12. MOLECULES OF WITCHCRAFT

FROM THE MIDDLE of the fourteenth until the late eighteenth century, a group of molecules contributed to the doom of hundreds of thousands of people. It can never be known exactly how many, in almost every country in Europe during these centuries, were burned at the stake, hanged, or tortured as witches. Estimates range from forty thousand to millions. Though accused witches included men, women, and children, aristocrats, peasants, and clergy, mostly the fingers were pointed at women—often poor and elderly women. Many reasons have been advanced for why women became the main victims of the waves of hysteria and delusion that threatened whole populations for hundreds of years. We speculate that certain molecules, while not wholly responsible for the centuries of persecution, played a substantial role in this discrimination.

Belief in sorcery and magic has always been part of human society, long before witch-hunts began at the end of the Middle Ages. Stone

Age carvings of female figures were supposedly venerated for their magical powers of fertility. Legends of all ancient civilizations abound in the supernatural: deities that take on animal form, monsters, goddesses who cast spells, enchanters, specters, goblins, ghosts, fearsome creatures who were half animal and half man, spirit-beings, and gods who lived in the sky, in forests, in lakes, in the ocean, and underground. Pre-Christian Europe, a world full of magic and superstition, was no exception.

As Christianity spread throughout Europe, many old pagan symbols and festivals were incorporated into the rituals and celebrations of the Church. We still celebrate as Halloween the great Celtic festival of the dead, marking the beginning of winter on October 31, although November 1, All Saints' Day, was the Church's attempt to divert attention away from the pagan festivities. Christmas Eve was originally the Roman feast day of Saturnalia. Christmas trees and many other symbols (holly, ivy, candles) that we now associate with Christmas are pagan in origin.

TOIL AND TROUBLE

Before 1350 witchcraft was regarded as the practice of sorcery, a method of trying to control nature in one's own interest. Using charms in the belief that they could protect crops or people, casting spells to influence or provide, and invoking spirits were commonplace. In most parts of Europe sorcery was an accepted part of life, and witchcraft was regarded as a crime only if harm resulted. Victims of *maleficium,* or evildoing by means of the occult, could seek legal recourse from a witch, but if they were unable to prove their case, they themselves became liable for a penalty and trial costs. By this method idle accusations were discouraged. Rarely were witches put to death. Witchcraft was neither an organized religion nor an organized opposition to religion. It was not even organized. It was just part of folklore.

But around the middle of the fourteenth century a new attitude

toward witchcraft became apparent. Christianity was not opposed to magic, provided it was sanctioned by the Church and known as a miracle. But magic conducted outside the Church was considered the work of Satan. Witches were in league with the devil. The Inquisition, a court of the Roman Catholic Church originally established around 1233 to deal with heretics—mainly in southern France—expanded its mandate to deal with witchcraft. Some authorities have suggested that once heretics had been virtually eliminated, the Inquisition, needing new victims, set its sights on sorcery. The number of potential witches throughout Europe was large; the potential source of income for the inquisitors, who shared with local authorities the confiscated properties and assets of the condemned, would also have been great. Soon witches were being convicted not for performing evil deeds but for supposedly entering into a pact with the devil.

This crime was considered so horrendous that, by the mid–fifteenth century, ordinary rules of law no longer applied to trials of witches. An accusation alone was treated as evidence. Torture was not only allowed, it was used routinely; a confession without torture was seen as unreliable—a view that seems strange today.

The deeds attributed to witches—orgiastic rituals, sex with demons, flying on broomsticks, child murdering, baby eating—were, for the most part, beyond rationality but were still fervently believed. About 90 percent of accused witches were women, and their accusers were just as likely also to be women as men. Whether so-called witch-hunts revealed an underlying paranoia aimed at women and female sexuality is still being argued. Wherever a natural disaster struck—a flood, a drought, a crop failure—no lack of witnesses would attest that some poor woman, or more likely women, had been seen cavorting with demons at a sabbat (or witches' gathering) or flying around the countryside with a familiar (a malevolent spirit in animal form, such as a cat) at their side.

The mania affected Catholic and Protestant countries alike. At the height of witch-hunt paranoia, from about 1500 to 1650, there were al-

most no women left alive in some Swiss villages. In regions of Germany there were some small villages where the whole population was burned at the stake. But in England and in Holland the witch craze never became as entrenched as in other parts of Europe. Torture was not allowed under English law, although suspected witches were subjected to the water test. Trussed and thrown into a pond, a true witch floated, to be retrieved and properly punished—by hanging. If the accused sank and drowned, she was considered to have been innocent of the charge of witchcraft—a comfort to the family but little use to the victim herself.

The witch-hunt terror faded only slowly. But with so many people

A Delft tile from the Netherlands (first part of the eighteenth century) showing a witch trial. The accused on the right, only her legs visible above the water, is sinking and would be proclaimed innocent. Satan's hand can be seen supporting the accused woman floating to the left, who—her guilt now proven—would be pulled from the water to be burned alive at the stake. (Courtesy of the Horvath Collection, Vancouver)

accused, economic well-being was threatened. As feudalism retreated and the Age of Enlightenment dawned, as the voices of brave men and women who themselves risked the gallows and the stake to oppose the madness became louder, the mania that had swept Europe for centuries gradually abated. In the Netherlands the last execution of a witch took place in 1610 and in England in 1685. The last witches executed in Scandinavia—eighty-five elderly women burned at the stake in 1699—were convicted solely on the basis of statements from young children who claimed to have flown with the women to sabbats.

By the eighteenth century, execution for witchcraft officially ceased: for Scotland in 1727, France in 1745, Germany in 1775, Switzerland in 1782, and Poland in 1793. But although the Church and the state no longer executed witches, the court of public opinion was less ready to give up the fear and loathing of witchcraft acquired by centuries of persecution. In more remote rural communities old beliefs still held sway, and many a suspected witch met a nasty, if unofficial, fate.

