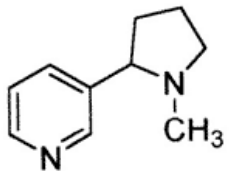
Catherine de Médicis, Queen of France. Smoking did not, however, meet with universal approval. Papal edicts banned the use of tobacco in church, and King James I of England is said to have authored a 1604 pamphlet decrying the "custome loathesome to the eye, hatefull to the nose, harmefull to the brain and daungerous to the lungs."

In 1634 smoking was outlawed in Russia. Punishment for breaking this law was extremely harsh—slitting of the lips, flogging, castration, or exile. Around fifty years later the ban was removed as Tsar Peter the Great, a smoker, promoted the use of tobacco. Just as Spanish and Portuguese sailors took chili peppers containing the capsaicin alkaloid around the world, so they introduced tobacco and the nicotine alkaloid to every port they visited. By the seventeenth century tobacco smoking had become widespread throughout the East, and draconian penalties, including torture, did little to stop its popularity. Although various countries, including Turkey, India, and Persia, at times prescribed the ultimate cure for addiction to tobacco—the death penalty—smoking is just as widespread in these places today as anywhere else.

From the beginning the supply of tobacco cultivated in Europe could not meet the demand. Spanish and English colonies in the New World soon started growing tobacco for export. Tobacco cultivation was highly labor intensive; weeds had to be kept under control, tobacco plants trimmed to the right height, suckers pruned, pests removed, and leaves manually harvested and prepared for drying. This work, done on plantations mainly by slaves, means that nicotine joins glucose, cellulose, and indigo as another molecule involved in slavery in the New World.

There are at least ten alkaloids in tobacco, the major one being nicotine. The content of nicotine in tobacco leaves varies from 2 to 8 percent, depending on the method of culture, climate, soil, and the process used to cure the leaves. In very small doses nicotine is a stimulant of the central nervous system and the heart, but eventually, or with larger doses, it acts as a depressant. This apparent paradox is explained by nicotine's ability to imitate the role of a neurotransmitter.



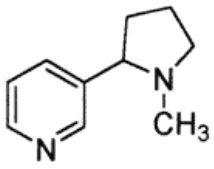
The structure of nicotine

The nicotine molecule forms a bridge at the junction between nerve cells, which initially heightens the transmission of a neurological impulse. But this connection is not readily cleared between impulses, so eventually the transmission site becomes obstructed. The stimulating effect of nicotine is lost, and muscle activity, particularly the heart, is slowed. Thus the blood circulation slows, and oxygen is delivered to the body and the brain at a lower rate, resulting in an overall sedative effect. This accounts for nicotine users who speak of needing a cigarette to calm their nerves, but nicotine is actually counterproductive in situations where an alert mind is required. As well, longtime tobacco users are more susceptible to infections such as gangrene that thrive in the low oxygen conditions from poor circulation.

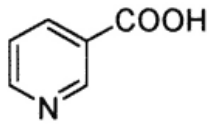
In larger doses nicotine is a lethal poison. Absorbing a dose as small as fifty milligrams can kill an adult in just a few minutes. But its toxicity depends not only on amount but also on how the nicotine enters the body. Nicotine is about a thousand times more potent when absorbed through the skin as when taken orally. Stomach acids presumably break down the nicotine molecule to some extent. In smoking much of the alkaloid content in tobacco is oxidized to less toxic products by the high temperature of burning. This does not mean tobacco smoking is harmless, just that if this oxidation of most of the nicotine and other tobacco alkaloids did not occur, smoking would invariably be fatal with only a few cigarettes. As it is, the nicotine that remains in tobacco smoke is particularly hazardous, being absorbed directly from the lungs into the bloodstream.

Nicotine is a potent natural insecticide. Many millions of pounds of nicotine were produced for use as an insecticide in the 1940s and 1950s

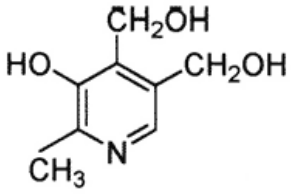
before synthetic pesticides were developed. Yet nicotinic acid and pyridoxine, with similar structures to nicotine, are not poisons. They are, in fact, beneficial—they are both B vitamins, essential nutrients for our health and survival. Once again a small change in chemical structure makes an enormous difference in properties.



