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THE PREHISTORY OF PSYCHOACTIVE DRUG USE

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Most adults regularly use at least one psychoactive drug. Globally popular options include caffeine (found in coffee, tea, soft drinks, and chocolate), alcohol, nicotine, arecoline and other psychoactive compounds in areca nuts (i.e., betel nuts, used by 10-20% of the global population), THC and other cannabinoids, opioids, amphetamine and its chemical analogs found in khat and other plants, and cocaine (Gupta & Warnakulasuriya, 2002; Peacock et al., 2018; Verster & Koenig, 2018). Few realize, however, the extraordinary time depth in which people have been interacting with these plants.

The most influential scientific account of human psychoactive substance use focuses on the *mesolimbic dopamine system* (MDS), a collection of dopamine neurons in the midbrain of humans and many other animals that plays a central role in Pavlovian conditioning and similar types of reinforcement learning. According to this view, the MDS evolved to reinforce behaviors that increased access to so-called *natural rewards*, such as food, sex, and other necessities of survival and reproduction (Glimcher, 2011; Wise, 1996).

Surprisingly, many popular psychoactive drugs also stimulate the MDS. This fact provides for a compelling theory of drug use: Drugs happen to activate behavior-reinforcement circuitry in the brain, thereby reinforcing drug consumption (cf. Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015; Everitt & Robbins, 2016; Koob & Volkow, 2010; Wise, 1996). But it also raises an important question: Why would drugs, which are often harmful to the user, activate brain circuitry that evolved to reinforce biologically beneficial behaviors like obtaining food and sex?

The hijack hypothesis

Neurons communicate using a variety of neurotransmitters such as dopamine, serotonin, and acetylcholine. Neural functions are therefore vulnerable to disruption by environmental compounds that resemble these signaling molecules. According to

the *hijack hypothesis*, the MDS evolved long before inventions such as pipes, cigarette papers, hypodermic syringes, and the ability to synthesize or purify drugs made drug addiction possible (Wise, 1996). The MDS is therefore vulnerable to hijacking by chemicals that are evolutionarily novel, especially in their purity or concentration, are consumed in a novel fashion, and provide no evolutionary fitness benefits (e.g., Kelly & Berridge, 2002; Hyman, 2005; Volkow, Baler, & Goldstein, 2011).

Although the hijack hypothesis is widely accepted, it has never been empirically tested, and there are many reasons to doubt it. A range of evidence from human physiology, animal behavior, plant biology, and archaeology indicates that the human lineage has been exposed to potent psychoactive substances for hundreds of millions of years, that we are well-adapted to these substances, and that they might provide pharmacological and other benefits (Hagen et al., 2009, 2013; Hagen & Sullivan, 2018; Sullivan, Hagen, & Hammerstein, 2008; Sullivan & Hagen, 2002).

The evolution of psychoactive drugs in an ancient evolutionary arms race

Organisms harvest free energy from the environment to promote their own survival and reproduction. The earliest organisms, which appeared sometime between 3.5 and 4 billion years ago, probably harvested chemical energy, perhaps near geothermal vents (Weiss et al., 2016), and shortly thereafter some evolved to obtain energy from sunlight (Judson, 2017). Organisms that harvest energy from such inorganic sources are termed *autotrophs*.

Organisms that harvest energy from organic sources, such as eating other organisms, are termed *heterotrophs*. Although there is still debate, the first heterotrophs appear to have evolved from autotrophs to, ironically, feed on autotrophs (Schönheit, Buckel, & Martin, 2016). Early on, heterotrophs probably fed on dead autotrophs because energy availability and hence growth rates were too low to support predation (Judson, 2017). But after the evolution of oxygenic photosynthesis in cyanobacteria, circa 2.4 billion years ago, the concentration of oxygen in the atmosphere began to increase dramatically, which increased the free energy available for newly evolving organisms to exploit (Hohmann-Marriott & Blankenship, 2011). The first eukaryotes appear during this epoch.

The increased availability of energy enabled the evolution of heterotrophs that could survive and reproduce by eating *living* autotrophs, as well as other heterotrophs. This set the stage for a critical evolutionary dynamic: an evolutionary arms race in which autotroph and heterotroph prey evolved defenses against heterotroph predators, which evolved to evade or neutralize those defenses, selecting for better prey defenses, and so forth (Dawkins & Krebs, 1979). Armor, for example, first appears in the fossil record circa 700–800 million years ago (Porter, 2011). Arms races between predators and prey were key evolutionary forces driving the diversification, first, of single-celled eukaryotes, some of which could consume other cells (phagocytosis), and later, multicellular organisms, including the first animals (for brief review, see Judson, 2017).

Toxins are a key prey defense against predators. Extant cyanobacterial and other phytoplankton species at the base of the marine food web are notorious for producing a wide range of deadly toxins (Wiegand & Pflugmacher, 2005). Toxins continued to play a critical defensive role when the arms race between autotrophs and heterotrophs expanded to terrestrial environments circa 400 million years ago with the evolution of terrestrial plants and animals. Tens of thousands of plant toxins have been identified, many of which specifically target animal nervous systems (Wink, 2015). Microbes, fungi, and many animals also produce or sequester toxins, including neurotoxins, for defense and other functions.

With the exception of alcohol, all globally popular recreational drugs, including caffeine, nicotine, THC, arecoline, opioids, amphetamines, and cocaine, are plant defensive neurotoxins or their close chemical analogs (Sullivan, Hagen, & Hammerstein, 2008; Sullivan & Hagen, 2002). Nicotine, one of the most addictive drugs, is an especially dangerous plant neurotoxin. Smokers absorb about 1 mg of nicotine per cigarette, and chewers about 4 mg per wad (Hukkanen, Jacob, & Benowitz, 2005). Slightly higher doses of 4–8 mg cause burning of the mouth and throat, nausea, vomiting, and diarrhea. Even higher doses result in dizziness, weakness, and confusion, progressing to convulsions, hypertension, and coma. Ingestion of concentrated nicotine pesticides can cause death within five minutes (Landoni, 1991).

Toxin defenses

Human physiology was profoundly shaped by our co-evolution with toxic plants. The human lineage, which extends from our recent plant-eating primate ancestors to our more distant marine vertebrate and early eukaryotic heterotrophic ancestors that might have fed on potentially toxic cyanobacteria and other phytoplanktons, has been exposed to toxic compounds for at least half a billion and perhaps one billion years or more. As a consequence, we have evolved an extremely sophisticated, multi-layered toxin defense system.

Animals evaluate food, in part, via its taste. Vertebrates, including fish, have repertoires of bitter taste receptor proteins, coded by the T2R gene family, that detect a wide range of toxic substances (Meyerhof et al., 2010). Carnivorous species have the fewest T2R genes, whereas herbivorous species have the most, suggesting that exposure to plant toxins was a major selective force shaping the evolution of these genes (Li & Zhang, 2013). Humans have about 25 T2R genes, similar to other primates (Dong, Jones, & Zhang, 2009). All common plant drugs taste bitter, indicating that human physiology correctly identifies them as toxic.

If, despite its bitter taste, a plant neurotoxin is ingested, it must pass through multiple toxin defense systems before reaching the brain. Our bodies can be conceived as a set of compartments, such as the intestines and lungs, that are separated by tissue barriers made up of epithelial or endothelial cells linked together with special proteins forming "tight junctions." These tissue barriers include our skin, gastrointestinal tract, respiratory tract, and the blood brain barrier (BBB). The

barriers have several functions, such as allowing an influx of essential chemicals like sugar and oxygen into a compartment, and simultaneously preventing an influx of microorganisms and toxins (Mullin, Agostino, Rendon-Huerta, & Thornton, 2005). The barriers achieve these effects by limiting or enhancing passive diffusion across the cells and tight junctions, and also by active mechanisms that transport essential chemicals into a compartment and that neutralize and transport toxins and other xenobiotics out of a compartment using networks of xenobiotic-sensing receptors, xenobiotic metabolizing enzymes, and xenobiotic transporter proteins. Many toxins are metabolized and excreted by the gastrointestinal barrier, or trigger nausea and are expelled by vomiting, while at the same time triggering aversive learning mechanisms in the CNS that will help prevent future consumption.

