

Arthur E. Guedel Memorial Anesthesia Center

Herbalists

By Merlin Larson, M.D.

Acoveted possession of the Guedel Museum are the artifacts collected by Richard and Ruth Gill on their arduous journey into the rain forest of Ecuador to collect curare paste. Richard Gill was an amateur ethnobiologist, and he collected many other indigenous medicinal plants in addition to curare. Upon their return to the United States, these plants were offered to various pharmaceutical firms for chemical analysis and clinical trials for various medical ailments ranging from dysentery to rheumatism. To Gill's dismay, there was no interest in his botanical collection and, except for the curare paste, it was eventually discarded.

The field notes written by Richard Gill are the property of the Guedel Museum, and these notes list his botanical collection in detail along with the indigenous



Figure 1. Gill's notes are property of the Guedel Museum and are used here with their permission. Each plant is carefully described along with the location where it grows and indications for how it was used by the native tribes. Ever the optimist, Gill describes this plant (Huito) as able to grow hair.

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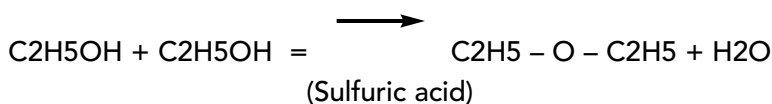
remedies for which each plant was used. Over 70 specimens were carefully catalogued and brought back to the United States for analysis and testing.

As such, extending the theme surrounding the use of plants in medicine seems like a natural topic for the Guedel section of this *Bulletin*. Recent reviews have highlighted the dangers inherent in the use of herbal remedies prior to anesthesia and surgery. It is somewhat ironic, therefore, that anesthesiology has its foundation in the plant kingdom and, in that sense, it can be considered to be herbal therapy, at least in the historical sense. Indeed, the origins of anesthetic agents are deeply embedded in botany.

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Ether

The botanical source of ether is the grape plant, *Vitis vinifera*. Valerius Cordus described the production of ether from distilled grape wine in 1540. The bulk of Cordus' classic treatise on ether is a description of how to produce sulfuric acid or, to use his name for it, oil of vitriol. Sulfuric acid is simply a dehydrating agent that removes one molecule of water from two alcohol molecules. Ether is the end product of heating alcohol and sulfuric acid, but there is no sulfur in the ether molecule. Diethyl ether is often referred to as sulfuric ether because of the synthetic method that requires sulfuric acid, but the latter compound is only a catalyst and is unchanged in the reaction. The production of ether takes place while heating concentrated alcohol in the following manner:



Highly concentrated alcohol was distilled from dilute wine in Europe as early as the 13th century. The word *alcohol* is an Arabic word whose roots are vague but imply the process of distillation. The distillation process was brought to Europe from Asia Minor during the Middle Ages. Sixty-five years after Cordus described ether, Paracelsus noted ether's soporific effect on chickens, but it was nearly 250 years later when it became widely used as a successful inhalation anesthetic. Commercially sold diethyl alcohol today is a by-product of the manufacture of organic compounds and is not obtained from the fermentation of wine or other plants.



Richard Gill at his hacienda in Ecuador, circa 1938.
Courtesy of the Guedel Museum.

Morphine

Papaverum somniferum has been the source of widespread personal tragedy, but it also ranks among the most useful medicinal plants known to mankind. Opium is derived from *Papaverum somniferum*, a plant indigenous to Asia Minor, and it has been part of medical therapy for over 3,000 years. Opioid adjuvants have become an integral element in contemporary anesthetic practice. Morphine is still one of the most widely used opioids and was isolated from opium by Serturmer in 1803. Its beneficial effects on the conduct of general anesthesia were first noted by Claude Bernard and confirmed by others. One hundred years after it was isolated from the juice of the yellow poppy, it still is in common use today. No processing of opium is required to produce its physiologic effects because opium is roughly 10 percent morphine.

Cocaine

The first local anesthetic, cocaine, is derived from *Erythroxilum coca*, a shrub-like plant that is indigenous to the South American Andes. An unremarkable plant in appearance, it contains 150 alkaloids in its leaves and has spurned decades of conflict in Ecuador, Bolivia, Columbia and Peru. The most active alkaloid, cocaine, was isolated from the leaves in 1860 by Albert Niemann and its local anesthetic properties were noted by von Anrepp in 1880. Regional anesthesia was launched on September 15, 1884, when Carl Koller and his

assistant, Joseph Brettauer, demonstrated cocaine's remarkable analgesic effect during surgery on the eye. The first neuraxial blocks were performed with cocaine injections into either the epidural or intrathecal spaces. Frolich and Loewi discovered the stimulating effect of cocaine on the sympathetic nervous system in 1910.

Scopolamine and Atropine

Scopolamine was commonly used as premedication during the era of ether anesthesia. The drug was isolated from *Atropa mandragora* by Lange in 1814. Mandrake or mandragora was the primary ingredient in ancient anesthetic potions and, because the plant contains high concentrations of scopolamine, it is likely that the effect of the plant was primarily due to this agent. Several plants contain both scopolamine and atropine; the latter drug was isolated from *Atropa belladonna* by Mein in 1831. In the early 20th century, scopolamine was used most commonly as an adjunct to morphine prior to surgery, and the combination usually produced a tranquil and sedated patient who very often would not remember the immediate preoperative period or the mask induction. The same combination was also used for labor analgesia in a technique known as twilight sleep. Scopolamine is also an antiemetic and is occasionally used today for that purpose in a transdermal delivery form.

