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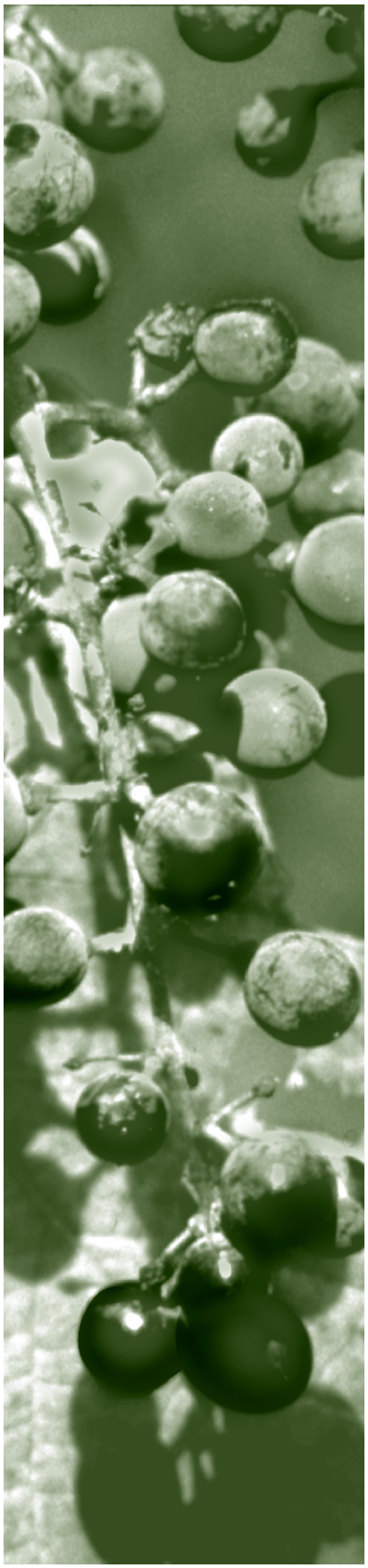

12

Wine, Food and Health

Wine and Food

Wine and its association with food encompass an incredible panoply of literature. Amazingly, almost none of its views and assumptions have come under scientific scrutiny. Only a few research papers deal with the topic. This may relate to the separation of enology and food science into separate departments. Also, the funding is different. That for enology and viticulture comes largely from governments and/or levies on vineyards and wineries. Funding in the food sciences comes largely from commercial firms, much of it done internally by food companies and proprietary. Funding from disparate industries provides little incentive for collaboration on interdisciplinary projects, such as food and wine combination.

Much of what is written on the subject comes from people with more of a background in history, sociology and journalism than science. Thus, in a field with little scientific rigor, but abundant imagination, opinion and instant experts, it is with some trepidation that I enter what has been largely considered an esthetic topic. This is especially so since scientists tend to be doubters; the issue is highly complex (controls difficult);

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experimental conditions make their relevance to 'real life' situations dubious; social pressures for conformity among consumers are often pronounced; and the context of the table often puts reality, and its perception, in conflict. Consequently, what I am about to say will likely not be taken with appreciation by the majority in the restaurant or retail wine trades. Nonetheless, fools, prophets (and occasionally scientists) often go where angels fear to tread. The author has already dared to comment on this topic at greater length in another work (Jackson, 2009). His head has a yet to roll, so one more, foreshortened, sortie into the topic may still be safe, buried as it is within a scientific text. It is added to give food for thought to those seriously interested in wine, and how it is most commonly used (or at least portrayed) in society.

The traditional view is that wine is in some fundamental way designed to be consumed with food. However, when one searches for the evidence, it seems to be a myth – a view that has been so oft repeated as to be assumed to be true, an example of social contagion of collective memory. The food/wine association only begins to appear in the literature during ancient Greek or Roman times. In the Near East and Egypt, wine was almost the exclusive preserve of the noble or priestly classes. The alcoholic beverage of the populace was beer. Wine is mentioned in the Bible, but seemingly recommended only in relation to religious ceremonies and weddings. It is only in regions where wild grapes grow indigenously that vines came to provide the drink for the masses. Its acidity, alcohol, and phenolic contents all enhanced its antimicrobial property, making it considerably safer to drink than water. This property of wine became increasingly important as population numbers grew, and hygienic conditions correspondingly deteriorated. Although production was seasonal (unlike beer based on a dry grain), its resistance to spoilage for several months, isolated from air, permitted it to become the preferred beverage where vines grew readily. Like beer, it could wash down food, and obliterate, for a short period, the afflictions of rigorous lives. Although safe and nutritious (caloric), there is nothing in its attributes that inherently makes wine ideal as a food beverage. It is actually better suited for its ancient secondary role, as a solvent in preparing extracts from medical herbs.

