This series of essays explores lessons and observations from fieldwork that might be of interest to the integrative medical community. In this context, the authors discuss "new" or less celebrated botanical medicines and unique healing practices that may contribute to the further development of contemporary integrative medical practices. Perhaps this column can facilitate an appreciation for our own roots and those of other cultures, before such ancient wisdom disappears forever.

POISON OR MEDICINE? A NOTE FROM THE FOREST

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Legend has it that Sir Walter Raleigh introduced a strange new arrow poison to the English court—Woorali, the Orinoco Indians called it, or "flying death." This strange black substance that coated the arrows of indigenous hunters in South America could kill the animals that were struck by the arrows—resulting in death in a few minutes in the case of birds, or 20 minutes in the case of large mammals. Asphyxia was the cause of death, as curare first relaxes then paralyses the voluntary muscles. This is caused by the effects of a powerful chemical, (+)-tubocurarine, in blocking nerve impulses to skeletal muscles at the myoneural junction. It is also said to produce a toxic action on blood vessels and a histamine-like effect.[1] Curiously, while the substance itself is toxic, the vapors given off during its preparation are not, and the animals it poisoned could be consumed without problem, as long as the toxin itself did not enter the blood system.

The first written documentation concerning the use of curare was by Pietro Martire d'Anghiera, an Italian priest in the court of Spain's Queen Isabella, writing in his book on the explorations of the New World *conquistadores*, *De Rebus Oceanis et Novo Orbe*.[2] There were many accounts of poisoned arrows and preparation of the poison in this volume. It has been suggested that at the time of the Conquest, poison tipped blowguns ranged from Central Mexico to Northern Bolivia.[3] In fact, it was Alexander Von Humboldt and Aimé Bonpland, traveling together in South America during 1799-1804 in search of botanical wonders, who were the first to witness and scientifically describe the preparation of curare. Von Humboldt brought curare back to Europe.[4] In the 1850s, Claude Bernard first described a localized paralytic action of curare. In the years that followed various discoveries were made about curare; for example that an animal poisoned with curare could be kept alive by artificial ventilation until recovery was complete.

Early preparations of curare were, curiously enough, categorized by the type of packaging they were made in—calabash curare, packed in a gourd; tube curare, packed in a bamboo stem; and pot curare, packed in a clay pot. The poison itself was a brown or black, shiny, resin-like substance with a bitter taste.[1] Recipes varied among tribes and ingredients were a closely guarded secret. Medical experiments were carried out with curare, but the lack of knowledge and standardization of the ingredients and preparation regimen kept it out of mainstream medical research. Enter Richard C. Gill, an American with a background in medicine.[4] A former resident of the Ecuadorian rainforest, he had become friendly with the local indigenous people, and studied their use of plants in healing. In 1932, he was diagnosed with multiple sclerosis and by 1934 was virtually paralyzed. His neurologist suggested that his muscle spasms might be treated if standardized supplies of curare were available. Hearing this, Gill arose from his sickbed and embarked on a training regimen to try and walk again, spending four years in the process. In 1938, he returned to the Ecuadorian forest, leading a large collecting team, walking while supported by a stick. That year he and his team returned with 12 kg of curare which was sent to the United States, most importantly with the first botanical specimens of the plant ingredient common to all of the curare preparations he studied. This plant was a vine in the moonseed family, the *Menispermaceae*. The dried, pressed plant specimens were delivered to Boris Krukoff, noted botanist at The New York Botanical Garden who was hard at work on the Curare problem and excitedly wrote that,

