Evolutionary Origins of Human Alcoholism in Primate Frugivory

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ABSTRACT

Evolutionary origins of alcohol consumption have rarely been considered in studies of ethanol addiction. However, the occurrence of ethanol in ripe and decaying fruit and the substantial heritability of alcoholism in humans suggest an important historical association between primate frugivory and alcohol consumption. Olfactory localization of ripe fruit via volatilized alcohols, the use of ethanol as an appetitive stimulant, and the consumption of fruits with substantial ethanol content potentially characterize all frugivorous primates, including hominoids and the lineage leading to modern humans. Patterns of alcohol use by humans in contemporary environments may thus reflect a maladaptive co-option of ancestral nutritional strategies. Although diverse factors contribute to the expression of alcoholism as a clinical syndrome, historical selection for the consumption of ethanol in the course of frugivory can be viewed as a subtle yet pervasive evolutionary influence on modern humans.

THE CONCEPT OF Darwinian medicine places the study of human disease within an evolutionary context (Williams and Nesse 1991, 1994; Nesse and Williams 1999). This is even true of efforts to understand addiction, the physiological dependence on a psychoactive or mind-influencing substance. As with addictions generally, the disease of alcoholism represents a major challenge to public health. Most interpretations of addiction in humans have emphasized the relative novelty of psychoactive chemicals; historical exposure to such substances is assumed to have been negligible, although ancestral neuroethological pathways are likely activated in contemporary manifestations of substance dependence (Nesse and Berridge 1997; Vallee 1998; Nesse 1999; Smith 1999). This perspective dominates current mechanistic investigations of the biological underpinnings of addiction. Relative to

other psychoactive compounds, however, ethanol occupies a unique position in the nutritional ecology of *Homo sapiens*. Hominoids, along with other animal frugivores, regularly ingest ethanol derived from yeast-based fermentation of naturally occurring fruit sugars. As a consequence, historical selection for finding and consuming ripe fruit has likely facilitated the evolution of appetitive behaviors that associate ethanol with caloric gain. This use of ethanol as a nutritional cue and substrate characterizes a diversity of frugivorous animal taxa, including various mammals, birds, *Drosophila*, and even fruit-feeding butterflies. The ethanol ingested during frugivory originates from the metabolic activity of sugar-feeding yeasts, and consumption of fermenting fruits thus represents a conceptual starting point for animal behaviors that ultimately may be expressed in patterns of alcohol abuse by modern humans.

FRUITS AND FERMENTATION

Since the work of Pasteur in the nineteenth century, fermentation of sugars by yeasts has been universally recognized. In nature, sugars within fruits represent the predominant substrate for such fermentation. Sugars naturally occur within the mesocarp (pulp) of fruit and serve as the primary nutritional reward for frugivores that subsequently disperse seeds from the fruit. Birds and mammals are the principal taxa involved in such behavior, and are typically attracted to and consume only ripe fruit. Although the condition is not well defined, ripeness indicates both readiness for consumption and the availability of associated nutritional rewards. For example, sugar concentrations within ripe fruits range from trace quantities to levels as high as 61% of fruit mass, with typical values of 5 to 15% (Whiting 1970; Tucker 1993; Baker et al. 1998).

By contrast, unripe fruit contains seeds in the state of maturation for which dispersal would be maladaptive. Accordingly, developing fruits express a variety of physical and chemical defenses that deter consumption by potential dispersers. Related measures protect against consumption by microbial pathogens (see Thompson and Willson 1979; Herrera 1982; Janzen 1983). The ripening of immature fruit is a complex biochemical process that yields changes in color, softening of texture, increased expression of volatiles, and conversion of starch to sugars (Brady 1987; Tucker 1993). The ripening process thus relaxes defenses against premature consumption by dispersers, but concomitantly renders the fruit more vulnerable to attack by microbes. Fruits are most susceptible to microbial decay once ripeness is attained, particularly given that a considerable period of time may pass before the fruit is consumed by a frugivore. Because such decay can potentially discourage or even preclude dispersal by vertebrates (e.g., Borowicz 1988; Cipollini and Stiles 1993a), fruit decomposition can be viewed as a race between microbes and dispersal agents to gain nutritional advantage (Janzen 1977).