The sharp acidity of many ancient wines, often extended with aged seawater and vinegar (especially for slaves), can hardly be considered an ideal food accompaniment from the modern perspective. The frequent presence of pitch is also less than appealing. The quality of the ordinary wine for the average Roman is probably best left to the imagination. Apparently, finer wines were available for the patrician classes. The most famous seem to have been, or became, concentrated, with aged versions being almost syrup-like. Nonetheless, several Roman poets eulogize the wonders of particular vintages, as do modern writers. Does this mean that ancient wines could be of equivalent quality, or at least acceptable to modern tastes? Probably some would have been, but it's likely most were simply the habitual everyday beverage.

Even modern wines, with their predominant acidic, bitterish, and astringent character have little to suggest food compatibility. These characteristics are simply the natural consequence of grape chemistry, not conscious intent. Admittedly, consuming wine with food does mollify its less pleasant aspects, unless one develops an appreciation for sour beverages with a bitter/astringent aspect. Some humans seem adept at coming to appreciate and crave what is initially abhorrent. Black coffee, capsicum peppers, and limberger cheese are classic examples. The mutual tapering of the sensation of both cheese and wine appears to be the major benefit of their combination at wine tastings (Nygren *et al.*, 2002, 2003a, 2003b). Other studies have confirmed these findings, as well as lending support to the idea that red wines marginally pair better with cheeses, with astringency being reduced and the perception of tannins appearing more silky (Bastian *et al.*, 2010). The bitterness-reducing aspect of cheese, which varies with the type of cheese and bitter tastant, appears to relate at least partially to its fatty acid content (Homma *et al.*, 2012). For example, oleic acid binds quinine, reducing its bitterness. In addition, some combinations fare worse, for example, pairing sweet wines with cheese (Bastian *et al.*, 2009).

In some instances, the iron content of the wine can induce a metallic sensation, by catalyzing lipid oxidation. This may be masked in combination with food. However, iron is considered to induce the fishy aftertaste associated with some white wines paired with seafood (Tamura *et al.*, 2009). In most 'compatible' combinations, both the cheese and wine appear better – not by enhancing their respective qualities, as usually interpreted, but by a mutual suppression of their less pleasing attributes. For example, the fatty acids in cheese, by coating taste receptors, reduce their exposure to wine acids and phenolics. Lipoproteins, typically found in foods, are known to react with hydrophobic regions of receptor membranes, suppressing the perception of bitterness (Katsuragi *et al.*, 1995). Suppression of unpleasantness of either component could easily be misinterpreted as an enhancement in pleasure – equating to compatibility. Similar situations could explain many other supposedly compatible food and wine associations. This is not what wine pundits and sommeliers profess, but seems far closer to the truth.

When one searches for commonalities among the attributes of food and wine, they are few and far between. Most table wines are distinctly on the sour side. This can be of value when wine is used as a marinade, promoting acid-induced hydrolysis of food proteins. As a marinade, wine antioxidants can also reduce the production of toxic heterocyclic amines during frying (Viegas *et al.*, 2012). Otherwise, sourness is rare as a principal element in most world cuisines (see Moskowitz *et al.*, 1975 for a marked exception). Acids typically are added only as a component in some condiments or flavorants, notably vinegar, lemon juice, or tamarind. They can enhance the flavor of otherwise bland foods. The bitterness and astringency of most red wines also finds no equivalent in meat or fish. Taking food with wine does, however, reduce both its sour and bitter/astringent attributes. The protein in solid food reacts with both wine acids and phenolics, limiting their availability to react with and stimulate gustatory receptors and trigeminal nerve endings.

The saltiness of most cheeses probably explains additional benefits, by suppressing the perception of bitterness (Frijters and Schifferstein, 1994; Breslin and Beauchamp, 1997; Keast *et al.*, 2001). Sodium chloride is effective at concentrations considerably lower than sugar (Nakamura *et al.*, 2002). Sugar is used extensively today to mask bitterness in modern beverages. Bitterness suppression appears to be one of the principal 'flavor-enhancing' aspects of adding salt to food. It might also explain the seemingly odd recommendation for adding seawater to wine by the Ancient Greeks – producing an esteemed wine called *oenos thalassikos* (see Younger, 1966). Pliny notes in *Historia Naturalis* (14.120) that salt enhanced the smoothness of wines. In addition, Columella recommends the addition of salt (*De Res Rustica* 12.41), apparently to avoid moldy tastes. Seawater was part of a recipe mentioned by Columella in preparing 'Greek' wine. Salt water was even recommended in preparing new barrels to receive wine in the recent past (Nègre and Françot, 1955). Glutamate and adenosine monophosphate, activators of umami receptors, can also suppress the perception of bitterness (Keast, 2008). Both are typical constituents of meat and cheese.

