the roles of HIF-1 in post-mitotic aging. We examined the effects of HIF-1 over-expression and of hif-1 loss-of-function mutations on longevity in C. elegans, a powerful genetic system in which adult somatic cells are post-mitotic. We constructed transgenic lines that expressed varying levels of HIF-1 protein and discovered a positive correlation between HIF-1 expression levels and lifespan. The data further showed that HIF-1 acted in parallel to the SKN-1/NRF and DAF-16/FOXO transcription factors to promote longevity. HIF-1 over-expression also conferred increased resistance to heat and oxidative stress. We isolated and characterized additional hif-1 mutations, and we found that each of 3 loss-of-function mutations conferred increased longevity in normal lab culture conditions, but, unlike HIF-1 over-expression, a hif-1 deletion mutation did not extend the lifespan of daf-16 or skn-1 mutants. We conclude that HIF-1 over-expression and hif-1 loss-of-function mutations
promote longevity by different pathways. These data establish HIF-1 as one of the key stress-responsive transcription factors that modulate longevity in C. elegans and advance our understanding of the regulatory networks that link oxygen homeostasis and aging.

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**One of the consequences of calorie restriction and certain other hermetic stresses on mitochondria is mitochondrial biogenesis.**

The impact described relates to electron transport chains, a topic introduced in the recent blog entry *Mitochondria in health and aging, and possibilities for life prolongation – Part 1: basics*. The situation is described in this diagram:
Mitochondrial Biogenesis and Reactive Oxygen Species. Shown is mitochondrial biogenesis during calorie restriction versus ad libitum feeding in mice and its proposed effects on reactive oxygen species (ROS). In the ad libitum case, the number of electron transport chains is low, and if the rate of entry of electrons (red e⁻) exceeds the slowest step of flow through the chain, stalling of electrons at mitochondrial complexes I and III (blue e⁻) and production of ROS will be favored. During calorie restriction, mitochondrial biogenesis increases the number of electron transport chains, thereby reducing the rate of electron entry per electron transport chain. Calorie restriction may also increase the fraction of electrons that bypass complex I by entering the electron transport chain via the electron transfer flavoprotein dehydrogenase (ETF). These effects may reduce the production of ROS during calorie restriction and hence mitigate cellular damage, aging, and disease.

A response to mitochondrial stress appears to be up-regulation of heat shock proteins.
The mitochondrial unfolded protein response (UPRmt) has been shown to play an important role in aging of C. elegans by studies from the Dillin Lab. The inhibition of mitochondrial activity can extend lifespan in worms. This is not simply the result of lowered oxidative damage, but requires induction of a mitochondrial stress response known as the UPRmt. The UPRmt is thought to signal from the mitochondria to the nucleus to cause changes in gene expression to improve mitochondrial protein homeostasis in a cell autonomous and non-autonomous fashion. We are performing genetic screens to identify key genes involved in this response in order to better understand communication between the mitochondria and nucleus and its important role in aging. These screens are being performed in both yeast and C. elegans in order to understand which aspects of the UPRmt have been evolutionarily conserved and whether the importance of this pathway in aging is also conserved.

Low-density lipoproteins induce hormesis, most likely via the Nrf2/Keap1 pathway.