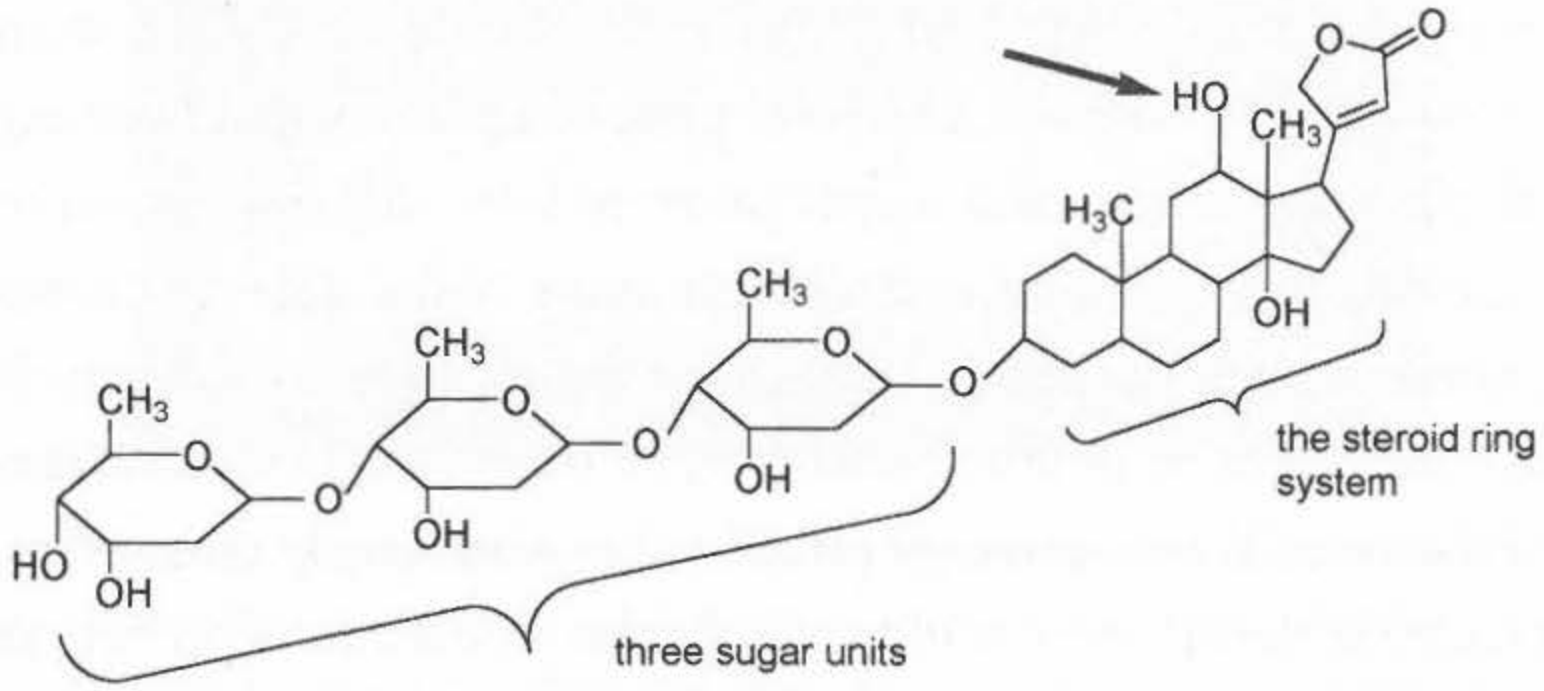
Many of the women accused of witchcraft were herbalists, skilled in the use of local plants to cure disease and provide relief from pain. Often they could also be relied upon to supply love potions, to cast spells, and to remove hexes. That some of their herbs did have healing powers would have seemed as magical as the incantations and rituals surrounding the rest of the ceremonies they would perform.

Using and prescribing herbal medicines would have been then—as it is now—a risky business. Different parts of a plant contain varying levels of effective compounds; plants gathered from different locations can vary in their ability to cure; and different times of the year can change the amount of a plant needed to produce an appropriate dose. Many plants in an elixir might be of little benefit, while others might contain medications that would be extremely effective but also deadly poisonous. The molecules in these plants could enhance the reputation of an herbalist as a sorcerer, but the very success of these molecules might eventually prove deadly for these women. Those herbalists whose healing skills were the greatest might be first to be branded a witch.

HEALING HERBS, HARMFUL HERBS

Salicylic acid, from the willow tree and the meadowsweet plant common throughout Europe, was known centuries before Bayer and Company began marketing aspirin in 1899 (see Chapter 10). The root of wild celery was prescribed to prevent muscle cramps, parsley was believed to induce a miscarriage, and ivy was used to relieve symptoms of asthma. Digitalis, an extract from the common foxglove *Digitalis purpurea,* contains molecules that have long been known to have a powerful effect on the heart—the *cardiac glycosides.* These molecules reduce the heart rate, regularize heart rhythm, and strengthen heartbeat, a potent combination in inexperienced hands. (They are also saponins, very similar to those found in sarsaparilla plants and wild Mexican yams from which the birth control pill norethindrone was synthesized; see Chapter 11.) An example of a cardiac glycoside is the digoxin molecule, one of the most widely prescribed drugs in the United States and a good example of a pharmaceutical based on folk medicine.

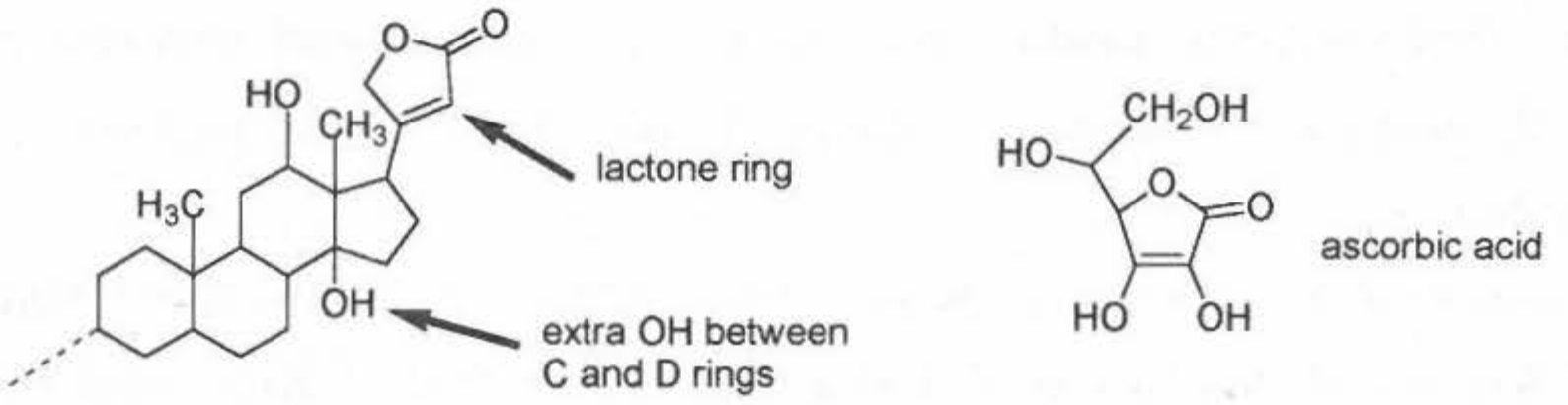
In 1795 a British physician named William Withering used extracts of foxglove to treat congestive heart failure after hearing rumors of the plant's curative abilities. But it was well over a century before chemists were able to isolate the molecules responsible.



