INTEGR. COMP. BIOL., 44:304–314 (2004)

Ferment in the Family Tree: Does a Frugivorous Dietary Heritage Influence Contemporary Patterns of Human Ethanol Use?[1]

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SYNOPSIS. **Humans and apes are placed together in the superfamily Hominoidea. The evolutionary trajectory of hominoids is intimately bound up with the exploitation of ripe, fleshy fruits. Fermentation of fruit sugars by yeasts produces a number of alcohols, particularly ethanol. Because of their pre-human frugivorous dietary heritage, it has been hypothesized that humans may show pre-existing sensory biases associating ethanol with nutritional rewards. This factor, in turn, could influence contemporary patterns of human ethanol use. At present, there seems little evidence to support a view of selection specifically for ethanol detection or its utilization over the course of hominoid evolution. Ethanol concentration in wild fruits consumed by monkeys and apes is predicted to be low. Wild monkeys and apes avoid consumption of over-ripe fruits, the class showing notable ethanol concentrations, and for this reason, ethanol plumes may act as deterrents rather than attractants. Any energetic benefits to wild primates from ingested ethanol appear negligible, at best. Mice and rats show patterns of ethanol self-administration similar to humans, indicating that a frugivorous dietary heritage is not necessary for such behaviors. In the natural environment, ethanol is predicted to be just one of many alcohols, esters and related compounds routinely encountered by frugivorous primates and of no particular significance. The strong attraction ethanol holds for some individuals could be due to a broad range of genetic and environmental factors. In some humans, the appetite for ethanol appears related to the appetite for sugar. The predisposition some individuals display toward excessive ethanol consumption could involve features of their genetics and biochemical similarities of ethanol and carbohydrate. Regular low ethanol intake is hypothesized to lower the incidence of cardiovascular disease in humans, perhaps through its effects on body fat distribution. Such a benefit, if confirmed, would appear to relate to features of the contemporary human rather than pre-human diet.**

INTRODUCTION

Humans show little evidence of innate nutritional wisdom (Carpenter, 1986, 2000; Galef, 1991) and individuals learn what to eat primarily through exposure to the eating habits of others. Until recently, most human societies ate time-tested diets, worked out over many generations by their ancestors. Today such traditional diets are largely a thing of the past, particularly in highly industrialized nations such as the United States. Here most people live in urban areas, totally removed from the sources of food production and largely out of touch with any former dietary traditions.

Dietary patterns are of interest because of the strong consensus that many current human health problems relate to diet. These include heart disease, hypertension, various of the leading cancers, obesity and type II diabetes—to name a few of the more obvious. To this list can be added the over-consumption of ethanol as considerable data indicate that this has and continues to be a health (as well as social and economic) problem of considerable magnitude (Lieber, 1982; Westermeyer, 1989). Excessive alcohol consumption is linked to various cancers, particularly those of the esophagus and colon, problems with cardiac and circulatory function, impaired vitamin and protein metabolism, central nervous system degeneration and potentially fatal gastric and liver disease (Lieber, 1982; Altura and Altura, 1989). Routine high consumption of alcohol during pregnancy can lead to fetal alcohol syndrome and even one ill-timed bout of binge drinking can cause permanent fetal damage (Wardlaw and Insel, 1996). The social and emotional costs of alcoholic excess are also well documented (Westermeyer, 1989). Alcohol use leads to the disruption of family and friends, spurs rapes and other forms of violence, much of it on college campuses, and figures in thousands of traffic fatalities each year (Wardlaw and Insel, 1996). In the United States, the annual economic burden attributed to alcohol abuse and alcoholism is placed at $185 billion due to lost productivity and medical, legal and property damages (Vivian *et al.*, 2001).

Given these grim statistics, it might seem a bit of a stretch to try and fit ethanol into a framework of Darwinian medicine (Williams and Nesse, 1991; Dudley, 2000). However, it is well appreciated that cultural change (that is, learned behaviors), can occur very rapidly whereas biological change (traits under genetic control) tends to occur only slowly. For this reason, disjunctions may appear between features of human biology and behavior. Dudley (2000, 2004) has hypothesized that humans, because of their past ancestral history as fruit-eating primates, may have an evolutionarily-based affinity for ethanol. Contemporary patterns of ethanol use may therefore reflect "a maladap-

[1] From the Symposium *In Vino Veritas: The Comparative Biology of Alcohol Consumption* presented at the Annual Meeting of the Society for Integrative and Comparative Biology, 5–9 January 2004, at New Orleans, Louisiana.

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tive co-option of ancestral nutritional strategies" (Dudley, 2000, p. 3).

In this hypothesis, ethanol plumes from ripening fruits may have served for millions of years to guide primates to ripening fruit crops and also served as an appetite stimulus and welcome source of dietary calories (Dudley, 2000, 2004). Just as we speak today of diabetes running wild in human populations due to excessive caloric intake (Diamond, 1992), so might we speak of ethanol running wild in human populations due to unlimited access to beverage ethanol and the tendency of many to drink to excess. Thus, biologically-based behaviors that might have served positive functions for pre-human, fruit-eating ancestors, could, under present-day environmental conditions, prove highly maladaptive. Below I examine some aspects of the possible evolutionary relationship between ethanol, fruits and wild primates and evaluate this information in terms of contemporary patterns of human ethanol use.

PRIMATE FRUGIVORY

The adaptive radiation and eventual dominance of angiosperms during the Cretaceous opened up a variety of new dietary possibilities for animals (Regal, 1977). Potential foods included not only pollinating insects of angiosperm flowers but also the pollens, nectars, fruits, seeds and foliage of angiosperms themselves. The Primate line is believed to have differentiated by the Middle Paleocene, arising from some type of terrestrial insectivorous stock (Eisenberg, 1973). However, if present day anthropoids are any indication, early primates were quick to take advantage of these new arboreal plant foods. With one exception (Tarsiodea), all extant primates take foods from the first trophic level but not all primates take food from the second, at least not intentionally. A few prosimians take much of the diet from animal source foods, but the overwhelming majority of extant primates have diets composed largely or exclusively of plant source foods (Milton, 1981, 1999). It is important to realize that, though Primates are viewed as omnivorous, they are omnivores of a very particular type in that the great majority of their foods each day come from plants (Milton, 1981). This indicates that the adaptive radiation of Primates, particularly the Anthropoids (higher primates—monkeys and apes), occurred by virtue of their ability to penetrate the as-yet unfilled arboreal plant food niche in the tropical forest canopy and radiate to the point where they came to dominate a strong subset of the available higher quality plant food resources in this environment (Milton, 1981).

