

# Ethanol, Fruit Ripening, and the Historical Origins of Human Alcoholism in Primate Frugivory<sup>1</sup>

ROBERT DUDLEY<sup>2</sup>

Department of Integrative Biology, University of California, Berkeley, Berkeley, California 94720 and Smithsonian Tropical Research Institute, P.O. Box 2072, Balboa, Republic of Panama

**SYNOPSIS.** Ethanol is a naturally occurring substance resulting from the fermentation by yeast of fruit sugars. The association between yeasts and angiosperms dates to the Cretaceous, and dietary exposure of diverse frugivorous taxa to ethanol is similarly ancient. Ethanol plumes can potentially be used to localize ripe fruit, and consumption of low-concentration ethanol within fruit may act as a feeding stimulant. Ripe and over-ripe fruits of the Neotropical palm *Astrocaryum standleyanum* contained ethanol within the pulp at concentrations averaging 0.9% and 4.5%, respectively. Fruit ripening was associated with significant changes in color, puncture resistance, sugar, and ethanol content. Natural consumption rates of ethanol via frugivory and associated blood levels are not known for any animal taxon. However, behavioral responses to ethanol may have been the target of natural selection for all frugivorous species, including many primates and the hominoid lineages ancestral to modern humans. Pre-existing sensory biases associating this ancient psychoactive compound with nutritional reward might accordingly underlie contemporary patterns of alcohol consumption and abuse.

## INTRODUCTION

The widespread occurrence of fermentative yeasts in ripening and ripe fruits indicates potential co-option of associated ethanol for use as a behavioral cue by vertebrate frugivores (Dudley, 2000, 2002). In particular, ethanol plumes might serve in localization of these transient nutritional resources, whereas ethanol consumed during the course of frugivory could act as an appetitive stimulant. Because humans are ancestrally derived from frugivorous primates, preference for and excessive consumption of alcohol by modern humans might accordingly result from pre-existing sensory biases associating ethanol with nutritional reward. Little is known, however, about either the natural occurrence of ethanol within fruits or the behavioral responses of frugivorous animals to such cues.

As agents of both microbial decay and fermentative activity, yeasts are widespread both on and inside fruits (see Last and Price, 1969; Cipollini and Stiles, 1992, 1993b; Spencer and Spencer, 1997). Anaerobic fermentation of sugars by yeasts yields ethanol. This metabolic pathway emerged in yeasts concomitantly with the shift by angiosperms from small wind-dispersed seeds to larger and more fleshy vertebrate-dispersed fruits during the late Cretaceous into the Paleocene (see Eriksson *et al.*, 2000; Benner *et al.*, 2002). Ethanol expression by fermentative yeasts appears to have specifically evolved to inhibit activity of bacterial competitors within ripe fruit (Ingram and Buttke, 1984), and ethanol plumes emanating from ripe fruit might thus have provided useful sensory information, both diurnally and nocturnally, from the very inception of mammalian frugivory. Given this historical presence of yeasts that consume sugars, plants correspond-

ingly express a diversity of antifungal compounds within developing and ripe fruit to impede decomposition (see Janzen, 1977; Borowicz, 1988b; Cipollini and Stiles, 1992; Cipollini and Levey, 1997a, b, c). Because microbial decay reduces the likelihood of vertebrate dispersal (Herrera, 1982; Borowicz, 1988a; Cipollini and Stiles, 1993a), the evolutionary pressures for effective antifungal measures that prevent spoilage are substantial.

The phenomenon of ripening, however, involves relaxation of defenses against premature consumption both by potential dispersers and by microbial pathogens (Thompson and Willson, 1979; Herrera, 1982; Janzen, 1983). Fruit ripening involves a coordinated series of changes in color, texture, volatile expression, and the conversion of starch to sugars (Brady, 1987; Tucker, 1993). In aggregate, these changes indicate suitability for consumption and dispersal by a vertebrate frugivore. As a consequence, fully ripe fruits are susceptible to microbial decay, an outcome that can interfere with the plant's evolutionary goal of consumption and dispersal by vertebrates (see Janzen, 1977; Borowicz, 1988a; Cipollini and Stiles, 1993a). Microbes, invertebrate fruit consumers (especially insect larvae), and vertebrate dispersers can thus be viewed as competitors for access to a rich but transient nutritional substrate.

In spite of the possible significance of ethanol for frugivore behavior and ecology (Levey and Martínez del Rio, 2001), knowledge of fermentation for non-domesticated fruits in natural ecosystems is confined to only several examples. Eriksson and Nummi (1982; see also Forsander, 1978) determined fairly low ethanol contents (0.05–0.3% w/w) for rowan berries, rosehips, and hawthorn fruits in autumn and winter conditions in Finland. Such temperate-zone fruits are unlikely, for reasons of low ambient temperatures alone, to be characterized by particularly high ethanol concentrations. Fermentation of fruit crops is instead more

<sup>1</sup> 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.

<sup>2</sup> E-mail: wings@socrates.berkeley.edu

pronounced in warm and humid environments that promote both yeast growth and rapid decomposition. Dudley (2002) presented ethanol data for three fruiting taxa in a Neotropical forest, and found that pulp of ripe and very ripe palm fruits (*Astrocaryum standleyanum*) contained ethanol at concentrations of about 0.5% and 0.6%, respectively.

The present study extends existing data on *A. standleyanum* to include parallel measures of texture and color for quantitative assessment of fruit ripeness, and also compares larger sample sizes of fruits taken both directly from the infructescence and from the ground where a greater range of decompositional conditions is available. *A. standleyanum* is a common palm species in lowland Panamanian rainforest, and bears large crops of orange fruits that are consumed by red-tailed squirrels, spiny rats, kinkajou, Central American agoutis, collared peccaries, and white-faced capuchin monkeys (Hladik and Hladik, 1969; Croat, 1978; Smythe, 1978, 1989; Hoch and Adler, 1997; Kays, 1999). This palm therefore represents an appropriate target species for evaluating the potential role of ethanol in the sensory and nutritional ecology of mammalian frugivores. Moreover, palm fruits have been proposed (together with figs) to be keystone resources for Neotropical vertebrate frugivores (Terborgh, 1980). Broad biogeographic and taxonomic screening of angiosperm fruits for ethanol content is beyond the scope of the present paper, but demonstration of ethanol-associated ripeness cues in palms may nonetheless be of general relevance for those frugivorous primates predominantly associated with tropical rain forest.

#### MATERIALS AND METHODS

Field collections and laboratory measurements were carried out on Barro Colorado Island (BCI), Republic of Panama, in May and June 2002 during the rainy season (ripe and over-ripe fruits), and in December 2002 (unripe fruits). Fruits were knocked down from infructescences using either a slingshot or thrown rocks (fruits thus obtained are hereafter referred to as hanging fruits), or were collected at the base of fruiting trees (*i.e.*, fallen fruits). Following transport of fruits within a closed plastic bag to the laboratory on BCI, measurements were made either immediately or within three hours of collection. In the latter case, individually bagged fruits were kept within a cold room at 10°C. Fruits were visually categorized as being either ripe or over-ripe; obviously rotting fruits were not used for measurements. Over-ripe fruits were never obtained from infructescences, and thus were only collected from the ground. Spatial heterogeneity of ripeness within an individual fruit was sometimes pronounced, particularly for fallen fruits. In these cases, all measurements were confined to a visually homogeneous region of the fruit. Wet masses of the exocarp (skin), mesocarp (pulp), and endocarp (seed) were also measured on twenty ripe fallen fruits.