Anecdotal statements that wine 'cuts through fat' are legion, but appear to be unsupported by corroborative data. If this view has a physicochemical basis, the partial fat solubility of ethanol may reduce the oily mouth-feel of fats, as well as limit the activation of taste receptors to fatty acids, but this is no more than speculation. The acids in wine might also have a similar effect. In addition, wine tannins might denature the G protein receptors responsible for detecting fatty acids in the oral epithelium (see Chapter 11), giving the impression of less fattiness. Conversely, fatty acids can reduce sensitivity to the sourness of organic acids and bitterness of some tastants (Mattes, 2007), possibly improving mouth-feel.

Phenolics are known to reduce (Jung *et al.*, 2000) or enhance (Mitropoulou *et al.*, 2011; Villamor *et al.*, 2013) volatility, depending on the phenolic and aromatic involved. Carbohydrates also have the ability to bind aromatics, reducing volatility, and significantly modify wine flavor and its retronasal attributes (Voilley and Lubbers, 1998; Villamor *et al.*, 2013). Thus, both synergies of flavor, as well as suppression, could be involved in 'ideal' pairings. Saliva-induced changes in flavor chemistry is another compounding issue little investigated. Whether such potential reactions are sufficiently marked and rapid to have significance, within the time frame of food consumption, is currently *terra incognita*.

When comparing the sapid profiles of food and wine, there appears to be little similarity. In contrast, there is extensive incongruity. Wine possesses gustatory attributes predominantly characterized as sour, bitter, astringent, and burning. In contrast, solid foods are variously distinguished by sweet, salty, savory (glutamate), and sebaceous (fatty acids) sensations. Sour, bitter, astringent, and spicy hot attributes are (or have been) less common in Western cooking, and then usually in condiments. The inherent, aversive reactions to such sensations probably arose during evolution, to avoid or limit the consumption of potentially toxic and rotten foods. Conversely, these compounds were probably selected during plant evolution to discourage their consumption, with the predominate exception being ripe fruit. During domestication, crop variants were selected with reduced aversive and enhanced pleasant tasting constituents. Thus, lettuce and other vegetables became less bitter; apples, cherries, and other fruits sweeter and less sour or astringent; citrus fruit less acidic; and legumes less flatulent. Cooking further facilitated these actions by inactivating or facilitating the removal of potential food toxins and anti-metabolites. Examples include mycotoxins in fungi, alkaloids in potatoes, and cyanogenic glycosides in casava. Cooking meat also facilitates digestion (collagen and protein fiber breakdown) and enhances flavor. Disappointingly, some cooking processes generate their own toxins, notably roasting and searing. Examples are acrylamide (a Maillard by-product), and a variety of toxic, pyrolytic, smoke by-products. Fermentation is another ancient technique that helped destroy anti-metabolites. For example, *Rhizopus oligosporus*, used in the production of tempeh, degrades the compounds that induce flatulence in soybeans. *Lactobacillus* can also destroy soy saponins. Fermentation also has the potential to break

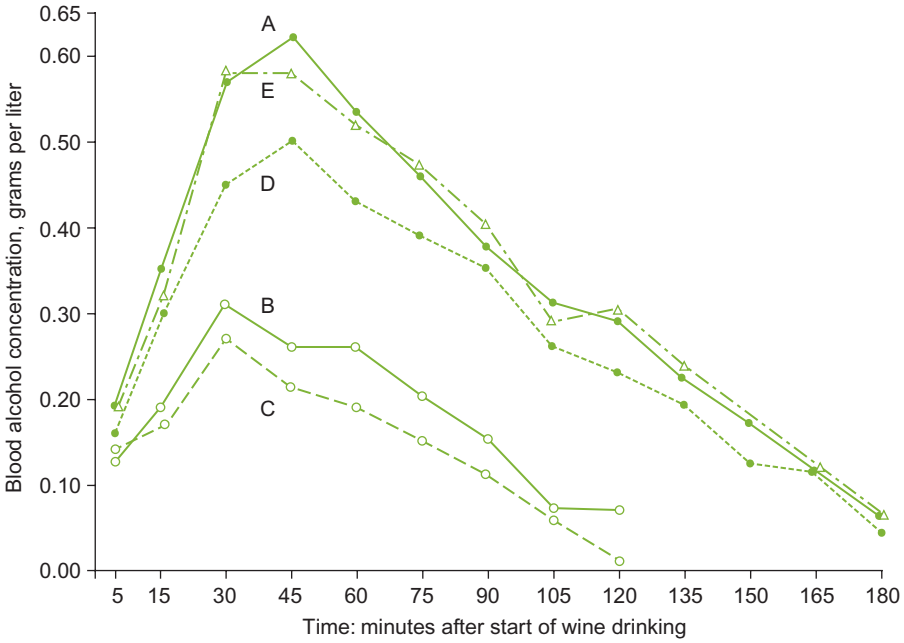

Figure 12.1 Blood alcohol concentrations after wine drinking in a single dose. A, fasting; B, during a meal; C, 2 hours after a meal; D, 4 hours after a meal; E, 6 hours after a meal. (From Serianni *et al.*, 1953, reproduced by permission.)

down difficult-to-digest oligosaccharides, and help preserve perishable foodstuffs.