The fruit-based diet of Hominoidea

Humans are placed in the Superfamily Hominoidea, a classification that reflects the close evolutionary relationship between humans and apes. The fossil record is replete with evidence supporting a plant-eating, basically frugivorous way of life for ancestral anthropoids, particularly hominoids (Kay, 1978; Andrews, 1981; Klein, 1999; Pilbeam, 2002). The dentition of fossil anthropoids from the Egyptian Fayum, dated at some 35–33 mya, shows adaptation to frugivory (Klein, 1999). The same frugivorous trend is reflected in the dentition of primitive apes from the early to middle Miocene (25–15 mya) (Kay, 1978; Fleagle, 1999). Though, on occasion, there is discussion as to which types of fruits certain fossil hominoids may have utilized, there is strong general consensus that the members of this lineage appear to have always been oriented toward the exploitation of ripe fruits as their principal source of dietary energy (Kay, 1978; Andrews, 1981; Fleagle, 1999; Klein, 1999). The dentition of fossil hominids (a bipedal family of African hominoids believed ancestral to the human (*Homo*) lineage) as, for example, *Australopithecus afarensis*, show dental adaptations suggestive of frugivory (Fleagle, 1999). All extant apes are very strongly frugivorous (Fleagle, 1999). For example, ≥90% of the annual diet of many hylobatids and chimpanzees is estimated to come from fruit and the diets of both lowland gorillas and orangutans are described as being dominated by a diverse array of fruits (Rodman, 1977; Wrangham, 1977; Curtin and Chivers, 1978; Goodall, 1986; Tutin *et al.*, 1991).

Fruit characteristics

Primates generally consume fruits described as *fleshy*—that is, fruits with an obvious edible mesocarp and usually notable sugar and water. Wild fruits differ from their cultivated counterparts in a number of important respects—as a class, tropical wild fruits are higher in protein, fiber and some micronutrients than cultivated fruits (Milton, 1999). The two major sugars in the flesh of wild fruits are hexoses—glucose and fructose—while the major sugar in cultivated fruits is sucrose, a disaccharide (Baker *et al.*, 1998; Milton, 1999). The notable difference in sugar composition between wild and cultivated fruits would seem to result from selective plant breeding aimed at production of a commercial product with a reliable strong sweet taste.

Fruit alcohols

Alcohols and esters are important contributors impacting the essence aroma of fruits. At least 200 different compounds are identified as making up the strawberry aroma—a mix of alcohols, aldehydes, esters, ketones and various other components. A fresh apple is estimated to contain 61 different alcohols and fresh orange juice 53 (Nijssen *et al.*, 1996). Ethanol is therefore only one of numerous fruit alcohols though it appears to be ubiquitous as it can be produced by cells of the fruit itself or by yeasts entering or sequestered within the fruit. Ethanol also tends to be by far the most abundant alcohol in fruits (Korine *et al.*, 2004).

Ethanol content of fruits

Few estimates exist for the ethanol content of wild fruits from tropical forest trees and vines. Dudley

(2004) found pulp from ripe fruits of the wild Panamanian palm *Astrocarium stanleyanum* to have an ethanol concentration of 0.56 ± 1.04%. In a Finnish study of ethanol ingestion by passerine birds, Eriksson and Nummi (1982) looked at ethanol concentrations of rowen berries, hawthorn haws and rose hips once per month between September 1979 and February 1980 at a site in the Helsinki area. The highest ethanol concentrations they recorded occurred in rowen berries in February (2.4 g ethanol/kg fresh wt berries or 0.0024% ethanol) and rose hips in January (3.2 g ethanol/kg fresh wt rose hips or 0.0032% ethanol). They concluded that *generally* ethanol levels in fruits in combination with metabolic rates of bird species under study were probably not high enough to have behavioral importance (see also Levey, 2004). Stevens (D. Stevens, personal communication) looked at ethanol concentrations of ripe commercial fruits in California supermarkets and found ethanol values ranging from 0.01% to 0.55% (average ethanol content = 0.18%, n = 7 commercial fruit types).

As ripe fruits age and become over-ripe, ethanol concentrations generally rise dramatically. Dudley (2004) found an ethanol concentration of 4.5 ± 0.61% in over-ripe fruits of the wild palm *Astrocarium stanleyanum* in Panama. A similar pattern was found by Stevens for commercial fruits in California. A supermarket mango with an ethanol concentration of 0.01% when ripe, showed a concentration of 0.52% when over-ripe. A ripe supermarket plum with an ethanol concentration of 0.05% showed a concentration of 0.54% when over-ripe. In all paired commercial samples (n = 7 pairs), as the ripe fruit aged, its sugar content dropped and its ethanol content rose (D. Stevens, personal communication). Fruit defenses weaken after maturation, facilitating invasions by yeasts and fungi (Biale, 1964). It is recognized that the terms *ripe* and *over-ripe* in the above context are subjective evaluations but, in general, a *ripe* fruit would be one judged to be at the end of stage 3 (*sensu* Biale, 1964), that is, a fruit at the climacteric or similar stage. An *over-ripe* fruit would be one that had passed this point and entered stage 4, senescence (Biale, 1964).