Color reflectance spectra, puncture resistance, sugar content of the pulp, and ethanol concentration of the

pulp were measured on all collected fruits. Reflectance spectra of the skins were determined using a portable spectroradiometer (Colortron II; Lightsource) that measured absolute reflectance at 10 nm intervals over the spectral range of 390–700 nm. An averaging feature of the device permitted continuous accumulation and time-averaging of spectra. A mean reflectance spectrum was determined for each individual fruit by slowly moving the spectroradiometer's measurement region ( $3 \times 4$  mm) about the fruit's circumference. Resistance to puncture was determined using a Chatillon Type 719 penetrometer with a tip radius of 4.7 mm. Force was slowly applied to the penetrometer until the exocarp visibly fractured at the region of contact with the tip of the device. Displacement of a sliding force indicator was used to determine the maximum applied force. Three separate measurements of puncture force were used to estimate an average value per fruit. It should be mentioned that the tip of the penetrometer was beveled, and that the force measured here is a comparative rather than absolute measure of fruit mechanical properties (see Lucas *et al.*, 2000).

Sugar and ethanol measurements were made excluding the exocarp and the endocarp (*i.e.*, the seed), given that the carbohydrate rewards for dispersers are located primarily if not exclusively within the pulp, wherein fermentative processes are also likely localized. Soluble carbohydrate content of macerated pulp was determined using a handheld Westover RHB-32 Brix refractometer calibrated against known sucrose standards. Ethanol concentrations of pulp were determined from equilibrium vapor pressure measurements made using an electrochemical ethanol sensor (PAS Systems, Fredericksburg, VA) calibrated against ethanol solutions of known concentration. A sample volume weighing 3.0 g of calibration fluid or of macerated and diluted mesocarp was placed in a plastic weighing boat such that a circular fluid surface (18 mm radius) was exposed. The average dilution factor for pulp from ripe and over-ripe fruits was 6.8; this dilution ensured release of pulp solutes from within a fibrous matrix, and was also necessary in some cases to yield an ethanol concentration within the sensor's range. No dilution was used for the pulp of unripe fruits because of their very low ethanol content. The weighing boat containing macerated fruit pulp was sealed within a 0.95 liter plastic bag that also contained the ethanol sensor.

The ethanol sensor was activated at fixed time intervals via a contact switch on the device; electrical leads running through the bag via glue-sealed holes were used to monitor voltage output of the ethanol sensor. Ethanol vapor pressures between air and dilute ethanol samples equilibrated rapidly (*e.g.*, 95% equilibration in 30 minutes). Measurements on all fruit samples were therefore taken at one hour following sample insertion to standardize comparisons while minimizing consequent ethanol production over this time period. All measurements were conducted at an approximately constant ambient air temperature determined from a

TABLE 1. Mean (s.d.) puncture force, mesocarp sugar content, and mesocarp ethanol content for unripe and ripe hanging fruits, and for over-ripe fallen fruits. No ethanol was detected in the pulp of unripe fruits.

Category	Puncture force (N)	Sugar (%)	Ethanol (%)
unripe hanging fruits (8)	78.5 (4.0)	8.1 (2.4)	0.0
ripe hanging fruits (15)	32.4 (6.3)	16.2 (2.4)	0.6 (1.0)
ripe fallen fruits (16)	24.6 (5.5)	17.3 (2.0)	0.9 (1.6)
over-ripe fallen fruits (9)	21.5 (3.4)	10.1 (4.0)	4.5 (2.6)

mercury thermometer inside the sealed plastic bag (mean [SD] = 26.0°C [0.6°C]). Measurements of ethanol concentration for diluted pulp solutions were multiplied by the aforementioned factor of dilution to obtain the corresponding estimate for non-diluted mesocarp.

### RESULTS

Pulp of ripe palm fruits contained ethanol at concentrations averaging 0.6–0.9%, whereas that of over-ripe fruit averaged 4.5% (Table 1). The highest value obtained for pulp of an individual (over-ripe) fruit was 8.1%. The mass of individual ripe fruits found on the ground averaged 27.97 g, 38% of which was pulp and 42% of which was the seed. Unripe, ripe (both hanging and fallen), and over-ripe fruits differed significantly in puncture force ( $F = 220.0$ ;  $df = 3,43$ ;  $P < 0.0001$ ), sugar content ( $F = 33.4$ ;  $df = 3,43$ ;  $P < 0.0001$ ), and ethanol content ( $F = 13.2$ ;  $df = 3,43$ ;  $P < 0.0001$ ). Most notably, green fruits contained no measurable ethanol (see Table 1), and over-ripe fruits had much higher ethanol concentrations than either hanging or fallen ripe fruits (Fisher's PLSD,  $P < 0.0001$  in both cases). Green fruits were much harder, as measured by penetration force, than ripe or over-ripe fruits (Fisher's PLSD,  $P < 0.0001$  in each case). Exocarp of green unripe fruits turned orange as they ripened, whereas over-ripe fruits were substantially more reflective in red than ripe fruits (Fig. 1). Sugar and ethanol content were inversely correlated when ripe and over-ripe fruits were pooled (Fig. 2).

### DISCUSSION

#### Palm fruits and ethanol production

In tropical rainforests, the majority of woody plant species disperse seeds via vertebrate frugivores (Fleming *et al.*, 1987; Jordano, 2000). The palm *A. standleyanum* exhibits a dispersal strategy mediated primarily by Central American agoutis (*Dasyprocta punctata*), whereby these rodents consume the pulp of fallen fruit and then cache the seed in the ground (see Smythe, 1970, 1978). Seed survivorship is enhanced by burial in a cache, and a certain fraction of the seeds thus buried are never recovered by the rodent. Such seeds experience a higher likelihood of germination (Smythe, 1989). In part, the large mesocarp of ripe fruits can be viewed as a necessary cost to the plant to facilitate caching behavior by the rodent. This mu-

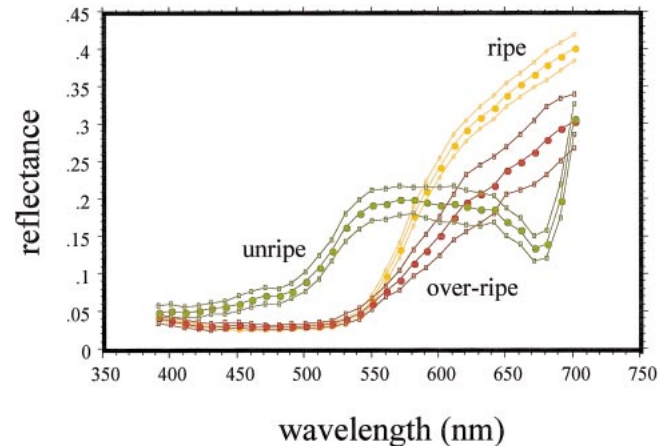


FIG. 1. Reflectance spectra of unripe, ripe, and over-ripe fruit. Ripe hanging and ripe fallen ripe fruits are pooled. Mean values and 95% confidence intervals are indicated for each measured wavelength.