Ephedrine

Ephedrine and epinephrine were the first sympathomimetic amines administered during anesthesia. Ephedrine was isolated from a spiny bush, *Ephedra sinica*, in the first part of the 20th century. It is now synthesized and prepared almost exclusively for use by anesthesiologists. There are several hundred *Ephedra* species, but only a few contain pharmaceutically active alkaloids. *Ephedra sinica* has a total alkaloid content of about 2 percent. Ephedrine constitutes about half of the alkaloid content, with the remainder consisting of pseudoephedrine. The dried plant, known as Ma Huang in traditional Chinese medicine, has been used as an herbal remedy for over 5,000 years. Ma Huang's prominent place in herbal therapy was curtailed in 2003 when the FDA banned the uncontrolled sale of dietary supplements containing *Ephedra*, citing an unreasonable risk of illness or injury. Its first use in anesthesia was to treat hypotension resulting from spinal anesthesia, and it is still used occasionally for the same purpose.

Curare

Chondrodendrum tomentosum is the representative plant of the Guedel Museum. Although Richard Gill brought back the gluey black paste used by the Jivaro and Canelos Indians to paint their poison darts, the essential ingredient that

was mixed with several others was the alkaloid (curare) present in the bark of the vine, *Chondrodendrum tomentosum*. Curare is found in other plants, notably *Strychnos toxifera*, but the Gill preparation was obtained from the bark of the *Chondrodendrum* species. Gill seemed almost desperate to find a use for his plant preparations. Sadly, initial experiments with curare were not encouraging, and even this indigenous concoction seemed to have no role to play in Western medicine at the time. The drug had a circuitous route before it entered the anesthesiologist's drug cabinet. The complete account has been told several times and is widely disseminated in the anesthesia literature. The Web site for the National Tropical Botanical Garden (www.ntbg.org) has several representative photographs of the vine. The plant must be observed in the primary rain forest of the Amazon Basin, as it has not reestablished itself in the secondary forests.

Physostigmine

Physostigmine is the chief alkaloid of the Calabar bean (*Physostigma venenosum*), which is native to West Africa and was employed there by native tribes in their trials of individuals suspected of witchcraft. Calabar bean extracts have a pronounced effect on the central nervous system, beginning with excitation and ending with depression and respiratory failure. The pure alkaloid was isolated by Jobst and Hesse in 1864 and named physostigmine. Dr. Mary Walker observed that it was an antidote to curare in 1934. The essential moiety is the methyl carbamate of a substituted phenol. The molecule was altered to produce the more popular drug Neostigmine, an alteration that prevented penetration of the blood brain barrier.

The following scenario might be a typical anesthetic given in the first half of the 20th century. Prior to arrival in the OR, the patient would have received an intramuscular injection of scopolamine (*Atropa mandragora*) and morphine (*Papaverum somniferum*). Anesthetic induction would commence with liquid ether (*Vitis vinifera*) applied to a handkerchief or gauge covering the mouth and nose. Cocaine (*Erythroxilim coca*) might be injected intrathecally or into the wound prior to incision. Hypotension might be treated by intramuscular injection of ephedrine (*Ephedra sinica*). With the introduction of curare (*Chondrodendrum tomentosum*) by Griffith and Johnson in 1942, this drug might be given intravenously to promote muscular relaxation. The drug would be injected directly into the vein and usually not through an indwelling intravenous catheter. Physostigmine (*Physostigma venenosum*) and atropine (*Atropa belladonna*, *Datura stramonium*) would similarly be given at the end of the case to reverse the effect of curare. Small doses of morphine (*Papaverum somniferum*) would be administered to alleviate pain on emergence. Anesthetic similar to this one are recorded in Gwathmey's and Lundy's textbooks, dating from the

Guedel (cont'd)

first half of the 20th century. Other plant-derived products that were used during that era include strychnine (*Strychnos toxifera*), tropococaine (*Erythroxilim coca*), theophylline (*Camellia sinensis* or “tea”) and picrotoxin (*Anamirta cocculus*).

Although scopolamine, atropine, and morphine are still in use today, the other drugs have been engineered to provide drugs with less toxicity and more favorable pharmacokinetics. Cocaine was replaced by procaine, dibucaine, and tetracaine in the first half of the 20th century. These three drugs are all para-aminobenzoic acid esters like cocaine. Lidocaine, the first amide local anesthetic, was discovered in 1956 and was originally derived from gramine, an alkaloid present in the barley plant (*Hordeum vulgare*). The amide local anesthetics were chemically modified to produce our modern drugs, bupivacaine and ropivacaine. Curare was displaced by gallamine, pancuronium, and rocuronium, but the structural similarity to the original alkaloid is still present in the modern drugs.

No single country or continent can claim these agents. Two came from South America, one from Asia Minor, one from China, one from Africa, and the others are found in several continents. Selecting these unique plant products from among the 422,000 total plant species in the world was the combined effort of thousands of individuals, including the indigenous peoples who discovered their effects on the body and in animals, the scientists who isolated and characterized the pure drugs, and the clinicians who were courageous enough to use them for the first time in human subjects. Over centuries of study, the pharmacological activities of these few plants were combined to produce a safe anesthetic. Regrettably, each piece of work was too small to be noticed by the committees that designate the major scientific awards, but the end product—modern anesthesia—is among the most remarkable medical discoveries of all time and has provided untold benefits to mankind.

References are available on request. Except for the Web site for the National Tropical Botanical Garden listed above, the best site to view images of these plants is <http://medphoto.wellcome.ac.uk/>.

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