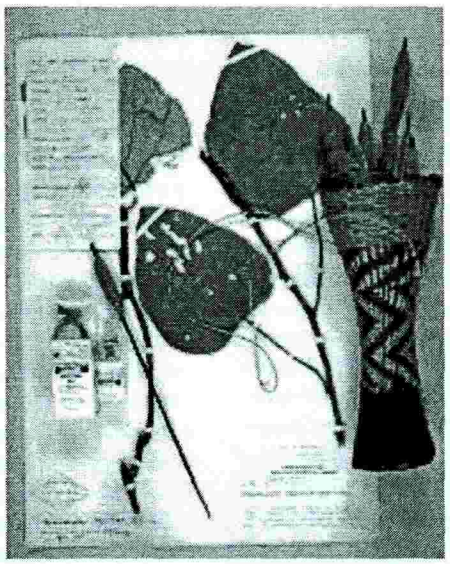
> "Now, through the courtesy of Mr. Richard C. Gill, we are able to examine specimens of the plant components of the Curare of the Canelos Indians of Ecuador...collected by Mr. Gill on the Gill-Merrill Ecuadorian Expedition in August to October, 1938, having been obtained in the Pacayacu-Sarayacu region, drained by the tributaries of Rio Pastaza in the Province of Napo-Pastaza. The collection is of unusual interest, since there appears to be no published record of the botanical identify of a single plant which the various Indian tribes of Ecuador use in preparing Curare."[5]

The New York Botanical Garden botanist identified the specimen as *Chondodendron tomentosum*, and reported that it seemed to be

the primary ingredient of many different curare mixtures. Once its identity was established, medical researchers could study the effects of the compounds in curare, which found numerous clinical applications over the years, including as a muscle relaxant in surgery, to control strychnine and tetanus-induced convulsions, as an adjunct in shock therapy, and diagnostic aid in myasthenia gravis.[1]

Walter Lewis and Memory Elvin-Lewis, in their wonderful new book, *Medical Botany: Plants Affecting Human Health*,[6] listed over one hundred different species of plants used to make blowgun dart poisons from South American plants. Of these, two plant families, the *Loganiaceae*—(the source of strychnos), and the *Menispermaceae*—(comprising dozens of species)—are said to provide the best curare. Beginning in the 1980's, two synthetic analogs of (+)-tubocurarine, atracurium and vecuronium, have replaced the natural substance in the practice of medicine.

The use of plant substances to poison the tips of arrows and darts is by no means restricted to South America. In Central Africa, there is a large vine that climbs to the top of the forest, bears three-parted leaves and curved pink or purple flowers. Its seeds are around 2 cm wide, kidney shaped, black-brown in color, shiny and extremely hard. The plant, known as *Physostigma venenosum*, has a long history of use as an arrow poison. It gained more notoriety as an ordeal poison, "...one of the most notorious trial by ordeal poisons in West Africa...."[7] The major alkaloid in this species, physostigmine, is used in ophthalmology, to improve neuromuscular impulse transmission (such as in the treatment of Myasthenia gravis), to treat poisonings with parasympatholytics (such as atropine, scopolamine, etc.) and in psychiatry (to treat anticholinergic syndromes such as hallucinations and alcoholic delirium).[7]



One of the original specimens of Chondodendron tomentosum collected by Richard Gill in the Ecuadorian Amazon; to the right of the specimen is a quiver of blowgun darts tipped with curare and to the left of the specimen is a sample of the contemporary pharmaceutical product. A single blowgun dart sits upon the plant specimen, with a tuft of kapock on one end tipped with curare on the other. Photo Courtesy of The New York Botanical Garden.

Nearly a decade ago, on a cold autumn night, I (MB) was cleaning out the closet in my home office, unpacking the boxes of indigenous artifacts that I had collected during my extended sojourn in the Amazon as a graduate student some 20 years before. I had been privileged to follow in the footsteps of my teacher, Professor Richard Evans Schultes, an intrepid Harvard professor, plant explorer and ethnobotanist who, beginning in the 1940s, spent many decades studying the indigenous use of plants in the Amazon Valley. As a specialist in psychoactive and poisonous plants, he trained his students to collect and appreciate the bioactive power of plants, and to collect and document the artifacts that were prepared from plants, along with the traditional botanical specimens themselves.