The 0820 publication *Characterization of oxidized low-density lipoprotein-induced hormesis-like effects in osteoblastic cells* reports: “Epidemiological studies indicate that patients suffering from atherosclerosis are predisposed to develop osteoporosis. Atherogenic determinants such as oxidized low-density lipoprotein (oxLDL) particles have been shown both to stimulate the proliferation and promote apoptosis of bone-
forming osteoblasts. Given such opposite responses, we characterized the oxLDL-induced hormesis-like effects in osteoblasts. Biphasic 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reductive activity responses were induced by oxLDL where low concentrations (10-50 microg/ml) increased and high concentrations (from 150 microg/ml) reduced the MTT activity. Cell proliferation stimulation by oxLDL partially accounted for the increased MTT activity. No alteration of mitochondria mass was noticed, whereas low concentrations of oxLDL induced mitochondria hyperpolarization and increased the cellular levels of reactive oxygen species (ROS). The oxLDL-induced MTT activity was not related to intracellular ROS levels. OxLDL increased NAD(P)H-associated cellular fluorescence and flavoenzyme inhibitor diphenyleneiodonium reduced basal and oxLDL-induced MTT activity, suggesting an enhancement of NAD(P)H-dependent cellular reduction potential. Low concentrations of oxLDL reduced cellular thiol content and increased metallothionein expression, suggesting the induction of compensatory mechanisms for the maintenance of cell redox state. These concentrations of oxLDL reduced osteoblast alkaline phosphatase activity and cell migration. Our results indicate that oxLDL particles cause hormesis-like response with the stimulation of both proliferation and cellular NAD(P)H-dependent reduction potential by low concentrations, whereas high concentrations lead to reduction of MTT activity associated with the cell death. Given the effects of low concentrations of oxLDL on osteoblast functions, oxLDL may contribute to the impairment of bone remodeling equilibrium.”

**Myocardial ischemic preconditioning**

Myocardial ischemic preconditioning (IPC) is an example of a hormetic process featuring the aspects of pulsing and increasing stress tolerance – even though the literature on IPC rarely if ever mentions the word “hormesis.” “IPC is an intrinsic process whereby repeated short episodes of ischaemia protect the myocardium against a subsequent ischaemic insult(Ref).” “The myocardium possesses innate physiologic adaptive processes that render it more resistant to potentially lethal ischemic injury. A number of these adaptive mechanisms have been identified; one is the phenomenon of ischemic preconditioning which provides the myocardium with the most powerful means of delaying myocardial infarction that has been identified. Ischemic preconditioning refers to the protection conferred to ischemic myocardium by preceding brief periods of sublethal ischemia(Ref)” “The 2002 review article Ischemic preconditioning of myocardium related in summary “Preconditioning of the myocardium with short episodes of sublethal ischemia will delay the onset of necrosis during a subsequent lethal ischemic insult. Ischemic preconditioning seems to involve a
variety of stress signals which include activation of membrane receptors and signaling molecules such as protein kinase C, mitogen-activated protein kinases, opening of ATP-sensitive potassium channel, and expression of many protective proteins."IPS is a powerful tool of hormesis that increasingly is being utilized in medical practice, particularly in open cardiac surgery(ref)(ref). The 2007 publication Ischemic preconditioning: Protection against myocardial necrosis and apoptosis reported: “The phenomenon of ischemic preconditioning has been recognized as one of the most potent mechanisms to protect against myocardial ischemic injury. In experimental animals and humans, a brief period of ischemia has been shown to protect the heart from more prolonged episodes of ischemia, reducing infarct size, attenuating the incidence, and severity of reperfusion-induced arrhythmias, and preventing endothelial cell dysfunction. Although the exact mechanism of ischemic preconditioning remains obscure, several reports indicate that this phenomenon may be a form of receptor-mediated cardiac protection and that the underlying intracellular signal transduction pathways involve activation of a number of protein kinases, including protein kinase C, and mitochondrial KATP channels. Apoptosis, a genetically programmed form of cell death, has been associated with cardiomyocyte cell loss in a variety of cardiac pathologies, including cardiac failure and those related to ischemia/reperfusion injury. While ischemic preconditioning significantly reduces DNA fragmentation and apoptotic myocyte death associated with ischemia-reperfusion, the potential mechanisms underlying this effect have not been fully clarified.”