The structure of the digoxin molecule. The three sugar units are different from those in the sarsaparilla or Mexican yam plants. The digitoxin molecule lacks the arrowed OH group on the steroid ring system.

In the *Digitalis* extract there are other very similar molecules to digoxin; for example the digitoxin molecule, which lacks only the OH, as indicated in the structure drawing. Similar cardiac glycoside molecules are found in other plants, usually members of the lily and ranunculus families, but foxglove is still the main source for today's drug. Herbalists have had little difficulty finding heart tonic plants in their own gardens and in local meadows. Ancient Egyptians and Romans used an extract from the sea onion, a member of the hyacinth family, as a heart tonic and (in larger doses) as a rat poison. We now know that this sea onion also contains a different cardiac glycoside molecule.

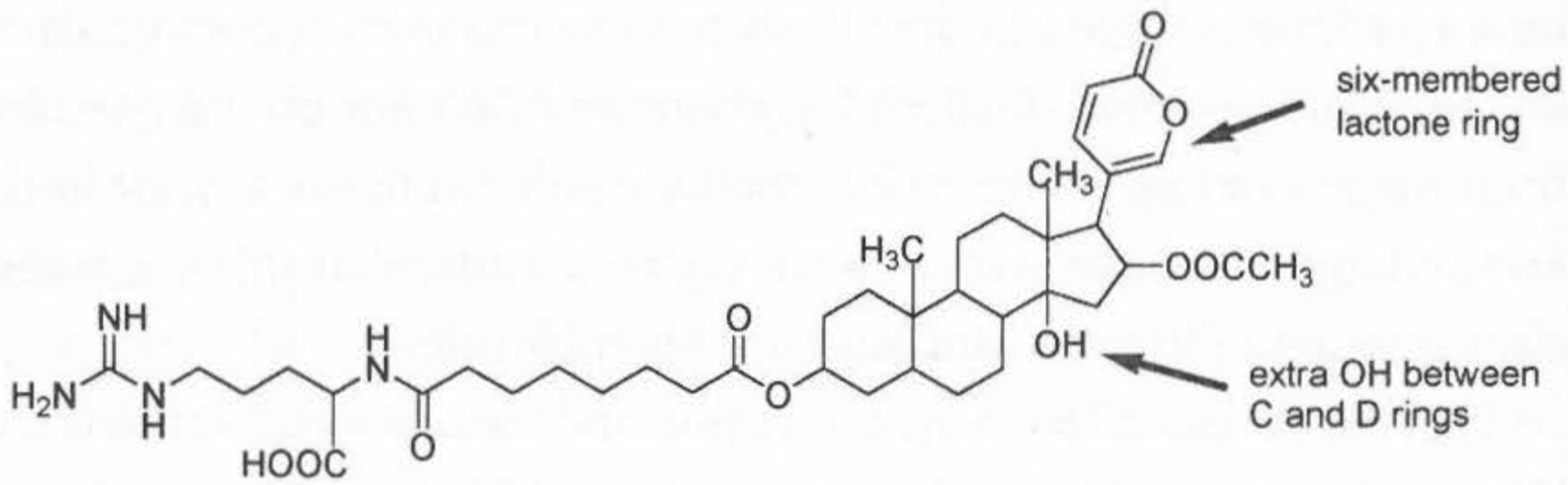
These molecules all have the same structural feature, which is therefore likely to be responsible for the cardiac effect. All have a five-membered lactone ring attached to the end of the steroid system and an extra OH between the C and D rings of the steroid system, as shown here:



The nonsugar portion of the digoxin molecule with the heart-affecting extra OH and the lactone ring arrowed. This lactone ring is also found in the ascorbic acid molecule (vitamin C).

Molecules that affect the heart are not found only in plants. Toxic compounds that are similar in structure to the cardiac glycosides are found in animals. These molecules do not contain sugars, nor are they used as heart stimulants. Rather, they are convulsive poisons and of little medical value. The source of these venoms is amphibians; extracts from toads and frogs have been used as arrow poisons in many parts of the world. Interestingly, the toad is, after the cat, the most common animal attributed in folklore as a familiar to a witch. Many potions prepared by so-called witches were said to contain parts of toads. The molecule *bufotoxin* is the active component of the venom of the common European

toad, *Bufo vulgaris,* and is one of the most toxic molecules known. Its structure shows a striking similarity at the steroid ring system to the digitoxin molecule, with the same extra OH between the C and D rings and a six-membered, instead of five-membered, lactone ring.



The bufotoxin from the common toad is structurally similar to digitoxin from the foxglove around the steroid portion of the molecule.

Bufotoxin, however, is a cardiac poison rather than a cardiac restorative. Between the cardiac glycosides of foxglove and venoms from toad, supposed witches had access to a potent arsenal of toxic compounds.

In addition to their penchant for toads, one of the most abiding myths about witches is that they were able to fly, often on broomsticks, to attend a sabbat—a midnight tryst, supposedly an orgiastic parody of the Christian mass. Many accused witches confessed, under torture, to flying to such sabbats. This is not surprising—we too would probably make such a confession if we were subject to the same horrific agonies perpetrated in the search for truth. The surprising thing is that a number of accused witches confessed, *before* torture, to the impossible feat of flying to a sabbat on a broomstick. As such a confession would not likely have helped these victims escape torture, it is quite possible that these women truly believed they had flown up the chimney on a broomstick and indulged in all sorts of sexual perversions. There may be a very good chemical explanation for their belief—a group of compounds known as alkaloids.

