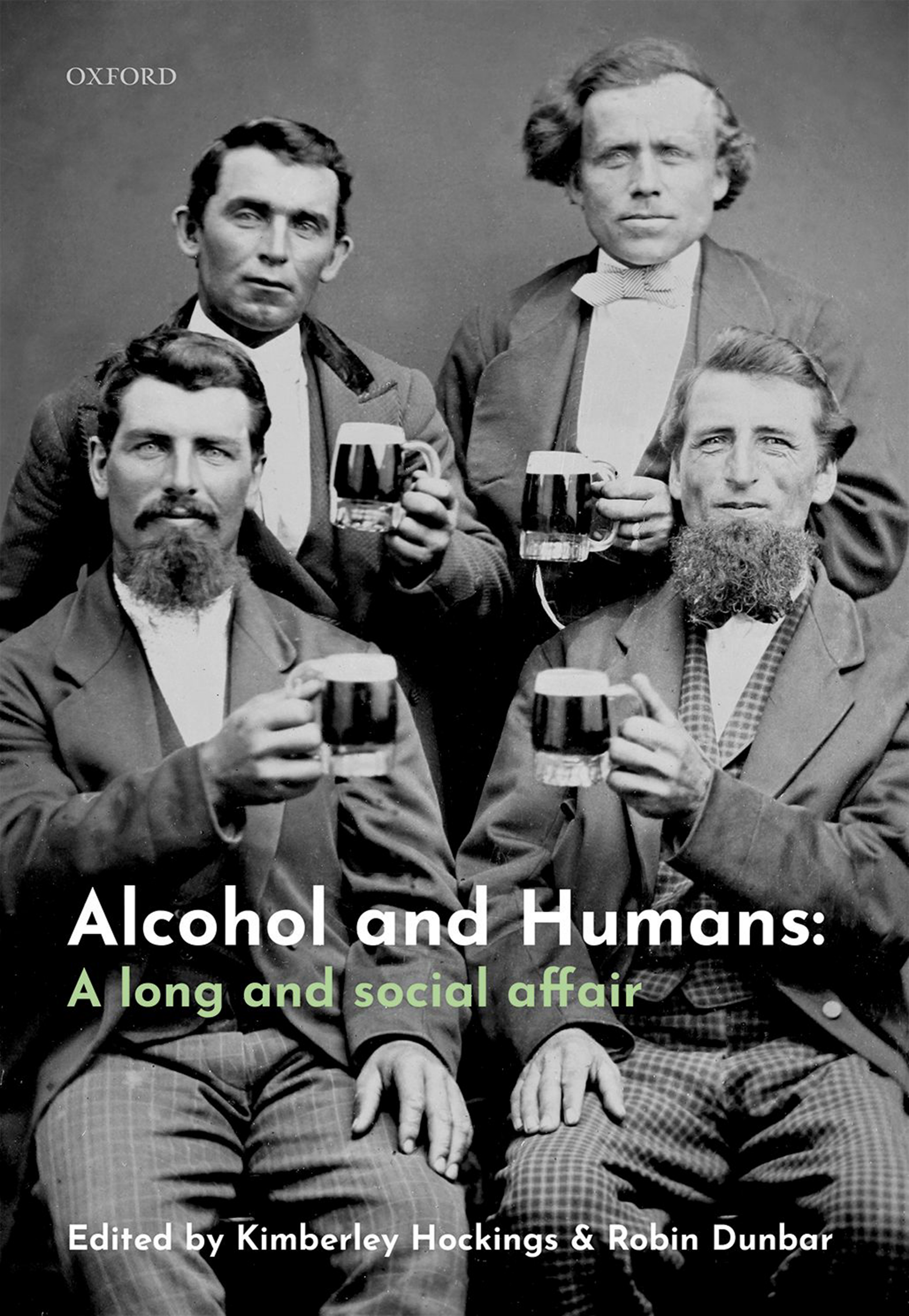

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Alcohol and Humans:
A long and social affair