Hormetic protectivity of polyphenols, as related to cellular stress and epigenetics

Again and again in these blog entries, I have highlighted the protective hormetic roles of plant-based polyphenol substances. I do so because I have become convinced that a dietary regimen that features consuming these substances when coupled with good lifestyle habits can produce significant health and longevity benefits right now. No need to wait for further research since enough is known already. No need to wait for new miracle drugs.
Image source: From the [Hormesis project, the National Institute of Aging](https://www.nia.nih.gov/research/hormesis) The slide shows the impacts of broccoli, garlic, hot peppers, turmeric, grape skins and numerous other phyto-substances on the Nrf2, Sirt1, FOXO3 and NF-kappaB pathways to create positive reactions in the nucleus of cells – hormetic effects. Note also that pathological stress and over-expression of the stress hormone cortisol can block the good benefits from happening.

**Molecular biology of the cold shock hormetic response**

Here are a couple of graphics that illustrate how the cold shock response works. As you can see, the complexity is significant.

The Shock Response Cold-inducible RNA binding Proteins: CIRP & RBM3
This review focuses on the roles of two major cold-inducible RNA binding proteins known in human cells: CIRP and RBM3. Both proteins were discovered when they were shown to be induced after exposure to a moderate cold-shock and other cellular stresses such as UV radiation and hypoxia. — Possible molecular pathways in which CIRP and RBM3, designated as CSP (cold-shock proteins), can modulate transcription and translation. Different mechanisms by which mammalian cells respond to some kinds of stresses are shown. Upon stresses such as cold-shock, hypoxia or UV treatment, two different and opposite pathways are shut down. One of them, which has a general effect on most mRNAs and proteins, is an anti-proliferative pathway (red arrow) that provokes a metabolic rate depression, general mRNA degradation and decrease in mRNA transcription and overall protein synthesis (which drops to ~10% compared to the control levels). Another pathway is a cell survival and/or proliferative pathway, where stress-induced proteins such as CSP are expressed. Remarkably, although the overall protein synthesis is suppressed, several genes show an increased expression rate against the overall trend. The proteins encoded by CSP are able to act through several pathways at different levels: (a) transcription: CSP bypass the general inhibition of most proteins in stressed cells, largely due to the 5′- and 3′-UTR of their transcripts. CSP are able to stabilize their own and other mRNAs under stress conditions to avoid the formation of secondary structures, or act as chaperones to stimulate their nuclear-cytoplasm transport. In addition, they have adaptive expression.
through alternative splicing or different promoters under stress; (b) translation: CSP are involved in the cap-independent (IRES) or cap-dependent translation by interacting with components of the basal transcriptional machinery and/or stimulating the activation of proteins involved in the initiation of translation (eIF4G, eIF4E, 4E-B-P1). In addition, cellular mRNAs that contain IRES within their 5′-UTR have diverse regulatory patterns. The mode of translation changes under stress conditions depending on the stress, for example when cap-dependent initiation decreases, then IRES-mediated initiation prevails; (c) CSP are able to modulate microRNAs or can be regulated by epigenetic mechanism such as methylation.” The Shock Response Cold
Cold-inducible RNA binding Proteins: CIRP & RBM3

Image source— “Many living organisms have adapted sophisticated strategies to allow their survival over a dynamic range of temperatures. The response to elevated temperatures has been extensively studied in both prokaryotic and eukaryotic systems and generally involves the induction of heat-shock proteins (HSPs), a family of proteins that are highly conserved between all organisms from bacteria to mammals. In contrast to the HSP response, the mechanisms involved in the response to sub-physiological temperatures are poorly understood and have been studied in few organisms. A number of plant genes are induced by low temperature stress, and in prokaryotes cold stress
induces several well-characterised cold-shock proteins (CSPs). — By contrast, the response of eukaryotic cells to cold-shock and the biological mechanisms that govern cellular response to sub-physiological temperatures are not well understood. Cold-stress exposures cells to two major stresses; those relating to changes in temperature and those related to changes in oxygen concentration due to higher dissolved oxygen concentrations at reduced temperatures. Although our understanding of the cold-shock response in eukaryotes is limited, several studies have demonstrated that induced CSPs are key determinants in the adaptation to growth and survival at lower temperatures although little is known about what effect changes in dissolved oxygen concentrations may play in these responses. What is becoming clear is that exposing eukaryotic cells to sub-optimal temperatures invokes a coordinated response involving modulation of the cell cycle, metabolism, transcription, translation, and the cell cytoskeleton. Moreover, the response of eukaryotes to cold stress has been implicated in adaptive thermogenesis, cold tolerance, storage of tissue, organs and cells, therapeutic treatment of brain damage, and as a method to improve recombinant protein production in mammalian cells.”

