Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover?

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ABSTRACT

In the field of addiction research, the possibility of ancestral exposure to psychoactive compounds has generally been excluded. A paleobiological approach to the human diet, however, illustrates the potential utility of historical data in interpreting modern-day addictive behaviors. Low-level dietary exposure to ethanol via ingestion of fermenting fruit has probably characterized the predominantly frugivorous anthropoid lineage for about 40 million years. Potentially adaptive primate behaviors associated with the natural occurrence of ethanol include the olfactory use of ethanol plumes to localize fruit crops, the use of ethanol as an appetitive stimulant to facilitate rapid consumption of transient nutritional resources, and the physiological exploitation of the caloric benefits of ethanol. Such behavioral and energetic advantages probably pertain to all animal taxa that consume fermenting fruit, and may have been retained in modern humans in spite of considerable dietary diversification over the last several million years. In contemporary human environments, excessive consumption of ethanol would then represent maladaptive cooption of ancestrally advantageous behaviors given essentially ad libitum access to a compound otherwise found only within scarce nutritional substrates. Epidemiologically demonstrated health benefits of low-level alcohol consumption are consistent with an ancient and potentially adaptive exposure of primate frugivores to this most common of the psychoactive substances.

KEYWORDS Alcoholism, ethanol, frugivory, fruit, primate.

INTRODUCTION

Evolutionary approaches to medicine provide a sometimes essential historical perspective to challenging questions of human health. In the last decade, evolutionary analysis has yielded substantial insight into such long-standing medical problems as the spread of antibiotic resistance among microbes, the high incidence rates of diabetes and obesity in many modern societies, and even sociological patterns of homicide and infanticide (see Daly & Wilson 1988; Williams & Nesse 1994; Buss 1999; Stearns 1999). By contrast, historical perspectives on substance abuse and drug addiction generally presume a fairly recent exposure of humans to psychoactive compounds, the approximately three million years of evolution in the genus *Homo* notwithstanding. Tacit assumption of such a restricted period of exposure is, in part, understandable. After all, intentional consumption by humans of a vast array of psychoactive substances is based largely on culturally transmitted information, and has probably arisen only within the last 50 000 years. Indigenous use of plant-derived narcotic

and medicinal substances, for example, requires often highly specific collection, preparation and manipulation of various chemical constituents (e.g. Schultes & Raffauf 1990). It is unlikely that such behaviors, together with sophisticated ritualization of usage, have much preceded the last 10 000 years.

On the other hand, incidental exposure to plant secondary compounds has been an inevitable consequence of foraging on wild plants throughout human evolution. Crop domestication dates only to about 8500 BCE (see Diamond 1999), whereas prior to this time humans would have ingested a wide variety of potentially psychoactive substances when consuming both vegetative and reproductive structures of plants, albeit at fairly low concentrations (Johns 1990, 1999). The presence of opiate and cannabinoid receptors in the human brain is also consistent with historical exposure to such compounds (Sullivan & Hagen 2001). Most importantly, unintentional dietary consumption of ethanol may have been a regular consequence of fruit-eating habits in many primates, including the lineage leading to modern humans. I recently suggested that the occurrence of ethanol within ripe and fermenting fruits indicates sustained historical exposure of all animal frugivores to this psychoactive and addictive compound (Dudley 2000). Here, I review probable evolutionary consequences of low-level dietary ingestion of ethanol, present preliminary data on ethanol content for some tropical fruits and discuss some possible implications for understanding modern-day patterns of alcohol consumption, metabolism and abuse.

ETHANOL, EVOLUTION AND HORMESIS

Although not usually thought of as a constituent of animal diets, ethanol is a molecule of widespread distribution within ripe fruit eaten by birds and mammals. Sugars within fruit pulp provide an energetic incentive for vertebrates to consume the fruit and subsequently to disperse seeds, but also serve as a substrate for fermentation by yeasts. Fruit-eating animals (i.e. frugivores) must then inevitably consume ethanol on a regular basis, although the actual ethanol content of wild fruits within natural environments has received remarkably little attention (see Dudley 2000). Agricultural fruits and fruit residues at various temperate-zone locations manifest ethanol concentrations ranging from 0 to 12% (e.g. Ainsley & Kitto 1975; McKenzie & Mckechnie 1979), but these values derive from domesticated and otherwise non-representative plants. The concentration of ethanol within naturally occurring fruits is remarkably little known. In what is perhaps the only such study, Eriksson & Nummi (1982) determined ethanol content for two fruiting shrub species from September to February in southern Finland. Ethanol concentrations reached a maximum of 0.3% for fruit of one species, although average values were much lower. It is also clear that the Scandinavian wintertime is unlikely to elicit substantial ethanol production by yeasts.