Nicotine



Nicotinic acid (niacin)



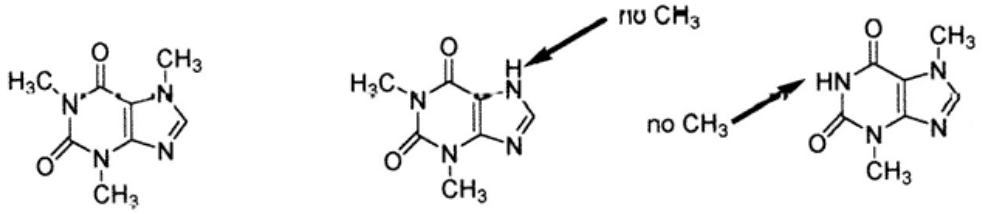
Pyridoxine (vitamin B_6)

In humans a dietary deficiency of nicotinic acid (also known as niacin) results in the disease pellagra, which is characterized by a set of three symptoms: dermatitis, diarrhea, and dementia. It is prevalent where the diet is almost entirely composed of corn and originally was thought to be an infectious disease, possibly a form of leprosy. Until pellagra was identified as caused by a lack of niacin, many of its victims were institutionalized in insane asylums. Pellagra was common in the southern United States in the early part of the twentieth century, but efforts by Joseph Goldberger, a doctor with the U.S. Public Health Service, convinced the medical community that it was indeed a deficiency disease. The name *nicotinic acid* was changed to *niacin* when commercial bakers did not want their vitamin-enriched white bread to bear a name that sounded too similar to nicotine.

THE STIMULATING STRUCTURE OF CAFFEINE

Caffeine, the third alkaloid connected to the Opium Wars, is also a psychoactive drug, but it is freely available almost everywhere in the world and is unregulated to such an extent that drinks laden with extra caf-

feine are manufactured and advertised as such. The structures of caffeine and the very closely related alkaloids theophylline and theobromine are shown below.



Caffeine *Theophylline* *Theobromine*

Theophylline, found in tea, and theobromine, in cocoa, differ from caffeine only in the number of CH_3 groups attached to the rings of the structure; caffeine having three and theophylline and theobromine each having two but in slightly different positions. This very small change of molecular structure accounts for the different physiological effect of these molecules. Caffeine is found naturally in coffee beans, tea leaves, and to a lesser extent cacao pods, cola nuts, and other plant sources mainly from South America, such as maté leaves, guarana seeds, and yoco bark.

Caffeine is a powerful central nervous stimulant and one of the most studied drugs in the world. The latest of numerous theories that have been suggested over the years to explain its effects on human physiology is that caffeine blocks the effect of adenosine in the brain and in other parts of the body. Adenosine is a neuromodulator, a molecule that decreases the rate of spontaneous nerve firing and thus slows the release of other neurotransmitters; therefore it can induce sleep. Caffeine cannot be said to wake us up, although it may feel like it does; its effect is really to hinder the normal role of adenosine in making us sleepy. When caffeine occupies adenosine receptors in other parts of the body, we experience a caffeine buzz: heartbeat rate increases, some blood vessels constrict while others open, and certain muscles more easily contract.

Caffeine is used medicinally to relieve and prevent asthma, to treat migraines, to increase blood pressure, as a diuretic, and for a host of other conditions. It is often found in both over-the-counter and prescription medications. Numerous studies have looked for possible negative side effects of caffeine, including its relationship to various forms of cancer, heart disease, osteoporosis, ulcers, liver disease, premenstrual syndrome, kidney disease, sperm motility, fertility, fetal development, hyperactivity, athletic performance, and mental dysfunction. So far there is no clear evidence that any of these can be linked to moderate amounts of caffeine consumption.

But caffeine is toxic; a fatal dose is estimated at about ten grams taken orally by an average-sized adult. Since the caffeine content for a cup of coffee varies between 80 to 180 milligrams, depending on the method of preparation, you would have to drink something like 55 to 125 cups, all at one time, in order to receive a lethal dose. Obviously, caffeine poisoning by this method is most unlikely, if not absolutely impossible. By dry weight, tea leaves have twice as much caffeine as coffee beans, but because less tea is used per cup and less caffeine is extracted by the normal method of making tea, a cup of tea ends up with about half the caffeine of a cup of coffee.