As most graduate students, I learned to do my best work at night, in the early hours of the morning when phones did not ring, classes were not held, and visitors did not come to one's door. To this day, I maintain the nocturnal habit, but on that particular night I had chosen to sort through and catalog some boxed materials, being too tired to put my full attention into a book I was working on. Holding a basket of curare darts in my hand that had been collected during one of my trips in the 1970s, I managed to stick myself in the hand while trying to organize the quiver. Just a small stick which, if done with a needle, would be barely noticeable--but in this case, with a curare dart! I thought about it for a few moments, suddenly realizing what I had managed to accomplish at 11:30 pm on a Saturday night, and immediately called the local poison control center. Reaching an understanding and helpful voice on the other end of the line, I explained that I had inadvertently stuck myself with a dart collected two decades before in the Amazon Valley, that probably contained a form of curare, a very toxic substance. "Well..." the voice said, "We don't usually get calls of this nature here at the poison control center. But I know someone that can help you figure this out—our specialist in this type of plant related poisoning is Dr. Michael Balick of The New York Botanical Garden, a world expert in these plant substances." "But," I protested, "this *is* Dr. Michael Balick of The New York Botanical Garden!" A protracted silence on the other end, which seemed like hours, but was probably only a minute or so, while my helpful new friend tried to figure out the next steps of this puzzle. "OK" I replied, to break the silence, "but what do I do now?" She then asked me to describe my symptoms, which as I recall at the time included a very dry mouth, lightheadedness, and a strange sense of doom, knowing well the literature on curare and the progression of its toxicity. As described in a modern web site (www.botgard.ucla.edu/html/ botanytextbooks/economic botany/curare/):

> "The horror of curare poisoning is that the victim is very much awake and aware of what is happening until the loss of consciousness. Consequently, the victim can feel the progressive paralysis but cannot do anything to call out or gesture. If artificial respiration is performed throughout the ordeal, the victim will recover and have no ill effects."

Not very reassuring at all. I did remember that Gill had reported somewhere that rubbing the wound with rock salt was a form of antidote to the poisonous effects of curare as he noted,

"...any Indian who receives a wound inflicted by a curare-laden weapon—which incidentally is a rare event—promptly incises the wound, ligates the area if it anatomically possible, and smears ordinary trade-goods rock salt into the puncture. He also drinks a copious amount of concentrated salt solution and, unless the mechanical wound caused by the weapon itself kills him, he usually survives the effects of the curare."[8]

So rub I did, immediately, while I spoke on the phone with the poison control person. "Get yourself to the hospital now!" was the command that suddenly came from the telephone and aroused me from my daze. After I called our local village ambulance, my next call was to the major county hospital emergency room, seeking to provide information that I might not able to offer after the twenty or so minutes it would take to get there. "I have a curare wound and I am coming in on the town ambulance" I said with a panicked voice to the resident in charge of the emergency room. "Right, but not tonight" she responded as she hung up the telephone, leaving me no option except to call a smaller but closer ER. Upon arrival to that hospital, I remember laying on the gurney, next to the several cases that were in the triage area—the car accident, the knife stabbing, the electrical shock, and, the Amazon curare wound. Guess who got the immediate interest of the resident at that ER? While everyone else waited, I was hooked up to the appropriate equipment and treated. "Never saw a curare dart wound up here in Westchester County" the young physician told me as I was given oxygen. "You are a very interesting case." "Thanks," I murmured gratefully. The next morning it was clear that the effects of the poison, if any, had passed, and I was free to go home—more present to the wisdom of keeping such toxins in my closet.

Poisons are an interesting group of plant compounds, many thought to be developed as defense mechanisms, as the plant fights its evolutionary battles against predators and infectious agents. Only the strongest survive, and thus the compounds that plants have developed are complex and powerful. Each year, poison control centers field millions of calls from patients and their physicians who fear that something toxic has been ingested.[9] Among the top five substances listed as the most common poison exposures plants are rated fourth. The first four (in order of greatest to least) are: cleaning substances, analgesics, cosmetic and personal care products, plants and foreign bodies.[9] The following plants are responsible for the greatest number of calls to poison information centers (the top 10 in order of their frequency from highest to lowest): *Spathyphyllum spp., Philodendron spp., Euphorbia pulcherrima, Ilex spp., Phytolacca americana, Ficus spp. Toxicodendron radicans, Dieffenbachia spp. Crassula spp*, and *Epipremnum aureum*.