Warmer and wetter climates more conducive to fermentative yeast metabolism include tropical rain forest and savannah habitats within which our hominoid ancestors (i.e. the human and anthropoid apes) evolved. In May 2000, ethanol concentrations were measured in fruits of three plant species from a well-studied Panamanian rain forest flora (see Croat 1978). Ripe fruits of the palm *Astrocaryum standleyanum* are eaten by a diversity of mammals, including white-faced capuchin monkeys, red-tailed squirrels, central american agoutis, and collared peccaries (Smythe 1989). Both ripe and unripe fruits of the shrub *Miconia argentea* are eaten by various birds and by white-faced capuchin monkeys (Croat 1978; pers. obs.), whereas ripe fruits of the shrub *Psychotria limonensis* are eaten by various bird species (B. Poulin, pers. comm.). Fruit ripeness was assessed qualitatively using criteria of color and texture. Ripe and very ripe fruits of *A. standleyanum* were obtained both from the fruit-bearing spadix and from recent falls beneath mother trees; unripe fruits from this palm were unavailable during the period of study. Fruits of the other two plant species were taken directly from the stem. Sugar content of ground fruit tissue, which included the pulp (mesocarp), the skin (exocarp) and seeds (for *M. argentata* and *P. limonensis*) was determined using a Westover RHB-32 Brix refractometer. The large seeds of palm fruits were removed prior to measurement. Ethanol concentration of fruit tissue was determined from vapor pressure measurements using an electrochemical ethanol sensor (PAS Systems, Fredericksburg, VA, USA) calibrated against ethanol solutions of known concentration.

Depending on taxonomic identity and ripeness, ethanol content of fruits ranged from trace quantities to values near 0.6% (Table 1). Such concentrations are not particularly high relative to those of alcoholic drinks consumed by humans, but one striking result of these measurements was the ubiquity of ethanol in ripe fruits. All such fruits were characterized by ethanol levels substantially higher than those of their unripe counterparts (Table 1), and also expressed the higher sugar content characteristic of ripeness (see Brady 1987). Ethanol concentrations of Table 1 are minimum estimates for concentrations in the fruit pulp alone, as neither the exocarp nor the small seeds of *M. argentata* and *P. limonensis* were removed from samples. Given the ubiquitous presence of yeast spores on plant structures, ethanol may well be a widespread constituent of sugar-rich fruits growing in wet tropical environments. These preliminary data

Table 1 Representative sugar and ethanol concentrations for fruits of three plant species on Barro Colorado Island, Republic of Panama. Sample size ***N*** refers to either the number of individual fruits (***Astrocaryum standleyanum***), or to the number of separate batches of fruit analyzed from different plants.

Species (family)	*Fruit condition*	*Color*	*Sugar (%)*	*Ethanol (%)*
Astrocaryum standleyanum (Palmae)	Ripe (*N* = 10)	Orange	15.9	0.52
	Very ripe (*N* = 9)	Dark orange	12.2	0.61
Miconia argentea (Melastomataceae)	Unripe (*N* = 4)	Green	5.6	0.04
	Ripe (*N* = 4)	Purple	15.5	0.09
Psychotria limonensis (Rubiaceae)	Unripe (*N* = 3)	Green	2.9	0.01
	Ripe (*N* = 3)	Orange	4.1	0.02
	Very ripe (*N* = 3)	Purple	6.4	0.08

suggest the utility of a more widespread screening of tropical fruits consumed by vertebrate frugivores, relying particularly on quantitative assays of ripeness, texture, color, and sugar and ethanol content. For example, both within- and among-plant variation in fruit ripeness can be substantial, and sample sizes must be high to establish statistically the overall levels of naturally occurring ethanol within a local fruit crop. The influence of ethanol content on fruit selection by frugivores is also unknown, yet is readily amenable to assessment under both natural and experimental circumstances.