tualism between agouti and palm is reinforced by the pronounced spines along the trunk and rachides of both fronds and infructescences of *A. standleyanum*. These spines presumably deter climbing by frugivorous taxa which might otherwise consume fruits directly from the infructescence without effecting either dispersal or caching. For example, white-nosed coatis climb into the canopy to eat ripe fruit of the palm *Attalea zonensis* on BCI (personal observation). Similarly, white-faced monkeys and red-tailed squirrels attain the infructescence of *A. standleyanum* via jumping into the crown, thus avoiding spines of the bole and consuming the fruit pulp with limited possibility for seed dispersal. Collared peccary likely consume and digest both pulp and seed of fallen *A. standleyanum* fruits, an outcome detrimental from the plant's evolutionary perspective.

For all aforementioned mammalian consumers of *A. standleyanum*, ingestion of either ripe or over-ripe fruits simultaneously involves ingestion of low-concentration ethanol. Pulp-ethanol concentrations within

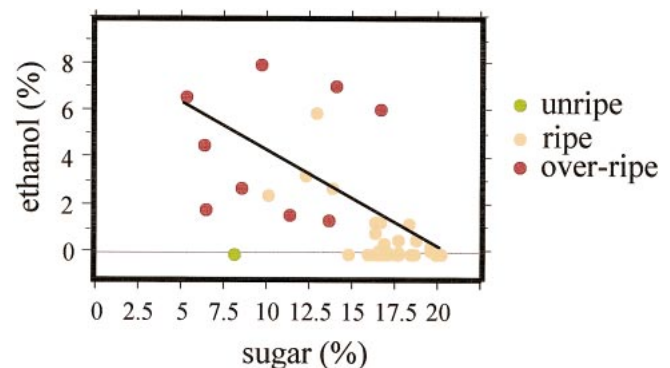


FIG. 2. Ethanol and sugar content of pulp for unripe (green symbol), ripe (orange symbols) and over-ripe (red symbols) fruits of the Neotropical palm *Astrocaryum standleyanum*. The regression for ripe and over-ripe fruits is given by  $y = -0.40x + 7.65$  ( $N = 40$ ;  $R^2 = 0.44$ ;  $P < 0.0001$ ).

ripe and over-ripe palm fruit averaged from 0.6% and 4.5%, respectively, representing a non-trivial absolute quantity given the substantial proportion of the fruit committed to pulp (~38% of wet fruit mass). As fruits ripened, coordinated changes in color, texture, and sugar content were all apparent. Fruits became softer and sweeter, both of which are characteristic changes in ripening that facilitate consumption (see Brady, 1987; Debussche *et al.*, 1987; Willson and Whelan, 1990; Tucker, 1993). The anthropogenic classification of palm fruits into either ripe or over-ripe corresponded, at least in part, to the extent of fermentative activity given the significantly higher ethanol content in fruits of the latter category. Dudley (2002) reported substantially lower pulp-ethanol concentrations (*i.e.*, a mean value of 0.6%) for over-ripe fruits of *Astrocaryum standleyanum*. The discrete categorization of fruits as either ripe or over-ripe, however, likely subsumes a diversity of microbial regimes according to age of fruit, thermal and hydric conditions, and within-fruit substrate heterogeneity. The dilution methods used here may have also more effectively homogenized pulp samples. Pulp-ethanol concentrations for those ripe fruits studied here were, by contrast, comparable to those reported by Dudley (2002). Unripe palm fruits contained negligible ethanol (Table 1), as would be anticipated given negligible presence of sugars and storage of carbohydrates as starch.

Two methodological issues pertain to the chemical analyses of fruit tissue used here. In a survey of fruit from thirty-seven temperate-zone species (White and Stiles, 1985), refractometry was found to substantially overestimate carbohydrate solute concentrations because of the contributions of nonsugar components, particularly lipids. White and Stiles (1985) accordingly cautioned against the use of refractometry in interspecific comparisons of fruit nutrient rewards, although this method may still be relevant in intraspecific comparisons if non-carbohydrate contributions to solute concentration remain proportionally constant. The data obtained here to estimate sugar concentrations likely indicate the overall relative trend among the discrete fruit categories (*i.e.*, unripe, ripe, and over-ripe), although chromatography would clearly be the preferred method to isolate and identify pulp sugars.

Similarly, the estimates of ethanol concentration used here involve a number of methodological assumptions. Contributions to total vapor pressure of non-ethanol volatiles are ignored. Ethanol is the predominant but not necessarily the only alcohol found in fermenting fruit. Perhaps more importantly, pulp samples were homogenized and then held for one hour prior to measurement of ethanol vapor content, in order to ensure equilibration of vapor pressure between sample and air. This period of time may have facilitated further fermentation and production of ethanol, particularly if fresh substrate were available to newly dispersed yeast populations. The relative importance of this effect is difficult to assess in the absence of pre- and post-homogenization measures of ethanol

content, although relative comparisons among fruit classes are unlikely to have been affected.

Because ripening occurs over a period of many weeks, fungi, bacteria, invertebrates, and destructive vertebrates have ample time to feed on fruit sugars prior to consumption of the fruit by an appropriate disperser (Thompson and Willson, 1978; Herrera, 1982). Intense competition both within and external to the fruit can therefore be expected. Production of ethanol by fermentative yeast may, in fact, be part of an evolved strategy to compete with other microbes for access to sugars. Ethanol inhibition of bacterial growth is strongly dose-dependent in the range of 1–10%, whereas fermenting *Saccharomyces* yeasts have a substantially higher tolerance, and also exhibit substantial genetic variability in this polygenic trait (see Ingram and Buttke, 1984; Casey and Ingledew, 1986). Ethanol tolerance in both yeasts and bacteria is temperature-dependent, with susceptibility increasing at higher temperatures (Ingram and Buttke, 1984). Medium composition also plays an important role in mediating tolerance to ethanol, although the relevance of homogeneous growth media to naturally occurring fungal ecologies is unclear. Microbial interactions within non-agricultural fruit of natural ecosystems seem never to have been examined from the perspective of ethanol and its potential role as a bactericide.