Dietary restriction and alternative day fasting are also hormetic means for health-induction and possibly slowing aging. See the blog entries Mechanisms and Effects of Dietary Restriction and Alternate-day Fasting – a better alternative. This interesting graphic illustrates how dietary restriction conveys
resistance to neurodegenerative and cardiovascular diseases via hormetic pathways.

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Image source: From the [Hormesis project, the National Institute of Aging](https://www.nia.nih.gov/research/hormesis), a web-page with much other interesting information.

With regard to both calorie restriction and every-other-day fasting, from the same NIA website: **1b. Dietary energy intake and age interact to modify cell stress pathways and stroke outcome.** "During the past 10 years we have demonstrated beneficial effects of dietary energy restriction, alternate day fasting (ADF) and limited daily feeding caloric restriction (CR) in reducing neuropathological processes and improving functional outcome in animal models of both acute and chronic neurodegenerative conditions. We showed that ADF and CR up-regulate the expression of genes in CNS cells that encode proteins that promote neuronal survival and plasticity (BDNF, HSP70, GRP78, UCPs). We recently performed an experiment aimed at addressing two major unanswered questions of considerable importance: 1) Does advancing age alter that ability of dietary energy restriction to activate neuro-protective pathways? 2) How do age and energy intake affect the outcome in an animal model of stroke? We employed a novel microchip-based immune-affinity capillary electrophoresis technology to measure a panel of neurotrophic factors, cytokines, and cellular stress resistance proteins in brain tissue samples from young, middle-aged, and old mice that had been maintained on control or ADF diets for 3 months prior to focal cerebral ischemia – reperfusion (3). Mortality from focal ischemic stroke was increased with advancing age and reduced by ADF. Brain damage and functional impairment were reduced by ADF in young and middle-aged mice, but not in old mice.
mice. The basal and poststroke levels of BDNF, bFGF, protein chaperones (heat shock protein 70 and glucose regulated protein 78), and the antioxidant enzyme heme oxygenase-1 were decreased, whereas levels of inflammatory cytokines were increased in the cerebral cortex and striatum of old mice compared with young and middle age mice. ADF coordinately increased levels of protective proteins and decreased inflammatory cytokines in young, but not in old mice. These findings suggest that the ability of ADF to activate adaptive neuronal stress response pathways and to suppress inflammation is impaired during the aging process, resulting in increased brain damage and poorer functional outcome."

We have touched here on several aspects of hormesis that go beyond those explored in previous blog entries. But the science of hormesis is hard science and as always there is much more that can be said. Please expect the hormesis concept to crop up frequently as we move forward with blog entries attempting to lay out what aging is and what can be done about it.

The Eductor technology can help apply the laws of homotoxicology and hormesis.
http://www.scienceofdetox.com
Chernobyl Children: what makes some Eastern Europeans born in 1985-1986 healthier from the rest of us?

By Kateryna Khinkulova and Victoria Angel

27/04 11:41 CET

Radiation hormesis in physiologic functions

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Ukraine marks anniversary of 1986 Chernobyl disaster

On April 26, 1986 a series of unsuccessful tests at the 4th reactor of Chernobyl nuclear power plant in the north-west of Ukraine caused an explosion which turned into an extensive fire, resulting in the world’s worst nuclear accident. The Soviet government attempted to cover up what happened but was forced to admit it after it was reported by a Swedish nuclear energy authority. But the science of hormesis tells us that a small exposure to a toxin can have a positive even stimulating effect on an organism.