Toxins that evade these barriers and pass into the bloodstream are immediately routed to the liver, an organ that is specialized for metabolizing toxins and other compounds. Should some quantities of plant neurotoxins remain, they then face the BBB, which prevents most toxins from entering the brain (Pardridge, 2012). The existence of the BBB is further evidence that neurotoxic compounds were a strong selection pressure on the human lineage (for a brief review of barrier and other toxin defenses, see Hagen & Sullivan, 2018, and references therein).

In summary, popular recreational drugs are neurotoxic plant pesticides, a diverse class of compounds that has infused the diets of human ancestors for hundreds of millions of years. These and other xenobiotics selected for a robust, multilayered toxin defense system that correctly identifies all drugs of abuse as toxins via bitter taste receptor and other xenobiotic-sensing proteins, and successfully metabolizes and excretes them. It is therefore doubtful that recreational plant drugs are best characterized as evolutionarily novel hijackers of reward circuitry (Hagen et al., 2009, 2013; Hagen & Sullivan, 2018; Sullivan et al., 2008).

The paradox of drug reward

Plants, such as tobacco, evolved neurotoxic pesticides, such as nicotine, to harm and deter herbivores, not reward them. Herbivores, in turn, evolved to avoid consuming toxic compounds. It is paradoxical that neurotoxic drugs of abuse activate reward and reinforcement mechanisms in the brain and that humans have long deliberately sought out and consumed them.

Self medication: the biological roots of human "recreational" and other psychoactive drug use?

Much of human physiology functions to safely extract nutrients, such as lipids, carbohydrates, and proteins, from plant and animal foods. These are then delivered to various tissues along with sufficient quantities of oxygen to provide the energy and resources necessary to run and maintain the body. Plant toxins have always been an important component of the stream of plant foods that coursed through the bodies

of human ancestors on a daily basis. The diverse array of toxin defense mechanisms shows that plant toxins posed a considerable threat to physiological functioning, but could plant toxins also have provided benefits?

Plant toxins evolved to harm plant pathogens and predators, which include microbes, fungi, helminths, insects and other arthropods, and vertebrates. The same categories of organisms that eat plants also eat animals. It is therefore conceivable that humans and other animals evolved to deliberately seek out and ingest limited quantities of plant toxins to self-medicate their own infections. Self-medication, originally proposed as a nonhuman primate behavior, is now documented in diverse nonhuman species, including fruit flies, ants, moths, butterflies, honey bees, birds, sheep, and goats (see references in Hagen et al., 2013). There is also increasing evidence that Neanderthals self-medicated with plant and fungal toxins (Weyrich et al., 2017).

Plant neurotoxins, in particular, target organisms with nervous systems, such as helminths, insects and other arthropods, and vertebrates. Human psychoactive drug-seeking might be grounded in an evolved, albeit unconscious, strategy to self-medicate infections of helminths, ticks, fleas, and other macroparasites (Hagen et al., 2009; Sullivan et al., 2008). It is intriguing that most popular recreational plant drugs, including coffee, tea, tobacco, cannabis, and betel nut, are toxic to helminths, and in hunter-gatherers, tobacco and cannabis use is negatively associated with helminth infections (Roulette et al., 2014; Roulette, Kazanji, Breurec, & Hagen, 2016a). Some helminth species have a larval stage that migrates through the lung, which perhaps was a selection pressure specifically to smoke neurotoxic plants. There are also robust but poorly understood interactions between the immune system and drug use, which could be hints of an adaptation to detect and self-medicate infections (see Hagen, Roulette, & Sullivan, 2013, for a brief review).

Psychoactive drugs are also often used for performance enhancement. Nicotine and caffeine, for example, appear to improve attention and memory (Einöther & Giesbrecht, 2013; Rezvani & Levin, 2001). Hagen et al. (2009) proposed that plants might be under selection to produce toxins with these cognitive-enhancement properties. Toxic and venomous animals have evolved distinctive sounds, odors, or coloring, such as the hornet's black and yellow bands, to improve the ability of potential predators to notice, recognize, and remember them, so as to better avoid them, a phenomenon termed aposematism. Toxic plants are similarly under selection to improve attention and memory in herbivores, so that herbivores notice, recognize, and remember which plant caused the toxic reaction so as to stop eating it and more reliably avoid eating it in the future. But plants need not rely solely on activating herbivore sensory organs. Instead, because toxic plants are ingested, they could potentially achieve the same effects by evolving compounds that "[pass] through the blood–brain barrier to directly trigger attention, aversion, and other learning mechanisms in the CNS" (Hagen et al., 2009, p. 77). If so, this could explain why some psychoactive plant drugs enhance aspects of cognitive performance (Hagen et al., 2009; for further evidence for this hypothesis, see Ejsmond and Provenza, 2018).

Hallucinogens such as mescaline, dimethyltryptamine, and psilocybin and ergot alkaloids (found in numerous species of fungi) are also toxins, and their hallucinogenic effects are probably byproducts of their neurotoxic effects. Aposematism, however, might have had some role to play in their evolution. Aposematic organisms typically have striking coloration, or produce distinctive odors or sounds. Hallucinogens also generate striking visualizations and other sensory experiences, usually accompanied by symptoms of toxification such as nausea and vomiting, that might improve an herbivore's ability to notice, recognize, and remember the toxic plant or fungus, so as to stop eating it and more reliably avoid it in the future (unlike, e.g., coloration, however, hallucinogenic plants only generate sensory effects once consumed).

The neurotoxin regulation hypothesis

Herbivore foods are almost always infused with toxins and other plant secondary compounds. Because avoidance of toxins was impossible, herbivores, including membes of the human lineage, should have evolved mechanisms to regulate their intake so as to avoid poisoning (Torregrossa and Dearing, 2009). If deliberate consumption of neurotoxic plants, which is extremely dangerous and potentially lethal, provided some fitness benefits to members of the human lineage, there would have been selection for neurophysiological mechanisms to maintain circulating levels of toxins by carefully regulating their intake and excretion. Psychoactivity, for instance, might itself be a cue of neurotoxicity that in some cases promotes consumption of neurotoxic plants (Hagen et al., 2009, 2013).

Salt intake provides a useful analogy. Many animals, including humans, seek out natural sources of salt and other minerals (Klaus & Schmidg, 1998). Prior to the discovery of sodium's role in body fluid homeostasis, our evolved appetite for salt was utterly mysterious. There are complex neuronal and endocrine mechanisms, including special salty taste receptors on the tongue, that regulate intake and excretion of milligrams of this valuable environmental chemical to maintain sodium homeostasis (Geerling & Loewy, 2008), even though there is no conscious awareness of its biological benefits. Similarly, bitter taste receptors and other xenosensors, in conjunction with neuronal, immunological, and other mechanisms, might regulate intake and excretion of milligrams of neurotoxins for their medicinal or social benefits without any conscious awareness of these benefits. Unlike the sodium regulation mechanism, however, the putative neurotoxin regulation mechanism must titrate a diverse range of compounds.

In support of regulated intake, cigarette smokers titrate nicotine, altering their smoking behavior in response to changes in nicotine content so as to maintain a relatively constant blood concentration of nicotine (Scherer & Lee, 2014). In support of regulated excretion of potentially therapeutic substances, whose levels should be maintained or increased when fighting an infection, there is a widespread downregulation of xenobiotic metabolizing enzymes and xenobiotic transporters during infections (including helminth infections), mediated by inflammatory cytokines.