The aromatic aspects of food and wine equally show little similarity on which supposed compatibility could be based. Wine aromas are most frequently described in terms of fresh fruit, jam, or flowers. None of these is characteristic of the main components of a meal, and would be considered odd if present. The 'apple' in Chardonnay wine may go well with chicken, the 'pepper' of a Shiraz pair with pepper steak, and the 'walnut' of some sherries combine with nut-containing salads (without vinaigrette). However, does the box wood or cat urine of Sauvignon blanc, the rose of Riesling, and the blackcurrant of Cabernet Sauvignon wines really match with any main course? In addition, does the vanilla/coconut of oak, or the leather aspect of aged red wines have any inherent compatibility with food? The supposed spiciness of Gewürztraminer wines is given as a reason for its combination with spicy Asian foods. However, the wine has more litchi aroma than spiciness, making the stated logic dubious. It is only its potential intense aroma that may permit its presence to remain noticeable. Personally, the best aspect of wine and food association is not their complementary natures but their contrasts. Each cleanses the palate between alternate samplings, allowing fresh perceptions of each. Thus, wine permits swift shifts in savory sensuality.

Without comparable tastes or flavors, where is the supposed inherent rapport between food and wine? Is its only justification the reduction of undesirable aspects of the partnership, and as a palate cleanser? Certainly, wine's ability to partially rinse the palate between food samples is important. It offers both gustatory, olfactory, and trigeminal receptors time to reestablish their native receptive state, countering adaptation and loss of sensory appeal. Thus, food appreciation is enhanced by being sampled afresh. Wine can, unromantically, be viewed as a savory mouthwash. In addition, volatility of food and wine flavorants is influenced by the dynamically changing concentrations of ethanol, phenols, carbohydrates, etc. supplied with the wine. Conversely, food dilutes, masks, and eliminates most wine flavors. The result being that the next sample can be appreciated to its full, adaptation having been avoided.

The other aspect of potential compatibility arises from their dissimilar attributes. They act in concert, in a manner similar to condiments, providing flavor accents to enhance and maintain flavor interest throughout the meal. The result can be the creation of a stimulating holistic experience. The typical starchy elements in a meal (rice, potatoes, pasta, bread) supplement it, in helping to cleanse the palate and generate a feeling of satiation.

In all the standard discussions of food and wine association, the obvious is never mentioned. It reduces wine's inebriating effect (Fig. 12.1). Its association with food is far more savory than dilution with water, a

frequent occurrence in Roman times. Then, the habit had the distinct benefit of partially disinfecting the water. Of little consequence today, it was of considerable value in the past. Roman generals knew well that even partially inebriated soldiers were better on the battlefield than those laid low with dysentery.

Many aspects of food preference appear to be established *in utero*, based on what the mother ate during pregnancy (Mennella *et al.*, 2004), as well as during early childhood. Thus, habituation is largely instrumental in the development of most personal preferences. Later on, peer pressure and cultural influences can combine to modify these early dispositions. Habituation may not be imbued with the emotional and social appeal associated with the image of predestined food and wine marriages, but far better fits the facts than any supposedly heaven-inspired pairings. Thus, it is little wonder that there is scant inclination to investigate the basis of lovingly held popular beliefs. It is almost like the proverbial attack on motherhood – to be avoid at any cost.

However, honesty does not have to destroy the pleasure of food and wine combination. Knowing that Michelangelo's Sistine Chapel consists of no more than brush strokes of pigment on plaster, perceived by photoreceptors in the eye, converted into synaptic impulses reconstructed piecemeal into a perception at the back of the brain need not destroy the pleasure of its appreciation. Ideally, it should enhance the glory of the perception, and the joy it brings. Scientific understanding augments sensory pleasure by adding new layers of appreciation. If supplemental knowledge were not considered to augment expectation and appreciation, why would connoisseurs be so concerned with vintage dates, wine geography, cultivars, or details of vineyard sites or wine producers? With knowledge, it really is the more the merrier.

Admittedly, an excess of scientific realism at the wrong time may limit sensory appreciation. For special events, psychological appeal can be more significant than sensory reality. As in other aspects of life, science can occasionally be set aside to permit spontaneity and anticipated pleasure to preside. The intrigue of magic is being fooled so effectively.