Two people died in the immediate explosion and 29 more in the hospital over the next few days. The 4th reactor continued to burn for almost three weeks and scores of people worked as so called “liquidators” putting the fire out. A lot of them died subsequently from health problems linked to exposure to radiation.
The total number of Chernobyl fatalities over the years is a disputed figure. International Agency for Research on Cancer (a UN body) claims that by 2065 40,000 people will have died from cancers that could be traced to Chernobyl. Many scientists put the figure well into six digits.

A 30 km exclusion zone was created and still remains around Chernobyl. Hundreds of thousands of people were evacuated from the areas around the plant, mainly the town of Prypiat and nearby villages. A temporary cover over the 4th reactor was erected in the summer of 1986 to be replaced later with a stronger structure. The building of the latter continues to this day, slowed down by the complexity of the project and high levels of radiation still present around the burnt-out reactor.

29 years after the accident Euronews spoke to three young Ukrainians, born within days of each other in that fateful month. We asked them: what is it like being a child of Chernobyl?

Olga Zakrevska is a professional photographer, running her own studio in Ukraine’s capital Kyiv. She was born on April 11, 1986 in Prypiat, a town nearest to the Chernobyl plant where many of the staff lived. Her father was a young nuclear energy expert.

“...after we moved away some parents would prevent their kids from playing with my brother and me, claiming that we were radioactive and contagious.”
“I lived in Prypiat for the first 15 days of my life. We left on April 26, 1986 and spent about a year staying with friends and family in Kyiv. I was tiny at the time and you could say I absorbed my mother’s anxieties and worries about our future. A year later we were given our own flat, which we were very grateful for. My father continued to travel to Chernobyl and work there.

“Chernobyl has been a part of my family’s story ever since I can remember. Our neighbors also worked at the plant. It was a part of our everyday life, a part of our relationship with the state. Chernobyl came up in the regular medical check-ups we had to have, the documents we had to file to receive assistance and aid.

“Right now I am trying to assess fully what Chernobyl meant for me. When I turned 25, I was suddenly struck by the fact that I grew up in the shadow of this event, this phenomenon. That’s why now I seek out other Chernobyl families, invite them to my photo studio. I photograph them, we talk. Many of my peers have their own families and kids now. We worry about our health, of course. When I was young the doctors kept saying: “We have no idea how the radiation might affect you.” Some things you can predict but many, well, you can’t.

“I feel that people, including those born in Prypiat, are still not ready to think and analyse what Chernobyl meant for us. Some would rather forget, push it to the back of their mind. Personally, I believe that since it happened, it is better to try and understand. Chernobyl traumatised us and through dealing with this trauma I think we can lead a better life in the future.

“Time heals but it never cures. Although I believe that some wounds can make you stronger. I think my peers and myself are strong people, perhaps stronger and more prepared to deal with life’s difficulties than others. One day our parents had to up and go, knowing they were never coming back. Afterwards we had to deal with prejudice: after we moved away some parents would prevent their kids from playing with my brother and I, claiming that we were radioactive and contagious.

“I have been photographing Chernobyl families for some time now and would like to turn this collection into a proper project one day. What’s more important for me personally though is to find my parents’ friends and colleagues, ones who worked at Chernobyl in 1986 and renew those bonds.”

Olexiy Starynets was born on April 26, 1986 in a small town a few kilometres south of the Ukrainian capital. Now he is a sports journalist living in Kyiv. Even though his birthday has always been a source of comments about a “Chernobyl baby”, he is optimistic about the future and believes in moving on.
“When I was little we moved a few times and at each new school I would have a medical check-up. I was always the healthiest!”