Ethanol preference patterns of laboratory animals

A study of oral self-administration of ethanol by captive cynomolgus monkeys classified monkeys into three phenotypes according to the amount of ethanol each consumed (Vivian *et al.*, 2001). Monkeys that drank >3.0 g/kg ethanol per day and obtained >20% of daily calories from ethanol were classified as "ethanol preferring" or "heavy drinkers"; monkeys that drank between 1.0 and 3.0 g/kg ethanol per day and obtained 10–20% of daily calories from ethanol were classified as "moderate drinkers"; and monkeys that drank <1.0 g/kg ethanol per day and obtained <10% of daily calories from ethanol were classified as "light drinkers" (Vivian *et al.*, 2001). The pattern of ethanol consumption shown by the light drinkers was described as "prandial," that is, monkeys tended to ingest ethanol when feeding (Vivian *et al.*, 2001). Any ethanol ingested by wild primates would always be in the context of feeding.

Not only humans and monkeys but also mice and rats show large individual differences in terms of voluntary ethanol intake (Crabbe, 2002). Under laboratory conditions, populations of mice or rats with notable genetic variability show a pattern of drinking similar to that of genetically variable human or monkey populations—that is, some mice or rats will drink significantly more ethanol than other mice or rats, some will drink little ethanol and so on (J. Crabbe, personal communication to KM). This suggests that proportions of populations of various mammal species are susceptible to genetic and environmental factors that can result in voluntary heavier or lighter ethanol consumption (Crabbe *et al.*, 1994; Vivian *et al.*, 2001; Crabbe, 2002). For this reason, a dietary heritage of frugivory does not seem necessary for such ethanol-related behaviors.

Estimates of ethanol intake by primates

How much ethanol would a wild primate ingest in a normal day's feeding if it consumed fruit pulp with an estimated ethanol concentration of 0.01%? If a 7 kg monkey took in some 1,600 g wet weight of fruit pulp over the course of a 12 hr day (an actual estimate made for wild spider monkeys) with an ethanol content of 0.01%, ethanol intake would be minute—around 0.16 grams of ethanol in total or less than 1/50th of a gram of ethanol per kilogram of body weight. If a higher ethanol estimate of 0.1% for ripe fruit pulp is used, estimated ethanol intake for the 7 kg monkey rises to 1.6 g total, which is still minute, particularly per kg. However, if animals consumed ripe fruit pulp with an ethanol concentration of 0.56% (the concentration Dudley [2004] reported for ripe palm fruits in Panama), their ethanol intake would rise notably to 8.9 g of ethanol per day or ~1.3 g ethanol per kg of body weight per day. However, this total would be ingested with food in two or more discrete feeding bouts over the course of a 12-hr day, so the maximum ethanol concentration the monkey would ingest at any one time would likely be <3 g ethanol in total or <0.43 g per kg. For comparative purposes, a 4 oz glass of red wine contains approximately 11 g ethanol and a martini 19 g (Wardlaw and Insel, 1995). A 68 kg man drinking 4 oz of red wine would therefore take in 0.16 g ethanol/kg body weight and if drinking a martini, 0.28 g ethanol/kg. This ethanol would be oxidized at a rate of 7 to 14 g per hour, depending on a wide variety of factors, including the individual's genetic make-up (Wardlaw and Insel, 1995).

Fruit stage preference survey

My field work has involved observations of the dietary behavior of various species of howler monkeys, spider monkeys, capuchins and tamarins as well as woolly spider monkeys. In my opinion, all of these species show a strong attraction to ripe (mature) fruits,

a few, on occasion, are attracted to select immature fruits and none appear attracted to over-ripe fruits. Curious about the stage of fruit maturation preferred by other wild primates, I sent out a brief survey. Twenty primatologists responsed, many of whom have worked at particular study sites for 15 or more years (see Appendix for respondent list). In combined data, survey respondents discussed the fruit stage preferences of 22 primate species and subspecies, including representatives of all of the great apes, various Old World and New World monkey species and one Malagasy prosimian. (See Appendix for species list.)

Two taxa in the survey sample, one subspecies of gorilla and one subspecies of sifaka were stated to rarely eat fruit and were omitted from further consideration. Sixteen (80%) of the remaining 20 primate taxa in the survey were stated to prefer ripe (mature) to immature or over-ripe fruits. Four species (20%), three Old World leaf-eating monkeys and one New World capuchin species were stated to prefer immature to mature or over-ripe fruits. No (0%) species was stated to prefer over-ripe fruits to mature or immature fruits. In fact, over-ripe fruits were stated to seldom or never be eaten. If over-ripe fruits were eaten, respondents stated this might occur inadvertently when animals were consuming ripe fruits.

From survey results, it seems safe to say that most wild primates do not appear attracted to and rarely, if ever, eat over-ripe fruits. For this reason, they would be unlikely to ingest any notable amount of ethanol. Flavor trials with humans involving Feutrell's Early mandarins stored at room temperature under different conditions showed that increased ethanol (and acetaldehyde) concentrations in fruits negatively and highly significantly lowered their flavor scores (Ahmad and Kahn, 1987). Over 90% of the variation in flavor scores could be explained by changes in ethanol and acetaldehyde content (Ahmad and Kahn, 1987). This suggests that humans prefer the flavor of fruits lower rather than higher in ethanol and the same may be true for wild primates. In trials, Egyptian fruit bats showed a significant decrease in food consumption with increasing ethanol concentrations (1% and 2% v/v) (Sanchez *et al.*, 2004). If low ethanol concentrations such as 0.001%, 0.01% and 0.1% turn out to be the norm for fruits eaten by wild monkeys and apes, then, by analogy, the amount of ethanol fruit-eating pre-human ancestors took in each day presumably was similarly low and therefore unlikely to have been of any notable behavioral or evolutionary consequence.

