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The Legacy of Atropos, the Fate Who Cut the Thread of Life

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In the days when no anesthetics were known, when the wounded or diseased must suffer the tortures of amputation, or the rough operations known in those days, with no relief till sheer pain should either kill or produce unconsciousness—here was a plant whose wonderful properties alone had the gift of showing mercy! Here was the ancient anaesthetic of the world, probably discovered by chance by the very witches who dropped its root into their bubbling pots for wicked incantation, and perhaps fell asleep as they inhaled its fumes or partook of their own magic potions. Here was a discovery indeed!¹

ANESTHESIOLOGISTS are familiar, at least historically, with the technique of "twilight sleep" used at the beginning of the 20th century, but the current use of anticholinergic agents as antagonists of the side effects of anesthetic and anticholinesterase agents is much more familiar. There was a time, however, when the botanical precursors of these modern drugs, *Atropa mandragora* (*A. mandragora*) and *Atropa belladonna* (*A. belladonna*), were the state of the art in pain relief. Alone, or in combination with other atropine-containing herbals such as henbane (*Hyoscyamus niger*) or hemlock (*Conium*), they were used as anodyne, soporific, and hallucinogenic agents. This article examines the medical use of these naturally occurring anticholinergic agents from ancient to modern times.

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Etymology

A. mandragora (also called love apple, devil's apple, mandrake, or *mandragora officinarum*), native to the Mediterranean and southern Europe, is a common plant throughout the Middle East. *Atropa*, found in the words atropine, *Atropa mandragora*, and *Atropa belladonna*, is derived from Atropos, the eldest of the Fates, whose duty it was to cut the thread of life^{2,3} (fig. 1).^{4,5} The derivation of the words *mandragora* and *mandrake* is less uncertain. The words may be a variation of the Greek *Mandragoritis*, an alternate name for Venus, or a compound of the Sanskrit *mandros* (sleep) and *agora* (object or substance). That the Greeks were acquainted with the dangerous properties of the *A. mandragora* root was shown by an alternate name, *Circeium*, derived from Circe, the sorceress who changed Odysseus's men into swine and who was celebrated for her knowledge of magic and venomous herbs.

A. belladonna (also called belladonna, deadly nightshade, or witch's berry), from which atropine (dl-hyoscyamine) and scopolamine (l-hyoscine) are derived, also was associated with Hecate, the Greek goddess of the underworld, night, and witchcraft. The term *belladonna* is typically translated as beautiful lady, as originally mentioned by Mattioli in 1554. Commonly thought to have been used as a cosmetic, a mydriatic, and an aphrodisiac agent in the sixteenth and seventeenth centuries, there is little evidence of the use of belladonna as a cosmetic anywhere other than Venice. In old Italian, *donna* is more properly translated as mistress or lady. The *bella donna* may have been a magical or beautiful lady (or spirit) of the forest, and the term may have been used euphemistically as a substitute for witch, suggesting an association with potions and herbalism. In the late Medieval period, servants too poor to have access to real doctors had to satisfy themselves with the potions prepared by a magician or witch, the *buona donna*.⁶

Establishment of Western Medical Herbalism

Theophrastus (370–285 before the common era [BCE]), a student of Plato (ca. 428–348 BCE) and Aristotle (384–322 BCE), classified plants and noted their medicinal properties. In contrast to earlier Egyptian, Chinese, and Indian writings that described combinations of plants or remedies with a single name, Theophrastus classified and evaluated single plant remedies such as *A. mandragora*⁷: “The leaf of (mandrake), they say, used with meal, is useful for wounds, and the root for erysipelas, when scraped and steeped in vinegar, and also for gout, for sleeplessness and for love potions.”⁸ It is clear that he believed that the leaf and the root of *A. mandragora* had multiple therapeutic benefits.