If the aforementioned concentrations of ethanol are indeed typical, it is then appropriate to consider potential evolutionary implications for animals that routinely consume these fruits. The three fruit species that were evaluated for ethanol content in Panama are dispersed by a variety of mammals and birds, and the co-evolutionary interaction between fruits of flowering plants and their vertebrate dispersal agents has been a vigorous one since the late Mesozoic (i.e. for 80–90 million years). Assuming that ethanol has been encountered regularly by frugivores over a geological time scale, what types of responses might we reasonably expect to have evolved? In general, physiological, morphological and behavioral traits that compose the phenotype can exhibit evolutionary change if such traits are at least partially heritable, and if there are forces of selection (either biotic or abiotic) acting on particular phenotypic features. One little-understood category of selective forces derives from low-level but chronic exposure to naturally occurring compounds or physical stressors. The effects of such stressors often follow a nutrient–toxin continuum, whereby low concentrations or exposures are stimulatory and beneficial, but higher concentrations are stressful and cause harm (see Calabrese & Baldwin 1998; Gerber *et al*. 1999). This phenomenon is termed hormesis, and has been documented for a diverse array of otherwise apparently stressful agents including toxic metals, radiation and various organic compounds (Calabrese & Baldwin 1998).

The evolutionary interpretation of hormesis relies on the assumption that natural selection maximizes relative fitness, and that organisms correspondingly evolve the necessary metabolic machinery to maximize benefits and to minimize costs of exposure to substances that occur at low concentration (Gerber *et al*. 1999). Because Darwinian fitness invokes life-time reproductive capacity, the possibility of trade-offs between short-term physiological benefits, life history traits and overall fecundity must also be considered (Forbes 2000). To date, hormetic effects of ethanol have been evaluated systematically for only one animal taxon, the fruit fly genus *Drosophila*. Larvae of many flies in this genus live within ripe and fermenting fruit, metabolizing not only fruit sugars but also yeasts, as well as the ethanol produced by yeast metabolism (see Ashburner 1998). Consistent with evolutionary expectation, the longevity of *Drosophila* species that naturally encounter fermenting nutritional substrates is enhanced at very low concentrations of ethanol (and of its conversion product, acetaldehyde), but is decreased at higher concentrations (Parsons 1983, 1989; see also Dudley 2000). Most importantly, not just longevity but also life-time fecundity of *Drosophila* increases in the presence of low-concentration ethanol vapor (Etges & Klassen 1989). These results are consistent with evolved metabolic responses that maximize physiological and overall fitness benefits of chronic environmental exposure to ethanol. Is such an outcome characteristic of other animals that feed on fermenting fruit? In particular, is the historical ecology of hominoid diets consistent with the ingestion of ethanol, and might modern humans possess the metabolic equipment necessary to obtain hormetic advantage from ethanol at suitably low concentrations?

HUMAN ANCESTRY AND ETHANOL CATABOLISM

Humans derive from a predominantly frugivorous lineage of primates, with ancestral fruit-based diets dating back to at least 24 million years ago, if not much earlier (Dudley 2000; see Fig. 1). With the sole exception of montane gorillas, all extant hominoid taxa (i.e. lowland gorillas, chimpanzees, orangutans and gibbons) are primarily frugivorous. Over the last two million years, the hominoid lineage leading to *Homo sapiens* increased

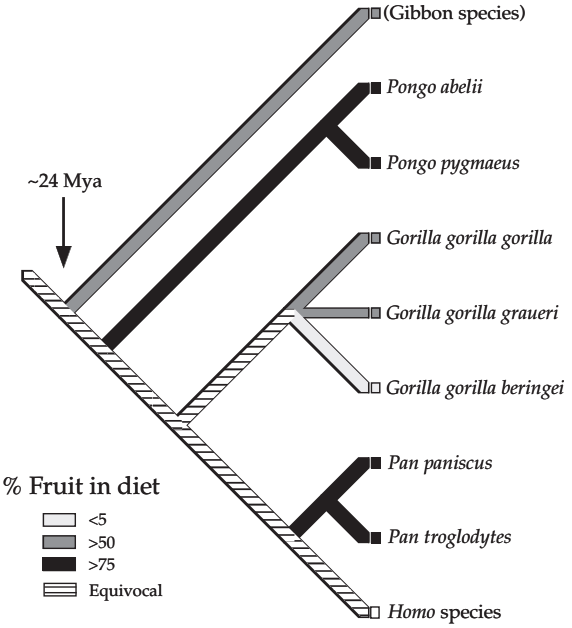

Figure 1 Phylogeny of extant hominoid taxa, the relative extent of frugivory for each taxon, and the most parsimonious reconstruction of frugivory for ancestral hominoids (from various sources; see Rowe 1996; Dudley 2000). The gorilla subspecies *G. g. beringei* is the mountain gorilla. The value for percentage frugivory in gibbons refers to a mean dietary percentage derived from data for 11 extant species. Homo species refer to premodern hominine taxa for which diets are not well-established but which were probably comparable to those of earlier hominids