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6

Uncorking the Past

Alcoholic Fermentation as Humankind's First Biotechnology

Patrick E. McGovern

Introduction

Clouds with billions of litres of simple alcohols—ethyl, methyl, and vinyl, as documented by far infrared and microwave telescopes (Turner & Apponi, 2001)—are an intrinsic part of our universe. They occur in star-forming regions near the centres of galaxies of which there are billions, the most distant of which occur some 13.8 billion light-years from Earth. The closest clouds are in our own Milky Way; for example, Sagittarius B2N is about 25 000 light-years (*ca*. 240 quadrillion kilometres) away. Neil deGrasse Tyson (2015) enticingly refers to them as the 'Milky Way Bar' (also see Tattershall et al., 2015). It is unlikely that our species any time soon will be mining extraterrestrial ethanol, the generic alcohol of the drinkable, non-poisonous variety.

We might ask why is there an alcoholic 'haze' at the centre of our galaxy, and what role did galactic alcohols play in jump-starting and sustaining life on our planet, especially the highly reactive vinyl compounds with double bonds? One may conjecture that alcohols and other prebiotic compounds, such as vitamin B_3 (nicotinic acid) (Smith et al., 2014), were brought to Earth by comets or meteorites, jump-starting the first forms of life, according to the Panspermia hypothesis. For example, spectroscopic measurements of Comet C/2014 Q2 in 2015 indicate that this interstellar body, otherwise known as Lovejoy, 'was releasing as much alcohol as in at least 500 bottles of wine every second during its peak activity' as it approached the sun (Biver et al., 2015).

Yet, we are far from knowing for certain how life arose on Earth, conceptually and factually, as it is believed to have happened about 4.5 billion years ago. It is difficult enough to reconstruct events from our childhoods or even last week, let alone to excavate and piece together an ancient culture, including its fermented foods and beverages from thousands of years ago. The available evidence, especially crucial organic compounds, has largely been destroyed, and inferences must be made using very narrow databases and by analogy to modern processes and phenomena which owe their existence to largely unknowable past events.

Creating a Ferment

A plausible theory for how life began is that single cells (prokaryotes) self-organized metabolic and replicative chemical pathways that enabled them to produce energy from simple sugars by an anaerobic fermentation process (glycolysis) (Cooper & Hausman,

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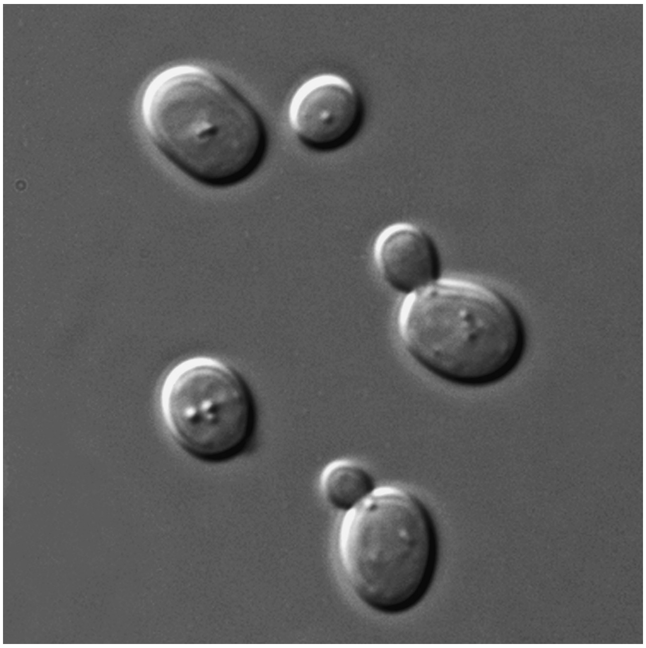

Figure 6.1 Microscopic view of budding of the wine/bread/baker's yeast (*Saccharomyces cerevisiae*).

2015), with alcohol and carbon dioxide as the possible end-products. A modified aerobic fermentation process—variously known as the citric acid, Krebs, or tricarboxylic acid cycle—still powers every living organism on Earth, including the approximately 40 trillion cells in our bodies. Although life is vastly more complex today, the essential process of energy production can then be envisioned as having been quite similar since the beginning.