In conjunction with the administration of mandrake wine, the Greek herbalist Dioscorides (ca. 40–90 of the common era [CE]) used the word anesthesia for the first time: “Using a cyathus† of it for such as cannot sleep, or are grievously pained, and upon whom being cut, or cauterized they wish to make a *not-feeling pain*.‡”¹² Three times in this same passage, Dioscorides pointed out that when physicians are about to cut or burn a patient, they should give him the wine of mandrake to cause insensibility, an idea viewed so positively by subsequent admirers that it seemed nothing short of divinely inspired (fig. 2).^{13,14}

As a well-traveled military physician, Dioscorides gathered a great deal of information about mandrake, which he recorded in *De Materia Medica*, including compre-



THE THREE FATES.—Thumann.

Fig. 1. The Fates: Clotho (the Spinner), Lachesis (the Apportioner), and Atropos (the Inflexible) were birth spirits who visited a newborn child and determined what his portion in life would be. Clotho, the youngest, spun the thread of life, in which the bright and dark lines were intermingled. Lachesis, the second, twisted it, and under her fingers, it was alternately strong then weak. Atropos, the third sister, armed with a huge pair of shears, cut the thread of life. “They also knew, but seldom revealed, what would be the fate of each Olympian god. Even Zeus feared them for that reason.”⁵ (Illustration by Thumann, in Guerber, American Book Company, 1893; quote from Graves.)

† In ancient Greece, the cyathus was a wine ladle, used as a server from a larger vessel, and its liquid measure was equal to one twelfth of a sextarius, ≈42 ml or 1.5 oz.

‡ Goodyear’s “Englished” translation of anesthesia, as used by Dioscorides. Similar translations such as “insensibility to pain” and “without . . . feeling pain” have been obtained from contemporaneous texts of other authors.^{9,10} The Greek “anaesthesia” (insensibility) is from a- (without) + aisthesis (perception), as distinct from anodyne, a pain-relieving remedy, derived from a- (without) + odune (pain).¹¹

§ An ancient Greek coin or weight equal to one sixth of a drachma. From the Latin obolus and Greek obolos (obelos), literally, “spit,” which also meant nail; nails were used as money, with six of them making a handful (drachmē).

|| A fermented or unfermented beverage of honey and water (from the Greek meli [honey] + kraton [from kerannynai—to mix]).

Form of hellebore, a poisonous herb of the genus helleborus or veratrum, containing alkaloids that may have been used variously as cardiac and respiratory depressant agents.

hensive descriptions of the preparation, expected benefits and toxic side effects of the plants:

Ye juice being drank ye muchness of ye quantity of 2 Oboli§ with Melicrate,|| doth expel upward Phlegm, and black choler, as Eleebore# doth, but being too much drank it drives out ye life . . . and being put up into ye seat for a suppository, it causeth sleep . . . Ye wine of ye bark of ye root is prepared without



Fig. 2. Dioscorides, seated in a chair, receives the mandrake from Euresis, the goddess of discovery. Immediately beneath the mandrake, a dog is rearing itself on its hindquarters, in *extremis* after the retrieval of the root. (Illustration in Thompson, from a miniature of an engraving in Lambecius, after the original in the Greek "Manuscript Anicia" of Dioscorides, in Venice.)

seething but you must cast in 3 pounds into a Metreta** of sweet wine, and that there be given of it 3 Cyathi to such as shall be cut, or cauterized, as is aforesaid. For they do not apprehend the pain, because they are overborn with dead sleep . . . but used too much they make men speechless . . . Physicians also, use this, when they are about to cut, or cauterize.¹²

Despite the care Dioscorides took to describe the medicinal uses of plants and to caution the ignorant, expectations of the public also were influenced by those who promoted ritualistic gathering of the plant. One of the most consistent stories used to justify ritualistic mandrake gathering was that of the dreadful shriek the mandrake produced when taken from the earth and the subsequent death of the person who had the presumption to drag the root from its bed. The mandrake, therefore, was ob-

** An ancient Greek liquid measure, equivalent to approximately nine gallons.

tained by fastening the plant to the tail of a dog, who drew the root from the ground. Theophrastus himself fell victim to this falsehood. He described the special precautions necessary for the collection of the mandrake, such as tracing a circle three times around the plant with a sword and cutting the plant while facing west. Pliny the Elder (23–79 CE) also advised keeping to the windward to avoid the foul stench of the uprooted plant.