According to Lewis Nelson, MD, Director, Fellowship in Medical Toxicology at New York City Poison Control Center, the most frequently reported "plant poisonings" received by his institution in New York City are by the members of the Araceae family—including the arums and dumbcanes, known to be rich in irritating oxylate crystals. He noted that that two compounds of plant origin, digoxin and heroin are the most common plant related toxicity seen by his office, and that there have been several deaths during recent years from herbal preparations used as laxatives that were contaminated with digitalis leaves—probably mistaken for psyllium leaves. The most intentionally ingested plant that results in poisoning, he reported, is *Datura stramonium*, taken internally in an attempt to hallucinate.

However, there is a more positive side to these powerful compounds, in that once they have been studied and standardized, they are the basis for many therapeutic compounds. According to Dr Nelson, "There are many clinically used plant "toxins." Morphine may represent our most commonly used medicine that is itself toxic in moderate dose. Atropine, a common murder weapon during Victorian times has moved to the fore. An immensely useful medicine against certain forms of nerve agents, it is now being stockpiled by the literal gallon." (L. Nelson, personal communication, November 2003).

Even Paracelsus (1493-1541), a great physician of the 15th Century and "Father of Pharmacology" observed that "all substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."[10] Paracelsus described quite aptly our general understanding of how most drugs create their beneficial effects and the means by which they become lethal. Through increasing graded doses, the therapeutic effects become magnified and eventually the substance crosses the threshold of benefit by becoming overly concentrated. The over-concentration of the drug creates its toxic effect either pharmacologically, pathologically or by creating genetic damage. An example of pharmacologic toxicity is excessive sleepiness caused by the use of a benzodiazepine such as diazepam (Valium). This is usually an effect that can be reversed with reducing or removing the drug. An example of a pathologic toxicity is liver injury (hepatotoxicity) caused by an overdose of acetaminophen (Tylenol). Whereas an example of genotoxicity or a gene damaging effect is the example of nitrogen mustard exposure. Nitrogen mustard is carcinogenic and exerts its effect by generating the negative biotransformation of the genetic material within the tissue. It is an electron thirsty chemical structure (electrophilic). The nitrogen mustard molecule gravitates towards the electron rich DNA of cells and chemically binds to it. The DNA becomes damaged. Tissues that are faster growing and exposed to nitrogen mustard are more susceptible to DNA damage. If the dose is right, the most rapidly dividing cells die. This is the principle by which the nitrogen mustards are used as chemotherapy agents. If the dose is too high other, more slowly dividing normal cells, become damaged and can become transformed into malignant cells. The premise of a linear dose curve is that the smallest doses of any substance have no effect, succeeding (increasing) doses have some effect—generally therapeutic—and, finally with super saturation, toxic effects are observed.

However, is everything in nature that we consider a poison really good for us at the proper (lower) dose? Until recently, thinking of environmental toxins such as dioxin, ionizing radiation, mercury, or pesticides my (RL) medical answer would be no! It turns out that I may need to reconsider this response. Over the last fifteen years, a toxicologist at the University of Massachusetts at Amerherst, Edward Calabrese, evaluated studies of the effects of

toxins and concluded that some toxins actually cause beneficial effects in very tiny doses. He observed that the dose response curve in these substances seem to have an observed benefit at a minute concentration, and a toxic effect in other concentrations. He compiled examples of environmental hazards that at low doses produce beneficial effects, thus challenging established theories of what is harmful. One example that illustrates this theory is dioxin, known to be one of the most lethal compounds on Earth. A rat exposed to 10 parts per billion of dioxin (the equivalent of 7 teaspoons diluted by enough water to fill an Olympic sized swimming pool will have a 50% chance of developing liver cancer.[11] Yet smaller concentrations fed to rats have been found to inhibit tumors and now this finding has become the focus of much study; modified dioxins are now being investigated as anti cancer agents. This concept of tiny doses creating a beneficial effect is known as hormesis.