#### *The comparative biology of ethanol consumption*

Data presented here for palms suggest that vertebrate dispersers consuming ripe fruit are also ingesting ethanol, and that sufficiently high levels of ingestion may yield elevated blood-ethanol levels. Low-concentration ethanol within fruit may act as an attractant to vertebrate frugivores, or even as a deterrent in some cases (Janzen, 1977; Levey and Martínez del Río, 2001) but no data are available that evaluate either possibility. The natural history of animal inebriation has been documented anecdotally (see Dennis, 1987; Dudley, 2000), but has received no scientific attention. In frugivorous birds, the best studied of such taxa, limited evidence suggests at least occasional dietary exposure to ethanol. Fitzgerald *et al.* (1990) documented ethanol toxicosis in cedar waxwings that had been feeding on fermenting hawthorn fruits. Eriksson and Nummi (1982) fed naturally fermenting fruits to three avian taxa, and found that the most specialized frugivore among the three also exhibited the fastest rates of ethanol clearance and the most active isozyme of alcohol dehydrogenase in the liver. Similarly, Prinzinger and Hakimi (1996) found the fastest activity of blood alcohol dehydrogenase in a frugivorous species among three sampled bird taxa. Mean and peak blood-ethanol concentrations have never been measured, however, for either insect or vertebrate taxa feeding on fruits.

One important consequence of fermentation within ripe and over-ripe fruits is generation of an ethanol plume around the infructescence and fallen fruit crops. Particularly in the tropics, ripe fruit is a highly tran-

sient and spatially heterogeneous resource (Richards, 1996; Leigh, 1999; Levey *et al.*, 2002). For both arboreal and ground-dwelling frugivores, rapid localization and consumption of fruits is preferred given ecological competition from other frugivorous taxa. Selection for foraging behaviors may have been associated with the initial elaboration of spatial memory in frugivorous primates (Milton, 1988, 1993), although little is known about the behavioral and physiological mechanisms of fruit localization by vertebrate frugivores over large spatial scales. However, the low molecular weight of ethanol and its substantial concentration within fruit pulp well suit this molecule for long-distance signaling of availability to appropriate consumers. Ripening involves production of a number of fruit volatiles (Nursten, 1970), but ethanol is perhaps the only olfactory commonality to an otherwise bewildering taxonomic array of angiosperm fruits. Under natural conditions, the three-dimensional structure of ethanol plumes emanating from fruit crops will reflect the often variable wind regimes within forest canopies (Lowman and Nadkarni, 1995). Upwind flight following contact with a plume can nonetheless be an efficient search strategy to locate an odor source. Although the olfactory sensitivity of primates to various alcohols is well-developed (Simmen, 1994; Laska and Seibt, 2002), anemotactic behavior to localize ethanol sources has not been demonstrated for any vertebrate frugivore.

Female *Drosophila* flies, however, are known to follow ethanol plumes to locate ripe fruit suitable for oviposition sites (Hoffmann and Parsons, 1984). Molecular pathways of inebriation are similar between fruitflies and humans (Miyakawa *et al.*, 1997; Moore *et al.*, 1998; Wolf and Heberlein, 2003), and evolutionary exposure to ethanol has yielded adaptation in ADH and ALDH activities corresponding to the extent to which ethanol occurs within larval substrates (*e.g.*, Geer *et al.*, 1990, 1993; Merçot *et al.*, 1994; Ashburner, 1998; Fry, 2001). Chronic environmental exposure to ethanol may thus result in physiological adaptation and overall fitness benefits to animal frugivores. For example, the lifespan of *Drosophila* species that naturally encounter fermenting nutritional substrates is increased at very low concentrations of ethanol, but decreases at zero exposure and at higher concentrations (Starmer *et al.*, 1977; Parsons, 1983, 1989). Similarly, lifetime fecundity of *Drosophila* is enhanced by the presence of low-concentration ethanol vapor (Etges and Klassen, 1989). Although perhaps an unlikely candidate to serve as a representative frugivorous taxon, fruitflies may be the most experimentally tractable group with which to evaluate natural ethanol exposure and inebriation under field conditions.

#### *An evolutionary perspective on alcohol consumption and abuse*

The presence of ethanol within ripe fruit suggests low-level but chronic dietary exposure to this molecule for all fruit-eating taxa. Volatilized alcohols from fruit

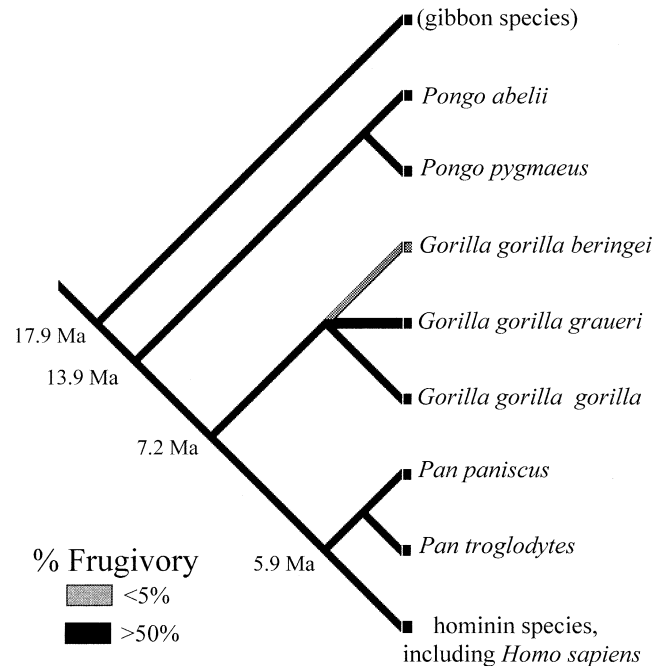


FIG. 3. Phylogeny and extent of frugivory for extant hominoid taxa. Extent of frugivory (%) refers to the proportion of fruit that contributes to total dietary intake. Taxonomic identifications as follows: *Pongo*, orangutans; *Gorilla*, gorillas; *Pan*, chimpanzees; hominins, human taxa subsequent to divergence from ape precursors. Branching dates are derived from Hacia (2001); Ma; mega-annum. Note that the most parsimonious reconstruction of hominid diets yields strong frugivory if an equivocal character state is initially assumed for these taxa.

potentially serve in olfactory localization of transient nutritional resources, whereas ethanol consumed during the course of frugivory may act as an appetitive stimulant (Dudley, 2000, 2002). As a consequence, natural selection may have acted on all frugivorous taxa, including human ancestors, to associate ethanol consumption with nutritional reward. Vertebrate frugivores in the wild would accordingly be predicted to selectively consume those fruits containing ethanol. Preference for and excessive consumption of alcohol by modern humans might then derive from pre-existing sensory biases associating ethanol with ancestral dietary strategies.

Frugivory characterizes many primate taxa, including most taxa ancestral to modern humans (Fig. 3). Basal primates were likely nocturnal and consumed both insects and fruits (Ravosa and Savakova, 2004; see also Bloch and Boyer, 2002; Ni *et al.*, 2004). Fruit-eating also characterized a number of now extinct hominoid lineages (*e.g.*, Afropithecinae, Dryopithecinae, Kenyapithecinae; see Teaford and Walker, 1984; Pickford, 1985; Teaford, 1988; Andrews and Martin, 1991; Andrews, 1992, 1996; Kay *et al.*, 1997). All extant hominoids with the exception of highland gorillas are strongly frugivorous. Our nearest living relatives, the chimpanzees, are characterized by a diet consisting primarily of ripe fruit (McGrew *et al.*, 1988; Wrangham *et al.*, 1991; Malenky and Wrangham,

1994). Humans diverged from chimpanzees about 5 Ma (mega-annum), but up until 2 Ma probably had a similar diet (Gaulin and Konner, 1977; Grine and Kay, 1988). Dietary diversification has characterized human evolution in the last two million years (Eaton *et al.*, 1997; Milton, 1999; Sponheimer and Lee-Thorp, 1999), but fruit consumption likely remained an important feature of the human diet until the Neolithic advent of agriculture. Consumption of low-concentration ethanol in the course of frugivory was thus characteristic of most hominoid taxa, including precursors to modern humans, over millions of years of evolution.