Evidence of intoxication in wild primates

I asked survey participants if they had ever seen a wild primate that appeared intoxicated. Andrew Ritchie, working as a field assistant in Madagascar for Erik Patel of Cornell University, reported that on two occasions during April–May 2003, he observed behaviors in the silky sifaka, *Propithecus diadema candidus*, that in his view indicated "drunkenness." Behaviors included lack of coordination with activity levels ranging from intense excitement to lethargy. Ritchie described animals as dazed, with eyes rolling around, apparently unable to focus, and mouths agape. Balance appeared compromised and in one case, a sifaka jumped on one of the observers. The experienced observer did not move and the animal did not appear to notice that it was resting on a person. In both cases, sifakas had just carried out long feeding bouts on seeds from over-ripe fallen fruits. The tree species was not identified. These sifakas generally do not feed on the flesh of ripe fruits, preferring instead to feed on leaves or seeds. Ritchie hypothesized that the animals became intoxicated while extracting seeds from the potentially ethanol-rich pulp. It is possible, however, that the seeds themselves contained some types of secondary compounds that produced the unusual behaviors observed (*e.g.*, Marais, 1969). As a class, seeds are noted for their toxic properties.

As this was the only positive report I received regarding possible primate intoxication in the wild, given the many thousands of hours of field observation represented by combined survey respondents, I conclude that if monkeys or apes ever do become intoxicated in the natural environment, this occurs extremely infrequently.

WHAT NUTRIENT FUNCTIONS DOES ETHANOL SERVE?

It seems popularly believed that ethanol might be a valuable dietary adjunct for wild primates due to its caloric content. Ethanol is an unusual substance. It is metabolized as a nutrient and could contribute to total caloric intake as it contains 7.1 cal per gram and has a thermogenic effect similar to carbohydrate when consumed in normal social drinking (*ca.* 10% of alcohol energy) (Sonko *et al.*, 1994). However, when ethanol is consumed at high dose, energetically wasteful metabolic pathways are activated (Pirola and Lieber, 1972). In humans, excessive ethanol intake is metabolized predominantly by the microsomal ethanol-oxidizing system (MEOS), which leads to an increased loss of energy from ethanol as heat (Lands and Zakhari, 1991; Suter *et al.*, 1992). As Lieber (1989) states, as a calorie source, alcohol is not as adequate as equivalent carbohydrate, particularly when taken chronically in large amounts.

Within the body, ethanol dominates oxidative pathways, taking precedence over carbohydrate, protein and fat oxidation, presumably because there is no storage capacity for ethanol within the body and because oxidative detoxification is imperative (Sonko *et al.*, 1994). Fat oxidation takes the lowest priority and is most easily displaced by the ingestion of alcohol (Sonko *et al.*, 1994). This appears to have led to the assumption that isoenergetic substitution of carbohydrate by ethanol causes net fat storage. In fact, ethanol does not induce lipogenic enzymes (Guthrie *et al.*, 1990) and isoenergetic subsitution of carbohydrate by ethanol is stated to have no effect on net fat storage (Sonko *et al.*, 1994). Alcohol should only induce fat storage when it is ingested along with other foods such that a

positive energy balance is created (Sonko *et al.*, 1994). In such cases, lipid storage would be favored with resulting weight gain (Suter *et al.*, 1992). Suter *et al.* (1992) stress that ethanol can be an important source of energy that is available to the body and note that subjects who wish to maintain a constant weight without giving up ethanol consumption should decrease their fat intake to allow for the additional energy from ethanol.

Given the modest amount of ethanol presumably taken in by wild primates, any fat storage related to ethanol ingestion is likely a non-issue. Too, the predominately fruit-based diet of most wild primates is already high in energy. Ethanol can also be considered "empty calories" as it provides no nutrient benefit other than energy. As pointed out by Lands and Zakari (1991; see also Colditz *et al.*, 1991), in humans, the carbon and calories in ethanol seem to make no contribution to weight or body mass index (BMI). Guthrie *et al.* (1990) reported that ethanol in diets of Sprague-Dawley rats actually caused shortening of the intestinal villi, something typically observed in starvation. Rats showed reduced growth characteristics even though the diets offered were nutritionally adequate with respect to protein, vitamins, minerals and total calories.

Do Primates Use Ethanol Plumes?

Tropical forests are noted for their high species diversity and wide array of phenological production patterns (Milton, 1980, 1981, 2000). As a class, ripe fruits are more patchily distributed in space and time in tropical forests than other categories of wild plant foods such as young leaves, immature fruits, or flowers (Milton, 1980, 1981). This raises the question of how primates are able to locate a sufficiency of ripe fruits each day. Primates, particularly anthropoids, are noted for their considerable cerebral complexity (Milton, 1981, 1988, 2000; Boinski and Garber, 2000). Extensive data show that wild primates often move rapidly and directly from one fruiting tree to another over long distances by the shortest possible route, suggesting that they have excellent memories and a high degree of spatial coordination (Milton, 2000; Boinski and Garber, 2000). However, it would seem that travel to fruiting trees could be greatly facilitated by olfactory cues. In particular, it has been hypothesized that frugivorous primates might use ethanol plumes to help locate ripening fruit crops (Dudley, 2000, 2004).

Olfaction has tended to be downplayed as an important sensory modality in food location by higher primates. However, Laska and Seibt (2002*a*, *b*) have recently shown that olfactory information of certain types is readily processed by and likely important to wild primates. In recent trials, they tested New World squirrel monkeys and Old World pig-tailed macaques for their olfactory sensitivity to aliphatic alcohols. Aliphatic alcohols were selected for study because, as a class, they are indicative of a fruit's stage of ripeness and for this reason their detection might be important to fruit-eating primates (Laska and Seibt, 2002*a*).

Results showed that in most cases, monkey species could discriminate alcohol concentrations below 1 part per million from the odourless solvent. Low carbon alcohols required higher concentrations for detection than longer chain alcohols. Neither monkey species could detect ethanol (C2) at a dilution lower than 1:300 (Laska and Seibt, 2002*a*). The same regular association between olfactory sensitivity and this molecular property of the odorants has been found in human subjects and in rats (Laska and Seibt, 2002*a*, *b*).