Under most circumstances, though, some basic rules of pairing should be kept in mind, to avoid glaring mistakes. In most fine cuisine, flavor balance, combined with suitable complexity, is central. Nonetheless, the vagueness of this concept is evidenced by the almost infinite variety of combinations seen in cookbooks, food magazines, and culinary shows. Accepted norms also vary markedly among cultures (Rozin, 1977, 1982). Thus, it should not be surprising that almost any wine can pair with almost any meal. There are limits, however, for example a dry Gewürztraminer with dessert, or a Riesling Auslese with bouillabaisse. To almost everyone, these would not be considered 'marriages made in heaven.' Cabernet Sauvignon and dark chocolate is another clash, but seeming appreciated by some connoisseurs. Except where there are clear flavor or intensity disparities, notably sweet/acid or sweet/bitter-astringent, almost any combination will be found pleasing to some, and acceptable to most.

Of the generalities oft quoted, the 'white with white, red with red' rubric bears logic, within the context of balanced flavor intensity. Nonetheless, it is often the food preparation mode (poached, fried, baked, broiled, barbequed) or the condiments added (chilies, curry, olive oil, tomato sauce, garlic, herbs) that have the greatest influence on flavor intensity, the basic character of the meal, and, correspondingly, a compatible wine.

In most instances, premium-quality table wines are best sampled prior to the meal, and premium-quality dessert wines after the meal. Because of their aromatic complexity, detection of these attributes is compromised by combination with food or dessert. Alternatively, the food or dessert should be designed to be a foil for the wine, and be mild in character. In contrast, the more markedly acidic or bitter/astringent the wine, the more effectively these features will be mollified by association with food. In addition, a lack in its aromatic interest can be camouflaged by flavors from the accompanying food. Where little attention is likely to be paid to the wine, inexpensive, neutral to off-balanced red or white wines are both financial and logical choices.

If some food and wine pairings are clearly inappropriate, are there seraphic duets? If so, I, for one, have experienced few. Some do pair better than others, but a transcendental experience, no! From my perspective, such paradisaical experiences are figments of the imagination, created to sell wine or spill ink on paper. It is not lack of flavor subtlety that denies these experiences from the great unwashed. Admittedly, as noted in Chapter 11, there is an incredible range in human sensory sensitivity, with those having higher than average acuity tending to prefer milder favored foods, and those with below average acuity tending to prefer more intensely flavored foods. But, these are no more than tendencies, with experience and social pressures capable of inducing significant shifts in preference, if not perception. Psychological influences and a desire to be influenced can distort perception, creating impressions that are 'real,' only because of the conditions under which the experience occurred. The more unexpected and astounding the sensation, the stronger the memory trace created. The more the mind is studied, the more we come to realize how the brain can distort perception. Experience generates mental models of reality,

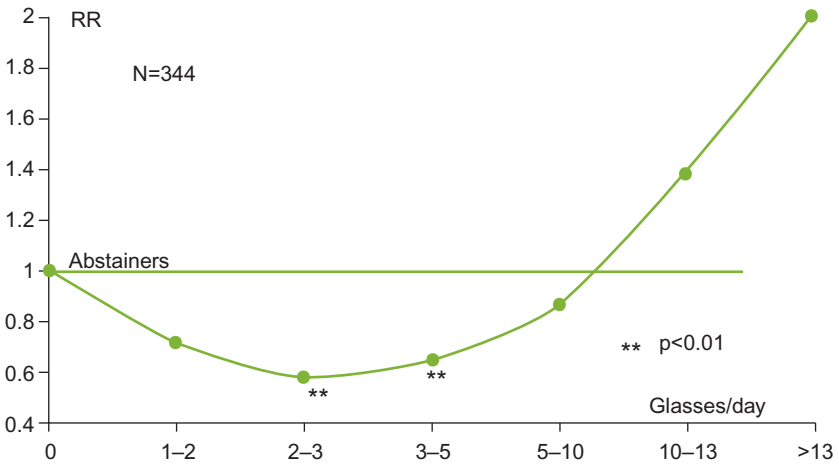

Figure 12.2 Death from other causes in wine drinkers of the Nancy cohort. Relative risk of death from all causes in relation to the intake of wine compared with abstainers, adjusted for age, smoking, BMI, and education. Other causes were the sum of the causes of death with the exception of cancer, cardiovascular causes, cirrhosis, and violent death. (From Renaud *et al.*, 2004, reproduced by permission.)

against which our sensations of reality are judged, interpreted, and potentially modified. Thus, it is wise to doubt perceptions and attempt to separate experience-based memory patterns from actuality, unless it is a selective choice to allow the mind to deceive us.