This evolutionary perspective raises the possibility of novel interpretations for the motivational mechanisms underlying both natural ethanol consumption as well as its abuse by humans. Among fruitfly species, preference for ethanol within larval medium is correlated with the ability to metabolize ethanol, suggesting a direct link between sensory motivation and physiological capacity for substrate utilization (Parsons, 1980; Depiereux *et al.*, 1985; Cadieu *et al.*, 1999). Intra- and interspecific variation in ADH and ALDH activity among extant frugivorous primates should similarly be correlated with the extent of dietary exposure to ethanol. Frugivorous lowland gorillas, for example, should both prefer and be more capable of metabolizing ethanol than their more folivorous montane counterparts (see Fig. 3). Both the natural occurrence of ethanol within fruits and the typical levels of ingestion and intoxication experienced by frugivores deserve quantitative attention, as do the sensory and behavioral responses of different vertebrate taxa to ethanol at naturally occurring concentrations.

Sustained evolutionary exposure to low-concentration ethanol will favor the evolution of metabolic adaptations that maximize physiological benefits associated with ethanol ingestion while concomitantly minimizing related costs. Exposure to higher concentrations of ethanol that are not naturally encountered may, by contrast, cause harm; such a nonlinear dosage-response curve is termed hormesis (Gerber and Williams, 1999; Forbes, 2000; Calabrese and Baldwin, 2003). As with longevity and fitness benefits of ethanol exposure in fruitflies, epidemiological studies in modern humans demonstrate a reduction in cardiovascular risk and overall mortality at low levels of ethanol consumption relative either to abstinence or to higher intake levels (*e.g.*, German and Walzem, 2000; Abramson *et al.*, 2001; Mukamal *et al.*, 2002; Vahtera *et al.*, 2002; Klatsky, 2003). The considerable variation in human behavioral responses to alcohol (see Marshall, 1979; Agarwal and Goedde, 1990) is also consistent with evolutionary predictions, namely that novel exposure to high concentrations of hormetic compounds increases phenotypic variance (Hoffmann and Parsons, 1997; Holloway *et al.*, 1997; Gerber and Williams, 1999). Unfortunately, consequences of chronic but low-level ethanol ingestion for reproductive fitness have not been determined for either modern humans or non-human primates.

Genetically-based behaviors that were once adaptive in ancestral environments can become disadvantageous in modern contexts that provide *ad libitum* access to nutritional substrates (Cronk, 1991; Williams and Nesse, 1994). If natural selection has acted on human ancestors to associate ethanol with nutritional reward, then excessive consumption by modern humans may be viewed as such a disease of nutritional excess. Availability of ethanol at concentrations higher than those attainable by yeast fermentation alone (*i.e.*, 10–12%) is a very recent event in human history (see Dudley, 2000, 2002). As an extreme of ethanol consumption, the biomedical and sociocultural phenomenon of alcoholism poses particular challenges. Alcoholism is known to be both partially heritable and polygenic in character (Cloninger, 1987; Cook and Gurling, 1990; Goldman, 1993), whereas the physiological response to ethanol can be correlated with enzymatic activity of particular ADH and ALDH isozymes both within and among human populations (Agarwal and Goedde, 1990; Goldman and Enoch, 1990; Osier *et al.*, 1999; Osier *et al.*, 2002). Rates of alcoholism, however constructed definitionally, tend to be much lower among East Asians than in West European and North American populations, consistent with deterrent effects on ethanol consumption associated from slow-acting ALDH isozymes and corresponding accumulation of toxic acetaldehyde (Agarwal and Goedde, 1986; Helzer and Canino, 1992). Such comparisons among human populations suffer, however, from the presence of potentially confounding cultural differences as well as definitional variation in the phenomenon termed alcoholism.

More convincing, however, are the recent intrapopulational studies of genetic influences on excessive consumption of alcohol. Japanese and Taiwanese alcoholics exhibit reduced frequencies of catalytically more effective ADH isozymes as well as higher frequencies of faster-acting ALDH isozymes relative to their non-alcoholic counterparts (Chen *et al.*, 1996; Shen *et al.*, 1997; Tanaka *et al.*, 1997; Harada *et al.*, 1999; Reich *et al.*, 1999). Although genotype-by-environment interactions are likely to be pronounced in the clinical emergence of alcoholism, these studies clearly implicate aversive acetaldehyde accumulation, derived from the interacting dynamics of ADH and ALDH activities, as being protective against excessive alcohol consumption (Li, 2000). Addictions in general, and alcoholism in particular, have usually been viewed as novel afflictions devoid of evolutionary context. However, ethanol ingestion via frugivory is ancestral in many primate taxa and may influence contemporary behavioral responses to this psychoactive compound by humans. Study of natural dietary consumption of ethanol in diverse frugivorous taxa may therefore contribute to our understanding of human patterns of alcohol consumption and abuse.

#### ACKNOWLEDGMENTS

I thank Brendan Borrell, Greg Byrnes, Chris Clark, Ryan Hill, Carmi Korine, Matt Medeiros, Nate Dom-

iny, Berry Pinshow, and Dustin Stephens for constructive comments on the manuscript, and the Smithsonian Tropical Research Institute for continuing access to research facilities on Barro Colorado Island.