As one of the primary agents of fruit decay, yeasts are common both on and inside fruits (see Batista et al. 1961; Last and Price 1969; Cipollini and Stiles 1992, 1993b; Spencer and Spencer 1997). Moreover, the widespread occurrence of antifungal agents within ripe fruits suggests considerable evolutionary pressure on plants to impede fungi-induced fermentation and decomposition (Cipollini and Stiles 1992; Cipollini and Levey 1997a–c). Fermentation of fruit sugars by yeasts yields a number of different alcohols, although ethanol is usually predominant. The production of ethanol by yeasts has been viewed as an evolved strategy that renders ripe fruit aversive to vertebrates (Janzen 1977), although there are no data that substantiate this possibility. Ethanol may similarly serve to inhibit the growth of microbial competitors, and yeast metabolism in laboratory and oenological contexts is itself substantially inhibited at ethanol concentrations greater than 12–15%. Unfortunately, the role of ethanol inhibition for wild yeast strains growing on natural substrates appears never to have been investigated. Also, the potential role of ethanol as a defense against consumption by either microbial or vertebrate consumers is likely to be both concentration-dependent and taxon-specific.

Nonetheless, the widespread occurrence of yeasts in fruits and the presence of abundant sugar for fermentation suggest that ripe fruits generally may contain substantial quantities of ethanol. Ethanol concentrations within ripe or decaying fruits that occur in nature seem

not to have been investigated. Instead, available data derive from domesticated fruits that are placed in the field as oviposition sites for the fly genus *Drosophila*. These studies record ethanol concentrations in decomposing fruit that range from trace quantities to values as high as 5% (see Gibson et al. 1981; McKechnie and Morgan 1982; Oakeshott et al. 1982). The relevance of these measurements to decomposition of wild fruit crops is not entirely clear. Cultivated fruits may be artificially selected either for reduced defense against microbial pathogens in order to yield greater productivity, or alternatively for increased postharvest defense to reduce microbial spoilage. Fermentation of fruit crops may also be more pronounced in warm and humid environments that promote both yeast growth and rapid decomposition. Of such habitats, tropical forests are of primary interest here, given the ecological associations of many frugivorous primates.

THE HISTORICAL ECOLOGY OF HOMINOID FRUGIVORY

Ripe fruit is a scarce commodity within tropical forests (Richards 1996; Leigh 1999). Temporal fruiting patterns of tropical trees are often highly seasonal, and the considerable distances between synchronously fruiting trees require extensive travel by fruit-eaters to move from one fruit crop to another. Intraspecific and interspecific competition among frugivores is intense, especially when fruit availability is highly variable. Such conditions require efficient foraging schemes in order to satisfy the nutritional requirements of frugivores, and may have promoted the elaboration of spatial memory and cognitive abilities among arboreal primates (Milton 1981, 1988, 1993). The mechanisms used to locate food in the wild have not been studied in primates, although olfactory cues are likely to be important for frugivorous taxa. Odor plumes from ripe fruit, including such low-molecular weight volatiles as ethanol and other alcohols (Nursten 1970), potentially function as long-distance signals that indicate fruit availability to appropriate dispersers. Selection for rapid consumption of ripe fruit is equally likely, given the competition from other frugivorous taxa and the presence of microbial agents of decay.

In this context, it is important to examine the frugivorous heritage of *Homo sapiens*. Ancestrally, frugivory emerged as a major dietary strategy among anthropoid taxa by the mid- to late Eocene (Kay et al. 1997), suggesting selective advantages for as many as 40 million years to taxa that efficiently foraged on fruits. Frugivorous adaptations among primates likely occurred even earlier, however, given the probable fruit-based diet of the catarrhine precursors to anthropoids (Andrews and Aiello 1984). Basal hominoids appeared approximately 24 million years ago (Ma), as seen in the fossil genus *Proconsul* and the clade leading to the extant gibbons. Teeth of *Proconsul* are consistent with a diet of soft fruit, and frugivory is similarly the predominant dietary mode of extant gibbons and siamangs (see Chivers 1977; Gittins and Raemaekers 1980; Andrews and Martin 1991). Additional hominoid lineages appearing subsequently to the origin of gibbons but prior to the hominids include the subfamilies Afropithecinae, Dryopithecinae, Kenyapithecinae, and the Ponginae (including the extinct genus *Sivapithecus* and the modern orangutans). With the exception of the unresolved dryopithecine diet, frugivory has been inferred for the aforementioned extinct lineages (see Kay 1977; Andrews and Aiello 1984; Teaford and Walker 1984; Pickford 1985; Teaford 1988; Andrews 1992, 1996). Similarly, extant orangutans are primarily frugivorous and feed mostly on ripe fruits (e.g., Rodman 1988; Leighton 1993).