The concept of hormesis, first described in 1888 by a German pharmacologist, Hugo Schultz, was stimulated by the observation that small doses of poisonous substances seemed to stimulate the growth of yeast. His observations were also observed in animal studies of drugs at very low doses performed by a German physician Rudolph Arndt. The shared observations became known as the Arndt-Shulz law. However, because Arndt was also a proponent of homeopathy, beginning around the 1920's the law lost credibility. Unlike homeopathy, substances described as "hormetic" involve concentrations at least 10,000 times higher than any homeopathic constituent; nevertheless, this detail was overlooked and the law remained discredited until Calabrese brought renewed interest to the theory.

In an article published in 1998, Edward Calabrese and his associate Linda Baldwin evaluated how frequently chemical hormesis occurred in medical literature. Four thousand publications were reviewed and of these, 350 studies were determined to have evidence of hormesis. Some of the findings included studies documenting plants dosed with herbicides growing more robustly, bacteria thriving in the presence of very tiny amounts of antibiotics, insects exposed to pesticides living longer, and rats fed with saccharine developing fewer tumors.

In a more recent analysis of hormesis published in February 2003 in *Toxicological Sciences*,[12] Calabrese evaluated the frequency of occurrence of hormesis in 195 publications. His inclusion criteria required that studies demonstrate dose response curves at least two doses below the no adverse effect level (NOEL) and a control. He reported that "hormetic dose-response curves outnumbered curves showing no effect at the lowest doses by 2.5 to 1."[11]

The likely explanation for this effect postulated by proponents of hormesis is that small doses of harmful substances stimulate a beneficial response that enhances normal function and provides resilience to the organism against subsequent stresses. The theory remains controversial. There are many other examples in environmental toxicology which do not show the biphasic hormetic response, (such as atrazine and bisphenol-A). Calabrese and other proponents suggest that the situation of hormetic response may not be completely uniform for all environmental toxins. Those challenging his hypothesis feel that the data analyzed—particularly the epidemiological studies which are postulated to be hormetic, may actually represent combined effects of several different biological or disease processes that result in a hormetic dose-response relationship.[13]

What are the implications of this theory to clinical medicine? Does chemical hormesis have applications in clinical practice? In order to address this question one must ask, do clinical examples exist demonstrating this biphasic effect? And if there are examples, are the phenomenon predictable in enough individuals to make them useful in clinical practice? If we think of natural physiological processes such as hormone regulation and pheromonic influences the concept of microdosing is not such a far out idea. Thyroid hormone is present at only one part per billion yet this is enough to regulate our entire body's processes.

However the most significant aspect of hormesis lies in its concept of non-linearity—not only does it advocate that minute doses have effects, but that sandwiched in between the favorable "beneficial effect" and the "no adverse effect level" (one level below when a toxic effect occurs) is an "ineffective zone" or null zone. This is a classic "U"- shaped curve. The potential for benefit in the clinical arena seems intriguing if, in fact U shape phenomena are reproducible in medicine. Perhaps we have been using the analogy to what could be described as a pharmacologic "hammer" in the current dosing schedules of some medications. Undoubtedly, if this effect is to be of use we will need more research to clarify its clinical applicability.

Jumping from the esoteric to the more utilitarian, a commonly acknowledged toxin, botulina, for which all of us have received vaccinations (tetanus) in childhood, serves as a recent 21st century example of a poison re-made into medicine. It is now used to treat a number of medical ailments that arise from unwanted intractable muscle spasms—by "poisoning" the undesired muscle activity; bringing relief to those who had few medical options before this was available. On the other hand, for a much less serious circumstance, botulina toxin is used cosmetically to "smooth" °out undesirable wrinkles. So as it is with other things in life—one person's poison may be another's medicine. As we ring in the New Year, once more, it seems that what is old becomes new again.

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