Alkaloids are plant compounds that have one or more nitrogen

atoms, usually as part of a ring of carbon atoms. We have already met a few alkaloid molecules—piperine in pepper, capsaicin in chili peppers, indigo, penicillin, and folic acid. It can be argued that, as a group, alkaloids have had a larger effect on the course of human history than have any other family of chemicals. Alkaloids are often physiologically active in humans, usually affecting the central nervous system, and are generally highly toxic. Some of these naturally occurring compounds have been used as medicines for thousands of years. Derivatives made from alkaloids form the basis of a number of our modern pharmaceuticals, such as the pain-relieving molecule codeine, the local anesthetic benzocaine, and chloroquine, an antimalarial agent

We have already mentioned the role that chemical substances play in protecting plants. Plants cannot run away from danger and cannot hide at the first sign of a predator; physical means of protection such as thorns do not always stop determined grazers. Chemicals are a passive but very effective form of protection from animals as well as fungi, bacteria, and viruses. Alkaloids are natural fungicides, insecticides, and pesticides. It has been estimated that, on average, each of us ingests about a gram and a half of natural pesticide every day, from the plants and plant products in our diet. The estimate for residues from synthetic pesticides is around 0.15 milligrams daily—about ten thousand times less than the natural dose!

In small amounts the physiological effects of alkaloids are often welcomed by humans. Many have been used medicinally for centuries. Acrecaidine, an alkaloid found in betel nuts from the betel palm, *Areca catechu,* has a long history of use in Africa and the East as a stimulant. Crushed betel nuts are wrapped in the betel palm leaves and chewed. Betel users are easily recognized by their characteristic dark-stained teeth and by their habit of spitting copious amounts of dark red saliva. Ephedrine, from *Ephedra sinica* or the ma huang plant, has been used in Chinese herbal medicine for thousands of years and is now used in the West as a decongestant and bronchodilator. Members of the vitamin B family, such as thiamine (B_1), riboflavin (B_2), and niacin (B_4), are all

classed as alkaloids. Reserpine, used in the treatment of high blood pressure and as a tranquilizer, is isolated from the Indian snakeroot plant, *Rauwolfia serpentina.*

Toxicity alone has been enough to ensure fame for some alkaloids. The poisonous component of the hemlock plant, *Conium maculatum,* responsible for the death of the philosopher Socrates in 399 B.C., is the alkaloid coniine. Socrates, convicted on charges of irreligion and the corruption of the young men of Athens, was sentenced to death by drinking a potion made from the fruit and seeds of hemlock. Coniine has one of the simplest structures of all the alkaloids, but it can be just as lethal a poison as more complicated alkaloid structures such as that of strychnine, from the seeds of the Asiatic tree *Strychnos nux-vomica.*

The structures of coniine (left) and strychnine (right)

In their "flying salves"—greases and ointments that supposedly promoted flight—witches often included extracts from mandrake, belladonna, and henbane. These plants all belong to the *Solanaceae* or nightshade family. The mandrake plant, *Mandragora officinarum,* with its branched root said to resemble the human form, is native to the Mediterranean region. It has been used since ancient times as a means of restoring sexual vitality and as a soporific. There are a number of curious legends surrounding the mandrake plant. When pulled from the ground, it was said to emit piercing screams. Whoever was in the vicinity was in danger from both the associated smell and the unearthly cry. That such a characteristic was common knowledge is reflected in Shakespeare's *Romeo and Juliet,* where Juliet says: ". . . with loathsome smells, and shrieks like mandrakes' torn out of the earth, / That living

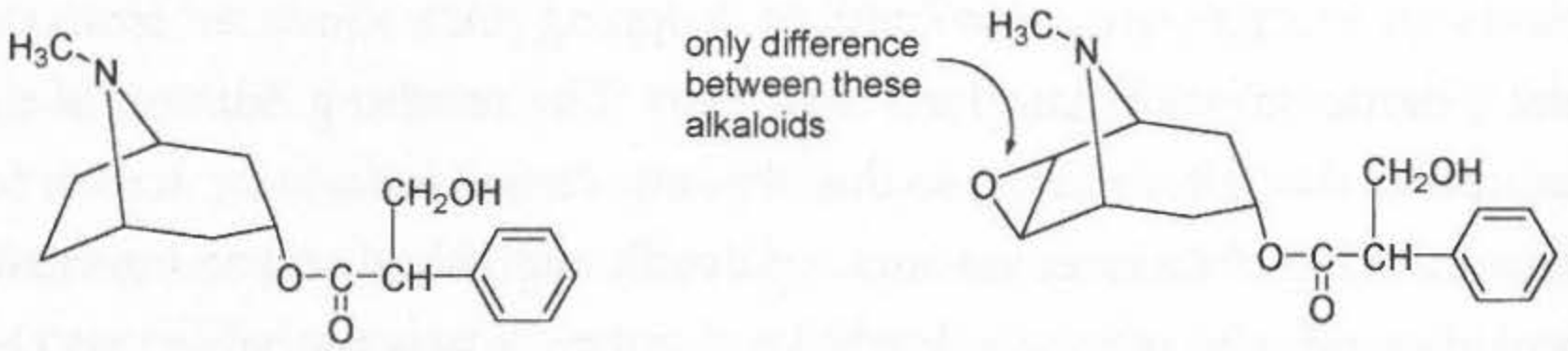
mortals, hearing them, run mad." The mandrake plant was rumored to grow beneath a gallows, springing to life from the released semen of the condemned men hanged there.

The second plant used in flying ointments was belladonna or deadly nightshade (*Atropa belladonna*). The name comes from the practice, common among women in Italy, of dropping juice squeezed from the black berries of this plant into their eyes. The resulting dilation of the pupil was thought to increase their beauty; hence *belladonna,* Italian for "beautiful lady." Greater amounts of deadly nightshade taken internally would eventually induce a deathlike slumber. It was probable that this was also commonly known and possible that this was the potion drunk by Juliet. Shakespeare wrote (in *Romeo and Juliet*) "through all thy veins shall run/A cold and drowsy humour, for no pulse shall keep," but eventually "in this borrow'd likeness of shrunk death/Thou shalt continue two and forty hours,/And then awake as from a pleasant sleep."

The third member of the nightshade family, henbane, was probably *Hyoscyamus niger,* though other species might also have been used in witch's potions. It has a long history as a soporific, a pain reliever (particularly for toothache), an anesthetic, and possibly a poison. The properties of henbane also seem to have been well known: Shakespeare was again only reflecting the common knowledge of his time when Hamlet was told by his father's ghost that "thy uncle stole, / With juice of cursed hebona in a vial, / And in the porches of mine ears did pour / The leperous distilment." The word *hebona* has been ascribed to both the yew and ebony trees as well as henbane, but from a chemical viewpoint we think henbane makes more sense.

Mandrake, deadly nightshade, and henbane all contain a number of very similar alkaloids. The two main ones, hyoscyamine and hyoscine, are found in all three plants in varying proportions. One form of hyoscyamine is known as atropine and is still valued today, in very dilute solutions, to dilate the pupil of the eye for ophthalmic examinations. Large concentrations produce blurry vision, agitation, and even delirium. One of the first symptoms of atropine poisoning is the drying

up of bodily fluids. This property is taken advantage of in prescribing atropine, where excess saliva or mucus secretion may interfere with surgery. Hyoscine, also known as scopolamine, has gained a probably undeserved reputation as a truth serum.