Today, two species of single-celled yeast (*Saccharomyces cerevisiae* [see Figure 6.1] and *S. bayanus*), encompassing a large group of wild and domesticated strains, carry on in this grand tradition, and serve as the worldwide workhorse fungi in making the alcohol in all fermented beverages (Boulton & Quain, 2006; also see Legras et al., 2007) Although hardly primitive now—having most of the same specialized organelles that other eukaryotes have, including a central nucleus which contains its chromosomal DNA—these yeasts thrive in low-oxygen environments but, of course, not the oxygen-free atmosphere such as we imagine existed on Earth when life began.

Specifically, *S. cerevisiae*, the wine-beer-and-bread (or baker's) yeast, is superbly adapted to killing off competitive microorganisms and producing the necessary energy for its existence. Because of the doubling of its genome, probably during the Cretaceous Period 145–65 million years ago, it has two versions of the alcohol dehydrogenase (*Adh*) gene, which produce two versions of the enzyme (ADH) (Thomson et al., 2005). One version of the enzyme (ADH1) converts acetaldehyde, the end-product of glycolysis, into alcohol in an oxygen-free environment. The yeast literally swamps its competitors in alcohol, and, since most microbes cannot tolerate alcohol levels above 5%, they die. The yeast cell can tolerate concentrations of 12–15%, sometimes more than 20%. The trade-off is that it produces less

ATP (adenosine triphosphate), the energy engine of the cell that enables synthesis of the essential organic compounds for life.

Once the competition has been eliminated and oxygen levels start to rise, the other version of the enzyme (ADH2) kicks in. It converts alcohol back into acetaldehyde and ultimately generates much more ATP through the citric acid/Krebs/tricarboxylic acid cycle that requires oxygen. The delayed gratification has been worth the wait, now that the competing microbes have been destroyed.

In short, a case can be made that fermentation is the basis for life on our planet. In the anaerobic environment of early Earth, we can even imagine that a kind of carbonated, alcoholic 'beverage' engulfed the globe for millions of years.

These developments set the stage for what followed, continuing on to the world we see around us today. We do not know when alcohol, as an energy-producing compound like sugar, began to be consumed. But by the Cretaceous Period, when dinosaurs roamed the Earth, there is no question of alcohol's importance in animal diets.

The first flowering fruit trees and shrubs appeared during the Cretaceous, which our ancestors later exploited for making alcoholic beverages. They provided food resources (fruit, nectars, and saps) for the animals, who in turn pollinated them. Honeybees came on the scene, taking these sweet essences and making the most concentrated source of sugar in nature: honey. Among many other insects which feed on both sugar and alcohol, fruit flies made their appearance. Like ourselves and most other animals, they sometimes overindulge and get drunk. They have been shown to have the same genes for inebriation as humans have, which are given such fanciful names as *amnesiac, barfly, cheapdate*, and *happyhour* (Heberlein et al., 2004). Other higher animals share the same genes. As another example, when zebra finches overindulge in fermented fruit, their songs become confused and more subdued due to alcohol's effect on their syrinx and brain (Olson et al., 2014). Likewise, when we get drunk, our homologous larynxes and brains can produce slurred and muffled speech.

Yeasts and other microorganisms took the newly available sugar resources and fermented them into alcoholic, aromatic concoctions that attract animals, who sense the pungent aromas, and happily consume the end products for energy and presumably enjoyment.

Over the course of the Cretaceous Period, new fruiting trees, new insects, new dinosaurs, and new yeasts emerged and were bound together into an intricate web of ecological symbiosis and mutualism. A new level of complexity was added when the supercontinent of Pangaea began to break up into the seven continents that we are familiar with today. Over millennia, land masses drifted apart, separating populations of flora, fauna, and microorganisms from one another and leading to new organisms and integrated communities (Almeida et al., 2014).

Despite geographical and temporal variations, the long-term availability of the alcohol molecule itself assured it a central, continuing role in the genetic and physiological processes of biological communities worldwide, some of which remained largely the same.