its intake of animal fat and protein significantly, although fruits and carbohydrates generally remain the major dietary component even in today's hunter-gatherer societies (see Eaton *et al*. 1997; Milton 1999). Although clearly not central to the diet of the various *Homo* species, fruit consumption would none the less have provided substantial caloric benefits to early humans. Accordingly, it can be hypothesized that our hominoid precursors were exposed routinely to low-concentration ethanol in the course of frugivory, and that this exposure in turn elicited corresponding physiological adaptations and preferences over an evolutionary time scale that are retained in modern humans.

One legacy of an ancestrally frugivorous diet is a well-developed ability to catabolize ethanol. Oxidation of ethanol in humans is catalyzed primarily by alcohol dehydrogenase (ADH) in the liver, and the ensuing aldehyde product is then degraded further to acetate via acetaldehyde dehydrogenase (ALDH; see Agarwal & Goedde 1990). The presence of these enzymes is, by itself, insufficient to establish strong dietary associations with ethanol as both ADH and ALDH are distributed widely among both unicellular and multicellular taxa (Brändén *et al.* 1973). However, genetically based variation among humans in both ADH and ALDH is substantial (Agarwal & Goedde 1989, 1990; Goedde & Agarwal 1989). As with *Drosophila* species (see below), these patterns are consistent with historically variable selective regimes for the ability to metabolize ethanol. Similar patterns of variation might be expected in comparisons of primate taxa that vary in the extent of frugivory (e.g. lowland versus montane gorillas; see Fig. 1). Much of primate evolution occurred in the context of warm equatorial climates where yeast-based fermentation of fruit sugars must occur quickly, and where regular dietary exposure to low-concentration ethanol has been a likely outcome. Moreover, associated metabolic specializations would be predicted to characterize not just frugivorous primates, but rather all animal taxa that regularly consume fruit (Dudley 2000).

Hormetic consequences of ethanol have only recently been investigated for *Homo sapiens*, but not via direct experimental manipulations. Instead, numerous epidemiological studies suggest a systematic reduction in cardiovascular risk and in overall mortality at low levels of ethanol consumption relative either to abstinence or to higher levels of intake (e.g. Camargo *et al*. 1997; McConnell *et al*. 1997; Cleophas 1999; Zakhari & Gordis 1999). Possibly parallel consequences for reproductive fitness have not been evaluated, but this issue is none the less logistically tractable. The well-known problem of potentially confounding economic, social and genetic factors necessarily indicates that sample sizes for such human studies would be large. By contrast, the use of non-human vertebrate models would provide for direct experimental tests of the potentially hormetic effects of ethanol. It is surprising that no such experiments evaluating effects of life-time exposure to ethanol have been carried out either for rodents or, more importantly, for primates. Studies of existing captive colonies of omnivorous (e.g. baboons) and frugivorous (e.g. chimpanzee) primate taxa would be particularly informative in this regard, given the possibilities for measuring overall reproductive fitness as well as the lifespan of known individuals.

EVOLUTIONARY UNDERPINNINGS TO ETHANOL ABUSE

What are the metabolic, sensory and behavioral mechanisms that contribute to excessive imbibition in modern circumstances? The well-established partial heritability of alcoholism indicates substantial genetic influences, yet this disorder is clearly polygenic and exhibits strong genotype × environment interactions. Intriguingly, heritable variation in the enzymatic pathways of ethanol degradation have been linked with propensity toward abuse both among and within particular population