Such patterns of frugivory, with a possible shift from soft to harder fruits, apparently persisted until the appearance of hominids, including the australopithecines, gorillas, chimpanzees, and the genus *Homo* (Walker 1981; Grine and Kay 1988; Andrews and Martin 1991; Andrews 1992). The *Homo-Pan* divergence occurred at 4.5–5.5 Ma, with an earlier split of *Gorilla* at 5.5–7 Ma (Goodman et al. 1994). Diets of early hominids are not known with any precision, but a similarity with the diet of modern chimpanzees has been inferred (e.g., Gaulin and Konner 1977; Grine and Kay 1988). Chimpanzees feed preferentially on plant material (approximately 94% of the diet), mostly in the form of energy-rich ripe fruits (Ghiglieri 1984; McGrew et al. 1988; Wrangham et al. 1991; Malenky and Wrangham 1994). Lowland gorillas consume large quanti-

ties of sugar-rich fruit in an opportunistic fashion, according to availability (Rogers et al. 1990; Williamson et al. 1990; Tutin et al. 1991; Kuroda et al. 1996; Yamagiwa et al. 1996; Remis 1997), and the generally folivorous (leaf-eating) mountain gorillas also engage seasonally in frugivory (Goodall 1977; Yamagiwa and Mwanza 1994). Dietary diversification has clearly characterized hominids within the last 5 Ma (e.g., Sponheimer and Lee-Thorp 1999), particularly with the inclusion of animal fat and protein. Even in modern hunter-gatherer societies, however, such sources of food represent less than 50% of the total diet (see Eaton and Konner 1985; Milton 1987). In sum, these observations suggest a deep-reaching frugivorous heritage for the human diet. Most suggestive is the predominantly frugivorous diet of our closest relatives, the chimpanzees, together with either nearly exclusive frugivory (gibbons, orangutans) or partial frugivory (gorillas) in all other extant hominoid taxa.

THE COMPARATIVE BIOLOGY OF ETHANOL INGESTION

Because ripe fruits may contain significant quantities of ethanol, animal frugivores can potentially use this substance as a sensory stimulant for resource localization and, by virtue of ethanol's association with sugars, for purposes of caloric gain. Unique among the addictive substances, however, ethanol can also represent a direct nutritional reward: the caloric value of ethanol (7.1 kcal/g) is nearly twice that for carbohydrates (4.1 kcal/g). The energetic gain associated with ethanol catabolism can thus be substantial. For example, humans who regularly consume alcoholic beverages may derive 2 to 10% of their total caloric intake from ethanol, whereas this value can be as high as 50% for alcoholics (Bebb et al. 1971; Lieber 1988). Such a high proportion of caloric intake derived from ethanol has also been used in clinical contexts to define alcoholism operationally.

Frugivores in general may display patterns of ethanol intoxication and addiction similar to those of modern humans. In the biomedical literature, nonhuman models of human alcoholism have generally been termed "animal" models. This term is misleading, however, and neglects naturally occurring inges-

tion of alcohol that potentially characterizes all frugivores, primate or otherwise. Considerable effort has been devoted to the experimental development of nonhuman models of alcoholism, primarily using rodents and primates (e.g., Lester and Freed 1973; Mello 1973; Cicero 1979; Pohorecky 1981; Ervin et al. 1990). Particularly with rodents, various experimental protocols have been developed for the administration of ethanol, and these experiments permit subsequent artificial selection for the genetically based expression of addictive behavior and withdrawal symptoms (see Cicero 1980; Li 1991). These and related experiments have demonstrated a substantial heritable component to ethanol addiction in rodents (Li 1991; Crabbe et al. 1994).