Tea also contains small amounts of theophylline, a molecule that has a similar effect to caffeine. Theophylline is widely used today in the treatment of asthma. It is a better bronchodilator, or bronchial tissue relaxant, than caffeine, while having less of an effect on the central nervous system. The cacao pod, the source of cocoa and chocolate, contains 1 to 2 percent of theobromine. This alkaloid molecule stimulates the central nervous system even less than theophylline, but as the amount of theobromine in cacao products is seven or eight times higher than the caffeine concentration, the effect is still apparent. Like morphine and nicotine, caffeine (and theophylline and theobromine) are addictive compounds; withdrawal symptoms include headaches, fatigue, drowsiness, and even—when caffeine intake has been excessive—nausea and vomiting. The good news is that caffeine clears the

body relatively quickly, a week at most—though few of us have any intention of giving up on the world's favorite addiction.

Caffeine-containing plants were probably known to prehistoric man. They were almost certainly used in ancient times, but it is not possible to know whether tea, cacao, or coffee was the first. Legend has it that Shen Nung, the mythical first emperor of China, introduced the practice of boiling the drinking water for his court as a precaution against illness. One day he noticed that leaves from a nearby bush had fallen into the boiling water being prepared by his servants. The resulting infusion was supposedly the first of what must now be trillions of cups of tea that have been enjoyed in the five thousand years since. Although legends refer to drinking of tea in earlier times, Chinese literature does not mention tea, or its ability to "make one think better," until the second century B.C. Other traditional Chinese stories indicate that tea may have been introduced from northern India or from Southeast Asia. Wherever the origin, tea has been a part of Chinese life for many centuries. In many Asian countries, particularly Japan, tea also became an important part of the national culture.

The Portuguese, with a trading post in Macao, were the first Europeans to establish a limited trade with China and become tea drinkers. But it was the Dutch who brought the first bale of tea to Europe at the beginning of the seventeenth century. Tea was initially very expensive, affordable only by the wealthy. As the volume of imported tea increased and import duties were gradually lowered, the price slowly fell. By the early eighteenth century tea was beginning to replace ale as the national beverage of England, and the stage was set for the role that tea (with its caffeine) would play in the Opium Wars and the opening of trade with China.

Tea is often seen as a major contributor to the American Revolution, although its role was more symbolic than real. By 1763 the British had successfully expelled the French from North America and were negotiating treaties with the natives, controlling expansion of settlements, and regulating trade. The colonists' unhappiness with control by the

British Parliament of what they saw as local matters threatened to turn from irritation to rebellion. Particularly galling was the high level of taxation on both internal and external trade. Though the Stamp Act of 1764–1765, which raised money by requiring revenue stamps for almost every type of document, was withdrawn, and though the duties on sugar, paper, paint, and glass were eliminated, tea was still subject to a heavy customs duty. On December 16, 1773, a cargo of tea was dumped into Boston Harbor by a group of irate citizens. The protest was really about "taxation without representation" rather than about tea, but the Boston Tea Party, as it was called, is sometimes considered the start of the American Revolution.

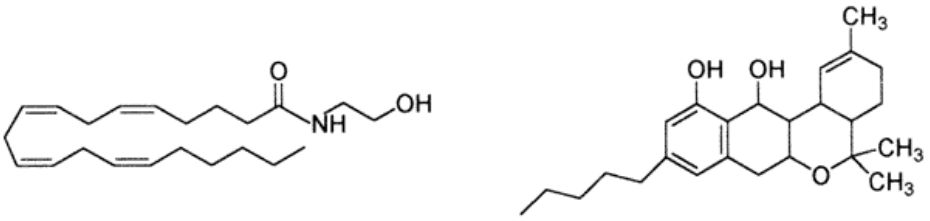
Archaeological discoveries indicate that the cacao bean was the first source of caffeine in the New World. It was used in Mexico as early as 1500 B.C.; the later Mayan and Toltec civilizations also cultivated this Mesoamerican source of the alkaloid. Columbus, upon returning from his fourth voyage to the New World in 1502, presented cacao pods to King Ferdinand of Spain. But it was not until 1528, when Hernán Cortés drank the bitter drink of the Aztecs in the court of Montezuma II, that Europeans recognized the stimulating effect of its alkaloids. Cortés referred to cacao by the Aztec description "drink of the gods," from which was to come the name of the predominant alkaloid, theobromine, found in the seeds (or beans) of the foot-long pods of the tropical tree *Theobroma cacao.* The names are from the Greek *theos,* meaning "god," and *broma,* meaning "food."