Data from other trials showed the two monkey species were considerable more sensitive to aliphatic esters than aliphatic alcohols (Laska and Seibt, 2000*b*). Though both alcohols and esters are important contributors impacting the essence aroma of fruits, it is esters which comprise the predominant aliphatic components in a wide variety of fruit odors throughout the ripening process (Laska and Seibt, 2002*a*). As alcohols only begun to occur notably as fruits become overripe, esters are likely to be of greater importance than alcohols as frugivore cues to ripening fruit crops (Laska, personal communication to KM). At present, there appear to be no data to show which fruit alcohols or esters (if any) primates might actually utilize to locate fruit crops in the natural environment. However it would seem that a *strong* ethanol plume, rather than acting as an attractant, might well act as a deterrent since field data indicate that wild primates actively avoid consumption of over-ripe fruits and primate species used in olfactory trials could only detect ethanol at relatively high concentrations.

Alcohol Dehydrogenase (ADH)

Ethanol is a toxic substance and its initial oxidation product, acedaldehyde, even more toxic. Animals consuming foods containing ethanol should possess efficient mechanisms to detoxify both of these compounds. Ethanol molecules are metabolized through reactions catalyzed initially by the enzyme alcohol dehydrogenase (ADH), a family of zinc-containing isozymes with universal distribution in living organisms, including plants and bacteria (Agarwal and Goedde, 1989). ADH serves to convert alcohols to their corresponding aldehydes using NAD+ as a cofactor (Seitz and Oneta, 1998) and this is usually visualized as its main function. However, as Agarwal and Goedde (1989) point out, at neutral pHs, ADH catalyzes irreversible aldehyde reactions and, at maximum velocity, the rate of aldehyde reduction is some 40 times greater than the rate of alcohol oxidation. ADH shows broad substrate specificity and numerous naturally occurring compounds have been suggested as substrates for ADH (Agarwal and Goedde, 1989). Various primary, secondary and aromatic alcohols arising from foodstuffs and fruits, including their corresponding aldehydes and ketones, are metabolized by ADH. Though the metabolism of acetaldehyde is of interest and importance in any discussion of ethanol detoxification, space limitations discourage such commentary. Those interested in details of this critical step in ethanol de-

toxification are referred to Goedde and Agarwal (1989).

Immunological studies show that ADH molecules from different mammalian species share common antigenic determinants and that common structures have been preserved over a long evolutionary period (Agarwal and Goedde, 1989). Human ADH exhibits multiple molecular forms, grouped into classes encoded by at least 7 genetic loci (Moreno *et al.*, 1994). These classes differ from one another in more than 30% of their amino acid sequence and exhibit distinct properties and specific tissue distributions. Most ADH activity in human tissues takes place in the liver but abundant activity also occurs in other tissues, particularly the esophagus and stomach as well as the large intestine, kidneys and lungs (Agarwal and Goedde, 1989; Seitz and Oneta, 1998). The human esophagus, like that of the baboon and rat, contains an ADH form with high activity and appears to serve as a first metabolic barrier against ingested alcohols and aldehydes (Seitz and Oneta, 1998). In humans, the rate of ethanol metabolism varies between individuals and is affected by numerous environmental and genetic factors. Generally, in adult humans, ethanol oxidation is in the range of 120 to 150 mg/hr/kg body weight (Agarwal and Goedde, 1989).

First pass metabolism and gastric ADH

On ingestion, ethanol is subjected to first pass metabolism (FPM)—that is the lowering of ethanol content through gastric and hepatic ADH prior to reaching the systemic circulation (DiPadova *et al.*, 1986; Haber *et al.*, 1996). The magnitude of FPM determines the bioavailability of alcohol and thus modulates its potential toxicity (DiPadova *et al.*, 1986; Haber *et al.*, 1996). Though FPM is primarily hepatic for other drugs, the stomach rather than the liver is predominately responsible for the first pass metabolism of ethanol not only in humans but also in baboons, rats, mice and Syrian golden hamsters (DiPadova *et al.*, 1986; Algar *et al.*, 1992; Haber *et al.*, 1996). In humans, within a range of moderate social drinking, gastric FPM appears to be dose dependent, but it is *maximally effective at very low ethanol dosage*—equivalent to one "drink" and gastric FPM is still significant at double that dose (DiPadova *et al.*, 1986). When alcohol is ingested at high dose, hepatic metabolism dominates.

In baboons, gastric ADH3 was found to be very active with ethanol at high concentrations and exhibited high K_{cat}values for hexanol and trans2-hexan-1-ol (Algar *et al.*, 1992). The kinetic properties of the enzyme suggest that it has evolved to turn over substrate rapidly where high concentrations might be encountered prior to their entry into the circulation (Algar *et al.*, 1992). K_{cat} values for ADH3 in baboons were 80-fold greater than for the corresponding human enzyme and 10-fold greater as compared with mouse and rat gastric ADHs (Algar *et al.*, 1992). Factors related to polymorphisms of gastric, hepatic and other ADH and the significance of such polymorphisms between individuals, populations and species are currently under study.

Ethanol metabolism by gastric ADH in various primate and rodent species suggests that this is a general property of the stomach of many mammals, *not just frugivorous mammals.* Even in the absence of its oral consumption, ethanol may be present within the lumen of the stomach, presumably as a result of microbial metabolism (Haber *et al.*, 1996). Thus the stomach may play a protective role through active metabolism of endogenous ethanol (Haber *et al.*, 1996).

Conditions in the natural environment

As noted above, fruits contain not only ethanol but numerous alcohols and esters. In baboons (and probably many other species), gastric ADH shows much greater affinity for some other alcohols than it does for ethanol and this affinity may alter the kinetics of gastric ethanol detoxification (Algar *et al.*, 1992). Fruits also contain dozens of other chemical constituents, including substantial amounts of glucose and fructose and some sucrose. High glucose and fructose concentrations in the blood of a human drinker are stated to reduce blood ethanol concentration, perhaps through enhanced oxidation of ethanol (Agarwal and Goedde, 1989). Fructose, either as a monosaccharide or in sucrose, was also found to decrease the negative effects of ethanol in rats (Guthrie *et al.*, 1990). Wild primates are taking in any ethanol in fruits along with considerable fructose, glucose and some sucrose as well as other alcohols and similar substrates. Results of human or animal studies which focus on the detoxification of beverage ethanol, often at high dose, may not accurately reflect normative wild primate-ethanol interactions.