This dramatic downregulation of xenobiotic defense gene expression is poorly understood, although it might serve to ensure sufficient haptic resources for the acute phase response to infection, e.g., upregulated expression of C-reactive protein (Klein et al., 2015). Because its effect is to maintain or increase circulating levels of xenobiotics (Keller et al., 2016; Klein et al., 2015; Mimche et al., 2014; Morgan, Lee, & Nyagode, 2011), however, such as potentially therapeutic plant toxins, it is worth considering that it might (also) be part of an evolved neurotoxin regulation system.

The important role of cultural transmission

Many, perhaps most, organisms use individual learning, such as associative learning, to optimize their behavior to local environmental conditions (van Duijn, 2017). Individual learning carries a cost, however. To discover the optimal behavior, an organism must often attempt behaviors that are suboptimal or even detrimental. To individually learn which plants are edible, for example, herbivores must sample unknown plants, which will include toxic plants, and will thus pay the occasional price of getting sick. Social learning, i.e., cultural transmission, avoids the cost of individual learning. Socially learning which plants are edible by observing the food choices of knowledgeable individuals provides the benefit of safe foods without paying the cost of occasional toxification (e.g., Rogers, 1988). Plant food choice was undoubtedly one of the selection pressures for the evolution of social learning in the human lineage. Infants look to adults before touching a plant (Elsner & Wertz, 2019), for example, and pregnant women in traditional societies learn from their mothers, grandmothers, and mothers-in-law which teratogenic foods to avoid (Henrich & Henrich, 2010; Placek & Hagen, 2015, Placek, Madhivanan, & Hagen, 2017). If there was natural selection on the human lineage to deliberately consume neurotoxic plants for medicinal or other purposes, the resulting adaptations for regulated neurotoxin intake would certainly rely heavily on socially learning to identify substances that maximize the benefits of ingestion and minimize the costs.

Does drug teratogenicity explain age and sex differences in drug use?

Global surveys of the prevalence of recreational drug use find dramatic age and sex differences. There is almost no drug use by children under the age of 10. Between the ages of 10 and 20, there is a rapid, switch-like transition to drug use by both sexes. Almost all users of a particular drug will have started use by early adulthood (Degenhardt, Stockings, Patton, Hall, & Lynskey, 2016). See Figure 25.1.

Sex differences in drug use are more variable across populations, type of drug, age, birth cohort, and other factors. By and large, though, the prevalence of drug use is greater in males than in females for most substances at most ages (e.g., tobacco use;

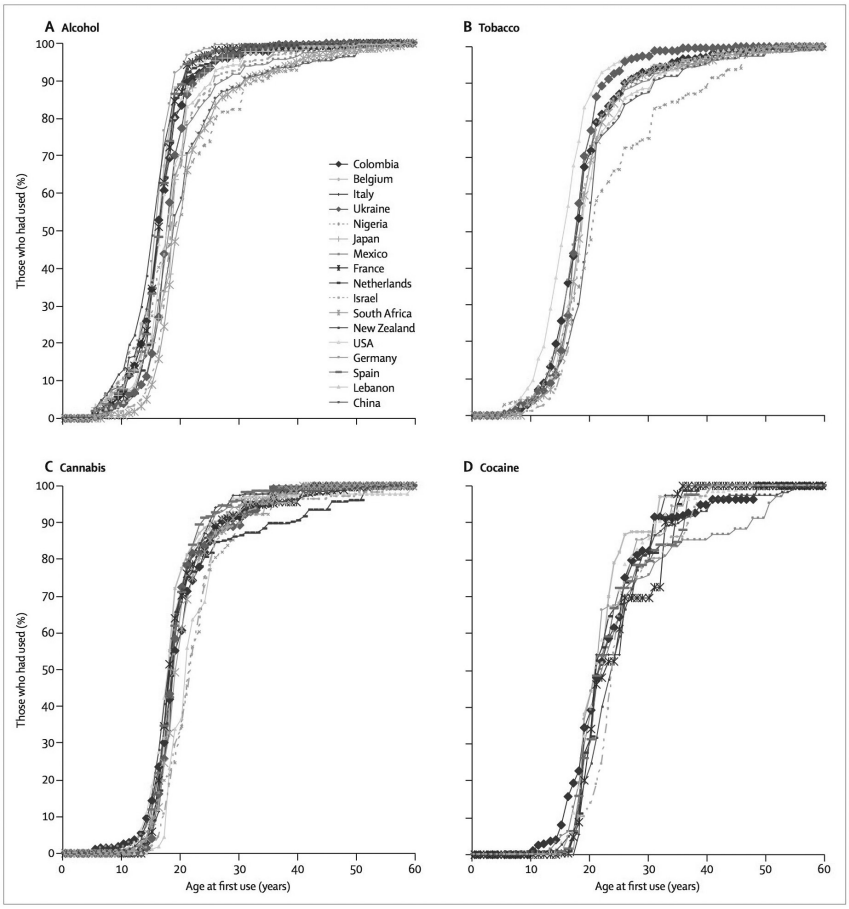

Figure 25.1 Cumulative distribution of self-reported age of first use of alcohol, tobacco, cannabis, and cocaine in a large (n = 85,052) cross-national sample of users of these substances. The similarities of these patterns across both drugs and countries suggest the existence of a developmental "switch" to drug use during adolescence.

Source: Figure from Degenhardt et al. (2016).

see Figure 25.2), a sex difference that tends to emerge in late adolescence and early adulthood (for review, see Hagen et al., 2013).

The near absence of drug use in children is typically assumed to be due to parental and other societal restrictions. Although to our knowledge this assumption has never been empirically tested, it is reasonable for tobacco, which is subject to numerous forms of control, such as laws in many countries that prevent sales to minors and extensive advertising campaigns that warn about health hazards. It is much less reasonable for caffeine, a bitter-tasting plant drug that shows promise as a pesticide

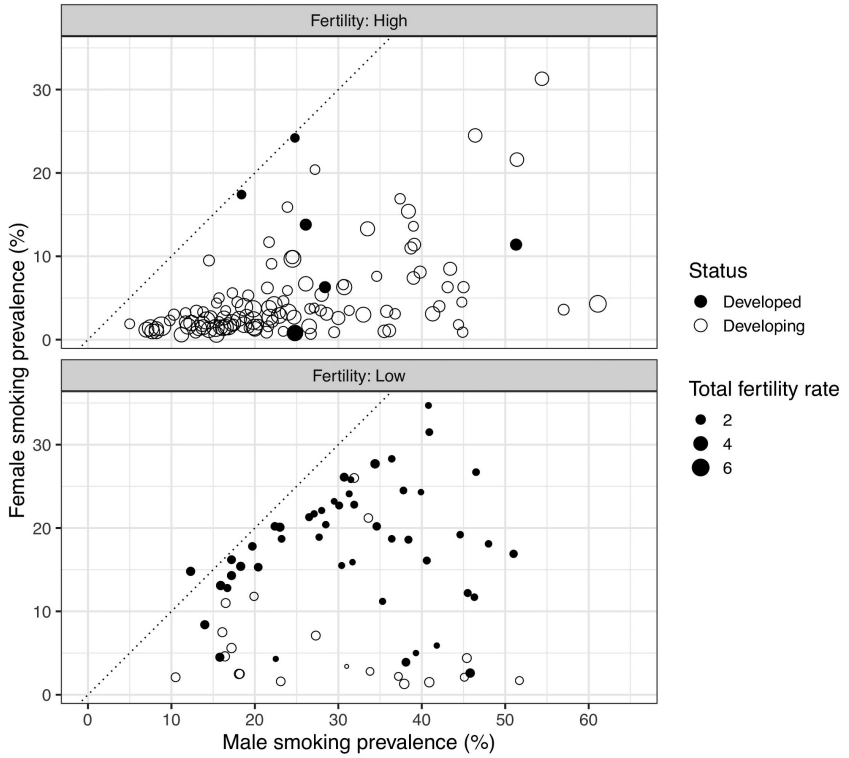

Figure 25.2 Prevalence of smoking by sex in 184 countries in 2012. Each dot is one country, and the size of the dot represents the total fertility rate (TFR). High fertility: TFR > 2; low fertility: TFR $\leq$ 2. Dotted line: equal smoking prevalence. Countries below the line have a prevalence of male smoking that is greater than the prevalence of female smoking. The prevalence of female smoking is generally much lower in developing countries that tend to have high TFR compared to developed countries that tend to have low TFR.