Atropine from hyoscyamine *Scopolamine (hyoscine)*

Combined with morphine, scopolamine is used as the anesthetic known as "twilight sleep," but whether one babbles the truth under its effect or just babbles is not clear. Still, writers of detective novels have always liked the thought of a truth serum, and it will probably continue to be quoted as such. Scopolamine, like atropine, has antisecretory and euphoric properties. In small amounts it combats travel sickness. U.S. astronauts use scopolamine as a treatment for motion sickness in space.

As bizarre as it might seem, the poisonous compound atropine acts as an antidote for groups of even more toxic compounds. Nerve gases such as sarin—released by terrorists in the Tokyo subway in April of 1995—and organophosphate insecticides, such as parathion, act by preventing the normal removal of a messenger molecule that transmits a signal across a nerve junction. When this messenger molecule is not removed, nerve endings are continuously stimulated, which leads to convulsions and, if the heart or lungs are affected, to death. Atropine blocks the production of this messenger molecule, so provided the right dosage is given, it is an effective remedy for sarin or parathion.

What is now known about the two alkaloids atropine and scopolamine, and was obviously known by the witches of Europe, is that neither is particularly soluble in water. As well, they would have recognized that swallowing these compounds might lead to death rather than the

euphoric and intoxicating sensations they wanted. Hence extracts of mandrake, belladonna, and henbane were dissolved in fats or oils, and these greases were applied to the skin. Absorption through the skin—transdermal delivery—is a standard method of taking certain medications today. The nicotine patch for those trying to quit smoking and some travel sickness remedies and hormonal replacement therapies use this route.

As the records of witches' flying salves show, the technique was known hundreds of years ago as well. Today we know that the most efficient absorption is where the skin is the thinnest and blood vessels lie just under the surface; thus vaginal and rectal suppositories are used to ensure rapid absorption of medications. Witches must also have known this fact of anatomy, as flying ointments were said to be smeared all over the body or rubbed under the arms and, coyly, "in other hairy places." Some reports said witches applied the grease to the long handle of a broom and, sitting astride, rubbed the atropine-and-scopolamine-containing mixture onto the genital membranes. The sexual connotations of these accounts are obvious, as are the early engravings of naked or partially clothed witches astride broomsticks, applying salves and dancing around cauldrons.

The chemical explanation is, of course, that the supposed witches did not fly on broomsticks to sabbats. The flights were ones of fancy, illusions brought on by the hallucinatory alkaloids. Modern accounts of hallucinogenic states from scopolamine and atropine sound remarkably like the midnight adventures of witches: the sensation of flying or falling, distorted vision, euphoria, hysteria, a feeling of leaving the body, swirling surroundings, and encounters with beasts. The final stage of the process is a deep, almost comalike sleep.

It is not difficult to imagine how, in a time steeped in sorcery and superstition, users of flying ointments really did believe they had flown through the night sky and taken part in wild dancing and wilder revelries. The hallucinations from atropine and scopolamine have been described as particularly vivid. A witch would have no reason to believe

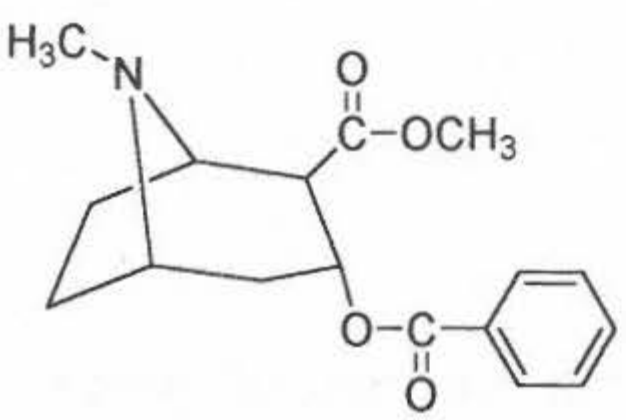
the effects of her flying ointment were solely in her mind. It is also not difficult to imagine how the knowledge of this wonderful secret was passed on—and it would have been considered a wonderful secret. Life for most women in these times was hard. Work was never ending, disease and poverty ever present, and a woman's control over her own destiny unheard of. A few hours of freedom, riding the skies to a gathering where one's sexual fantasies were played out, then waking up safely in one's own bed must have been a great temptation. But unfortunately the temporary escape from reality created by the molecules of atropine and scopolamine often proved fatal, as women accused of witchcraft who confessed to such imagined midnight exploits were burned at the stake.

Along with mandrake, deadly nightshade, and henbane, other plants were included in flying ointments: foxglove, parsley, monkshood, hemlock, and thorn apple are listed in historical accounts. There are toxic alkaloids in monkshood and hemlock, toxic glycosides in foxglove, hallucinogenic myristicin in parsley, and atropine and scopolamine in thorn apple. Thorn apple is a *Datura;* devil's apple, angel's trumpet, stinkweed, and jimsonweed are some of the other plants in this genus. Now widely distributed in the warmer parts of the world, *Datura* furnished alkaloids for witches in Europe as well as for initiation rites and other ceremonial occasions in Asia and the Americas. Folklore associated with *Datura* usage in these countries reveals hallucinations involving animals, a very common aspect of witches' flights. In parts of Asia and Africa *Datura* seeds are included in mixtures to be smoked. Absorption into the bloodstream through the lungs is a very rapid method of obtaining a "hit" from an alkaloid, as European tobacco smokers later discovered in the sixteenth century. Cases of atropine poisoning are still reported today, with thrill-seekers using flowers, leaves, or seeds of *Datura* to pursue a high.

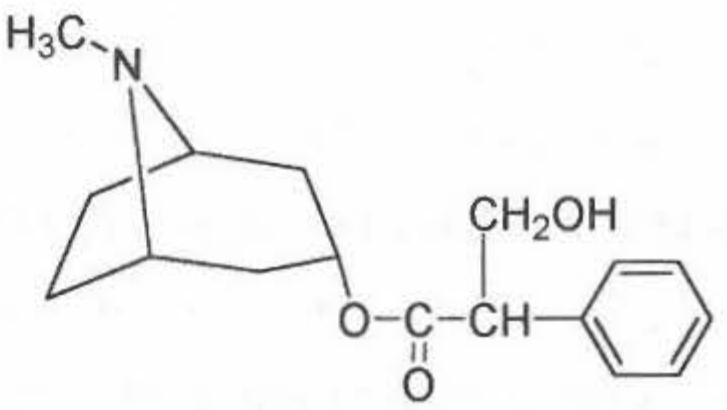
A number of plants from the nightshade family were introduced into Europe from the New World soon after the journeys of Columbus. Some that contained alkaloids—tobacco (*Nicotiana*) and peppers (*Cap-*

sicum)—gained immediate acceptance, but surprisingly, other members of this family—tomatoes and potatoes—were initially regarded with great suspicion.