How effective the ancient anodyne agents were has been a matter of some controversy. If Dioscorides observed the efficacy of such preparations, why were they not used more often? Part of the answer may be embedded in the Hippocratic oath itself, which discouraged the practice of surgery by physicians, including "cutting even for the stone." The opening of abscesses, the use of cautery, the setting of fractures, and the reduction of dislocations, however, were not considered surgery. Suitable drugs such as alcohol and beer in Pharaonic Egypt, opium imported from Cyprus, and possibly hemp seed (*cannabis*) were available for producing major pain relief, if not genuine surgical anesthesia, in the second millennium BCE.¹⁰

The Early and Late Medieval Period and the Renaissance

The Saracens conquered Alexandria in 640 CE. By 711 CE, they were patrons of learning, translating Greek texts, including the ancient herbals, into Syriac and spreading this knowledge throughout the East. Avicenna (Abu Ali Hussain ibn Abdullah ibn Sina, 980–1037 CE) wrote his *Canon of Medicine* in the early eleventh century. In it, he recognized the medical usefulness of opium, henbane and mandrake¹⁵:

If it is desirable to procure a deeply unconscious state, so as to enable the pain to be borne . . . administer fumitory opium, hyoscyamus (half dram dose of each) . . . Add this to the wine, and take as much as is necessary for the purpose. Or boil black hyoscyamus in water, with mandragora bark, until it becomes red, and then add this to the wine.

Western monks collected medicinal recipes and cultivated herbs during the Early Medieval Period (500–950 CE, The Dark Ages). Nonetheless, even as medical studies and practice were becoming more widespread in monastic circles, the Council of Clermont (1130 CE) forbade the practice of medicine by the monks, and the Council of Tours (1163 CE) clarified this proscription with "Ecclesia abhorret a sanguine" ("the Church does not shed blood"). The practice of surgery was effectively taken out of the hands of physicians, because most physicians were also members of the clergy. The

only exception was in Italy and southern France, where the secular tradition still held, and some physicians continued to practice the art of surgery.¹⁶ They further incorporated into their practice a knowledge of herbalism acquired from Islamic scholars, who preserved such information after the fall of Rome and throughout the Crusades. This information entered Europe principally *via* Salerno, an important trade center on the southwest coast of Italy. Salerno thus was a geographic, political, and philosophical crossroads for herbal lore from Greco-Roman tradition, monastic medicine, and Jewish-Arabic and Oriental practices of the Middle East and northern Africa.¹⁷ Those who cared for the sick may have had ready access to secular reference works, which were no problem to obtain along the trade routes.¹⁸

It was because of this secular view that surgery could remain within the doctor's purview and include concepts of pain relief and unconsciousness.¹⁷ *Practica Chirurgiae*, written in 1170 CE by the surgeon Roger Frugardi (Roger of Salerno), mentions a sponge soaked in "narcotics" and held to the patient's nose. Hugh of Lucca (ca. 1160–1252 CE) prepared such a sleeping sponge according to a prescription later described by Theodoric of Cervia (ca. 1205–1296 CE) as containing opium, the juice of unripe mulberry, hyoscyamus, spurge flax, leaves of mandragora, ivy, climbing ivy, lettuce seed, lapathum seed, and hemlock.¹⁹ The description of the soporific sponge of Theodoric survived through the Renaissance, largely because of Guy de Chauliac's (1300–1367 CE) *The Grand Surgery* and the clinical practices of Hans von Gersdorff (c. 1519 CE) and Giambattista della Porta (1535–1615 CE), who used essentially the same formula. The herbalist William Turner (1510–1568 CE) described the "forgetful and sleepish drowsiness" after the ingestion of a potion containing mandragora root and the pragmatic warning "they that smell too much of the apples, become dumb."²⁰