GENDER-ASSOCIATED DIFFERENCES IN ETHANOL CONSUMPTION AND METABOLISM

Higher male preference for ethanol

Great apes, hominids and humans (fossil and extant) show intraspecific body size dimorphism, at times considerable body size dimorphism, with adult males larger than adult females (Milton, 1983; Klein, 1999; Fleagle, 1999; McHenry, 1996). Human males typically have greater body water content, distribution space and lean body mass than human females (Kwo *et al.*, 1998). All else being equal, it would be predicted that, at the same ethanol dose, human males would show less immediate effects of ethanol ingestion than human females. A wealth of data indicate that, for whatever reasons, men are far more likely to over-consume ethanol than women. A cross-cultural survey of the use of ethanol in 139 largely preliterate human societies, showed that in all societies in which drinking was present in one sex but not in the other, it was present in males (Child *et al.*, 1964). For all societies for which statistics were available, data also showed that men were much more likely than women to become alcoholics (Bacon *et al.*, 1964). Epidemiological data on alcohol drinking patterns in the US and elsewhere

suggest that men are more likely to drink and drink heavily than women and have a higher likelihood of legal and psychosocial problems related to their consumption of ethanol compared with women.

Trials on cynomolgus monkeys, described as an excellent model for the study of human alcohol abuse, concluded that male monkeys were at greater risk of drinking ethanol excessively than females (Vivian *et al.*, 2001). Female rhesus monkeys were less likely to initiate and maintain ethanol consumption than males or demonstrated no sex difference in ethanol self administration across a range of ethanol concentrations. (Vivian *et al.*, 2001). In contrast, data for rodents (Long-Evans rats) suggest that females voluntarily drink more ethanol than males (Lancaster and Spiegel, 1992). Readers are referred to primary sources for details of experimental protocols as these could affect results. For example beer containing 5% ethanol was offered to Long-Evans rats (Lancaster and Spiegel, 1992). The nutrient value of beer might have influenced female preference.

On the whole, data suggest that male primates are more likely to self-administer higher doses of ethanol than female primates. This pattern may prevail because, as discussed below, male health seems less likely to be negatively impacted on by ethanol consumption, at least initially, and male fitness seems far less likely to be affected by ethanol consumption than female fitness. In ethanol self-administration trials with cynomolgus monkeys, though ethanol intakes were lower in females compared with males, profound changes in menstrual cycle quality were associated with higher ethanol intakes. These perturbations in ovarian progesterone in the heavier-drinking female monkeys were consistent with disruption of reproductive functions observed in human females and documented in female rhesus monkeys (Vivian *et al.*, 2002).

Gender differences in gastric FPM

Data suggest that women under the age of 40–50 show significantly decreased gastric ADH activity and lower gastric FPM than male counterparts. (Frezza *et al.*, 1990; Seitz and Onata, 1998; Thomasson, 1995; Parlesak, *et al.*, 2002). Numerous factors have been suggested to contribute to this difference, which is not well understood (Frezza *et al.*, 1990; Thomasson, 1995; Parlesak *et al.*, 2002). A study of ADH activity in samples of gastric mucosa from one adult male and one adult female rhesus macaque showed that gastric ADH activity in the male sample was 1.5 times that of the female sample (A. Almquist personal communication). In Sprague-Dawley rats, in contrast, gastric ADH activity and enzyme protein levels are higher in female than in male rats (Mezey *et al.*, 1992).

If *gastric* FPM is less effective in young women then, all else being equal, more ethanol should initially reach the female liver and bloodstream and females should react accordingly. A heightened female sensitivity to ingested ethanol could possibly serve useful functions. In mammals, the reproductively active female has a set of metabolic constraints placed on her feeding processes quite unlike those of her male counterpart (Demment, 1983). Not only are females responsible for bearing all costs of gestation (and lactation) but they must also protect the fetus from harm. A heightened female sensitivity to the presence of ethanol in fruits could serve as an early warning detection device regarding ingestion of this potentially teratogenic substance.

Ethanol and the developing fetus

Ethanol has known teratogenic effects. In humans, orally ingested ethanol can reach fetal blood within 15 minutes, with effects 10 times greater on the fetus than on the mother (Wardlaw and Insel, 1995). Exposure to ethanol in the preimplantation period is associated with lethality. Structural and functional malformations can result from ethanol exposure during the period of organogenesis, approximately 18 through 60 days post conception in the human (Chernoff, 1980). After this critical period, the human fetus becomes increasingly resistant to structural malformation but remains susceptible to ethanol-induced deficiencies in growth and maturation. Intermittent exposure during a short period of development would be expected to cause only a portion of the total syndrome (Chernoff, 1980). In pregnant human females, one ill-timed bout of binge drinking may produce permanent fetal damage (Wardlaw and Insel, 1995). In humans and rats, prenatal exposure to ethanol during organogenesis can result in delayed sexual maturation of daughters (Robe *et al.*, 1980). Ingested ethanol can also interfere with the absorption or function of various micronutrients, including folate (Wardlaw and Insel, 1995).

Laboratory trials on cynomolgus monkeys showed that once weekly administration of 1.8 g ethanol/kg to pregnant female monkeys for a period of 6 weeks or for the entire 24 weeks of gestation resulted in cohorts of infants uniformly abnormal in behavior and inconsistently abnormal in physical development relative to controls (Clarren *et al.*, 1992). Problems with motor development and coordination were noted in the entire 24 week cohort and in one infant in the 6-week cohort. As most primates are arboreal and/or feed in trees, they require a high degree of balance and coordination and ethanol-impacted infants should fare poorly. Locomotor coordination problems have also been reported for ethanol-impacted rat pups (Meyer *et al.*, 1990). Though for humans, the question of fetal damages due to low to moderate drinking during pregnancy is still controversial (Abel and Sokol, 1989), women in the US are now warned to avoid alcohol entirely during pregnancy or when there is a chance pregnancy might occur (Wardlaw and Insel, 1995).