## REFERENCES

- Abramson, J. L., S. A. Williams, H. M. Krumholz, and V. Vaccarino. 2001. Moderate alcohol consumption and risk of heart failure among older persons. *JAMA* 285:1971–1977.
- Agarwal, D. P. and H. W. Goedde. 1986. Ethanol oxidation: Ethnic variations in metabolism and response. In W. Kalow, H. W. Goedde, and D. P. Agarwal (eds.), *Ethnic differences in reactions to drugs and xenobiotics*, pp. 99–111. Alan R. Liss, New York.
- Agarwal, D. P. and H. W. Goedde. 1990. *Alcohol metabolism, alcohol intolerance, and alcoholism: Biochemical and pharmacogenetic approaches*. Springer-Verlag, Berlin.
- Andrews, P. 1992. Evolution and environment in the Hominoidea. *Nature* 360:641–646.
- Andrews, P. 1996. Palaeoecology and hominoid palaeoenvironments. *Biol. Rev.* 71:257–300.
- Andrews, P. and L. Martin. 1991. Hominoid dietary evolution. *Phil. Trans. R. Soc. London B* 334:199–209.
- Ashburner, M. 1998. Speculations on the subject of alcohol dehydrogenase and its properties in *Drosophila* and other flies. *BioEssays* 20:949–954.
- Benner, S. A., M. D. Caraco, J. M. Thomson, and E. A. Gaucher. 2002. Planetary biology—paleontological, geological, and molecular histories of life. *Science* 296:864–868.
- Bloch, J. I. and D. M. Boyer. 2002. Grasping primate origins. *Science* 298:1606–1610.
- Borowicz, V. A. 1988a. Do vertebrates reject decaying fruit? An experimental test with *Cornus amomum* fruits. *Oikos* 53:74–78.
- Borowicz, V. A. 1988b. Pulp composition and the invasion and decay of fruits by microbes. *Can. J. Bot.* 66:1068–1072.
- Brady, C. J. 1987. Fruit ripening. *Ann. Rev. Plant Physiol.* 38:155–178.
- Cadiou, N., J.-C. Cadiou, L. El Ghadraoui, A. Grimal, and Y. Lamboeuf. 1999. Conditioning to ethanol in the fruit fly—a study using an inhibitor of ADH. *J. Insect Physiol.* 45:579–586.
- Calabrese, E. J. and L. A. Baldwin. 2003. Toxicology rethinks its central belief. *Nature* 421:691–692.
- Casey, G. P. and W. M. Ingledew. 1986. Ethanol tolerance in yeasts. *CRC Crit. Rev. Microbiol.* 13:219–280.
- Chen, W. J., E. W. Loh, Y.-P. P. Hsu, C.-C. Chen, J.-M. Yu, and A. T. A. Cheng. 1996. Alcohol-metabolising genes and alcoholism among Taiwanese Han men: Independent effect of ADH2, ADH3, and ALDH2. *Brit. J. Psych.* 168:762–767.
- Cipollini, M. L. and D. J. Levey. 1997a. Antifungal activity of *Solanum* fruit glycoalkaloids: Implications for frugivory and seed dispersal. *Ecology* 78:799–809.
- Cipollini, M. L. and D. J. Levey. 1997b. Secondary metabolites of fleshy vertebrate-dispersed fruits: Adaptive hypotheses and implications for seed dispersal. *Am. Nat.* 150:346–372.
- Cipollini, M. L. and D. J. Levey. 1997c. Why are some fruits toxic? Glycoalkaloids in *Solanum* and fruit choice by vertebrates. *Ecology* 78:782–798.
- Cipollini, M. L. and E. W. Stiles. 1992. Relative risks of microbial rot for fleshy fruits: Significance with respect to dispersal and selection for secondary defense. *Adv. Ecol. Res.* 23:35–91.
- Cipollini, M. L. and E. W. Stiles. 1993a. Fruit rot, antifungal defense, and palatability of fleshy fruits for frugivorous birds. *Ecology* 74:751–762.
- Cipollini, M. L. and E. W. Stiles. 1993b. Fungi as biotic defense agents of fleshy fruits: Alternative hypotheses, predictions, and evidence. *Am. Nat.* 141:663–673.
- Cloninger, C. R. 1987. Neurogenetic adaptive mechanisms in alcoholism. *Science* 236:410–416.
- Cook, C. C. H. and H. M. D. Gurling. 1990. The genetic aspects of alcoholism and substance abuse: A review. In G. Edwards and M. Lader (eds.), *The nature of drug dependence*, pp. 75–102. Oxford University Press, Oxford.
- Croat, T. B. 1978. *Flora of Barro Colorado Island*. Stanford University Press, Stanford.
- Cronk, L. 1991. Human behavioral ecology. *Ann. Rev. Anthropol.* 20:25–53.
- Debussche, M., J. Cortez, and I. Rimbault. 1987. Variation in fleshy fruit composition in the Mediterranean region: The importance of ripening season, life-form, fruit type and geographical distribution. *Oikos* 49:244–252.
- Dennis, J. V. 1987. If you drink, don't fly. *Birder's World* 1:15–19.
- Depiereux, E., N. Hougouto, J. Lechien, M. Libion-Mannaert, M.-C. Liétaert, E. Feytmans, and A. Elens. 1985. Larval behavioral response to environmental ethanol in relation to alcohol dehydrogenase activity level in *Drosophila melanogaster*. *Behav. Genet.* 15:181–188.
- Dudley, R. 2000. Evolutionary origins of human alcoholism in primate frugivory. *Q. Rev. Biol.* 75:3–15.
- Dudley, R. 2002. Fermenting fruit and the historical ecology of ethanol ingestion: Is alcoholism in modern humans an evolutionary hangover? *Addiction* 97:381–388.
- Eaton, S. B., S. B. Eaton, III, and M. J. Konner. 1997. Paleolithic nutrition revisited: A twelve-year retrospective on its nature and implications. *Eur. J. Clin. Nutr.* 51:207–216.
- Eriksson, K. and H. Nummi. 1982. Alcohol accumulation from ingested berries and alcohol metabolism in passerine birds. *Ornis Fennica* 60:2–9.
- Eriksson, O., E. M. Friis, and P. Löfgren. 2000. Seed size, fruit size, and dispersal systems in angiosperms from the Early Cretaceous to the Late Tertiary. *Am. Nat.* 156:47–58.
- Etges, W. J. and C. S. Klassen. 1989. Influences of atmospheric ethanol on adult *Drosophila mojavensis*: Altered metabolic rates and increases in fitnesses among populations. *Physiol. Zool.* 62:170–193.
- Fitzgerald, S. D., J. M. Sullivan, and R. J. Everson. 1990. Suspected ethanol toxicosis in two wild cedar waxwings. *Avian Diseases* 34:488–490.
- Fleming, T. H., R. Breitwisch, and G. H. Whitesides. 1987. Patterns of tropical vertebrate frugivore diversity. *Ann. Rev. Ecol. Syst.* 18:91–109.
- Forbes, V. E. 2000. Is hormesis an evolutionary expectation? *Funct. Ecol.* 14:12–24.
- Forsander, O. 1978. Alkoholien esiintymisen luonnossa. [The occurrence of alcohol in nature]. *Luonnon Tutkija* 82:1–3. (In Finnish, with English summary).
- Fry, J. D. 2001. Direct and correlated responses to selection for larval ethanol tolerance in *Drosophila melanogaster*. *J. Evol. Biol.* 14:296–309.
- Gaulin, S. J. C. and M. Konner. 1977. On the natural diet of primates, including humans. In R. J. Wurtman and J. J. Wurtman (eds.), *Nutrition and the brain*, Vol. 1, pp. 1–86. Raven Press, New York.
- Geer, B. W., P. W. H. Heinstra, A. M. Kapoun, and A. van der Zel. 1990. Alcohol dehydrogenase and alcohol tolerance in *Drosophila melanogaster*. In J. S. F. Barker, W. T. Starmer, and R. J. MacIntyre (eds.), *Ecological and evolutionary genetics of Drosophila*, pp. 231–252. Plenum Press, New York.
- Geer, B. W., P. W. Heinstra, and S. W. McKechnie. 1993. The biological basis of ethanol tolerance in *Drosophila*. *Comp. Biochem. Physiol.* 105B:203–229.
- Gerber, L. M. and G. C. Williams. 1999. The nutrient-toxin dosage continuum in human evolution and modern health. *Q. Rev. Biol.* 74:273–289.
- German, J. B. and R. L. Walzem. 2000. The health benefits of wine. *Annu. Rev. Nutr.* 20:561–593.
- Goldman, D. and M.-A. Enoch. 1990. Genetic epidemiology of ethanol metabolic enzymes: A role for selection. In A. P. Simopoulos and B. Childs (eds.), *Genetic variation and nutrition*, pp. 143–160. Karger, Basel.
- Grine, F. E. and R. F. Kay. 1988. Early hominid diets from quantitative image analysis of dental microwear. *Nature* 333:765–768.
- Harada, S., T. Okubo, T. Nakamura, C. Fujii, F. Nomura, S. Higuchi, and M. Tsutsumi. 1999. A novel polymorphism (-357 G/A) of