The Thirsty Treeshrew, Drunken Monkey, and *Homo imbibens*

The revolutionary Cretaceous era sets the stage for what was to follow, up to the present, as alcohol continued to play a leading role in directing the course of evolution. We have only to look at the diminutive, nocturnal pen-tailed Malaysian treeshrew (*Ptilocercus lowii*), a close relative of primates whose family, the treeshrews (Tupaiidae), diverged from the order Primates about 55 million years ago (Janecka et al., 2007). These creatures binge on fermented bertam palm nectar all night long (Wiens et al., 2008), drinking the equivalent of nine glasses of 12% alcoholic wine for the average human. In contrast to us, who would be certifiably drunk at this stage, the treeshrew shows no signs of inebriation.

Moving along the phylogenetic ladder in our direction, it has been shown that modern primates generally have diets comprised of about 75% fruit in keeping with their dentition (small molars and canines) which is best-suited for soft foods, and they are known to eat as much fermented fruit or drink as possible when available. Robert Dudley (2014) in his book, *The Drunken Monkey*, demonstrates this for howler monkeys in Panama which consume a fermented palm fruit, putting away the equivalent of about two bottles of grape wine in 20 minutes (see also Dudley, Chapter 2). Kimberley Hockings and colleagues (2015) report how, in Guinea, wild chimpanzees, who are closest to us genetically (96% correspondence), improvise leaf 'sponges' to facilitate lapping up about one bottle of a 3–6% alcoholic palm wine (see also Hockings et al., Chapter 4). West African chimpanzees have also been observed improvising tools, including sharp-ended sticks and long, flexible vines, to extract honey from natural beehives (Ghislain & Yamagiwa, 2014) in advance of human efforts in this direction to make a fermented beverage, viz. mead (see below).

Our hominin and human ancestors in Africa were likely genetically and physiologically endowed to consume and enjoy an alcoholic beverage, as we and other primates are today. Soft tissues and other organic evidence for the Palaeolithic Period, going back some four million years and representing 99% of human existence, may be very thin on the ground. But fossil skeletons, not so dissimilar to our own, imply that our forerunners had the necessary sensory apparatus—the colour vision to be attracted to brightly hued, readily fermentable fruit; olfactory bulbs to detect alcohol and associated aromatics; and taste buds to appreciate a myriad of flavours produced by glycolysis. Brain endocasts bear out these conclusions (Falk, 2014), besides implying that the requisite structures and presumably the neurotransmitters (dopamine, serotonin, opioids, and other compounds) for cellular intercommunication were already present for unleashing a 'pleasure cascade' and mind-altering experience when alcohol was consumed (Nestler et al., 2015).

The relatively small teeth of Palaeolithic hominins again point to a diet of soft foods, which has been bolstered by isotopic and phytolith studies of natural products embedded in plaque, principally fruits and leaves of the C3 metabolic pathway (e.g. Henry et al., 2012).

Moreover, like yeast, a suite of alcohol dehydrogenase enzymes was available to hominins for converting alcohol into energy. A comparative study of variants of the ADH4 enzyme (Carrigan et al., 2015), present in the mouths, throats, and stomachs of some primates as well as humans, indicates that it came into existence about 10 million years ago when the human and ape lineages separated and humans began to exploit the resources of the African savannah in addition to forest fruits (see Carrigan, Chapter 3). This enzyme would have increased our ancestors' ability to digest alcoholic foods and beverages, which is mainly carried out by ADH1 and ADH2 in the liver. Human livers, the real powerhouses for churning out energy from both sugar and alcohol, are comprised of about 10% of these metabolic enzymes.

Fermentation by countless bacteria, fungi, and other microorganisms of food stuffs outside the body, during a 'predigestive' phase, was likely also important to prehistoric humans.

Such food processing would have been followed up by the communities of beneficial and symbiotic microorganisms inhabiting theirs and our gastrointestinal tracts.