The soporific sponge of the Salernitan surgeons and their successors contained varying mixtures of opium (as the primary ingredient) with henbane, nightshade, mandrake, and hemlock as secondary ingredients, but how effective was it? Baur cast doubt on its efficacy in 1927 when she concocted the mixture from locally purchased herbs, moistened a sponge, and found that guinea pigs would neither become stuporous nor anesthetized when placed in a bell jar with the sponge.²¹ In their attempt to study rat responses after duplicating the soporific sponge, Infusino *et al.* found that only

three of five rats became even slightly sedated.²² Armstrong Davison claimed that the soporific sponge is one of many examples that show how much magic and superstition were a part of therapeutics in the early Middle Ages.²³ The first physician to devote his practice to the administration of anesthetic agents, John Snow (1813–1858 CE), noted that mandrake can cause unconsciousness, especially after intoxication with the drug.²⁴ Moreover, in 1888 Benjamin Ward Richardson reported his effort at producing mandragora wine, including its lack of efficacy if prepared as a tincture "with strong alcohol." He noted, however, that "the active principle of mandragora is most soluble in water, as is also the active principle of atropa belladonna," and went on to state:

The effects produced were those of narcotism, dilatation of the pupil, paralysis of motion and sensation, excitement during the stage of recovery, if the dose were not fatal, and sleep and paralysis if the dose were too potent. The action was found to extend to all classes of animals.

He specifically reported pigeons and rabbits, and noted that "the heart . . . continued in action longer than any other part, and indeed, was found to be pulsating after the respiration had for many minutes ceased." He concluded, "The whole of the facts indeed lead clearly to the acceptance of the belief that the medicinal use of mandragora in ancient times has been correctly recorded. The wine of mandragora is a general anesthetic of the most potent quality." It also seemed in keeping with contemporaneous medical thought regarding the heart's vital function in survival to believe that the routine use of this preparation would confer protection from the adverse effects of anesthetics because:

. . . from the circumstance that the heart continues to beat after the respiration has ceased, we may infer that as a general anaesthetic the alkaloid might, under necessity, be once more employed, as in the olden time, to deaden the pain of a surgical operation, and that too with comparatively little risk to life.²⁵

In more recent times, atropine toxicity therapy was used in psychiatric treatment. With a routine dose of 30–50 mg atropine, recovery from coma was noted as "spontaneous and complete in six to nine hours."²⁶

Orally administered potions and the soporific sponge were not the only methods of drug delivery. Combined with fats or oils, active ingredients of the plant would penetrate the skin or be absorbed by sweat ducts (in the armpits) or in body orifices (*e.g.*, vagina, rectum). This would allow the psychoactive alkaloid agents, es-

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pecially hyoscine, access to the blood and brain without passage through the gut. John Arderne (1307–1380 CE) provided eloquent descriptive testimonial to the efficacy of “oyntments”:

... the juice of henbane, mandragora, hemlock, lettuce, black and white poppy ... with sufficient lard ... anoint the forehead, the pulses, the temples, the armpits, the palms of the hands and the soles of the feet and immediately the patient will sleep so soundly that he will not feel any cutting.^{27,28}

He added advice, however, about appropriate interventions for the recognized risks of such a practice: “And know that it is well to tweak the nose, to pinch the cheeks or to pluck the beard of such a sleeper to quicken his spirits lest he sleep too deeply.”

Andres De Laguna (1499–1560 CE), physician to Emperor Charles V and Philip II, provided an unambiguous description of an experiment with an ointment he discovered in the home of a couple accused of witchcraft:

... a pot full of a certain green ointment ... with which they were anointing themselves ... was composed of herbs ... such as hemlock, nightshade, henbane, and mandrake ... I had the wife of the public executioner annointed with it from head to foot ... she ... had completely lost power of sleep ... no sooner did I annoint her than she opened her eyes, wide like a rabbit, and soon they looked like those of a cooked hare when she fell into such a profound sleep that I thought I should never be able to awake her ... after a lapse of thirty-six hours, I restored her to her senses and sanity.