groups. Individuals from East Asian and indigenous South American populations tend to exhibit a heightened sensitivity to ethanol that derives from the presence of slow-acting ALDH isozymes and adverse physiological responses to acetaldehyde build-up (see Goedde & Agarwal 1989). In a similar vein, alcoholics within particular East Asian populations are much more likely to express both slow-acting ADH as well as fast-acting ALDH isozymes than are their non-alcoholic counterparts (Chen *et al*. 1996; Shen *et al*. 1997; Tanaka *et al*. 1997; Osier *et al*. 1999; Reich *et al*. 1999). Net acetaldehyde accumulation must be influenced by the interacting dynamics of ADH and ALDH, and the aversive response to such accumulation is apparently protective against excessive alcohol consumption (Li 2000). Interestingly, indigenous North Americans are much more likely to express fast- rather than slow-acting ALDH isozymes (Goedde & Agarwal 1989), but none the less exhibit high rates of alcoholism consistent with substantial genotype × environment effects. The wide range of contemporary behavioral responses to alcohol (see Agarwal & Goedde 1990) is consistent, furthermore, with evolutionary and hormetic predictions, namely that exposure to novel concentrations of toxic compounds increases overall phenotypic variance (see Hoffmann & Parsons 1997; Holloway *et al*. 1997; Gerber *et al*. 1999).

Similar patterns of genetic variability in ethanol metabolism characterize other frugivorous taxa. The fly genus *Drosophila* includes many species with obligately frugivorous larvae as well as adults that opportunistically feed on fermenting fruits. Among *Drosophila* species, variation in ADH and ALDH activity correlates well with the relative extent to which ethanol is naturally encountered in the environment (see Merçot *et al.* 1994; Dudley 2000). Such an evolutionary outcome is not confined to ethanol metabolism, as fruit flies also demonstrate specific behavioral responses to ethanol that are apparently advantageous and that have been the target of natural selection. For example, adult fruit flies use ethanol vapor as a long-distance cue in localizing ripe fruit crops, a strategy that is potentially available to all frugivores. Fruit-eating mammals may track ethanol plumes upwind in order to find ripe fruit crops (see Singh 1985), and it is possible that genetic selection on rodents for strains that prefer ethanol (Crabbe *et al*. 1994) may also yield correlated selection for differences in olfactory responses to fermenting food and in the ability to metabolize ethanol.

Ethanol may also serve frugivores as a feeding stimulant, given its obligate association with valuable nutritional resources. Given widespread competition for ripe fruit from microbes, insect larvae and diverse vertebrates, one possible short-term correlate of low-level ethanol ingestion might be to increase the rate of food ingestion, which in turn would increase blood-ethanol content and stimulate further feeding. This behavioral possibility can easily be tested, but relies necessarily on direct physical association between ethanol and fruit sugars. The caloric contribution of ethanol within fruits may also be of significance to vertebrate frugivores. Particularly relevant to primate nutritional ecology are the large and sugar-rich fruits of tropical palms. Using data of Table 1 for the average ethanol content of ripe and very ripe palm fruits, and assuming complete catabolism of sugars and ethanol (with the exclusion of other constituents), the caloric value of ethanol alone represents from 6% to 9% of total energy content.

Similar calculations for the predominantly avian-dispersed fruits of Table 1 would yield lower percentages, however, and natural consumption rates of ethanol via frugivory are unfortunately not known for any animal taxon. Fruits with higher ethanol concentrations might also be selectively found or preferred for consumption. In sum, a variety of advantageous metabolic and behavioral responses to ethanol may have evolved in animal frugivores.

Addictive responses to ethanol, as to other psychoactive substances, must derive from pre-existing neural substrates and pathways (Nesse & Berridge 1997; Nesse 1999). In both fruit flies and humans, extensive neuropharmacological studies have demonstrated a variety of neural pathways and mechanisms that influence behavioral sensitivity to ethanol (see Miyakawa *et al*. 1997; Eckhardt *et al*. 1998; Harris *et al*. 1998; Koob *et al*. 1998; Moore *et al*. 1998). Of these pathways, the mesolimbic dopaminergic system appears to play a major role in addiction (Self & Nestler 1995; Wise 1998; Di Chiara 1999). Rather than acting as a reward system *per se*, this system reinforces novel, rewarding or even aversive stimuli which result in arousal and then influence subsequent motivation (see Newlin 1999; Spanagel & Weiss 1999; Horvitz 2000). Is dopaminergic stimulation by low-concentration dietary ethanol an ancestrally advantageous neural response that is now coopted by high-concentration ethanol solutions, and possibly by other psychoactive drugs? Some involvement of serotonergic pathways is also indicated in the modulation of ethanol intake. In particular, reinforcement mechanisms underlying voluntary ethanol intake seem to involve interactions between serotonin and dopamine release (see LeMarquand *et al*. 1994; Eckhardt *et al*. 1998).