“My first memory of Chernobyl? My earliest birthday memory, of course! People always talked about it, at home and at school, since I was born on the day of the actual explosion. My mum and Grandma told me that they heard about the disaster on day one. At the maternity ward where my mum gave birth to me they would shut the windows to keep the radiation out and washed the floors more often. The explosion happened in the early hours of April 26. I was born around 6 pm that day.

“When I was little we moved a few times and at each new school I would have a medical check-up. I was always the healthiest! Of course, my parents never stopped thinking and worrying about effects of Chernobyl since we lived only 250 km away from it and often went closer than that!

“No, I don’t think of myself as a Chernobyl child. It hasn’t affected my health for one reason or another. I feel completely normal. I have not been to Prypiat, to the Chernobyl power plant that is. I am sure I will go one day just to see what it’s like.

“I am very positive about nuclear energy. If dealt with correctly, it is safe and environmentally sound. As far as I understand the accident at Chernobyl was caused by human error.
“Yes, of course Chernobyl is a part of our history but I don’t think about it too much. My friends always remember my birthday though!”

Yuri Vyshnevsky is also a journalist living in Kyiv. He was born on April 1, 1986. His father worked in the exclusion zone in the months after the accident.

“I feel that since a lot of countries don’t have sufficient natural resources in the 21st century nuclear energy is necessary.”

“My mum went to stay with my Grandma in Moldova after the accident and my Dad came to visit whenever he could. We mentioned Chernobyl occasionally but luckily it has not affected our family that much. We are all quite healthy though the environment in Ukraine is very polluted.

“Chernobyl is a massive part of our history. Ukraine became known in Europe in the worst possible way, we can’t forget that. There have been plenty of other events, though, which make me proud to be Ukrainian: the declaration of state independence, sporting victories of my compatriots like footballers from Dynamo Kyiv, boxing champions the Klitschko brothers and Ukrainian Olympians. However, all these positive things cannot make me forget about this huge environmental disaster, which harmed not just Ukraine but also other European countries.

“I don’t think of myself as a child of Chernobyl really. It hasn’t affected my health, luckily. But through my work I see kids whose parents have been ill or who are sick themselves. It is very sad.”
“I have never been to the exclusion zone but a lot of my friends have. Now it’s quite easy to go there on a guided tour, so the “exclusion” is really quite limited.

The science of hormesis tells us that a small exposure to a toxin can have a positive even stimulating effect on an organism. So while the negative close exposure toxic effects of Chernobyl were horrendous the long distance subtle exposure could have a positive life and immune enhancing effect. This is part of the principles of homeopathy were the effect of a large dose of a poison is reversed with a small doses of the toxin. This is known as the Arndt-Schultz principle of pharmacology taught in the IMUNE courses.


“Is nuclear power a good idea? I feel that since a lot of countries don’t have sufficient natural resources in the 21st century, nuclear energy is necessary. It’s important to be responsible with it though to prevent disasters which hurt humans and nature.”

Hormesis has proven one of the great principles of homeopathy that when it comes to poisons “Let Like Treat Like”.

Although skeptics of homeopathy may assume that homeopathic doses are still too small to have any biological action, such assumptions have also been proven wrong. The multi-disciplinary field of small dose effects is called "hormesis," and approximately 1,000 studies from a wide variety of scientific specialties have confirmed significant and sometimes substantial biological effects from extremely small doses of certain substances on certain biological systems.

http://www.downloads.imune.net/medicalbooks/Scientific%20Research%20In%20Homeopathy%202012.pdf

http://www.downloads.imune.net/medicalbooks/The%20Natural%20Repertory%20of%20Prof.%20Nelson%20-%20An%20In%20Depth%20Understanding%20of%20Nelsonian%20Homeopathy%201988.pdf
Victoria Angel (Rita born in late 1985 was a Chernobyl baby and now a world class body builder) has shown us the Hormesis effect. And helped us to understand that fear of toxins is unneeded in a world where a small exposure to toxins makes you stronger.
International Atomic Energy Agency on Chernobyl
Town of Pripyat official website
New Scientist journal on Chernobyl death toll

http://medicalexpose.org/
The Spirit of Hormesis

Let’s face it. Most “nootropics” don’t work well for youngish healthy individuals, at least in my experience. As my health problems disappeared, I naturally started to search for the best tools for enhancement and I realized everything that was highly effective fell into 2 categories. They either corrected a deficiency or worked by hormesis.