Wine and Health

The contrasting social and antisocial effects of alcohol consumption must have become evident shortly after the discovery of winemaking. Time has only augmented our understanding of the multifaceted nature of this Dr Jekyll–Mr Hyde phenomenon. It is clear that excessive alcohol consumption, both acute and chronic, can have devastating effects on physical and mental well-being. Abusive ethanol consumption can cause cirrhosis of the liver, increase the likelihood of hypertension and stroke, favor the development of breast and digestive tract cancers, and induce fetal alcohol syndrome. Many of these effects may stem from the activation of free-radical damage induced by high alcohol intake (Meagher *et al.*, 1999). Others may arise indirectly, via the accumulation of acetaldehyde, a major breakdown product of ethanol metabolism (Lachenmeier *et al.*, 2009). Because the problems associated with alcoholism (Abrams *et al.*, 1987; Schmitz and Gray, 1998), and its eventual, irreversible, chemical modifications in the brain (Nestler and Malenka, 2004; Heinz, 2006), have been well documented, they will not be discussed here. On the other hand, it is becoming equally clear that moderate wine consumption (up to about one-third of a 750-ml bottle per day) can potentially have health benefits. This is considerably less than the two bottles that Brillat-Savarin (1848) considered a healthy man could consume per day and live long; or the amounts considered appropriate in times past (Younger, 1966, pg 367). Mark Twain expressed moderation best in his expression:

> *"Temperate temperance is best," from Notebook, 1896.*

Multiple epidemiological studies suggest that daily, moderate, alcohol consumption (Thun *et al.*, 1997; Doll *et al.*, 2005), and notably wine (Grønbæk *et al.*, 2000; Renaud *et al.*, 2004), is associated with a reduction in all-cause mortality. This is expressed in the now famous J-shaped curve (Fig. 12.2), with earlier mortality being associated with both excess alcohol intake and abstinence. This is particularly evident in the reduced incidence of cardiovascular disease in moderate alcohol consumers. In addition, it reduces the likelihood of type 2 diabetes, combats hypertension, and is correlated with reduced frequency of certain cancers and other diseases (see below).

These epidemiological correlations are being supported by *in vivo* studies that provide potential molecular explanations for these associations. The principal elements missing, in confirming a causal relationship, involves detailed information on the dynamics of absorption, metabolism, and elimination of the proposed active ingredients. Another aspect missing is data on the relationship with morbidity. The general assumption is that the trends are the same.

Although important, data on this aspect are much more difficult to obtain, partially because morbidity is far more difficult to quantify and syndromes it should include are ill-defined. The same situation applies to data on the effects of obesity on mortality vs. morbidity (Gibbs, 2005).

Faced with a chemical and beverage that can be not only salubrious but also addictive, the fluctuations in society's attitude toward alcohol are not surprising (Musto, 1996; Pittman, 1996; Vallee, 1998). Thankfully for those in the wine industry, wine drinkers appear less likely to become heavy drinkers (Jensen *et al.*, 2002), or to illustrate those alcohol-related problems that have given alcohol a bad reputation (Smart and Walsh, 1999). In addition, wine has a more positive social image than other alcohol-containing beverages (Klein and Pittman, 1990). The major caveat is the derogatory epithet, *wino*, ascribed to some unfortunate members of society.

The use of wine as a medicine, or even more frequently as a carrier for pharmaceuticals, has a long history. It goes back at least to the Pharaohic Egyptians (Lucia, 1963). Ancient Greek and Roman society used wine extensively as a solvent for herbal infusions. This practice continued largely unabated until the beginning of the twentieth century. The excessive abuse of distilled alcoholic beverages, combined with religious and political conservatism, created a backlash against all beverages containing alcohol, notably in North America. Alcohol was viewed as an agent of corruption to be annihilated. Following the failure of Prohibition, humans themselves, not alcohol, came to be viewed as the source of iniquity. Alcoholism is now appropriately viewed as a developmental, multistage, chronic dependence, possessing a complex etiology (Nurnberger and Bierut, 2007), with both genetic and environmental aspects. In this regard, it is similar to other addictions (Ersche *et al.*, 2012). Thus, the social climate is changing, and the relationship between wine (as opposed to alcohol) and health is again being reassessed, and finally investigated seriously.

It is unlikely that doctors will soon be prescribing wine for its health benefits. Too often, people have difficulty recognizing the limits of rational use, and differ markedly in their metabolism (Gross *et al.*, 2010). In addition, detrimental influences rapidly counter any benefits at more than light to moderate consumption (often viewed as <30 mg ethanol/day) (Rehm *et al.*, 2010). Erring on the side of restraint seems judicious, without excessively assuaging pleasure, especially if combined with food. Even dietary flavonoid supplements (one of the benefits of wine consumption) can be detrimental, if taken in excess (Skibola and Smith, 2003). Wine can be wonderful in moderation, but is no panacea.

Alcohol Metabolism

Alcohol is the primary by-product of fermentative metabolism in many organisms. Ethanol is also an energy source for an even larger number of species. Thus, it is not surprising that enzymes involved in ethanol oxidation are found in most life forms. In humans, ethanol enters the bloodstream either via the consumption of beverages containing alcohol, and/or from ethanol synthesized by the bacterial flora in the intestinal tract. When the concentration of alcohol is low, most of it is metabolized in the liver, before it enters the systemic blood supply. Most of the blood coming from the digestive tract passes through the liver before being dispersed to the rest of the body.