To make a long story shorter, the modern human is preprogrammed to detect, process, and enjoy an alcoholic beverage. From the moment we take a sip of our drink of choice and alcohol crosses the blood–brain barrier—and even before when we consider the possibilities of what the natural product has in store for us—genes and enzymes go into action. It doesn't take a great leap of imagination then to posit that early humans some 100 000 years ago in Africa were already acting in the role of *Homo imbibens*, making wines, beers, and mixed or extreme beverages with many ingredients, from wild fruits (maybe figs, dates, or palm fruit), honey, chewed grains and roots, and all manner of herbs and spices culled from their environments. The only caveat is that, because of the limited possibilities for drinking an alcoholic beverage in Palaeolithic times, our bodies and brains are adapted to moderate consumption. When we overindulge in alcohol (thus violating the general biological principle of hormesis in which moderate consumption of a substance, which might be dangerous when taken to excess, can be positively good for you), we pay the medical consequences.

In addition to fruit juice, tree saps and flower nectars readily ferment to wines, because of resident yeast. Honey can also easily be fermented to mead when diluted down with water at a ratio of about 30% honey to 70% water. Under these conditions, native hyperosmotic yeast in the honey become active.

Roger Morse (1980), who wrote the pioneering book on the subject, proposed that mead-making was the first biotechnology of humans. He theorized that a honey hunter, a well-respected 'occupation' in Mesolithic and Neolithic times (as shown in African and European rock art), when making his/her rounds, might have discovered a beehive in a hollow of a dead tree that had fallen to the ground. After the cavity was filled with the requisite amount of rain water, the honey would have been converted into mead. One smell of the new aromas emanating from the hive and one taste of the mind-stunning liquid were likely all it might have taken to spawn the idea that perhaps a fermented honey beverage could be produced on a regular basis with a little help from man (or more likely a woman in this instance, since females were generally the fermented beverage-makers of antiquity). A container would be needed, and that might have been improvised from wood, an animal skin, or woven grass. Unfortunately, containers have yet to be recovered from Stone Age sites, and definitive analytical support for this hypothesis is thus far lacking since organic materials readily degrade and disappear.

Hominin production of a fermented beverage from a carbohydrate resource, such as a wild grain, tuber, or plant leaves and stems, also cannot be ruled out. The enzyme ptyalin in our saliva, and likely in that of our ancestors, belongs to the amylase/diastase class, which are active in the saccharification (malting) process of beer-making in which starches are cleaved into sugars to be fermented. Given the natural impulses to suck and chew, our ancestors might well have masticated plant products and observed that their sweetness was intensified. If they then spit out the liquid, the latter might have been inoculated with yeast by an insect feeding on the sugar, thus producing a fermented beverage.

Corn *chicha* has long been made by the chewing-and-spitting method throughout the Americas (see Rosinger & Bethancourt, Chapter 10), and was incorporated into the social and religious traditions of the principal cultures, including Inca, Maya, and Aztec (Blake, 2015). A strong archaeological, genetic, and isotopic case can be made that chewing maize in Archaic (Upper Palaeolithic) caves of west-central Mexico, as attested by masticated cakes or quids, contributed to human fascination with the plant, ultimately leading to its domestication from the wild grass teosinte (Smalley & Blake, 2003). The primary goal of all this chewing, in addition to the creation of a highly concentrated and nutritious sugar resource, was to make an alcoholic beverage. It should be noted that one kernel of corn is equivalent to that of an entire teosinte plant, and there are 500 or more kernels in a single ear of corn.

The goal of making a fermented beverage, probably originally by the chewing-and-spitting method, appears to have led to the domestication of other major cereals worldwide, including barley, wheat, rice, sorghum, and millet. Modern examples, probably with long precedence, include women in the eastern Sahel of Africa making a sorghum beer this way and groups of women similarly chewing rice in Japan and Taiwan to prepare a traditional beer there for marriage ceremonies.

Ancient fermented beverages were no ordinary drinks, but had significant social and biological ramifications. Besides the sheer psychoactive delight in their new-found beverages, fermentation produced more nutritious, sensory appealing, and preservable foods than the starting materials. They served to bring people together as a group in its role as a 'social lubricant' by breaking down inhibitions between individuals. We can still see this going on around us today in taverns and homes, and at celebrations of every kind. An alcoholic beverage was additionally a combination relaxant (perhaps after a hard day of hunting and gathering), sleep-inducer, and aphrodisiac.