The damaging effects of ethanol on the human fetus appear to have long been appreciated by humans and many societies had/have sanctions against ethanol intake by young or pregnant women. The Old Testament, for example, contains numerous strong admonitions

regarding ethanol ingestion by pregnant women or those wishing to become pregnant, *e.g.*, "Of all that I said unto the woman let her beware. She may not eat of any thing that cometh of the vine, neither let her drink wine or strong drink. . . " (Judges 13:13–14, King James version. The Holy Bible). After menopause, such sanctions are often relaxed, suggesting that the association between female fecundity, ethanol ingestion and fetal damages are recognized (Almquist and Matsuda, 1998).

Hepatic detoxification of ethanol

In the natural environment, ethanol intake by nonhuman primates is presumed to generally be quite low and for this reason unlikely to pose problems. Daily ethanol detoxification is likely no more or less important to wild primates, including pregnant females, than the routine detoxification of numerous other common plant compounds. But because of their dietary focus on wild plant foods, higher primates, unlike many mammals, have been exposed to potentially toxic or psychoactive compounds over their entire evolutionary history and for this reason might be particularly well equipped to deal with them.

In primates, the liver is the principal detoxification site for ethanol and numerous other compounds (Frezza *et al.*, 1990; Maly and Sasse, 1991; Wardlaw and Insel, 1995). Higher primates are noted for large liver size and scant data suggest that folivorous primates, which should encounter toxic compounds in foods at a higher rate and concentration than frugivorous primates, show higher liver/body weight ratios (Querling, 1950). Kwo *et al.* (1998) have data suggesting that in adult humans, the average female liver does not differ significantly in mass from the average male liver in spite of generally larger body size in human males. This suggests that natural selection may have favored a more powerful hepatic detoxification system in females than males, a feature which could relate to selective pressures placed on female metabolism during gestation.

Women of reproductive age are also reported to show higher hepatic ADH activity (Maly and Sasse, 1991) and to exhibit faster ethanol metabolic rates than similar-aged males (Thomasson, 1995). Female rats and mice also have higher hepatic ADH activity and/or faster rates of ethanol metabolism than male rats and mice (Thomasson, 1995; Harada *et al.*, 1998; Ritsuko *et al.*, 2002). Yet, at the same time, women *are more susceptible* than men to the adverse effects of ethanol and develop ethanol cirrhosis and ethanol hepatitis at younger ages and at lower accumulated ethanol intakes than men. (Schenker and Speeg, 1990; Thomasson, 1995; Kwo *et al.*, 1998). Female rats likewise exhibit greater susceptibility to early alcohol–induced liver injury than male rats (Iimuro *et al.*, 1997). Factors that might cause women (and some other female mammals) to be more vulnerable to ethanol damages are not yet established and information on this topic is often conflicting (Lieber, 1994; Thomasson, 1995; Iimuro *et al.*, 1997).

The initial bioavailability of ethanol should be greater in women because of their lower gastric FPM of ethanol (Frezza *et al.*, 1990). At the same ethanol dose, this should result in more ethanol reaching the female liver, perhaps contributing to the higher vulnerability to hepatic injury in women (Frezza *et al.*, 1990). Hormonally-mediated interactions particular to or more acute in cycling or pregnant females may also play a role. For example, faster hepatic ethanol oxidation in females may expose liver tissue to higher levels of acetaldehyde, a highly reactive molecule that forms adducts with cell surface and blood proteins, and is suggested to contribute to the development of cirrhosis (Thomasson, 1995).

Human ethanol production

For thousands of years, human ingenuity has made low ethanol beverages (mead, beer, wine) available in quantity and, since around A.D. 700, distilled ethanol has been available at concentrations not possible in the natural environment of the fermenting fruit (Westermeyer, 1989; Vallee, 1998). An enzymatic system easily able to deal with detoxification activities related to routine small quantities of ethanol and similar substances in fruits or other foods, and capable, though the microsomal enzyme oxidizing system (MEOS) and peroxisomal catalase, of handling an occasional high ethanol dose in foods, might not be able to function efficiently when exposed to consistent high beverage ethanol concentrations. Studies show that numerous and wide ranging differences develop between the ethanol metabolism of the occasional social drinker and that of the alcoholic (Lieber, 1989). For example, alcoholic men display reduced gastric ADH levels and reduced first pass metabolism relative to normal healthy controls (Algar *et al.*, 1992). They also show reduced testosterone levels, a factor which appears to increase the alcoholic male's ability to metabolize ethanol (Cole-Harding and Wilson, 1987). In considering possible ethanol-related adaptations in frugivorous primates, it is important to bear in mind that their day-to-day exposure to ethanol is likely to be low. Information or insights derived from studies of high ethanol dose or prolonged high ethanol intake may be misleading if viewed from the perspective of the wild primate situation.

Why are some humans so strongly attracted to ethanol?

Why some humans are particularly attracted to ethanol is not known though a diverse array of genetic and environmental factors are implicated (Vesell, 1989; Crabbe *et al.*, 1994). Fruit sugars have been the primary source of dietary energy for hominoids over most or all of their entire evolutionary past. Apes and humans therefore have an ancient and perhaps special relationship with such sugars, particularly fructose and glucose. In some manner, the strong attraction ethanol

holds for certain individuals may relate to interactions between their particular genotypes and certain biochemical similarities between ethanol and carbohydrate. Both ethanol and carbohydrate are metabolized by a common pathway to fatty acids from acetyl-coenzyme A by lipogenic enzymes (Guthrie *et al.*, 1990). Humans are stated to have no regulatory or satiation point either for ethanol (Lands and Zakhari, 1991) or lipids and neither substrate can be metabolized to produce glucose. The large primate brain, and, in particular the unusually large human brain, utilizes considerable glucose each day. In adult humans, an estimated 23% of daily basal metabolic rate relates to energy demands of the brain alone (Holliday, 1978).