The liver metabolizes about 95% of alcohol in the plasma, at about 15 mL/h. The rest tends to be lost in the breath, or secreted in the urine and other bodily fluids. The liver possesses two enzymic pathways for ethanol metabolism. The primary, constitutive mechanism involves the oxidation of ethanol to acetaldehyde, through the action of cytoplasmic alcohol dehydrogenases (ADHs). Of the seven known *ADH* genes (Crabb *et al.*, 2004), three function in the liver. The others act in the gastric epithelium and other tissues. Subsequent oxidation converts acetaldehyde to acetic acid. This occurs principally under the action of mitochondrial acetaldehyde dehydrogenase (ALDH2). Cytoplasmic acetaldehyde dehydrogenase (ALDH1) is less active. Acetic acid may be released into the blood or converted to acetyl CoA. From this point, metabolism may flow along any standard biochemical pathway (see Fig. 7.20).

Alcohol metabolizing enzymes frequently occur in allelic forms (isozymes). Their relative occurrence also tends to vary among ethnic groups. Some of the isozymes possess distinct physiological attributes. For example, *ADH1B*1* codes for an isozyme subunit that oxidizes ethanol slowly, whereas *ADH1B*2* encodes for a highly active subunit of the dimeric enzyme (about 30 times more efficient) (Thomasson *et al.*, 1995). Correspondingly, those individuals who are homo- or heterozygous for the *ADH1B*2* subunit, eliminate alcohol from their blood more rapidly. Rapid alcohol oxidation may donate a degree of protection against alcoholism, by quickly converting ethanol to acetaldehyde. Such individuals tend to consume less alcohol and show more rapid and marked negative consequences to alcohol consumption (headaches and hangovers) than do those metabolizing alcohol more slowly (Wall *et al.*, 2005). This 'protection' is apparently enhanced when combined with slow-acting alleles for acetaldehyde dehydrogenase (*ALDH2*) (Crabb *et al.*, 2004). Although viewed as a beneficial trait, rapid alcohol degradation probably reduces some of

the health benefits of ethanol consumption. Slow acetaldehyde metabolism also appears to predispose individuals for cancers of the oropharynx and esophagus.

A second, ethanol-degradation pathway becomes activated only when the blood alcohol concentration reaches high levels. It involves a microsomal cytochrome, P4502E1. The cytochrome oxidizes ethanol to acetaldehyde, using molecular oxygen rather than NAD^+. The activation of the microsomal oxidation pathway has the undesirable side-effect of generating free oxygen radicals[1] (Meagher *et al.*, 1999). The free-radical activity can remain long after alcohol intake has ceased. Although most free oxygen radicals are inactivated by glutathione, superoxide dismutase, and catalase, long-term exposure to trace amounts of oxygen radicals may induce the slow, progressive accumulation of irreparable cellular damage. Subsequent oxidation of acetaldehyde, generated by the microsomal pathway, to acetic acid is identical to that derived via alcohol dehydrogenase.

The metabolism of ethanol to acetate (acetic acid) has the advantage that tissue cells can regulate its transport. This is not the situation with ethanol, which can diffuse freely across cell membranes. Transport control is a central tenet in proper cellular function.

Physiological Actions

The ability of ethanol to displace water, and its unregulated passage cross cell membranes, explains much of alcohol's toxicity. In addition, its oxidation to acetaldehyde is more rapid than acetaldehyde's oxidation to acetate. Thus, acetaldehyde may accumulate in the blood and other bodily fluids. This is often viewed as an important contributor to the toxicity associated with excessive alcohol consumption (Lachenmeier *et al.*, 2009). Differentiating between these direct and indirect toxic effects of excessive ethanol intake has proven difficult.

One of the first physiologic effects of alcohol consumption is a suppression of cognitive brain function. This is most noticeable in enhanced sociability – by blocking social inhibitions regulated by higher brain functions. For others, it quickly induces drowsiness (Stone, 1980). This probably explains why taking a small amount of wine before going to sleep (90–180 ml) often helps people, notably the elderly suffering from insomnia (Kastenbaum, 1982). Half a glass of wine provides the benefits of sleep induction, without causing subsequent agitation and sleep apnea – often associated with greater alcohol consumption. The effect on sleep may arise from alcohol facilitating the transmission of inhibitory γ-aminobutyric acid (GABA), while suppressing the action of excitatory glutamate receptors (Haddad, 2004). GABA and glutamate are estimated to be involved in about 80% of neuronal circuitry in the brain.

Another effect on brain function results from a reduction in hormonal secretion – notably vasopressin. As a consequence, urine production increases, producing the frequently reported diuretic effect associated with alcohol consumption. Less well known is how alcohol acts as a crucial regulator of the hypothalamic–pituitary–adrenal axis, modulating the release of hormones such as adrenocorticotropic hormone (ACTH) and corticosterone (Haddad, 2004).