This passage is redolent of the description of belladonna alkaloid poisoning “hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a wet hen.”²⁹

De Laguna’s personal commentaries accompanying the above text included the astute observation: “From all this we may infer that all that those wretched witches do and say is caused by potions and ointments which so corrupt their memory and their imagination that they create their own woes, for they firmly believe when awake all that they had dreamed when asleep,” making him perhaps the first physician to correlate herbal intoxication with the rituals of witchcraft and to imply that confessions extracted from such drug users might represent the delusional speech of a deranged mind.³⁰

De Laguna was not the sole commentator about the relationship of mind-altering drugs and witchcraft in the 16th century. In *De Praestigiis Daemonum*, which Freud called one of the 10 most significant books of all time, Johann Weyer (1515–1588 CE) concluded hen-



THE DEPARTURE FOR THE SABBAT
David Teniers

Fig. 3. A sabbat was the nighttime gathering of a witches’ coven, their weekly meeting to practice magic rites. It was believed widely that witches traveled through the air to these nighttime gatherings and would therefore make use of flying ointments. (Engraving of *Départ pour le Sabat* by Jacques Aliamet, after David Teniers the Younger [1610–1690 CE], courtesy of the Wellcome Institute Library, London and the Bibliothèque Nationale de France; with permission.)

bane was a principal ingredient of witches’ brew, along with deadly nightshade and mandrake.³¹ According to Weyer, there were other ointments, but the essential ingredients remained the same in all. The preparations, when applied to the upper thighs or genitals, were said to induce the sensation of rising into the air or flying. Witches were thought to anoint a chair or broomstick with the devil’s ointment, and after self-application, would fly through the air to meet for devil worship at the sabbat³² (figs. 3 and 4). Francis Bacon (1561–1626 CE) observed that “... the witches themselves are imaginative, and believe oftentimes they do that, which they do not ... transforming themselves into other bodies ... not by incantations or ceremonies, but by ointments, and annointing themselves all over.”³³



Fig. 4. An engraving of witches, traditionally titled *Witches' Sabbath*, by the German artist Hans Baldung Grien (c. 1484–1545 CE). Two women are shown in the act of anointing themselves from the pot, probably containing flying ointment in the center of the print. The goats and cats in the woodcut were witches familiars (an attendant spirit or demon to obey the command or serve the pleasure of the witch, often taking animal form) and also symbols of lust. (Illustration courtesy of the Bibliothèque Nationale de France; with permission.)

In an extensive review of psychotropic plant ointments of the Renaissance, Piomelli and Pollio examined transcripts of witchcraft trials, writings on demonology, and the botanical composition of ointments that alleged witches used on themselves during the 15th and 16th centuries.²⁷ Despite the difficulty with accurate identification of the plants, the documents reported consis-

tent pharmacologic effects. Further, the biochemical logic of applying these plants in a fat-based unguent was sound, as it would promote passage of the alkaloids through the intact skin and mucosa. The use of soot (slightly alkaline) likely would enhance the passage of organic bases because a weakly alkaline environment would be sufficient to neutralize the positive ionic charge. That this is an effective ethnobotanical technique may be seen with Peruvian coca chewers, who mix in their mouths the cocaine-containing leaves with alkaline cinders to enhance uptake. There is even experimental evidence for believing that a fatty base was used in these ointments; an ointment from the 13th or 14th century, found accidentally, was subjected to chemical analysis and had an animal fat content of 40%.³⁴

Folk practices and magical beliefs coexisted with these vivid descriptions of pharmacologic efficacy.³⁵ Among these beliefs was that the mandrake root protected against bad fortune and danger. The Germans formed little idols of the roots of the mandrake, called *Alrunen*, dressed them every day, and consulted them as oracles. They were brought to England in the time of Henry VIII (1509–1547 CE) and met with eager purchasers who were told that, with the assistance of some mystic words, whatever money was placed near them would increase.^{1,3} Among French peasants, the mandrake was the abode of a little elf, called *main-de-gloire* or *maglore*, who had to be appeased with daily offerings of food. Reminiscent of earlier apocryphal Greco-Roman fables, the roots of these plants were alleged to grow from the flesh of criminals who fell from the gallows; others pretended that this plant was obtained from the Far East, and then only after the greatest risk and danger.⁷