Source: Smoking and country developmental status from Ng et al. (2014). Total fertility rate data from United Nations, Department of Economic and Social Affairs, Population Division (2015).

and repellent for slugs, snails, birds, and insects, yet which is present in, or added to, many foods marketed to children, such as soft drinks, energy drinks, and chocolate. Despite children's ready access to caffeine, their consumption of caffeine is quite low compared to adults, and begins to increase in adolescence, just like consumption of other drugs (Hagen & Sullivan, 2018).

The sex difference in drug use is also widely thought to be due to societal restrictions on women's drug use. According to this view, differences in traditional sex roles translate into gendered social norms, such as disapproval of female drug use and social rewards for male rebelliousness and drug use. Cross-national variation in female smoking prevalence is similarly tied to cross-national variation in women's

social, political, and economic power, that is, to variation in gender inequality. In countries with high gender inequality, women might face considerable social and economic barriers to obtaining and smoking cigarettes, whereas in countries with low gender inequality, women might face fewer such barriers (Hagen, Garfield, & Sullivan, 2016; Hitchman & Fong, 2011). We refer to these ideas as the *social restriction model* of age and sex differences in drug use.

Alternatively, many plant defensive chemicals, including psychoactive plant toxins, are teratogenic, i.e., disrupt development (Panter, Welch, & Gardner, 2017). Nicotine, for example, is a teratogen that interferes with acetylcholine signaling, which has a unique trophic role in brain development. Nicotine exposure can disrupt all phases of brain assembly (Dwyer, Broide, & Leslie, 2008), and smoking during pregnancy causes poor fetal growth, and is associated with increased risk of number of other poor pregnancy outcomes, such as spontaneous abortions and stillbirths (Cnattingius, 2004). The costs of plant toxin ingestion are therefore higher for individuals whose brains and other organs are still developing, i.e., fetuses and children. There is considerable evidence that toxin defense mechanisms are upregulated in children and pregnant women. Infants are more hesitant to touch plants compared to other objects (Wertz & Wynn, 2014). Children are neophobic and picky about food, have a higher density of taste buds on the tip of the tongue, and are more sensitive to bitter substances. Women also have more taste buds than men, appear to have higher bitter taste sensitivity, and during pregnancy are averse to spicy foods and have upregulated activities in most xenobiotic metabolizing enzymes (Hagen et al., 2013).

According to the neurotoxin regulation hypothesis, then, the higher costs of exposure to plant teratogens suffered by children should reduce their drug consumption relative to other segments of the population. As the development of the brain and other organs nears completion, the costs of teratogen exposure are reduced, so drug consumption should increase (i.e., in adolescence and early adulthood). Similarly, pregnant women, and women in their reproductive years more generally, should have lower drug use compared to postmenopausal women and men. Because the transition to drug use occurs in adolescence and early adulthood (see Figure 25.1), an early transition to motherhood might preempt the transition to drug use. The reduction in female drug use should therefore be more pronounced in traditional (developing) populations with an earlier age at first marriage and first birth, and higher total fertility rates. Indeed, whereas the prevalence of male smoking is virtually identical in developing vs. developed countries (32% vs. 30.1%, respectively), the prevalence of female smoking is dramatically lower in developing countries (3.1%) than in developed countries (17.2%) (Ng et al., 2014). We refer to this view as the *developmental disruption model* of age and sex differences in drug use. See Figure 25.3.

In support of the developmental disruption model, Hagen et al. (2016) found that, controlling for gender inequality and per capita income, countries with higher total fertility rates (TFR) had lower female smoking rates. They also found that the prevalence of female smoking increased in older, postmenopausal women relative to younger women, and that this increase was greater in countries with high TFR (see also Roulette, Hagen, & Hewlett, 2016b).

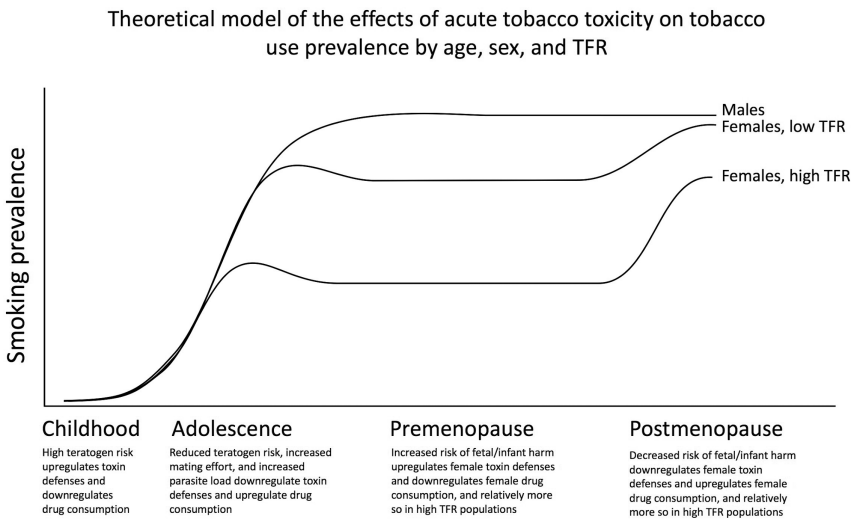

Figure 25.3 Theoretical model of age and sex differences in use of tobacco and other plant drugs; TFR: total fertility rate

Source: Figure from Hagen et al. (2016).

If the stark age and sex differences in psychoactive drug use seen in contemporary populations also characterized ancestral populations (but see the following text), then it is possible that conspicuous consumption of psychoactive substances could serve as social signals. For instance, the transition to drug use in adolescence could be an honest signal of developmental maturity, i.e., that one has transitioned from the juvenile to the adult phase of life, which is information that would be valuable to potential mates and other social partners. Conspicuous consumption by reproductive-age women might signal that they are not pregnant, information that is valuable to potential mates (Hagen et al., 2013).

Age and sex differences in drug use could be altered by the following factors: If the anti-parasitic or other benefits of drug use outweighed the risk of disrupted development, individuals might start using drugs at younger ages, or during their reproductive years. In addition, avoidances of toxic and teratogenic substances are often acquired by social learning. If a particular drug is not among the substances identified as dangerous during pregnancy by, e.g., mothers, grandmothers, or mothers-in-law, then women who are pregnant or in their reproductive years might not avoid it.

There is some overlap between the social restriction model and the disrupted development model of age and sex differences in drug use in that both involve authority figures, such as parents, warning against the use of psychoactive substances. In the case of the social restrictions model, however, there is either an implicit or explicit assumption that there is a conflict between the innately rewarding experience

of drug consumption regardless of age or sex and the warnings from authority figures who aim to prevent drug use by certain others despite often enjoying these substances themselves. According to the disrupted development model, in contrast, the interests of children and pregnant women are aligned with those of the authority figures, all of whom are keen to avoid developmental harm to the child or fetus, and there is a synergy between bitter taste and other cues of toxicity, and warnings from parents and trusted others.