Hormesis is the best method for enhancement for people who are already healthy. Hormesis is the concept of introducing an acute stress to the body, in which case the body will have a reaction that will prep it for future stressors that are even stronger. By being prepped, the body can be shifted into a state of higher performance.

Vaccines work in this manner. You introduce a tiny dose of a pathogen and the body responds with developing immunity to an even bigger onslaught of that pathogen. When you introduce small stressors, the body will super-compensate and become stronger.
Exercise mainly works by hormesis as well, which is why it’s an effective enhancement tool for people who are already very healthy.

The American ethos, though, has a hard time digesting this concept and using it properly. We like the concept of becoming stronger but we lack the culture of moderation and the wisdom that less is more. We view hormesis as what doesn’t kill you makes you stronger.

In reality, what doesn’t *harm you too much* makes you stronger. We like to take things to the extreme, though. If something is good we’ll do more of it. Exercise is healthy? Great. Time to run marathons.

The dose used in hormesis must be carefully applied according to the individual’s initial condition. For example, someone who hasn’t exercised in years shouldn’t suddenly engage in exhaustive exercise. In the same vein, someone with a ‘leaky gut’ should not be exercising exhaustively or drinking alcohol because these things exacerbate such a condition. With hormesis, the dose is key. A little is a great and a lot is terrible.

The conditional nature of hormesis adds complexity and naturally humans don’t like this because we tend to view the world in a binary fashion, where things are either good or bad. If it’s good, we like it and if it’s not we don’t. A nuanced approach is missing here, where the answer isn’t “yes” or “no” but rather “it depends.”

The human body is a complex system that requires nuance more than less complex systems. By categorizing things clearly, nuance gets lost in the jungle of labels. By not truly accepting this idea that less is more, many bloggers and people tend to take things too far. If we don’t use hormesis properly it can cause more harm than good.

**Examples of Hormesis in Health**

- Cold Showers
- Fasting
- Protein Restriction
- Calorie Restriction
- Sun
- Interval exercise – sprints, weight lifting
- Using an oxygen tank- or breathing exercises
- Yoga
- Psychological stress
- Dual N-Back
- Meditation – has some aspects of it
- Alcohol
- Getting glycogen depletes
- Vaccines
- Herbal supplements – Adaptogens, Curcumin, Resveratrol, Berberine, Gynostemma, Grapeseed extract, etc..
- Vegetables, plant based-foods – plant toxins
- Methylene Blue
- LLLT
- Caffeine – alkaloids in general work by hormesis
- Ketosis
- Short term nutrient deficiency
- Very low doses of environmental toxins – even heavy metals. The problem is we’re exposed to them chronically often….
- Getting sick – I don’t recommend it for adults, but kids growing up have a better developed immune system when they play with germs.
Tips for Using Hormesis

- It’s better to have all the basic building blocks (i.e. proper diet and nutrition) before you start hormetic types of enhancements
- The dose is everything
- The proper dose can be different for different people in different circumstances
- Less is more
- Do not “stack”
- You must fully heal before taking the next dose
- Take breaks. Use different kinds of stressors during these breaks that stress different aspects of the body/mind.
- Do not use stressors to improve performance during or immediately after. Performance actually takes a dip right after the stimulus. Effects accrue over time, though.
- When you stop feeling an effect, up the dosage by a little.

http://www.scienceofdetox.com
When small minds attack
Natural Medicine IMUNE stands
Firm on the Bridge and Says
"You will NOT Pass"