Most such studies with rodents and other nonhuman taxa explicitly attempt to simulate alcohol consumption in modern humans, providing ethanol in dilute form as an adjunct to an otherwise solid diet. Sometimes this approach is justified by the claim that ethanol consumption has not historically been important for the animal taxon under consideration (e.g., Deitrich and McClearn 1981; Higley et al. 1991). Ethanol-seeking behavior of hominid taxa in natural contexts has never been evaluated, and experimental studies of alcoholism in primates have instead emphasized liquid consumption of low-concentration ethanol (e.g., Fitz-Gerald 1972; Pieper et al. 1972; Higley et al. 1991). Recognition of a frugivorous diet in taxa studied, however, suggests that further insight might be derived by evaluating nutritional and addictive responses to ethanol under more natural conditions. The caloric implications of ethanol consumption also deserve further experimental attention, given the obligate association of ethanol and sugars within fermenting fruit. Sugars and ethanol potentially interact to stimulate feeding—rodents increase their consumption of liquid ethanol when sucrose is added to the solution, although the incremental caloric gain is small relative to that of simultaneously available solid food (Samson et al. 1996). Preference for varying ethanol concentrations in either solid or semisolid nutritional media that simulate fermenting fruit can similarly be investigated, particularly through the use of binary choice tests that evaluate taste thresh-

olds and above-threshold preferences (e.g., Simmen 1994). Olfactory mechanisms by which frugivorous taxa locate fermenting fruit over long distances are similarly amenable to laboratory investigation.

Ethanol molecules are metabolized through reactions catalyzed initially by the enzyme alcohol dehydrogenase (ADH) to yield acetaldehyde, and then by the enzyme aldehyde dehydrogenase (ALDH) to yield acetate that subsequently enters the Krebs cycle (see Agarwal and Goedde 1989, 1990a; Goedde and Agarwal 1989). The extensive variation seen among diverse animal taxa in both ADH and ALDH suggests that historically there have been a number of variable selective regimes for ethanol utilization (Sund and Theorell 1963; Bränden et al. 1973; Smith 1986). The genus *Drosophila* exemplifies intraspecific and interspecific differences in ADH activity (e.g., McKenzie and Parsons 1972, 1974). Adult female fruit flies use ethanol and acetaldehyde plumes to locate suitable oviposition sites, whereas their larvae consume yeasts and metabolize associated alcohols within the larval medium (Hoffmann and Parsons 1984). *Drosophila* genotypes with higher ADH activity typically exhibit greater tolerance for ethanol as adults, and an increased preference for ethanol-supplemented larval media (see McDonald and Avise 1976; Oakeshott 1976; Cavener 1979; Hickey and McLean 1980; Holmes et al. 1980; Geer et al. 1990; Merçot et al. 1994). Ironically, the fairly homogeneous and ethanol-rich substrates provided by temperate-zone vineyards and wine seeps have apparently selected for particularly high levels of ethanol tolerance in fruit flies. *Drosophila* holds considerable promise as a useful model for study of human alcohol preference and consumption, in that genetic analysis can potentially pinpoint molecular bases to a susceptibility for inebriation (Miyakawa et al. 1997; Moore et al. 1998).

Additional nonhuman models of ethanol intoxication can be identified both within the insect taxa and among frugivorous vertebrates other than rodents. Particularly in the tropics, many butterflies feed on rotting fruits, and lepidopterists have traditionally used these and other fermenting substances to attract particular species of butterflies and moths (Utrio

and Eriksson 1977). Behavioral observations suggest intoxication of butterflies through consumption both of rotting fruits and of alcoholic beverages (Gómez 1977; Miller 1997). Anecdotal accounts also document fruit-induced inebriation in wild birds, mammals, and hymenopterans (see Janzen 1977; Siegel 1989), perhaps most strikingly in elephants feeding on fermenting fruits (Siegel and Brodie 1984). Although blood-ethanol concentrations have never been measured on apparently inebriated frugivores, these behavioral observations are consistent with occasional ethanol intoxication in diverse animal taxa. Preference for ethanol and addictive behavior in humans obviously involves a variety of factors other than those based on dietary associations, but one potentially important feature of alcoholism may be co-option of molecular pathways and sensory biases common to many frugivorous taxa.