The mind-altering effects of a fermented beverage, as well as the mysterious process of fermentation itself, in which a liquid is radically transformed with the violent evolution of a gas (NB, yeasts were seen microscopically for the first time in the seventeenth century and their biological function was elucidated by Louis Pasteur only a century and a half ago), probably account for why fermented beverages were so readily incorporated into religions around the world. While rice and millet beers took hold in East Asia, becoming central to religions there, grape wine emerged as the most significant fermented beverage in the Middle East and Western countries. In Africa, where our species began, modern cultures, which perpetuate more ancient traditions that can be broadly characterized as shamanistic, are awash in sorghum and millet beers, honey mead, and banana and palm wines.

During prehistoric times when synthetic drugs were unavailable and your life span, if you survived birth and childhood, was 20–30 years, a fermented beverage's health benefits were obvious—alcohol relieved pain, stopped infection, and seemingly cured disease. It could be readily administered by drinking or applying to the skin. Those who drank fermented beverages, rather than raw water which could be tainted with harmful microorganisms and other parasites, lived longer and consequently reproduced more. Herbal or tree resin compounds with medicinal properties could also be more easily dissolved in an alcoholic medium than in water.

Alcoholic beverages additionally might well have opened the human mind to new possibilities of thought. Among many creative activities, perhaps some grunts might have been varied to produce a kind of music or communication, which eventually led to true language; syncopated body movements might have resulted in dance; and visual representations might have led on to cave art. Some modern thinkers, musicians, and artists carry on such primitivist traditions.

Wherever we look in the ancient or modern world, humans have shown remarkable ingenuity in discovering how to make fermented beverages and incorporating them into their cultures. In Africa, where humans originated, these fermented alcoholic drinks, especially those made from cereals, are estimated to provide today more than half of the energy needs of over a billion people. Each community generally has its own preferred alcoholic drink. Very often, the brewery or other production facility is placed at the centre of a village, reflecting how fermented beverages were and continue to be fully integrated into a society.

Ancient China: A Paradigmatic Example of theCultural and Biological Significance of Alcoholic Beverages

I would argue that no single fermented beverage took precedence over any other in being discovered first, whether a wine, mead, beer, or more complex concoctions with numerous and diverse ingredients, so-called extreme fermented beverages. All the biological pieces of the puzzle for intentionally making an alcoholic beverage were there—the natural products, the inquisitive hominin and human brain, the sensory awareness, and much more—and in place from the 'beginning' of our species, as it were. Our omnivorous diet is testimony to our openness to trying out new foods and mixing them together.

We may never know how, when, and where the initial discovery of an alcoholic beverage took place during the Palaeolithic Period, but as new archaeological excavations are carried out and scientific instrumentation continues to improve, we will undoubtedly learn more. We can imagine, but not yet prove, that an enterprising 'first fermented beverage-maker' likely threw some ripe fruit, honey, or masticated wild grain into a primitive container made of wood, woven grass, or an animal skin, and voilà, you had your drink! Lacking the glass bottle and cork of much later times, however, you had to consume it quickly before it went to vinegar. You could call it a Stone-Age Beaujolais Nouveau or sour ale or mead. The drink might have been passed around to the assembled group for their opinions, later to become a staple or traditional drink.

But we now have a starting point (a *terminus ante quem* in archaeological parlance) from which to look back on the great expanse of early hominin and human existence and its drinking proclivities. The Early Neolithic site of Jiahu (Henan Provincial Institute of Cultural Relics and Archaeology, 1999) in the Yellow River valley of China currently holds this distinction. According to chemical and radiocarbon analyses, the village people there were making, drinking, celebrating with, and enjoying an extreme fermented concoction of wild grapes, hawthorn tree fruit, honey, and rice around 7000–6000 BC.

You might have thought, as I first did as a Middle Eastern archaeologist, that the Fertile Crescent of the Near East, the so-called Cradle of Civilization, would have come first (and that may still be the case as we continue analysis of stone vats from Göbekli Tepe in eastern Turkey: Dietrich et al., 2012; see also Dietrich & Dietrich, Chapter 7). China had at least one point in its favour: pottery was being made there as early as 16 000 BC, some 10 000 years in advance of its production in the Near East. Once pottery enters the picture, the prospects for preserving and identifying ancient organics change markedly. Porous earthenware pottery, made from aluminosilicate clays, was able to absorb ancient organic compounds, especially as liquids, and retain them relatively intact for centuries, even millennia.