Ethanol

Ethanol is a globally popular psychoactive drug that is not a plant toxin but is instead a metabolic byproduct of yeast metabolism. It would therefore seem to be a glaring exception to the foregoing theoretical framework, which emphasizes the co-evolution of the human lineage with neurotoxic wild foods.

Ethanol could be less of an exception than it seems, however, as it might have evolved to serve as a toxic defensive chemical for yeast. Adenosine triphosphate (ATP) is a critical molecule that provides energy for cellular processes. Yeasts can typically use two different pathways to produce ATP from sugars: respiration and fermentation. Respiration, which requires oxygen, metabolizes sugar to CO_2 to produce a high yield of ATP (e.g., 18 ATP per glucose in *S. cerevisiae*), whereas fermentation, which does not require oxygen, metabolizes sugar to ethanol to produce a low yield of ATP (e.g., 2 ATP per glucose). Interestingly, many yeasts, including *S. cerevisiae*, use fermentation even in the presence of oxygen, termed the Crabtree effect, resulting in a much lower yield of ATP than they would if they used respiration. Why would many yeasts have evolved to pay this price? One influential hypothesis is that ethanol is toxic to other microbes, such as bacteria, that are competing for the same sugars in fruit. Thus, instead of defending themselves with toxins, yeasts are defending their food supply (Piškur, Rozpędowska, Polakova, Merico, & Compagno, 2006). An alternative hypothesis for the Crabtree effect is that although the yield of ATP in fermentation is low compared to respiration, its rate of production is higher, which would provide a competitive growth advantage (Pfeiffer & Morley, 2014). The two hypotheses are not mutually exclusive.

Whatever the evolutionary explanation for the Crabtree effect, ethanol is a small, toxic organic molecule infusing plant foods, such as rotting fruit, and it therefore might trigger the same toxin defense mechanisms and putative neurotoxin regulation mechanisms as other plant neurotoxins (Sullivan, 2017). In support, the distribution of ages of onset for alcohol use is very similar to that of plant drugs (see Figure 25.1).

There is more to the story, however. Humans and other primates possess several genes for alcohol dehydrogenases (ADH), enzymes that metabolize alcohol to acetaldehyde, which suggests that the human lineage has long been exposed to alcohol, and that there was some fitness benefit to metabolizing it. Fruits, an important plant food, often ferment, and ethanol has more calories per gram than carbohydrates (7.1 vs. 4.1). Primates might have evolved to be attracted to ethanol both as a cue of food

and as food itself (Dudley, 2000, 2014). In a breakthrough, Carrigan et al. (2015) discovered that in early human ancestors prior to our divergence from orangutans, ADH4, the first enzyme exposed to alcohols in the digestive tract, was efficient at metabolizing long-chain alcohols that are common in plants, but it was quite inefficient at metabolizing ethanol. About ten million years ago, however, a mutation occurred in ADH4 in the lineage leading to the extant African apes that dramatically increased its catalytic activity for ethanol, but reduced its activity on long-chain alcohols. Carrigan et al. argue that around this time there was a shift to a more terrestrial lifestyle in this lineage, and fermenting fruit on the ground became an important fallback food. The change in ADH4 would have allowed more efficient exploitation of this ethanol-rich resource. Thus, ethanol might have been an important component of the diet in the human lineage for millions of years.

A further twist involves much more recent evolution of ADH in modern humans, as well as of aldehyde dehydrogenase (ALDH), which metabolizes acetaldehyde to acetic acid. Most research has focused on functional alleles of ADH1B, the alcohol dehydrogenase enzyme with the highest concentration in the adult liver. A derived allele that is at high frequency in modern East Asian populations (rs1229984), but low frequency in African and European populations, underwent recent positive selection that is geographically and temporally associated with the advent of rice cultivation, circa 7,000–10,000 ybp (Peng et al., 2010; Wang et al., 2016). The resulting enzyme has substantially higher activity metabolizing ethanol compared to the ancestral allele, and there is evidence of convergent evolution of the same allele in European populations (Galinsky et al., 2016).

Additionally, there is an inactive allele of ALDH2 (rs671) that is at relatively high frequency in East Asia and virtually absent elsewhere. Enzyme activity is greatly reduced in heterozygotes for this allele and abolished in homozygotes.

Several hypotheses have been put forward for positive selection on these ADH1B and ALDH2 alleles. Rice cultivation and storage in Asia were probably associated with both inadvertent and deliberate fermentation and increased consumption of ethanol. The effect of the ADH1B allele is to accelerate the formation of acetaldehyde, and that of the ALDH2 allele to inhibit the metabolism of acetaldehyde. The joint effect is therefore to increase levels of circulating acetaldehyde. Because acetaldehyde, like its chemical cousin formaldehyde, is highly toxic, one set of hypotheses proposes that these alleles were positively selected because acetaldehyde helps defend against infection by one or more pathogens (e.g., Goldman & Enoch, 1990). A more intensively researched hypothesis is that because acetaldehyde is responsible for many of the aversive effects of ethanol consumption, these alleles were selected because they deter alcohol use, thereby reducing the risk of alcoholism. Both alleles are, in fact, associated with reduced risk of alcoholism (for review, see Polimanti & Gelernter, 2018).

There are problems with both hypotheses, however. Whereas there is solid evidence of positive selection on the ADH1B allele, so far there is little compelling evidence of positive selection on the rs671 ALDH2 allele (Polimanti & Gelernter, 2018). If rs671 was not positively selected, this undercuts hypotheses that depend on

selection for increased levels of acetaldehyde. In addition, although the negative association of these alleles with alcoholism is large relative to other findings of genome-wide association studies, it explains little of the variance in alcohol use behaviors. Finally, ADH1B is expressed in many tissues and metabolizes many substrates other than ethanol, so positive selection on the ADH1B allele could be unrelated to ethanol metabolism. For a review, see Polimanti and Gelernter (2018).

Nevertheless, the most parsimonious hypothesis for positive selection on the Asian ADH1B allele is that, similar to the scenario described earlier for ADH4, the transition to agriculture increased exposure to ethanol, an environmental toxin (and nutrient), and there has subsequently been selection for increased ability to metabolize it. This hypothesis is supported by the facts that the Asian ADH1B allele increases enzyme activity, there has been convergent selection on the same allele in Europe, there is a similar African-specific allele of ADH1B (rs2066702) that also increases enzyme activity, and there seems to have been global recent positive selection on ethanol metabolic pathways (Johnson & Voight, 2018). The selection pressure might have involved ethanol's toxic effects. Ethanol is a teratogen (Goodlett, Horn, & Zhou, 2005), for instance, and its consumption has been generally (though not consistently) associated with pregnancy loss (Avalos, Roberts, Kaskutas, Block, & Li, 2014). Improved pregnancy and child developmental outcomes might therefore have been one selection pressure for improved ethanol metabolism during the transition to agriculture.

Archaeological evidence for prehistoric psychoactive drug use

Archaeology offers a deep time perspective into coupled human-plant interactions. While there has been a much greater emphasis on studies of plant for food (i.e., subsistence studies, domestication, and agriculture), a growing number of archaeologists are investigating evolutionary aspects of addiction and drug use by people, sometimes over very great time depths. The present status and use patterns of these substances have been influenced by thousands of years of co-evolution with human beings – and human manipulation seems to have enhanced the intoxicant properties of several of these plants, spreading them to areas where they may have not previously naturally occurred and in some cases leading to new species or domesticated varieties (e.g., tobacco).

As in modern times, humans have used an array of psychoactive plants not only as food but also for social, ceremonial, recreational, and medicinal reasons. Many societies have individuals, such as shamans, traditional healers, and doctors, who specialize in learning the medicinal benefits of toxic plants. Archaeologists often rely on early written records, explorer journals, and ethnographies to understand intoxicant plant use in traditional societies and interpret archaeological findings. From such records, coupled with a growing body of archaeological data, it is clear that intoxicant plants played (and continue to play) a central role in the ceremony and religion of many cultures.