For the rest of the sixteenth century the drinking of chocolate, as it came to be called, remained the preserve of the wealthy and aristocratic in Spain, spreading eventually to Italy, France, and Holland and then to the rest of Europe. Thus the caffeine in cacao, though present in smaller concentrations, predates European caffeine use from either tea or coffee.

Chocolate contains another interesting compound, anandamide, which has been shown to bind to the same receptor in the brain as the phenolic compound tetrahydrocannabinol (THC), the active ingredient in marijuana, even though the structure of anandamine is quite differ-

Cacao pods from the Theobroma cacao *tree.* (Photo by Peter Le Couteur)

ent from the structure of THC. If anandamide is responsible for the feel-good appeal that many people claim for chocolate, then we could ask a provocative question: What is it that we want to outlaw, the THC molecule or its mood-altering effect? If it is the mood-altering effect, should we be considering making chocolate illegal?



Anandamide (left) from chocolate and THC (right) from marijuana are structurally different.

Caffeine was introduced to Europe through chocolate. It was at least a century later that a more concentrated brew of the alkaloid arrived in the form of coffee, but by then coffee had been used in the Middle East

for hundreds of years. The earliest surviving record of coffee drinking is from Rhazes, an Arabian physician of the tenth century. Doubtless coffee was known well before this time as the Ethiopian myth of Kaldi, the goatherd, suggests. Kaldi's goats, nibbling on the leaves and berries of a tree he had never noticed before, became frisky and started to dance on their hind legs. Kaldi decided to taste the bright red berries himself and found the effects as exhilarating as had his goats. He took a sample to a local Islamic holy man who, disapproving of their use, threw the berries on a fire. A wonderful aroma arose from the flames. The roasted beans were retrieved from the embers and used to make the first cup of coffee. Although it is a nice story, there is little evidence that Kaldi's goats were the true discoverers of caffeine from the *Coffea arabica* tree, but coffee may have originated somewhere in the highlands of Ethiopia and spread across northeastern Africa and into Arabia. Caffeine in the form of coffee was not always accepted, and sometimes it was even forbidden; nevertheless by the end of the fifteenth century Muslim pilgrims had carried it to all parts of the Islamic world.

A similar pattern followed the introduction of coffee to Europe during the seventeenth century. The lure of caffeine eventually won over the initial apprehension of officials of the Church and government as well as physicians. Sold on the streets of Italy, in cafés in Venice and Vienna, in Paris and Amsterdam, in Germany and Scandinavia, coffee has been credited with bringing greater sobriety to the population of Europe. To a certain extent it took the place of wine in southern Europe and beer in the north. No longer did workingmen consume ale for breakfast. By 1700 there were over two thousand coffeehouses in London; patronized exclusively by men, many came to be associated with a specific religion or trade or profession. Sailors and merchants gathered at Edward Lloyd's coffeehouse to peruse shipping lists, an activity that eventually led to the underwriting of trade voyages and the establishment of the famous insurance company Lloyd's of London. Various banks, newspapers, and magazines as well as the stock exchange are all supposed to have started life in London's coffeehouses.

The cultivation of coffee played an enormous role in the development of regions of the New World, especially Brazil and countries in Central America. Coffee trees were first grown in Haiti in 1734. Fifty years later half of the world's coffee derived from this source. The political and economic circumstances of Haitian society today are often attributed to the long and bloody slave uprising that started in 1791 as a revolt against the appalling conditions imposed on slaves toiling to produce coffee and sugar. When the coffee trade declined in the West Indies, plantations in other countries—Brazil, Colombia, the Central American states, India, Ceylon, Java, and Sumatra—rushed their product to the rapidly growing world market.