We focused our efforts at Jiahu on jars with high necks and flaring rims (Figure 6.2), which were ideally shaped to hold and serve liquids. The question was: What was the beverage? We used a battery of chemical tests, including infrared spectrometry, gas chromatography-mass spectrometry (GC-MS), isotope analysis, and purge-and-trap thermal desorption GC-MS, to ferret out the fingerprint compounds or biomarkers of the natural product ingredients of the original beverage.

As we analysed the extracts from one pottery vessel after another, the same chemical compounds kept showing up (McGovern et al., 2004). There were beeswax compounds, which we had already detected in the Midas extreme fermented beverage from central Turkey (McGovern et al., 1999), showing that one of the constituents was high-sugar honey. Despite the sugar itself having decomposed and been lost, the beeswax compounds reliably marked the presence of honey in the residues, because it was impossible to filter them out completely using early methods of processing of honey. We also found tartaric acid, the biomarker of grape and wine in the Middle East. In China, however, it could also mark the presence of hawthorn tree fruit (*Crataegus pinnatifida* and *C. cuneata*) which contains three times more of the acid than that found in grapes. We don't know yet whether only a wild Chinese grape species or hawthorn fruit, or both, went into the beverage. (After we published our chemical results, an archaeobotanical study showed that only those two fruits and no others were in fact present at the site. While this nicely corroborated our findings, we were still left uncertain as to whether both were used for the fermented beverages or only one.) Finally, close chemical matches with phytosterol ferulate esters pointed to rice as the third main ingredient, whose presence was also archaeobotanically confirmed by grains intermediate in form between

Figure 6.2 Early Neolithic jars, with high flaring necks and rims, from Jiahu (Henan province, China), *ca*. 6000–5500 BC. Analyses by the author and his colleagues showed that such jars contained a mixed fermented beverage of rice, honey, and fruit (hawthorn fruit and/or grape).
Photograph courtesy of J. Zhang, University of Science and Technology in China, and Henan Institute of Cultural Relics and Archaeology, nos. M252:1, M482:1, and M253:1 [left to right], height 20 cm [leftmost jar]).

wild and domesticated. Yeasts associated with the high-sugar fruits and honey would have assured the liquid's fermentation.

You could call this extreme fermented beverage a 'Neolithic grog' (or cocktail). It combined honey mead, a rice beer, and a grape and/or hawthorn tree fruit wine. As such, it was the earliest wine, beer, and mead in the world, albeit in combined form. Such a hybrid fermented beverage might sound strange and unappetizing, as had the Midas beverage. As we've learned over the past two decades, however, mixed fermented drinks were generally the rule in antiquity, especially during Neolithic times when plants were first domesticated and fermented beverages began to be produced in quantity. By combining multiple sugar sources, our ancestors appear to have accidentally hit upon a solution to a never-ending quest: upping the alcohol content of a fermented beverage as much as possible.

The Jiahu beverage was improvised during a revolutionary era when many plants and animals were being domesticated, thus laying the foundation for year-round habitation and civilization as we know it. Jiahu led the way in this new way of life with the earliest playable musical instruments (bird bone flutes), silk textiles, domesticated rice and pigs, fish-breeding, possible pictographic writing on tortoise shells for divination, and, of course, a suitably complex and delicious alcoholic beverage to sustain oneself, especially in the afterlife.

China is all about long traditions, and today people in China still communicate with their dead ancestors via a high-alcohol rice or millet beer. A family intermediary consumes nine large goblets, some 4.5 litres of a 10–12% alcoholic drink, enough to assure inebriation. This is only fitting, since 'the spirits are all drunk' (Paper, 1995) and drunkenness is the only way to communicate with them. Bells are rung and drums beaten at the ceremony's conclusion. We can imagine that, 7000 years earlier, the Neolithic flutes in the Jiahu tombs might well have served a similar purpose at funerary ceremonies. The jars with the 'Neolithic cocktail' were carefully placed near the mouths of the deceased, perhaps for easier drinking in the hereafter. The practice of communicating with the dead via a fermented beverage goes back at least to the Shang Dynasty (*ca.* 1200–1046 BC) when written documentation first becomes available.