Other alkaloids that are chemically similar to atropine are found in the leaves of several species of *Erythroxylon,* the coca tree, native to parts of South America. The coca tree is not a member of the nightshade family—an unusual situation, as related chemicals are normally found in related species. But historically plants were classified on morphological features. Revisions now consider chemical components and DNA evidence.



Cocaine



Atropine

The main alkaloid in the coca tree is cocaine. Coca leaves have been used as a stimulant for hundreds of years in the highland areas of Peru, Ecuador, and Bolivia. The leaves are mixed with a paste of lime, then tucked between the gum and the cheek, where the alkaloids, released slowly, help counter fatigue, hunger, and thirst. It has been estimated that the amount of cocaine absorbed this way is less than half a gram daily, which is not addictive. This traditional method of coca alkaloid use is similar to our use of the alkaloid caffeine in coffee and tea. But cocaine, extracted and purified, is a different matter.

Isolated in the 1880s, cocaine was considered to be a wonder drug. It had amazingly effective local anesthetic properties. Psychiatrist Sigmund Freud considered cocaine a medical panacea and prescribed it for its stimulating properties. He also used it to treat morphine addiction. But it soon became obvious that cocaine itself was extremely addictive, as addictive as any other known substance. It produces a rapid and ex-

treme euphoria, followed by an equally extreme depression, leaving the user craving another euphoric high. The disastrous consequences on human health and modern society of abuse of cocaine are well known. The cocaine structure is, however, the basis for a number of extremely useful molecules developed as topical and local anesthetics. Benzocaine, novocaine, and lidocaine are compounds that mimic the pain-destroying action of cocaine by blocking transmission of nerve impulses, but they lack cocaine's ability to stimulate the nervous system or disrupt heart rhythm. Many of us have thankfully experienced the numbing effect of these compounds in the dentist's chair or the hospital emergency room.

THE ERGOT ALKALOIDS

Another group of alkaloids of quite different structure was probably, although indirectly, responsible for thousands of witch burnings in Europe. But these compounds were not used in hallucinogenic ointments. The effects of some of the alkaloid molecules from this group can be so devastating that whole communities, afflicted with horrendous suffering, assumed that the catastrophe was the result of an evil spell cast by local witches. This group of alkaloids is found in the ergot fungus, *Claviceps purpurea,* that infects many cereal grains but especially rye. Ergotism or ergot poisoning was until fairly recently the next-largest microbial killer after bacteria and viruses. One of these alkaloids, ergotamine, causes blood vessels to constrict; another, ergonovine, induces spontaneous abortions in humans and livestock; while others cause neurological disturbances. Symptoms of ergotism vary depending on the amount of the different ergot alkaloids present but can include convulsions, seizures, diarrhea, lethargy, manic behavior, hallucinations, distortion of the limbs, vomiting, twitching, a crawling sensation on the skin, numbness in the hands and feet, and a burning sensation becoming excruciatingly painful as gangrene from decreased circulation eventually sets in. In

medieval times this disease was known by various names: holy fire, Saint Anthony's fire, occult fire, and Saint Vitus' dance. The reference to fire relates to the terrible searing pain and blackened extremities caused by the progression of gangrene. Often there was loss of hands, feet, or genitals. Saint Anthony was considered to have special powers against fire, infection, and epilepsy, making him the saint to appeal to for relief from ergotism. The "dance" of Saint Vitus' dance refers to twitching and convulsive contortions due to the neurological effects of some of the ergot alkaloids.

It is not hard to envisage a situation where a large number of villagers or townsfolk were struck by ergotism. A particularly rainy period just before harvest would encourage fungus growth on rye; poor storage of the cereal in damp conditions would promote further growth. Only a small percent of ergot in flour is needed to cause ergot poisoning. As more and more of a town's inhabitants displayed the dreaded symptoms, people might start to wonder why their community had been singled out for disaster, especially as adjacent towns had no sign of the disease. It could have seemed quite plausible that their village had been bewitched. As in many natural disasters, the blame was often placed on the innocent head of an elderly woman, someone who was no longer useful for childbearing and who may have had no family support. Such women often lived on the outskirts of the community, perhaps surviving on their skills as herbalists and unable to afford even the modest sum required to purchase flour from the miller in town. This level of poverty would have saved a woman from ergotism but ironically, as maybe the only person untouched by the ergot poisons, she became even more vulnerable to the accusation of witchcraft.

Ergotism has been known for a long time. Its cause was hinted at in reports from as early as 600 B.C., when the Assyrians noted "a noxious pustule in the ear of grain." That ergot alkaloids from "noxious grasses" could cause miscarriages in cattle was recorded in Persia around 400 B.C. In Europe the knowledge that fungus or mold on grains was the cause of the problem seems to have been lost—if it was ever known—

during the Middle Ages. With damp winters and improper storage, mold and fungus flourished. In the face of famine, infected grain would have been used rather than discarded.

The first recorded occurrence of ergotism in Europe, in A.D. 857, is from Germany's Rhine valley. Documented reports of forty thousand deaths in France in the year 994 are now attributed to ergotism, as are another twelve thousand in 1129. Periodic outbreaks occurred throughout the centuries and continued into the twentieth century. In 1926–1927 more than eleven thousand people were afflicted with ergotism in an area of Russia near the Ural Mountains. Two hundred cases were reported in England in 1927. In Provence, France, in 1951, four died and hundreds more became ill from ergotism after ergot-infected rye was milled and the flour sold to a baker, although the farmer, miller, and baker were supposedly all aware of the problem.

There are at least four occasions when ergot alkaloids are claimed to have played a role in history. During a campaign in Gaul, in the first century B.C., an epidemic of ergotism among Julius Caesar's legions caused great suffering, reduced the effectiveness of his army, and possibly curtailed Caesar's ambitions to enlarge the Roman Empire. In the summer of 1722 Peter the Great's Cossacks camped at Astrakhan, at the mouth of the Volga River on the Caspian Sea. Both the soldiers and their horses ate contaminated rye. The resulting ergotism supposedly killed twenty thousand troops and so crippled the tsar's army that his planned campaign against the Turks was aborted. Thus Russia's goal of a southern port on the Black Sea was stopped by ergot alkaloids.