Physicians and herbalists began to bridge these worlds of witchcraft and medicine. Paracelsus (Aureolus Theophrastus Bombastus von Hohenheim, 1493–1541 CE) pursued the pharmacologic value of the witches' experience, and probably took advantage of their fund of knowledge: "Not all things the physician must know are taught in the academies. Now and then he must turn to old women, to Tartars who are called gypsies, to itinerant magicians, to elderly country folk and many others who are frequently held in contempt."³⁶

John Gerard (1545–1607 CE) in his *Herbal or General Historie of Plantes* further challenged the mysticism shrouding mandrake root cultivation by stating that "many ridiculous tales (had been) brought up of this plant, whether of old wives, or some runagate surgeons, or physike-mongers, I know not."³⁷ William Turner

(d. 1658 CE), in referring to mandrake, wrote that the roots "which are counterfeited and made like little puppettes and mammettes . . . are nothing else but foolish feigned trifles, and not natural."³⁸ Turner used his *Herball* to expose, for the protection of the public, the secret methods of "fetching" drugs, "to eschew ye frawde of them that selleth it."³⁸

Controversy and ambivalence persisted nevertheless, and it was reflected in popular literature by no less noted a writer than William Shakespeare (a neighbor of Gerard, from whom he may have learned a great deal about herbalism³⁹) in several plays, for example, *Romeo and Juliet* ("[a]nd shrieks like mandrakes' torn out of the earth, that living mortals hearing them run mad")⁴⁰ and *Othello* ("[n]ot poppy, nor mandragora nor all the drowsy syrups of the world shall ever medicine thee to that sweet sleep which thou owedst [sic] yesterday").⁴¹

The development of printing from moveable type made scholarship publicly and inexpensively available at the beginning of the Renaissance. Many of the early books were herbals, authored by Renaissance voyagers who were perhaps influenced by accounts of new drugs from exotic places. Unfortunately, a drug-induced sleep in the setting of medical or surgical treatment was often associated with death and undoubtedly discouraged many physicians and patients from attempting to relieve surgical pain.⁴² Multiple explanations may exist for skepticism on the part of patients and physicians. To the extent that compounds were used rather than single remedies ("simples"), either an incorrect component could have been added or an inappropriate balance of components prepared. Side effects such as respiratory depression or apnea, or complications such as aspiration, could have occurred. Complications of the surgery or intercurrent illness, blamed on the anesthetic agent, have certainly occurred in modern times, and we would have no reason to think that the use of herbals escaped such criticism.⁴³ In referring to *A. belladonna*, Gerard warns ". . . this kind of Nightshade causeth sleepe . . . it bringeth such as have eaten thereof into a ded sleepe wherein many have died."³⁷ For the ancients (as for modern physicians), therapeutic effects and toxicity existed on a continuum; the Greek word *pharmaka* means both drugs and poisons.⁴⁴ Avicenna attributed the anesthetic action of the various medicinal plants used to a shared poisonous property of variable strength, with opium the most powerful, followed by mandrake, papaveris, henbane, and hemlock.⁴⁵ By the end of the sixteenth century such "anesthetic agents" had largely fallen into disrepute. If physicians tried to use "nar-

cotic" herbals in the middle of the seventeenth century, they were condemned, arrested, and fined or tried for practicing witchcraft.²⁰

Early Science, Pharmacology, and Anesthesia

Attempts to develop quantitative methodology characterized science in the seventeenth and eighteenth centuries, and at the forefront of these attempts was the chemical analysis of the active ingredients in medicinal plants. The English philosopher John Locke (1632–1704 CE), who argued that governments depend on the consent of the governed and thus became the philosophical compass for the Declaration of Independence, also observed astutely "did we know the mechanical affections of the particles of rhubarb, hemlock, opium and a man, as a watchmaker does those of a watch . . . we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep . . ."⁴⁶ At the same time, European interest in trade and commerce was renewed; once again, as at the turn of the millenium, information and new drugs passed freely through the trade routes.⁷ Rational thought, early experimentation, shared information, and the secularization of pain and its management⁴⁷ added to the divergence of herbalism from witchcraft and medicine in the seventeenth century.