- the ALDH2 gene: Linkage disequilibrium and an association with alcoholism. *Alcohol. Clin. Exp. Res.* 23:958–962.
- Hacia, J. G. 2001. Genome of the apes. *Trends Genet.* 17:637–645.
- Helzer, J. E. and G. J. Canino. (eds.). 1992. *Alcoholism in North America, Europe, and Asia*. Oxford University Press, New York.
- Herrera, C. M. 1982. Defense of ripe fruit from pests: Its significance in relation to plant-disperser interactions. *Am. Nat.* 120:218–241.
- Hines, L. M., M. H. Stampfer, M. Jing, J. M. Gaziano, P. M. Ridker, S. E. Hankinson, F. Sacks, E. B. Rimm, and D. J. Hunter. 2001. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N. Engl. J. Med.* 344:549–555.
- Hladik, A. and C. M. Hladik. 1969. Rapports trophiques entre végétation et primates dans la forêt de Barro Colorado (Panama). *La Terre et la Vie* (ser. 2) 23:25–117.
- Hoch, G. and G. Adler. 1997. Removal of black palm (*Astrocaryum standleyanum*) seeds by spiny rats (*Proechimys semispinosus*). *J. Trop. Biol.* 13:51–58.
- Hoffmann, A. A. and P. A. Parsons. 1984. Olfactory response and resource utilization in *Drosophila*: Interspecific comparisons. *Biol. J. Linn. Soc.* 22:45–53.
- Hoffmann, A. A. and P. A. Parsons. 1997. *Extreme environmental change and evolution*. Cambridge University Press, Cambridge.
- Holloway, G. J., H. J. Crocker, and A. Callaghan. 1997. The effects of novel and stressful environments on trait distributions. *Funct. Ecol.* 11:579–584.
- Ingram, L. O. and T. M. Buttke. 1984. Effects of alcohols on microorganisms. *Adv. Microbial Physiol.* 25:253–300.
- Janzen, D. H. 1977. Why fruits rot, seeds mold, and meat spoils. *Am. Nat.* 111:691–713.
- Janzen, D. H. 1983. Physiological ecology of fruits and their seeds. In O. L. Lange, P. S. Nobel, C. B. Osmond, and H. Ziegler (eds.), *Physiological plant ecology III. Responses to the chemical and biological environment*, pp. 625–655. Springer Verlag, Berlin.
- Jordano, P. 2000. Fruits and frugivory. In M. Fenner (ed.), *Seeds: The ecology of regeneration in plant communities*, 2nd ed., pp. 125–165. CABI Publishing, Wallingford.
- Kay, R. F., C. Ross, and B. A. Williams. 1997. Anthropoid origins. *Science* 275:797–804.
- Kays, R. W. 1999. Food preferences of kinkajous (*Potos flavus*): A frugivorous carnivore. *J. Mammal.* 80:589–599.
- Klatsky, A. L. 2003. Drink to your health? *Sci. Amer.* February: 75–81.
- Laska, M. and A. Seibt. 2002. Olfactory sensitivity for aliphatic alcohols in squirrel monkeys and pigtail macaques. *J. Exp. Biol.* 205:1633–1643.
- Last, F. T. and D. Price. 1969. Yeasts associated with living plants and their environs. In A. H. Rose and J. S. Harrison (eds.), *The yeasts*, Vol. 1, pp. 183–218. Academic Press, London.
- Leigh, E. G. 1999. *Tropical forest ecology: A view from Barro Colorado Island*. Oxford University Press, New York.
- Levey, D. J. and C. Martínez del Río. 2001. It takes guts (and more) to eat fruit: Lessons from avian nutritional ecology. *The Auk* 118:819–831.
- Levey, D. J., W. R. Silva, and M. Galetti. (eds.). 2002. *Seed dispersal and frugivory: Ecology, evolution and conservation*. CABI Publishing, Wallingford.
- Li, T.-K. 2000. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. *J. Stud. Alcohol.* 61:5–12.
- Lowman, M. D. and N. M. Nadkarni. (eds.). 1995. *Forest canopies*. Academic Press, San Diego.
- Lucas, P. W., I. M. Turner, N. J. Dominy, and N. Yamashita. 2000. Mechanical defences to herbivory. *Ann. Bot.* 86:913–920.
- Malenky, R. K. and R. W. Wrangham. 1994. A quantitative comparison of terrestrial herbaceous food consumption by *Pan paniscus* in the Lomako Forest, Zaire, and *Pan troglodytes* in the Kibale Forest, Uganda. *Am. J. Primatol.* 32:1–12.
- Marshall, M. (ed.). 1979. *Beliefs, behaviors, & alcoholic beverages: A cross-cultural survey*. University of Michigan Press, Ann Arbor.
- McGrew, W. C., P. J. Baldwin, and C. E. G. Tutin. 1988. Diet of wild chimpanzees (*Pan troglodytes verus*) at Mt. Assirik, Senegal: I. Composition. *Am. J. Primatol.* 16:213–226.
- Merçot, H., D. Defaye, P. Cappy, E. Pla, and J. R. David. 1994. Alcohol tolerance, ADH activity, and ecological niche of *Drosophila* species. *Evolution* 48:746–757.
- Milton, K. M. 1988. Foraging behavior and the evolution of primate intelligence. In R. W. Byrne and A. Whiten (eds.), *Machiavellian intelligence: Social expertise and the evolution of intellect in monkeys, apes, and humans*, pp. 285–305. Clarendon Press, Oxford.
- Milton, K. 1993. Diet and primate evolution. *Sci. Amer.* August: 86–93.
- Milton, K. 1999. Nutritional characteristics of wild primate foods: Do the diets of our closest living relatives have lessons for us? *Nutrition* 15:488–498.
- Miyakawa, T., T. Yagi, H. Kitazawa, M. Yasuda, N. Kawai, K. Tsuboi, and H. Niki. 1997. Fyn-kinase as a determinant of ethanol sensitivity: Relation to NMDA-receptor function. *Science* 278: 698–701.
- Mukamal, K. J., M. Maclure, J. E. Muller, J. B. Sherwood, and M. A. Mittleman. 2002. Prior alcohol consumption and mortality following acute myocardial infarction. *JAMA* 285:1965–1970.
- Moore, M. S., J. DeZazzo, A. Y. Luk, T. Tully, C. M. Singh, and U. Heberlein. 1998. Ethanol intoxication in *Drosophila*: Genetic and pharmacological evidence for regulation by the cAMP pathway. *Cell* 93:997–1007.
- Ni, X., Y. Wang, Y. Hu, and C. Li. 2004. A euprimate skull from the early Eocene of China. *Nature* 427:65–68.
- Nursten, H. E. 1970. Volatile compounds: The aroma of fruits. In A. C. Hulme (ed.), *The biochemistry of fruits and their products*, pp. 239–268. Academic Press, London.
- Osier, M., A. J. Pakstis, J. R. Kidd, J.-F. Lee, S.-J. Yin, H.-C. Ko, H. J. Edenberg, R.-B. Lu, and K. K. Kidd. 1999. Linkage disequilibrium at the *ADH2* and *ADH3* loci and risk of alcoholism. *Am. J. Hum. Genet.* 64:1147–1157.
- Osier, M., A. J. Pakstis, H. Soodyall, D. Comas, D. Goldman, A. Odunsi, F. Okonofua, J. Parnas, L. O. Schulz, J. Bertranpetit, B. Bonne-Tamier, R.-B. Lu, J. R. Kidd, and K. K. Kidd. 2002. A global perspective on genetic variation at the *ADH* genes reveals unusual patterns of linkage disequilibrium and diversity. *Am. J. Hum. Genet.* 71:84–99.
- Parsons, P. A. 1980. Responses of *Drosophila* to environmental ethanol from ecologically optimal and extreme habitats. *Experientia* 36:1070–1071.
- Parsons, P. A. 1983. Ecobehavioral genetics: Habitats and colonists. *Ann. Rev. Ecol. Syst.* 14:35–55.
- Parsons, P. A. 1989. Acetaldehyde utilization in *Drosophila*: An example of hormesis. *Biol. J. Linn. Soc.* 37:183–189.
- Pickford, M. 1985. A new look at *Kenyanthropus* based on recent discoveries in Western Kenya. *J. Hum. Evol.* 14:113–143.
- Prinzinger, R. and G. A. Hakimi. 1996. Alcohol resorption and alcohol degradation in the European Starling *Sturnus vulgaris*. *J. Orn.* 137:319–327.
- Ravosa, M. J. and D. G. Savakova. 2004. Euprimate origins: The eyes have it. *J. Hum. Evol.* 46:355–362.
- Reich, T., A. Hinrichs, R. Culverhouse, and L. Bierut. 1999. Genetic studies of alcoholism and substance dependence. *Am. J. Hum. Genet.* 65:599–605.
- Richards, P. W. 1996. *The tropical rain forest: An ecological study*, 2nd ed. Cambridge University Press, Cambridge.
- Shen, Y.-C., J.-H. Fan, H. J. Edenberg, T.-K. Li, Y.-H. Cui, Y.-F. Wang, C.-H. Tian, C.-F. Zhou, R.-L. Zhou, J. Wang, Z.-L. Zhao, and G.-Y. Xia. 1997. Polymorphism of ADH and ALDH genes among four ethnic groups in China and effects upon the risk for alcoholism. *Alcohol. Clin. Exp. Res.* 21:1272–1277.
- Simmen, B. 1994. Taste discrimination and diet differentiation among New World primates. In D. J. Chivers and P. Langer (eds.), *The digestive system in mammals: Food, form, and function*, pp. 150–165. Cambridge University Press, Cambridge.
- Smythe, N. 1970. Relationships between fruiting seasons and seed dispersal methods in a Neotropical forest. *Am. Nat.* 104:25–35.