Tracking ancient substance use

The widespread use of drugs and their importance in many cultures suggest that people *really like drugs*, and that they have liked them for a very long time. Firm evidence of psychoactive drug use in the past is possible through the identification of charred plant material, pollen, and other palaeoenvironmental data, but this can be complicated due to the rarity of charred seeds and costs of such analyses. The presence of certain ceremonial vessels, storage containers, and drug uptake-related artifacts (e.g., pipes, snuff trays) can signal use of intoxicant plants, and biochemical studies are increasing the precision with which we can identify prehistoric use of specific species or classes of plants. Chemical residue analysis and identification of alkaloid biomarkers via radioimmunoassay and, more commonly, liquid or gas chromatography-time of flight mass spectrometry (LC-TOFMS/GC-TOFMS) offer novel means of approaching these issues, and over the past 15 years a number of studies have produced compelling results demonstrating the global scale and deep time use of such substances.

Ancient roots of psychoactive drugs in shamanism and medicine

Shamanism is often associated with rituals involving out of body experiences, vision quests, and similar pursuits designed to connect individuals with spirit worlds through altered states of consciousness (ASC). ASC bring a heightened awareness or the sense of alternate realities to individuals and may be induced through a variety of means, including repetitive or trance-inducing percussion, fasting, withholding sleep, as well as the use of a wide array of hallucinogenic plants and substances (e.g., Carod-Artal, 2015; Torres, 1995). Some of the better known of these entheogens include datura (*Datura* sp.), peyote (*Lophophora williamsii*), *Anadenanthera* snuff, Belladonna (*Atropa belladonna*), blue lotus (*Nymphaea caerulea*), certain mushrooms (*Psilocybe* sp., *Amanita muscaria*), and bufotoxins secreted by some toads (*Bufo* sp.), but there are many others, and even great quantities of some potent species of tobacco are documented to have induced hallucinogenic states (Janiger & de Rios, 1976). *Ritual healing theory* suggests that such practices have very deep roots. In this line of thinking (see useful review in Sosis & Alcorta, 2003), early nonhuman primates engaged in rudimentary rituals (such as grooming) as a means of alleviating social stress; such rituals became increasingly complex as humans engaged in ASC and were common among hunting and gathering communities throughout the world (de Rios & Winkelman, 1989; McClenon, 1997). McClenon (1997, p. 345) argues that "shamanic/hypnotic suggestion may reduce pain, enhance healing, control blood loss, facilitate childbirth, and alleviate psychological disorders," and thus ASC ritual offered evolutionary benefits for individuals "more responsive to such suggestions." While intriguing, such behavior is difficult to track archaeologically and is not without controversy.

The "flower burial" at Shandihar Cave in northern Iraq, which dates to Middle Palaeolithic times (circa 60,000 BC), is widely regarded as the earliest possible

evidence of shamanistic intoxicant plant use in the world. The burial contained the skeleton of an adult male Neanderthal (*Homo neanderthalensis*) argued to have been a shaman, an idea largely based on the presence of a wide range of medicinal plant "pollen clusters" including the *Ephedra altissima*, a plant associated with the stimulant ephedra (Leroi-Gourhan, 1975; Lietava, 1992), though this has been disputed (Sommer, 1999).

Many regard European Palaeolithic rock art created by early *H. sapiens* as being associated with ASC and psychoactive drugs. In their neurological model of "entoptic phenomena," Lewis-Williams and Dowson (1988) linked Palaeolithic art with ASC and drug use. The logic goes like this: Neurologically, human brains remained the same since Palaeolithic times, thus, people experienced ASC in the same way they do today, with abstract geometric patterns and visual hallucinations common (Sacks, 2012). In other words, "the abstract patterns and visual hallucinations created under ASC are universal, since they are effects of the central nervous system" (Guerra-Doce, 2015, p. 97). However, this line of thinking is not without debate (e.g., Guerra-Doce, 2015); see also *Current Anthropology* commentaries following Lewis-Williams and Dowson (1988). After the Neolithic there is increasing evidence of ancient drug consumption in many parts of Europe and Asia, for example, through the presence of artifacts interpreted to be associated with the consumption of plants such as opium (*Papaver somniferum*) and cannabis.

Since they first colonized the New World 14,000 or more years ago, Early Americans likely used psychoactive plants for medicinal, ceremonial, and shamanistic reasons. In the absence of chemical and archaeobotanical evidence, many researchers who track ancient use rely on the same logic linking Old World Palaeolithic art with ASC and drug use, as well as a rich ethnographic record linking certain artifact types, designs, and the like with shamanism and ritual drug use. This includes studies that posit that rock art and some types of painted and decorated ceramics are associated with datura and tobacco shamanism (Litzinger, 1981; VanPool, 2009). If taken in large doses, tobacco, a very common intoxicant plant used throughout the Americas (see the following text), can cause ASC experiences, hallucinations, and visions, and is documented as having been sought after for its mind altering effects by shamans for vision quests, curing, and other religious purposes (Janiger & De Rios, 1976; Siegel, 1989; Wilbert, 1987). In South America wooden "snuff trays" and tubes signal anadenanthera snuffing practices in South American shamanism (Torres & Repke, 2014), although identifying key chemical compounds associated with the plant has proven difficult in at least one study (Echeverría & Niemeyer, 2013).

Ethanol and fermented beverage consumption

Fermented beverages are commonly associated with ceremony, feasting, and ritual practices in different areas of the globe. Production of ethanol-containing drinks is a relatively straightforward process that was discovered independently by ancient peoples in different parts of the world. Archaeologists track the development of fermented beer, wine, and grog through early written records

and hieroglyphics, and in a growing number of studies, through chemical and archaeobotanical analysis.

China has the longest established records of fermented beverage consumption. Written records of millet and barley or wheat based beer production occur as early as the Shang dynasty in China (circa 1,250–1,046 BC) (Wang et al., 2016; Zhang, 1994). A study of Chinese ceramics dating to as early as 700 BC identified residues suggesting the artifacts were associated with a concoction of "rice, honey, and fruit (hawthorn fruit and/or grape)" and that such drinks "paved the way for unique cereal beverages used in later times" (McGovern et al., 2004, p. 17593). A multi-proxy record of starch grain, phytolyth, and chemical data associated with a "beer-making tool kit" (ceramic pots, funnels, amphorae) discovered in northern China reveals an ancient beer "recipe" consisting of barley, broomcorn millet, Job's tears, and tubers, and supports a much earlier (5,000-year) record of beer production in China (Wang et al., 2016).

Later dating but no less revealing studies have employed chemical trace analysis to track grog consumption in Nordic Europe (McGovern, Hall, & Mirzoian, 2013), herbal medicinal wines in Egypt (McGovern, Mirzoian, & Hall, 2009), and a 2,500-year-old record of grape wine production in southern France, an industry that possibly set the stage for the spread of wine in other parts of Europe and the world (McGovern et al., 2013). Tree resin additives were common in the ancient world and served to protect against "wine disease," to cover "off-tastes and off-aromas," as well as for medicinal purposes. Similarly, herbs such as rosemary, mint, thyme, and mugwort were often added to wines and beers in ancient Egypt, China, and Etrusca, for medicine and taste (McGovern, 2010; McGovern et al., 2009, 2013). As one leading scholar of the archaeology of fermented beverages put it, "ancient wine . . . served as more than a social lubricant or aromatic beverage, as is customary today. In addition to its eventual role as a powerful religious symbol, grape wine and other alcoholic beverages were the medicines of antiquity. . . . alcoholic beverages were an excellent means to dissolve and administer botanical concoctions externally and internally" (McGovern et al., 2013, p. 10151).