In France, in July 1789, thousands of peasants rioted against wealthy landowners. There is evidence that this episode, termed *La Grande Peur* (the Great Fear), was more than just civil unrest associated with the French Revolution. Records attribute the destructive spree to a bout of insanity in the peasant population and cite "bad flour" as a possible cause. The spring and summer of 1789 in northern France had been abnormally wet and warm—perfect conditions for the growth of the ergot fungus. Was ergotism, much more prevalent among the poor, who

ate moldy bread out of necessity, a key factor in the French Revolution? Ergotism was also reported to be rife in Napoleon's army during its journey across the Russian plains in the fall of 1812. So maybe the ergot alkaloids, along with the tin in uniform buttons, share some responsibility for the Grande Armée's collapse on the retreat from Moscow.

A number of experts have concluded that ergot poisoning was ultimately responsible for the accusations of witchcraft against some 250 people (mainly women) during 1692 in Salem, Massachusetts. The evidence does indicate an involvement of the ergot alkaloids. Rye was grown in the area in the late seventeenth century; records show warm, rainy weather during the spring and summer of 1691; and the village of Salem was located close to swampy meadows. All of these facts point to the possibility of fungal infestation of the grain used for the community's flour. The symptoms displayed by the victims were consistent with ergotism, particularly convulsive ergotism: diarrhea, vomiting, convulsions, hallucinations, seizures, babbling, bizarre distortions of the limbs, tingling sensations, and acute sensory disturbances.

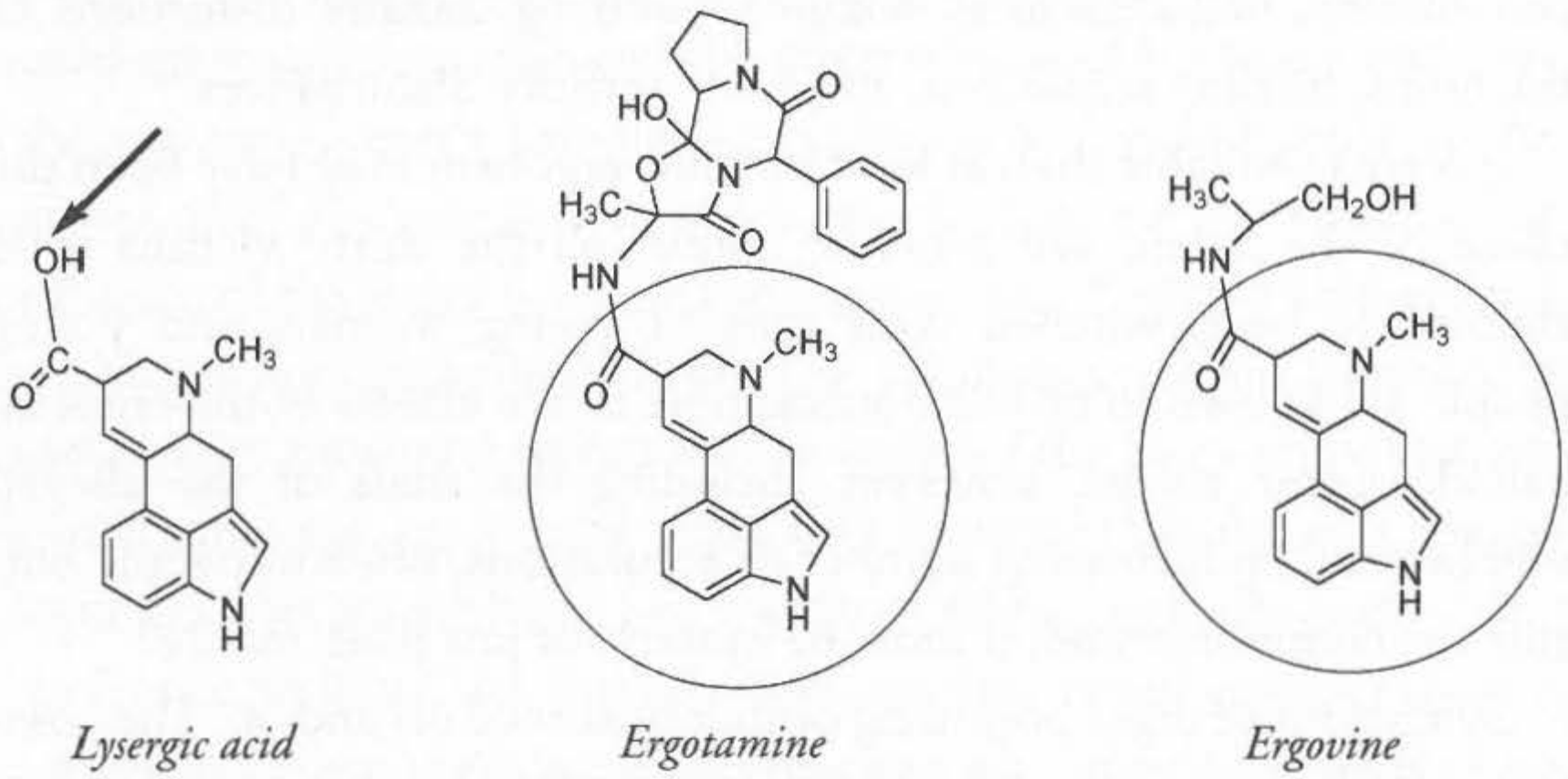
It seems probable that, at least initially, ergotism may have been the cause of the Salem witch-hunts; almost all the thirty victims who claimed to be bewitched were girls or young women, and young people are known to be more susceptible to the effects of the ergot alkaloids. Later events, however, including the trials of the alleged witches and an increasing number of accusations, often of people outside the community, point more to hysteria or just plain malice.

Symptoms of ergot poisoning cannot be turned off and on. The common phenomenon in the trials—victims throwing a convulsive fit when confronted by the accused witch—is not consistent with ergotism. No doubt relishing the attention and realizing the power they wielded, the so-called victims would denounce neighbors they knew and townsfolk they had scarcely heard of. The suffering of the real victims of the Salem witch-hunts—the nineteen hanged (and one pressed to death by a pile of rocks), those tortured and imprisoned, the families

destroyed—may be traced to ergot molecules, but human frailty must bear ultimate responsibility.