It has been proposed that men and women who regularly drink alcohol may have different dietary preferences than non-drinkers (Colditz *et al.*, 1991). Dietary preferences are likely influenced to some extent by genetic factors. A genetic predisposition to consume ethanol, particularly notable doses of ethanol, could relate to its pharmacological (drug) effects or to its taste, smell or caloric value (Crabbe *et al.*, 1994). In humans, the consumption of candy and sugar is inversely related to ethanol intake, raising the possibility that appetite for ethanol may be related to appetite for sugar (Colditz *et al.*, 1991). In the Nurses' Health Study, a clear inverse relationship between alcohol consumption and BMI was noted in women but not in men (Colditz *et al.*, 1991). In both genders, a consistent decrease in the use of added sugar with increasing ethanol consumption was found but in female subjects, energy from alcohol intake displaced sugar in the diet while in male subjects, calories from alcohol were added to energy intake from other sources. Factors underlying this gender-based difference are not known.

Alcohol-potentiated reactive hypolyglycaemia is stated to depend on the nature of the carbohydrate mixer ingested with ethanol. In human males in the fasted state, when ethanol is drunk with a simple sugar mixer, reactive hypoglycaemia may result due to an augmented insulin response (Baker *et al.*, 1984). This does not occur when ethanol is consumed with a starch mixer, as in sorghum beer or commercial bottled beer (Baker *et al.*, 1984). For whatever reason(s), it also seems to be the case that many of the same human populations currently suffering from a high incidence of obesity and type II diabetes are also suffering from problems related to the over-consumption of ethanol. The ambiguous status of ethanol as a nutrient that is not exactly a nutrient, a food that is not exactly a food, may resonate in some manner with certain biochemical attributes of human biology in ways some individuals find difficult to resist.

Hormetic effects of ethanol?

Humans in highly technological nations suffer a high incidence of cardiovascular disease and strokes (Altura and Altura, 1989). Some data suggest that regular light-to-moderate drinking may protect against coronary heart disease (CHD)—in other words, that individuals routinely consuming modest amounts of ethanol may show a lower incidence of CHD than individuals either abstaining from or drinking higher amounts of ethanol (Klatsky *et al.*, 1981; Altura and Altura, 1989; Klatsky, 2004). A number of mechanisms have been suggested to explain the means by which routine modest alcohol consumption could exert such protection but to date, there is no consensus and the topic remains controversial (Altura and Altrua, 1989).

Drinking patterns have recently been suggested to differentially affect central adiposity as measured by abdominal height in women and men (Dorn *et al.*, 2003). Central adiposity, particularly the amount of visceral fat, is implicated as an important risk factor for cardiovascular disease (CVD), including both stroke and CHD mortality (Dorn *et al.*, 2003). It is hypothesized that ethanol may affect insulin sensitivity such that less visceral fat can be deposited, lowering this cardiovascular risk (Dorn *et al.*, 2003). If this possibility is confirmed, it appears to relate to features of the contemporary human diet and health problems stemming from this diet in relation to human biology rather than to any biological heritage features associated with ancestral fruit ethanol consumption.

In summary

On the whole, this examination of ethanol, fruits and wild primates has failed to detect any convincing evidence suggesting the presence of fruit ethanol-based *biological* heritage features that might predispose humans to seek out or desire ethanol any more or less than might be the case for various other non-primate species. The panhuman interest in beverage ethanol may relate to the fact that human foodways are largely *learned* behaviors and alcoholic beverages have figured strongly in the foodways of most human societies for thousands of years (Westermeyer, 1989; Vallee, 1998). As cultural animals, humans have little innate nutritional wisdom (Carpenter, 1986, 2000; Galef, 1991) and for this reason may have unusual difficulty in determining when it is prudent to quit ingesting ethanol. Humans also appear to be the only animals with a highly developed sense of self-awareness and thus they may be the only animals that might wish to escape from their own consciousness. Ethanol offers humans this psychopharmacologic effect.

ACKNOWLEDGMENTS

Special thanks to Robert Dudley and Michael Dickinson for inviting me to present a paper on ethanol, frugivory and human evolution in the In Vino Veritas symposium they organized for the 2004 SICB annual meetings. Thanks also to Russell Jones and Loy Volkman for considerable useful information on plant biochemistry, to Kevin L. Goodner for timely information on ethanol and related compounds in fruits, to John Crabbe for information on mice and ethanol preferences and to Vittorio Maestro for suggesting the better half of the paper's title. My thanks also to all of those

who took the time to share their knowledge by participating in the fruit preference and intoxication survey. Access to the reference collection of the Alcohol Research Group at Berkeley was invaluable in preparing this paper and very much appreciated as was additional aid with references provided by Ingrid Radkey, Reference Librarian, Bio Science and Natural Resources Library, U. Cal. Berkeley.

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APPENDIX

Individuals participating in the fruit preference and intoxication survey included the following (listed in alphabetical order by last name): Colin Chapman, Linda Fedigan, Eduardo Fernandez-Duque, Ken Glander, Alexander Harcourt, Gottfried Hoffman, Lynn Isbell, Cheryl Knott, Joanna Lambert, William McGrew, John Mitani, John Oates, Ryne Palombit, Susan Perry, Vernon Reynolds, Andrew Ritchie, Scott Suarez, Carolyn Tutin, Richard Wrangham, Pat Wright.

Common names of primates included in the fruit preference and intoxication survey included the following (listed in alphabetical order): black-faced black spider monkeys, black-handed spider monkeys, black and white colobus monkeys, blue monkeys, bonobos, chacma baboons, common chimpanzees (4 sites), lowland gorillas (subspecies), mangabeys, mantled howler monkeys, Milne Edward's sifakas (subspecies), mountain gorillas (subspecies), night monkeys, olive baboons, olive colobus monkeys, orangutans, patas monkeys, red colobus monkeys, red-tailed monkeys, silky sifakas (subspecies), vervets, white-throated capuchins.