Evidence for fermented beverages is largely absent in North America, but South American examples include archaeological studies of ancient chicha (maize) beer drinking in the Peruvian Andes via plant microfossil studies (Logan, Hastorf, & Pearsall, 2012). Archaeological studies suggest the possibility of ancient fermented cacao drinks in addition to better known "chocolate" drinks (see next section). For example, Henderson, Joyce, Hall, Hurst, and McGovern (2007) found that ceramic vessels from the Puerto Escondido site in Honduras differ significantly in form from later Classic period vessels. Earlier dating pots do not seem to facilitate frothing (associated with traditional Mesoamerican style chocolate drinks), so the study authors hypothesize that they may have been associated with another cacao preparation method, such as a fermented beverage. Fermented cacao is also suggested in some hieroglyphics on Classic Maya polychrome vessels, which refer to "tree-fresh" cacao, which evokes the concoction resulting from the initial period of fermentation from the pulp of the cacao pod (Stuart, 2006). While intriguing, the use of fermented cacao drinks has yet to be confirmed chemically.

Stimulants: ancient performance enhancers?

Ancient stimulants include a wide range of products including coffee (thought to originate in Ethiopia), oolong and many other teas (Asia), betel nut (Southeast Asia), tobacco (North and South America), coca (South American Andes), cacao or chocolate (*Theobroma cacao*, South America, Mesoamerica, southwestern US), and cassina (*Ilex vomitoria*) (southeastern United States). Coca is used by many people living in the South American Andes. Several studies including Cartmell, Aufderheide, Springfield, Weems, and Arriaza (1991) and Rivera, Aufderheide, Cartmell, Torres, and Langsjoen (2005) have confirmed a 2,000–3,000 year record of coca use via the detection of biomarkers including benzoylecgonine (BZE), a metabolic product of cocaine in the hair of male and female burials.

Some stimulants were associated with high status ceremonials and purgative rituals. Cassina and cacao were derived of psychoactive plants used in elite ceremonials in North America. Chemical evidence tracing the ritual use of these plants archaeologically has been a major emphasis in recent years, and based on such work it seems clear that both cacao and cassina were highly esteemed ceremonial drink plants used by elites for hundreds if not thousands of years (e.g., Crown et al., 2012; Crown & Hurst, 2009; Henderson et al., 2007; Washburn, Washburn, & Shipkova, 2011).

Traditionally reddened teeth associated with betel nut chewing was seen as a mark of beauty among many societies in Southeast Asia. Betel nut chewing involves a mixture of limestone paste, areca nut, Piper betel vine leaves, and sometimes tobacco (in more recent times). Archaeological evidence of the practice includes archaeobotanical remains of betel vine and areca found at a site in Timor dating to as early as 13,000 years before present, and numerous cases of stained teeth in human burials at sites throughout the region dating to after 5,000 years ago (Fitzpatrick, Nelson, & Reeves, 2001).

Pathways to domestication? The origins of tobacco and cannabis ritual

Tobacco (*Nicotiana* sp.) and cannabis (*Cannabis* sp.) are thought to have been some of the earliest cultivated plants in the world. Cannabis is thought to have evolved in the steppes of central Asia (Mongolia and Siberia) possibly 12,000 years ago, and later spread throughout the Asian and European continents. As with tobacco in the New World, cannabis is thought to have been one of the earliest plant cultigens in the Old World. There is some debate about when cannabis was first used as a psychoactive, however. Cannabis plant parts have been found in early archaeological sites, but in many cases may have been associated with non-psychoactive use; hemp or non-psychoactive cannabis has a variety of uses, especially as a fiber for cloth, paper, and rope/cordage, and continues to be used by many groups for such purposes to the present day. Palaeoenvironmental and archaeological evidence reveals an 8,000-year record of cannabis use throughout Eurasia, though an increase in key markers suggests an increase in psychoactive use around 5,000–4,000 years ago (Long, Wagner,

Demske, Leipe, & Tarasov, 2017). Psychoactive use is strongly suggested by the presence of numerous cannabis plants/plant parts in tombs found in the Turpan Basin of Central Eurasia, including a remarkable 2,800–2,400 year-old burial of a man who was shrouded in 13 complete cannabis plants (Jiang et al., 2016).

Tobacco has New World origins and is thought to have been first domesticated in the Andes region of South America about 6,000–8,000 years ago (Goodspeed, 1954; Winter, 2000a). At contact, numerous tobacco species were used by indigenous peoples throughout the Americas who regarded it as a sacred plant with great power. Winter (2000a) hypothesized that tobacco was not only the earliest domesticated plant in the Americas, perhaps even predating and setting the stage for maize agriculture, but one of the first plants used by the initial colonists of the Americas. In this scenario, early Ice Age hunter-gatherers came from Siberia around 13,000 years or more ago, and this was a place with an existing complex of shamanistic practices and medicinal plant use. Early groups would have readily recognized the special qualities of tobacco and thus were likely to have adopted the plant quite early in time.

Domesticated tobaccos such as *N. rustica* and *N. tabaccum* were used primarily by farmers throughout South America, Mesoamerica, the Caribbean, and the eastern US, while hunter-gatherer fishers used numerous indigenous (coyote) tobacco species (Figure 25.4a). While once regarded as a largely "wild" species, it is clear that hunter-gatherers regarded tobacco as a special plant, and cultivation practices seem to have resulted in new tobacco varieties as well as anthropogenically extending tobacco to places far outside of its natural range (Turner & Taylor, 1972; Tushingham & Eerkens, 2016).

At contact tobacco was ingested in a variety of ways – through snuffing, chewing, eating, and smoking (in pipes, cigars, and cigarettes) and by enema. Of these techniques smoking in pipes is the most likely to be recognized archaeologically. Archaeological pipes (Rafferty, Lednev, Virkler, & Chovanec, 2012, refers to them as "nicotine delivery devices") are an innovation that dates to as early as 4,000–5,000 ybp in North America, but they become much more common after approximately 2,000 years ago. In any case, without direct chemical or archaeobotanical evidence it should not be assumed that people used the pipes at all times and in all places to smoke tobacco since historic native groups in North America smoked 100 or so different species of plants, including tobacco (Moerman, 1998). To date the earliest chemical evidence of tobacco use via the identification of nicotine in pipes is associated with artifacts in the eastern US (Carmody et al., 2018; Rafferty, Lednev, Virkler, & Chovanec, 2012), but biochemical discoveries in northwestern North America are demonstrating deep time continuity of tobacco smoking and possibly cultivation practices by hunter-gatherer-fishers, including the far interior Northwest, a region where tobacco was previously depicted as being introduced by traders and explorers after contact, demonstrating deep time continuity of indigenous tobacco smoking in a place where tobacco has been depicted as being introduced by early Euro-American traders and explorers (Tushingham et al., 2013; Tushingham et al., 2018b) (Figure 25.4).