Like cocaine, ergot alkaloids, although toxic and dangerous, have had a long history of therapeutic use, and ergot derivatives still play a role in medicine. For centuries herbalists, midwives, and doctors used extracts of ergot to hasten childbirth or produce abortions. Today ergot alkaloids or chemical modifications of these compounds are used as vasoconstrictors for migraine headaches, to treat postpartum bleeding, and as stimulants for uterine contractions in childbirth.

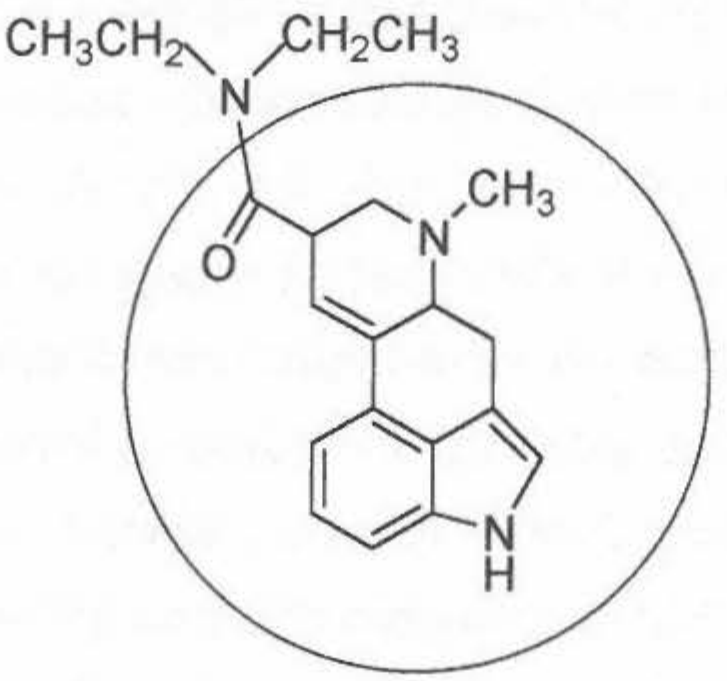
The alkaloids of ergot all have the same common chemical feature; they are derivatives of a molecule known as lysergic acid. The OH group (indicated with an arrow, below) of lysergic acid is replaced by a larger side group, as shown in the ergotamine molecule (used to treat severe migraine headaches) and the ergovine molecule (used to treat postpartum hemorrhages). In these two molecules the lysergic acid portion is circled.



Lysergic acid *Ergotamine* *Ergovine*

In 1938, having already prepared a number of synthetic derivatives of lysergic acid of which some had proved useful, Albert Hofmann, a chemist working in the research laboratories of the Swiss pharmaceutical company Sandoz, in Basel, prepared another derivative. It was the twenty-fifth derivative he had made, so he called lysergic acid diethyl-

amide LSD-25, now known, of course, as just LSD. Nothing exceptional was noted about the properties of LSD.



Lysergic acid diethylamide (LSD-25), or LSD as it was to become known. The lysergic acid part is circled.

It was not until 1943, when Hofmann again made this derivative, that he inadvertently experienced the first of what was to become known in the 1960s as an acid trip. LSD is not absorbed through the skin, so Hofmann probably transferred LSD from his fingers to his mouth. Even a slight trace would have produced what he described as an experience of "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense kaleidoscope play of colors."

Hofmann decided to deliberately take LSD to test his assumption that this was the compound producing the hallucinations. The medical dosage for lysergic acid derivatives such as ergotamine was at least a few milligrams. Thinking, no doubt, that he was being cautious, he swallowed only a quarter of a milligram, an amount at least five times that needed to produce the now well-known hallucinogenic effects. LSD is ten thousand times more potent as a hallucinogen than naturally occurring mescaline, found in the peyote cactus of Texas and northern Mexico and used for centuries by native Americans in their religious ceremonies.

Rapidly growing dizzy, Hofmann asked his assistant to accompany

him as he rode his bicycle home through the streets of Basel. For the next few hours he went through the full range of experiences that later users came to know as a bad trip. As well as having visual hallucinations, he became paranoid, alternated between feelings of intense restlessness and paralysis, babbled incoherently, feared choking, felt he had left his body, and perceived sounds visually. At some point Hofmann even considered the possibility that he might have suffered permanent brain damage. His symptoms gradually subsided, though his visual disturbances persisted for some time. Hofmann awoke the morning after this experience feeling totally normal, with a complete memory of what had happened but seemingly with no side effects.

In 1947 the Sandoz company began to market LSD as a tool in psychotherapy and in particular for the treatment of alcoholic schizophrenia. In the 1960s LSD became a popular drug for young people around the world. It was promoted by Timothy Leary, a psychologist and one-time member of the Harvard University Center for Research in Personality, as the religion of the twenty-first century and the way to spiritual and creative fulfillment. Thousands followed his advice to "turn on, tune in, drop out." Was this alkaloid-induced escape from everyday life in the twentieth century so different from that experienced by women accused of witchcraft a few hundred years before? Though centuries apart, the psychedelic experiences were not always positive. For the flower children of the 1960s, taking the alkaloid-derivative LSD could lead to flashbacks, permanent psychoses, and in extreme cases suicide; for the witches of Europe, absorbing the alkaloids atropine and scopolamine from their flying salves could lead to the stake.

The atropine and ergot alkaloids did not cause witchcraft. Their effects, however, were interpreted as evidence against large numbers of innocent women, usually the poorest and most vulnerable in society. Accusers would make a chemical case against the witch: "She must be a

witch, she says she can fly" or "she must be guilty, the whole village is bewitched." The attitudes that had allowed four centuries of persecution of women as witches did not change immediately once the burnings were stopped. Did these alkaloid molecules contribute to a perceived heritage of prejudice against women—a view that may still linger in our society?

In medieval Europe the very same women who were persecuted kept alive the important knowledge of medicinal plants, as did native people in other parts of the world. Without these herbal traditions we might never have produced our present-day range of pharmaceuticals. But today, while we no longer execute those who value potent remedies from the plant world, we are eliminating the plants instead. The continuing loss of the world's tropical rain forests, now estimated at almost two million hectares each year, may deprive us of the discovery of other alkaloids that would be even more effective in treating a variety of conditions and diseases.

We may never know that there are molecules with antitumor properties, that are active against HIV, or that could be wonder drugs for schizophrenia, for Alzheimer's or Parkinson's disease in the tropical plants that are daily becoming closer to extinction. From a molecular point of view, the folklore of the past may be a key to our survival in the future.