Getting drunk to communicate with the dead was one use for an extreme fermented beverage. Another advantage of such a drink was its health-giving properties, including both the alcohol itself and any botanicals with medicinal value dissolved into it. Since we have not yet analysed the extracted residues from the Jiahu jars for low-molecular-weight aromatic compounds, it is not known whether any herbs or spices, which might have anticancer or other medicinal properties, were added to the ancient mixed beverage. The primary natural ingredients in the Jiahu extreme fermented beverage, especially honey (Olaitan et al., 2007), hawthorn fruit (Tadić et al., 2008), and grapes (Stockwell et al., 2008), have positive health benefits and are still used today in traditional Chinese medicine (TCM).

Our chemical studies of later Shang Dynasty fermented beverages (McGovern et al., 2010) did reveal the presence of likely botanicals derived from a wormwood or mugwort species (*Artemisia annua* and *A. argyi*, respectively) in a rice beer. Amazingly, the sample that we analysed from Changzikou, not far from Jiahu, had remained liquid for 3000 years, because of the tight lid on the bronze vessel and its subsequent corrosion to the vessel's neck. Before the remaining liquid inside the vessel had been hermetically sealed off, the liquid had evaporated down to about a third or less of its full capacity.

Once we knew that a wormwood/mugwort herb was probably added to the ancient rice beer, we followed up with anticancer testing of one specific compound of known medicinal value (artemisinin) at the Penn Medical and Abramson Cancer centres, as part of our 'Digging for Drug Discovery' (D^3) project. We showed by testing cancer tissues *in vitro* that the compound and its main derivative, artesunate, are highly effective against all kinds of cancers, including those of the lung (Lewis lung carcinoma), colon (adenocarcinoma), eye, liver, ovary, nervous system, pancreas, and blood. The compound is still undergoing *in vivo* testing in mice against cancers, and clinical trials are underway for cancer treatment in humans (Efferth, 2007). Artemisinin/artesunate has also been shown to be a powerful antimalarial agent, and often the medication of last resort for that disease (Nosten & White, 2007).

A. annua and *A. argyi* have long been important in TCM (Huang, 2000), and are still very popular in China today. They are usually equated with plants with the Chinese names Qinghao and Ai Ye. Both are used to treat haemorrhoids and as general sexual and medicinal tonics. Leaves of Ai Ye are also burned on the tips of acupuncture needles, and applied to the key body points in a practice called moxibustion. The monumental *Compendium of Materia Medica* by Li Shizhen, published in 1596 AD, attests to the long medicinal use of *Artemisia* herbs by citing the polymath Ge Hong's *Handbook of Prescriptions for Emergency Treatment* of the fourth century AD. The herbs are also cited in the earliest Chinese medical prescriptions, which were written on bamboo and silk strips, found in the extraordinary tomb of a noblewoman at Mawangdui in Hunan province, dating to 168 BC (Harper, 1998). She is said to be the most well-preserved human ever discovered, with the tissues of her internal organs intact and moist. It is possible that the use of these wormwood/mugwort plants in fermented beverages, in addition to many other botanicals that make up the ancient and modern *materia medica* of TCM, goes back much earlier, perhaps even to Neolithic times at Jiahu. Further study is needed, especially by employing ever-improving archaeological, archaeobotanical, chemical, and other scientific techniques and strategies.

Ancient China provides an excellent example with significant findings to date of how alcoholic beverages were well integrated into human cultures after our ancestors 'came out of Africa' about 100 000 years ago. Whether by applying prior traditions that they brought with them on their travels or by the innovative experimentation of our species, humans successfully took newly found natural products of a region, variously discovering their sensory and medicinal properties, and converting them into nutritious, healthful, and socially significant fermented beverages, often of the extreme type. As one follows human peregrinations around the world, many other alcoholic beverages made from every kind of ingredient can be documented (McGovern, 2009; McGovern, 2017). They are indeed the universal elixir of humankind.

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