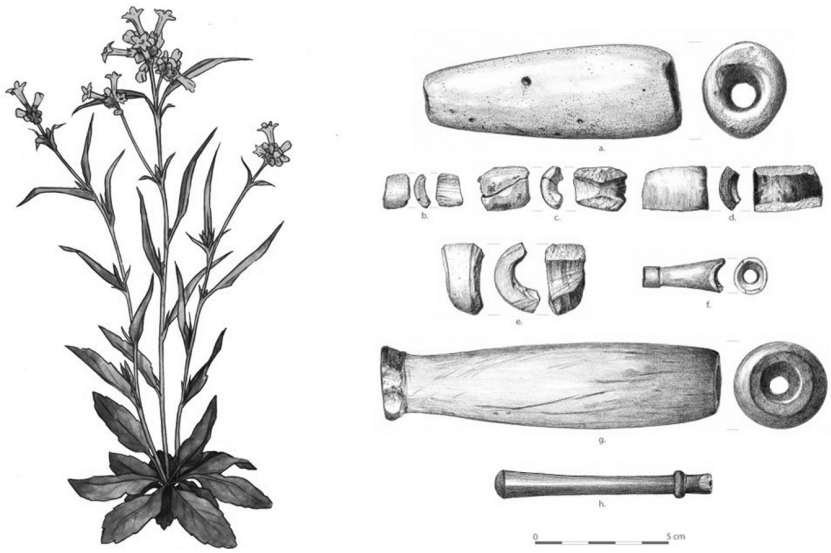

Figure 25.4 Tobacco, often smoked in pipes, was a widespread intoxicant plant used by indigenous groups throughout the Americas for thousands of years. Image at left: *Nicotiana quadrivalvis*, a preferred indigenous tobacco species widely used by hunter-gatherer-fisher groups in western North America (illustration by Emily H. Hull). Image at right: the northernmost biochemical evidence of pre-contact tobacco use is represented by these nicotine positive pipes from archaeological sites in the northwestern Plateau (illustration by Tammara Norton; see Tushingham et al., (2018b).

Figure 25.4 is to be made available as a downloadable e-resource at [URL to be supplied].

Ancient gender and age patterns of drug use

While the vast majority of archaeometric studies work with residues extracted from archaeological artifacts, recent innovations have made it possible to identify drug alkaloids in the human hair of mummies (Cartmell et al., 1991; Echeverría & Niemeyer, 2013; Niemeyer, de Souza, Camilo, & Echeverria, 2018; Rivera et al., 2005) as well as the dental calculus (mineralized plaque) scraped from ancient human teeth (Eerkens et al., 2018; Tushingham et al., 2018a). When coupled with demographic data about individual burials (e.g., age, sex, health, status based on grave goods, etc.) these innovations are giving archaeologists an unprecedented window into understanding drug use patterns in ancient societies.

Tobacco use is a major focus in recent chemical studies of human hair and dental calculus, and several of these studies are providing insight into several evolutionary models reviewed earlier, for example, those positing that avoidance of plant toxins is an evolved response by women of reproductive age (to protect fetuses and nursing infants from harmful biochemicals) and younger children (to avoid deleterious growth effects). If true, tobacco use should be reduced in children and reproductive

age women compared to adult men and post-reproductive women (Hagen et al., 2016; Roulette et al., 2014). See Figures 25.2 and 25.3.

Tobacco's harmful effects on infants are well-known today, a fact that is reflected in one provocative study from South America, where Niemeyer et al. (2018) identified nicotine and cotinine in a chemical analysis of hair from a perinate from northern Chile. Quantitative segmental hair analysis suggested the perinate died shortly after or during delivery, leading the authors to posit that the mother consumed very high quantities of tobacco and thus was a "tobacco shamaness" who "might have experienced a miscarriage, since tobacco consumption by pregnant women is strongly associated to spontaneous abortions and perinatal death" (Niemeyer et al., 2018, p. 130). It is indeed a puzzle why a pregnant woman would ingest so much tobacco, as the deleterious effects on infants must have been known by prehistoric people. However, it is unclear whether this was an anomaly, or if there was some other reason. Tobacco is documented as a "strong medicine," used to treat a wide range of ailments (e.g., Groark, 2010, pp. 14–16; Stewart, 1967), as well as an abortifacient (Breedlove & Laughlin, 1993; Noumi & Djeumen, 2007). Thus, although speculative, it is possible the woman had ingested high amounts of tobacco because it was used to treat a serious illness, because she had or was in the process of having a miscarriage and was ingesting tobacco to speed the process along, or simply because she no longer wanted to bring her child to term.

The greater frequency of dental calculus in the archaeological record (preserved human teeth are much more common than preserved human hair) is giving archaeologists an expanded understanding of tobacco use in larger populations. A pilot study investigating patterns of tobacco use in pre-contact Native American populations analyzed dental calculus samples from burials excavated from sites in central California (Eerkens et al., 2018). Nicotine was identified in 2 of the 10 analyzed samples, a male and an older female, providing support for the evolutionary models reviewed earlier. However, a follow up study is providing mixed results: Tushingham et al. (2018a) identified nicotine in 7 of 60 tested dental calculus samples from another central California site, but the researchers were surprised to discover that the majority (6 of the 7) of the samples were associated with females, suggesting women may have been more commonly tobacco users than the ethno-historic record would suggest. Also, tobacco use was not as age restricted as expected, with nicotine positive female burials including overlapping estimated individual age ranges from 20–25, 25–34, 30–34, 40–45, and 40–44 years of age, at the time of death.

Unfortunately, at least at this point, it is difficult to say much about degree of use. In other words, although the chemical evidence tells us that these women were tobacco users, we do not know enough about the process of uptake and preservation of nicotine in dental calculus to know much about the *amount* of tobacco they were using. Tushingham et al. (2018a) suggest the women were tobacco chewers since most of their nicotine positive teeth were in posterior areas of the mouth (versus males who tended to have positive anterior teeth, possibly a sign of pipe use). It could be that women were chewing relatively low amounts of tobacco as self medication or performance enhancement (see the preceding text), for example,

as a mild stimulant on a daily basis, high enough to reach the limits of detection by archaeologists, but too low to adversely impact unborn children.

In addition, mortality rates in such populations are highest among young children and the elderly, and lowest among those of reproductive age (e.g., Burger, Baudisch, & Vaupel, 2012). Thus, the presence of young adult women in this sample is somewhat unusual. Perhaps they were severely ill, and self-medicating with tobacco. There are many challenges to inferring the distributions of health and health-related behaviors in prehistoric populations from skeletal samples, however (the so-called osteological paradox; DeWitte & Stojanowski, 2015; Wood et al., 1992). The apparent use of tobacco by reproductive age women should therefore be interpreted cautiously. Nevertheless, there are contemporary high fertility populations in which the prevalence of female tobacco use is relatively high (see Figure 25.2).

It is interesting that ethnohistorically, tobacco was both smoked and chewed with a mixture of shell lime in many places in central California (Winter, 2000b), and among the Yokuts of this area, most men and women drank a "lime and tobacco emetic" in winter months for fasting purposes and to "dream of supernatural beings" (Winter, 2000b, p. 35). Additional research is clearly needed to flesh out these patterns, and work is currently underway that involves studies of the dental calculus of modern drug users (to better understand preservation dynamics and expand ancient dental calculus studies to other drugs in addition to tobacco), in addition to significantly expanding sample sizes of archaeological studies, in terms of both number of archaeological sites and individuals analyzed.

While few adults today have not used or been impacted by one or more of the substances discussed in this chapter, few realize the deep time history of humanity's interactions with these plants. In many cases, psychoactive plants used by prehistoric humans have in recent times been refined into incredibly potent and addictive substances, with profound global health consequences. Studies that investigate the evolutionary history of psychoactive drug use by humans provide a deep time perspective on addiction, self-medication, and other complex cultural and physical interactions of psychoactive substances.

Concluding remarks

For hundreds of millions of years, human and other lineages of plant-eating animals were exposed to dietary toxins, including neurotoxins, on a nearly daily basis, as evidenced by the evolution of extremely sophisticated and effective toxin defense mechanisms such as the blood brain barrier and other barrier tissues, large families of genes for bitter taste and other xenobiotic-sensing receptors, xenobiotic metabolism enzymes, xenobiotic transporter proteins, and aversive learning circuitry in the CNS that is triggered by toxin exposure. The archaeological record provides increasing evidence that deliberate human psychoactive substance use is not simply a modern phenomenon. The correct evolutionary explanation for human psychoactive substance seeking is not yet known. Self-medication, a behavior documented in many other species, is one promising hypothesis, however, especially since the medical

use of plants is ubiquitous across cultures and there is increasing evidence for self-medication in the archaeological record.

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