- Smythe, N. 1978. The natural history of the Central American agouti (*Dasyprocta punctata*). *Smithson. Contrib. Zool.* 257:1–52.
- Smythe, N. 1989. Seed survival in the palm *Astrocaryum standleyanum*: Evidence for dependence upon its seed dispersers. *Biotropica* 21:50–56.
- Spencer, J. F. T. and D. M. Spencer. 1997. Ecology: Where yeasts live. In J. F. T. Spencer and D. M. Spencer (eds.), *Yeasts in natural and artificial habitats*, pp. 33–58. Springer-Verlag, Berlin.
- Sponheimer, M. and J. A. Lee-Thorp. 1999. Isotopic evidence for the diet of an early hominid, *Australopithecus africanus*. *Science* 283:368–370.
- Starmer, W. T., W. B. Heed, and E. S. Rockwood-Sluss. 1977. Extension of longevity in *Drosophila mojavensis* by environmental ethanol: Differences between substrates. *Proc. Natl. Acad. Sci. U.S.A.* 74:387–391.
- Tanaka, F. Y., Y. Shiratori, O. Yokosuka, F. Imazeki, Y. Tsukada, and M. Omata. 1997. Polymorphism of alcohol-metabolizing genes affects drinking behavior and alcoholic liver disease in Japanese men. *Alcohol. Clin. Exp. Res.* 21:596–601.
- Teaford, M. F. 1988. A review of dental microwear and diet in modern mammals. *Scann. Microsc.* 2:1149–1166.
- Teaford, M. F. and A. C. Walker. 1984. Quantitative differences in dental microwear between primate species with different diets and a comment on the presumed diet of *Sivapithecus*. *Am. J. Phys. Anthropol.* 64:191–200.
- Terborgh, J. 1980. Keystone plant resources in the tropical forest. In M. E. Soulé and B. A. Wilcox (eds.), *Conservation biology: An evolutionary-ecological perspective*, pp. 349–382. Sinauer Associates, Sunderland.
- Thompson, J. N. and M. F. Willson. 1978. Disturbance and the dispersal of fleshy fruits. *Science* 200:1161–1163.
- Thompson, J. N. and M. F. Willson. 1979. Evolution of temperate fruit/bird interactions: Phenological strategies. *Evolution* 33:973–982.
- Tucker, G. A. 1993. Introduction. In G. B. Seymour, J. E. Taylor, and G. A. Tucker (eds.), *Biochemistry of fruit ripening*, pp. 1–51. Chapman & Hall, London.
- Vahtera, J., K. Poikolainen, M. Kivimäki, L. Ala-Mursula, and J. Pentti. 2002. Alcohol intake and sickness absence: A curvilinear relation. *Am. J. Epidemiol.* 156:969–976.
- White, D. W. and E. W. Stiles. 1985. The use of refractometry to estimate nutrient rewards in vertebrate-dispersed fruits. *Ecology* 66:303–307.
- Williams, G. C. and R. M. Nesse. 1994. *Why we get sick: The new science of Darwinian medicine*. Times Books, New York.
- Willson, M. F. and C. J. Whelan. 1990. The evolution of fruit color in fleshy-fruited plants. *Am. Nat.* 136:790–809.
- Wolf, F. W. and U. Heberlein. 2003. Invertebrate models of drug abuse. *J. Neurobiol.* 54:161–178.
- Wrangham, R. W., N. L. Conklin, C. A. Chapman, and K. D. Hunt. 1991. The significance of fibrous foods for Kibale Forest chimpanzees. *Phil. Trans. R. Soc. London B* 334:171–178.