AN EVOLUTIONARY HYPOTHESIS FOR HUMAN ALCOHOLISM

If selection for ethanol consumption during frugivory has been significant for human ancestors, then alcoholism in modern humans may be viewed conceptually as a disease of nutritional excess (see Cronk 1991; Williams and Nesse 1991; Nesse and Berridge 1997). In this perspective, genetically-based behaviors adaptive in the ancestral environment become disadvantageous in a modern human environment that provides *ad libitum* access to nutritional substrates, including ethanol. This interpretation of alcoholism is thus analogous to hypotheses that link high rates of obesity and diabetes in modern humans to the ready availability of fats and carbohydrates in industrialized societies. Contemporary interpopulational variation in susceptibility to diabetes has similarly been attributed to historically variable selective regimes in the diet of early humans (see Neel 1962, 1982; O'Dea 1992).

In contrast, evolutionary perspectives are conspicuously absent from the literature on human alcoholism. Phylogenetic origins of alcoholic behavior do not figure in suggestions that alcoholism will be gradually outbred because of its deleterious effects (e.g., Milam and Ketcham 1981; Carpenter and Ewing 1989; Nesse 1994), or that this apparently maladaptive behavior actually promotes advantageous

social conformity (Logan and Qirko 1996). An explicit application of Darwinian theory to psychiatry similarly provides no phylogenetic perspective on ethanol consumption, suggesting instead that alcoholism is "in part a strategy to offset the undesirable consequences associated with actual or perceived failures" (McGuire and Troisi 1998). None of these various possibilities are precluded by an ancestral predilection for ethanol consumption during frugivory, but neither do they address the important issue of the phylogenetic origins of such behavior.

Phenotypic traits may be modified when selection acts on heritable variation. In humans, the genetic components of alcoholism are well-established, with estimates of narrow-sense heritability for alcohol dependence ranging from 0.2 to 0.6 (see Cloninger 1987; Cook and Gurling 1990; Goldman 1993). Susceptibility to alcoholism is also polygenic in character. Interestingly, contemporary human populations differ considerably in their physiological sensitivity to ethanol (see Wolff 1972; Agarwal and Goedde 1986, 1990b; Goedde and Agarwal 1986; Smith 1986; Helzer and Canino 1992). Many East Asians and Native Americans, for example, tend to be more susceptible than Caucasians to the immediately adverse effects of ethanol ingestion (e.g., cutaneous flushing, vasodilation, tachycardia; see Agarwal and Goedde 1986). Much of this variation can be correlated with the presence of particular ADH and ALDH isozymes (Goedde et al. 1979; Agarwal and Goedde 1990a; Goldman and Enoch 1990; Shen et al. 1997; Osier et al. 1999). For example, frequencies of a deficient ALDH I allele tend to be higher in East Asians and indigenous South Americans than in Caucasians, which in part explains acetaldehyde buildup and greater overall sensitivity to ethanol in the first two groups (Goedde and Agarwal 1986, 1989). Between Native Americans and Caucasians, however, ADH activity and rates of ethanol degradation are similar, in contrast to anecdotal accounts of greater susceptibility to "firewater" in the former group (see Reed 1978; Schaefer 1981; Agarwal and Goedde 1986). Within-group variation in diet and genetic background may also influence the ability to clear ethanol. Indigenous peoples of northern Canada, for example, historically consumed virtually no carbohydrates and appear to metabolize ethanol more slowly than do Caucasians and Native Americans from more equatorial latitudes (see Schaefer 1986).