Independently of the neural pathways mediating consumption, however, ethanol alone may elicit the positive motivational responses normally associated with feeding and nutritional gain. If so, it is tempting to suggest that contemporary imbibition of dilute ethanol continues, on average, to the point of blood-ethanol concentrations attained historically in the course of frugivory. Cessation of imbibition (i.e. satiation) may derive in fact from such

a signal. In this manner, the ancestral associations of ethanol with fruit consumption would be falsely indicated as fitness benefits, possibly motivating repeated consumption and facilitating addiction. This postulated relationship between ethanol intake and dietary satiation is necessarily speculative, but is based on the commonality of the dopamine pathway in reinforcement of various stimuli, and deserves experimental attention.

THE NATURAL HISTORY OF ALCOHOL INGESTION

Apart from occasional behavioral observations, the effects of ethanol on animal frugivores in the wild have never been investigated. Numerous anecdotal accounts of drunkenness among elephants, primates, warthogs, birds and butterflies probably represent extremes of environmental exposure (see Dudley 2000), but the natural occurrence of ethanol ingestion is undocumented in any quantitative sense. Knowledge of blood-ethanol concentrations following fruit ingestion is particularly important in this regard. Eriksson & Nummi (1982) fed naturally fermenting fruits to captive individuals of two bird species, and recorded maximum blood-ethanol concentrations of about 0.02%. Similarly, Fitzgerald *et al.* (1990) documented ethanol toxicosis in cedar waxwings that had been feeding on fermenting hawthorn fruits. Data on ethanol ingestion by primate frugivores under natural circumstances would clearly be desirable, but are not currently available. However, a preliminary calculation of blood-ethanol concentrations assuming consumption of the palm fruits indicated in Table 1 is suggestive. If we assume conservatively an ingested fruit mass that is 1% of the body mass, a blood volume equal in mass to 7% of body mass (in mammals; see Calder 1984), full absorption of ingested ethanol and a 10-fold reduction in concentration to account for digestion kinetics, then ingestion of these fruits would yield a blood-ethanol concentration of about 0.01%. By comparison, legally defined inebriation levels in the United States range from 0.08 to 0.10%. Lower ethanol content of ingested fruits (e.g. *M. argentea* or *P. limonensis*; see Table 1), relatively smaller ingested fruit masses and less efficient absorbtion would obviously yield lower blood-ethanol concentrations. None the less, this exercise suggests the potential for low-level intoxication with few behavioral effects, but also statistically predicts occasional events of overt drunkenness.

In this regard, one of the most pressing experimental needs is to determine both the natural occurrence of ethanol within fruits and the typical levels of ingestion and intoxication experienced by mammalian frugivores, including primates. The ripening and fermentation of non-domesticated fruit in natural ecosystems is virtually unstudied, and ample opportunity exists to determine patterns of temporal variation in ethanol expression. Similarly, large numbers of frugivorous vertebrate taxa together with diverse invertebrate and microbial consumers of fermenting fruit suggest a taxonomically broad-based ecology of fruit decomposition and dispersal. If this is indeed the setting within which human preferences for alcohol originally evolved, then sensory and behavioral responses of animal frugivores to ethanol under natural conditions provide a far more realistic context for the development of non-human models of alcoholism than do emulations of human drinking behavior using laboratory rodents. The confounding caloric benefits of ethanol were recognized early on in the development of such non-human models, but the provisioning of dilute ethanol as an adjunct to solid food fully decouples ethanol from its biological origins and nutritional associations. The general relevance of behavioral and addictive responses under such circumstances is thus unclear, particularly if ethanol ingestion via frugivory contributes to feeding responses and ultimately to the sense of satiation. This possibility is, however, readily amenable to experimental investigation (Dudley 2000).

In a well-known work entitled *The Natural History of Alcoholism*, Vaillant (1983) described results of a multidecadal study of drinking habits and disease progression in several cohorts of Boston residents. 'Natural history', in this context, indicated the temporal development of alcoholic behavior for a modern hominoid species living in a twentieth-century industrialized society. By contrast, use of the phrase 'natural history' connotes, at least to organismal biologists, the behavior and ecology of animals, plants and fungi within natural environments. The natural history of alcohol consumption, as argued above, pertains to a variety of animal taxa within the specific behavioral and ecological context of frugivory. From this perspective, patterns of alcohol consumption and abuse in modern humans emerge from ancestral primate and particularly hominoid nutritional behaviors. Novel insights into human alcoholism might thus derive from greater study and understanding of the natural biology of alcohol consumption.

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