In Brazil in particular coffee cultivation came to dominate agriculture and commerce. Huge areas of land that had already been established as sugar plantations switched to growing coffee trees in the expectation of huge profits to be reaped from the bean. In Brazil the abolition of slavery was delayed through the political power of coffee growers, who needed cheap labor. Not until 1850 was the importation of new slaves into Brazil banned. From 1871 all children born to slaves were considered legally free, ensuring the country's eventual, although gradual, abolition of slavery. In 1888, years after other Western nations, slavery in Brazil was finally completely outlawed.

Coffee cultivation fueled economic growth for Brazil as railways were built from coffee-growing regions to major ports. When slave labor vanished, thousands of new immigrants, mainly poor Italians, arrived to work on the coffee plantations, thus changing the ethnic and cultural face of the country.

Continued coffee growing has radically changed Brazil's environment. Huge swaths of land have been cleared, natural forest cut down or burned, and native animals destroyed for the vast coffee plantations that cover the countryside. Grown as a monoculture, the coffee tree quickly exhausts soil fertility, requiring new land to be developed as the old becomes less and less productive. Tropical rain forests can take centuries to regenerate; without suitable plant covering erosion can re-

move what little soil is present, effectively destroying any hope of forest renewal. Overreliance on one crop generally means local populations forgo planting more traditional necessities, making them even more vulnerable to the vagaries of world markets. Monoculture is also highly susceptible to devastating pest infestations, like coffee leaf rust, that can wipe out a plantation in a matter of days.

A similar pattern of exploitation of people and the environment occurred in most of the coffee-growing countries of Central America. Starting in the last decades of the nineteenth century, the indigenous Mayan people in Guatemala, El Salvador, Nicaragua, and Mexico were systematically forced from their lands as coffee monoculture spread up the hillsides, which offered perfect conditions for cultivation of the coffee shrub. Labor was provided through coercion of the displaced population; men, women, and children worked long hours for a pittance and, as forced laborers, had few rights. The elite—the coffee plantation owners—controlled the wealth of the state and directed government policies in the pursuit of profit, fomenting decades of bitterness over social inequality. The history of political unrest and violent revolution in these countries is partly a legacy of people's desire for coffee.

From its beginning as a valuable medicinal herb of the eastern Mediterranean, the opium poppy spread throughout Europe and Asia. Today profit from illegal trafficking in opium continues to finance organized crime and international terrorism. The health and happiness of millions have been destroyed, directly or indirectly, by alkaloids from the opium poppy, yet at the same time many millions more have benefited from the judicious medical application of their amazing pain-relieving properties.

Just as opium has been alternately sanctioned and prohibited, so has nicotine been both encouraged and forbidden. Tobacco was once considered to have advantageous health effects and was employed as a cure for numerous maladies, but at other times and places the use of to-

bacco was outlawed as a dangerous and depraved habit. For the first half of the twentieth century tobacco use was more than tolerated—it was promoted in many societies. Smoking was upheld as a symbol of the emancipated woman and the sophisticated man. At the beginning of the twenty-first century the pendulum has swung the other way, and in many places nicotine is being treated more like the alkaloids from opium: controlled, taxed, proscribed, and banned.

In contrast, caffeine—although once subject to edicts and religious injunctions—is now readily available. There are no laws or regulations to keep children or teenagers from consuming this alkaloid. In fact, parents in many cultures routinely provide their children with caffeinated drinks. Governments now restrict opium alkaloid use to regulated medical purposes, but they reap large tax benefits from the sale of caffeine and nicotine, making it unlikely that they will give up such a lucrative and reliable source of income and ban either of these two alkaloids.

It was the human desire for three molecules—morphine, nicotine, and caffeine—that initiated the events leading to the Opium Wars of the mid-1800s. The results of these conflicts are now seen as the beginning of the transformation of a social system that had been the basis of Chinese life for centuries. But the role these compounds have played in history has been even greater. Grown in lands far from their origins, opium, tobacco, tea, and coffee have had a dramatic effect on local populations and on those people who have cultivated these plants. In many cases the ecology of these regions changed dramatically as native flora were destroyed to make way for acres of poppies, fields of tobacco, and verdant hillsides covered with tea bushes or coffee trees. The alkaloid molecules in these plants have spurred trade, generated fortunes, fueled wars, propped up governments, funded coups, and enslaved millions—all because of our eternal craving for a quick chemical fix.