After his clinical observation of poisoning in children who had mistaken water hemlock for parsnip root, Johann Jakob Wepfer (1620–1695 CE) demonstrated the dose-dependent toxic effects in dogs of the alkaloids eventually isolated as strychnine, nicotine, and conine. He recorded these experiments carefully, including the animal used, the time of administration, the dose, and the development of symptoms along with the results of either a vivisection or *post mortem* examination.⁴⁸ Claims of therapeutic efficacy in cancer treatment, based on dose-response tests on himself and dogs, were made by Anton Storck (1731–1803 CE) of Vienna using hemlock, stramonium (*Datura stramonium*), and henbane, although these claims were disputed.^{49–}

⁵² In the laboratory, Philipp Lounz Geiger (1785–1836 CE) of Heidelberg with his pupil Germain Henri Hess (1802–1850 CE) isolated atropine from belladonna leaves and hyoscyamine from henbane. These advances in pharmaceutical isolation and preparation along with the acceptance of the dose-response concept were concurrent with the beginning of ether and chloroform surgical anesthesia.

Unwanted side effects and complications of anesthetic agents did not escape attention. Snow, as a meticulous chronicler of his clinical practice, noted the increase in salivation with ether and chloroform.⁵³ Unexplained deaths with chloroform led to the selection by the Royal Medical and Chirurgical Society of an investigative Chloroform Commission. In 1864, this commission reported a death rate of approximately 1:3,000 with chloroform anesthesia compared with 1:14,000 with ether.⁵⁴ The committee report suggested that vagal stimulation as a result of local laryngeal irritation on first inhaling chloroform might be enough to stop the heart, yet the use of atropine was not suggested until J. A. F. Dastre (1844–1917 CE) of Paris recommended premedication with atropine in accordance with proposed physiologic principles of vagally mediated cardiac arrest.⁵⁵ Puschmann⁵⁶ cites Von Pitha as the first to administer an extract of *A. belladonna* per rectum as an intentional premedicant. In 1930, von der Porten recommended premedication with morphine and atropine administered subcutaneously to decrease psychological stress during the induction of anesthesia, to reduce the consumption of anesthetic drugs, to eliminate salivation, to reduce postanesthetic vomiting, and to reduce respiratory depression.⁵⁷ Phelps,⁵⁸ Stephen *et al.*,⁵⁹ and Eger⁶⁰ reviewed the use of anticholinergic drugs in preanesthetic medication for almost identical indications. After thousands of years as an intoxicant and anodyne, atropine was transformed into a prophylactic medication and antidote for the new intoxicants and anodynes of the nineteenth and twentieth centuries.

Conclusion

Hardly a practitioner of anesthesia begins administration of an anesthetic agent without the ready availability of atropine. That the infrequent use of the ancient anodyne agents was so rapidly replaced by the almost universal use of volatile anesthetic agents after 1846 has been the subject of essays examining the confluence of social, ethical, and scientific developments of the nineteenth century.^{47,61–63} Throughout this long history of pain relief, no matter whether the anodyne agents have been ancient or modern, the principle of safeguarding the thread of life has remained the core of anesthetic practice. The legacy of Atropos, the Fate who cut the thread of life, and her namesake roots *A. mandragora* and *A. belladonna*, used as anodyne, soporific,

and hallucinogenic agents for millennia, reminds us that we practice the art and science of anesthesiology against a backdrop of legendary proportion.

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