Both among and within human populations, differential propensities toward alcoholism are at least partially correlated with variability in the metabolic pathways that degrade ethanol and acetaldehyde. For example, rates of alcoholism among East Asians tend to be much lower than those in Caucasian populations (see Chafetz 1964; Sue 1987), consistent with deterrent effects on ethanol consumption owing to deficient ALDH I alleles and corresponding accumulation of acetaldehyde. However, the high vulnerability of indigenous North Americans to alcoholism (Brod 1975) cannot be attributed to deficient ALDH I alone, as allele frequencies for this isozyme are low and are much more similar to those of Caucasians than of East Asians (Goedde and Agarwal 1989). Alcoholism rates among indigenous North and South Americans also tend to be similar in spite of the much higher rate of occurrence of deficient ALDH I in the latter group (see Goedde and Agarwal 1989, Everett et al. 1996). Instead, susceptibility to alcoholism may in part derive from the interacting dynamics of ethanol degradation (via ADH) and acetaldehyde accumulation (via slow-acting ALDH). Alcoholics within particular Asian populations, for example, exhibit reduced frequencies of catalytically more effective ADH alleles, as well as higher frequencies of faster-acting ALDH alleles (see Chen et al. 1996; Shen et al. 1997; Tanaka et al. 1997; Harada et al. 1999; Osier et al. 1999). In general, genotype-by-environment interactions, coupled with polygenic effects, are likely to be pronounced in the emergence of alcoholism as a clinical syndrome. Nonetheless, partial genetic contributions to alcohol abuse in humans have been clearly established.

This hypothesis thus proposes that natural selection has acted on human ancestors to associate ethanol with nutritional reward, promoting rapid identification and consumption of ethanol-containing fruit resources. Alcohol-seeking in humans has in fact been termed an exploratory appetitive behavior (Cloninger 1987). An immediate prediction of the hypothesis that links alcohol consumption to

frugivory is that hominids in the wild preferentially select and consume ripe fruits that contain ethanol. Quantitative assays of fruit ripeness, ethanol content, and palatability are clearly essential for any such analysis. As in *Drosophila*, intraspecific and interspecific variation in ADH and ALDH activity among extant frugivorous primates would be predicted to follow the relative dietary inclusion of ethanol. For example, frugivorous lowland gorillas should be more capable of metabolizing ethanol than are the more folivorous montane gorillas. Similar variability in ethanol-degrading enzymes should be indicated in interspecific comparisons of frugivorous mammals and birds with their nonfrugivorous sister taxa (e.g., fruit-eating megachiropteran bats versus insectivorous microchiropterans). Overall, any general tendency toward addiction would be predicted to follow both the relative extent of natural ethanol consumption and the aforementioned human patterns of genetic variation in the efficacy of ethanol and acetaldehyde degradation.

Many chemical compounds that are stressful or toxic at high concentrations are, somewhat paradoxically, beneficial at low dosages. Such a nutrient-toxin continuum is termed hormesis (Calabrese et al. 1987; Calabrese and Baldwin 1998; Gerber et al. 1999), and in many cases may reflect evolutionary exposure and adaptation to substances that naturally occur in the environment at low concentrations. For animal frugivores, specific hormetic advantages may derive from historical exposure to ethanol and fermentation products. In *Drosophila* species that oviposit on fermented fruit, for example, adult longevity is enhanced by exposure to ethanol and acetic acid vapors relative to controls exposed to water vapor (Parsons 1983). Similarly, adult survivorship of *Drosophila melanogaster*, as of its hymenopteran parasitoid, is maximal at acetaldehyde vapor concentrations near 0.1% and declines rapidly at higher concentrations (Owen 1985; Parsons 1989). An evolutionary perspective on hormesis suggests that behavioral responses towards particular compounds should vary according to relative availability and predictability in the diet (Gerber et al. 1999). If regular exposure to low concentrations of ethanol is an inevitable consequence of ripe fruit con-

sumption, then selection will favor the evolution of metabolic adaptations that maximize physiological benefits and minimize any costs associated with ethanol ingestion. This argument pertains, however, only to those ethanol concentrations historically encountered by frugivorous hominoids. Exposure to much higher concentrations of a hormetic substance would, by contrast, induce maladaptive responses (Gerber et al. 1999).

The intentional fermentation of fruits and grain to yield ethanol arose only recently within human history. Archeological evidence dates the production of wine and beer to Mesopotamian civilizations in the fourth millennium BCE (see Katz and Voigt 1986; McGovern et al. 1995). Although widespread in the ancient world (Lutz 1922; Forbes 1964), production of alcoholic beverages was apparently limited to the low ethanol concentrations yielded by the fermentation process alone (i.e., 10–15%). The freezing of dilute alcohol solutions to produce high-concentration ethanol (known literally as "frozen-out wine") appeared in central Asia by 300 CE (Needham 1980). Distillation as a chemical process dates to the Hellenistic alchemists of Alexandria (0 to 200 CE), although specific distillation of high-concentration ethanol apparently first arose in seventh-century China (see Needham 1980). This method subsequently spread into Central Asia and Arabia, although in western Europe the distillation of ethanol can be reliably dated only to 1100 CE, at Salerno (Forbes 1948). Medicinal use of alcoholic tinctures also facilitated a rapid spread of this technology throughout medieval Europe, as beverages with higher alcohol concentrations became ever more popular. Relative to the geological duration of the hominid lineage, therefore, exposure of humans to concentrations of ethanol higher than those attained by fermentation alone is strikingly recent.

Complex historical and cultural attitudes inform contemporary views of alcoholism (Lender and Martin 1987; Vallee 1998). In the United States, the remarkable diversity of addiction treatments developed over the last two centuries is ample testimony to the complexity of biological as well as social factors that influence this persistent medical issue (White 1998). An evolutionary perspective, however, raises

the possibility of novel interpretations for the motivational mechanisms underlying both ethanol consumption and actual addiction. It is tempting to speculate, for example, that hormetic effects underlie recently demonstrated reductions in cardiovascular risk and overall mortality that are associated with low-level alcohol consumption (e.g., Doll et al. 1994; Goldberg et al. 1994; Camargo et al. 1997; McConnell et al. 1997). By contrast, widespread availability of ethanol at high and stressful concentrations not only demonstrates vulnerability in contemporary humans, but also should elicit a greater range of heritable responses than was evident in the ancestral environment (see Gerber et al. 1999). The aforementioned ethnic and populational differences, both in physiological reactions to ethanol and in susceptibility to alcoholism, are consistent with this prediction. Such observations are tantalizingly suggestive of hormesis, although validation of this hypothesis requires detailed empirical evaluation of dose-dependent costs and benefits (Gerber et al. 1999). The hormetic range evoked by ethanol may also vary in modern humans according to ancestral as well as present-day dietary practices of particular populations.

Recognition of historically frugivorous diets among hominoids suggests multiple directions for research into the natural occurrence of ethanol consumption. In the wild, what are the sensory mechanisms by which primates and other frugivorous taxa localize ripe fruit over long distances? What are typical ethanol concentrations within consumed fruit, and to what extent and how frequently do animal frugivores actually become inebriated? Does ethanol act as a feeding stimulant under certain circumstances? What are the hormetic effects of ethanol on extant hominids? Answers to these and related questions are likely to be taxon-specific, but they will also depend strongly

on local ecological conditions. Within tropical and subtropical environments, for example, the broad taxonomic diversity of potential fruit crops (and yeasts), coupled with a high degree of seasonal variability, suggests a corresponding diversity in historical patterns of selection for efficient fruit consumption. This diversity may, in turn, have promoted evolution of a variety of sensory mechanisms that mediate ethanol ingestion via frugivory. Does the presence of particular mechanisms predispose or motivate certain taxa to excessive consumption of ethanol under abnormal conditions of availability? Because human alcoholism (and drug addictions generally) are apparently unique in the animal kingdom, our perception and treatment of these diseases have been largely decoupled from the biological context within which our nutritional and sensory physiology evolved. However, an evolutionary perspective places intraspecific and interspecific variation in preference for ethanol, together with hormetic effects of this substance, within a broader and perhaps methodologically more tractable framework. Identification of the behavioral, physiological, and genetic mechanisms underlying abuse of ethanol has to date proven to be a formidable task. Nonetheless, ethanol ingestion via frugivory is ancestral in hominoids and may influence contemporary behavioral responses by humans. Studies of historical exposure to this substance can accordingly provide information for interpreting modern patterns of alcohol consumption and abuse.

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