Although alcohol has a general depressive action on brain function, the levels of some brain modulators show transitory increases. Examples are serotonin and histamine. The latter may activate a cascade of reactions leading to headache production.

Another of the multiple influences of alcohol is the conversion of hepatic glycogen to sugar. This results in a short-lived increase in plasma glucose content. This, in turn, can cause glucose loss in the urine, as well as an increase in insulin release by the pancreas. Both result in a drop in blood sugar content. If sufficiently marked, hypoglycemia results. This apparently causes the temporary weakness occasionally associated with alcohol consumption, especially excess intake.

In addition to direct effects, the accumulation of acetaldehyde, as a by-product of ethanol metabolism, may have several undesirable consequences. At low rates of alcohol intake, acetaldehyde metabolism is sufficiently rapid to limit its accumulation and liberation from the liver. At higher concentrations, acetaldehyde production rapidly consumes the liver's glutathione reserves – a central cellular antioxidant. This coincides with activation of the microsomal ethanol oxidation pathway that generates toxic free-oxygen radicals. In the absence of sufficient glutathione, free-oxygen radicals can accumulate, disrupting mitochondrial function. Elsewhere in the body, acetaldehyde can bind with proteins and cellular constituents, forming stable complexes (Niemela and Parkkila, 2004). These can lead to the production of immunogenic determinants, which can stimulate antibody production against acetaldehyde adducts. This may induce some of the chronic tissue damage associated with alcohol abuse (Niemela and Israel, 1992). The binding of acetaldehyde to the plasma membrane of red blood cells is known to increase rigidity. By limiting their ability to squeeze through the narrowest capillaries, oxygen supply to

[1] Free radicals are molecules (or their fragments) with one or more unpaired electrons that give them high reactivity.

tissue cells may be restricted. This could participate in suppressed brain function. It is estimated that the brain consumes up to 20% of the blood's oxygen supply, but constitutes only about 2.5% of body mass.

Although ethanol and acetaldehyde can produce severe, progressive, and long-term damage to various organs, and incite alcohol dependence, these consequences are minimal to undetectable when alcohol consumption is moderate and taken with meals. As the sections below demonstrate, moderate, daily, wine consumption can have health benefits for the majority of people.

Food Value

Wine's major nutritional value comes from its rapidly metabolized, ethanolic, caloric content. Alcohol does not need to be digested, prior to being absorbed through the intestinal wall. In rural viticultural areas, wine historically provided a significant source of metabolic energy for the adult population. The caloric value of ethanol (7.1 kcal/g) is nearly twice that of carbohydrates (4.1 kcal/g). Wine was a food. Wine also supplied a safe source of water, being itself almost 90% water. Added to other sources of water, wine helped to disinfect the supply.

Wine contains small quantities of several vitamins, notably several B vitamins, such as B_1 (thiamine), B_2 (riboflavin), and B_{12} (cobalamin). However, wine is virtually devoid of vitamins A, C, D, and K. In excess, ethanol can impair vitamin uptake.

Wine contains various minerals in readily available forms, especially potassium and iron (in the ferrous state). Nevertheless, excessive alcohol consumption can disturb the uptake of calcium, magnesium, selenium, and zinc, and increase the excretion of zinc via the kidneys. The low sodium/high potassium content of wine makes it one of the more effective sources of potassium for individuals on diuretics.

Although wine contains soluble dietary fiber, especially red wines (Díaz-Rubio and Saura-Calixto, 2006), it is insufficient to contribute significantly to the daily recommended fiber content in the human diet.

Digestion

Wine has several direct and indirect effects on food digestion. Its phenolic (Hyde and Pangborn, 1978) and alcohol (Martin and Pangborn, 1971) contents activate the release of saliva. In addition, wine promotes the release of gastrin as well as gastric juices. Succinic acid is apparently the principal constituent activating the release of gastric juices in red wines, whereas in white wines it is malic acid (Liszt *et al.*, 2012). It does not, however, activate gastrin release. The substance(s) involved in stimulating gastrin secretion are unknown. Wine also significantly delays gastric emptying, both on an empty stomach (Franke *et al.*, 2004), or when consumed with food (Benini *et al.*, 2003). The latter favors digestion by extending acid hydrolysis.

Delayed gastric emptying may be a consequence of wine phenolics activating STC-1 cells in the stomach. These possess the same T_2R system as bitter-sensitive receptors in the mouth (see Finger and Kinnamon, 2011). On stimulus, they release cholcystokinin, a peptide hormone that reduces gut mobility.

In addition, wine slows plasma glucose uptake, independent of any insulin response (Benini *et al.*, 2003). Furthermore, at the levels found in most table wines, ethanol activates bile release in the intestines. Wine acids and aromatics also have the same effects. In contrast, the high alcohol content of distilled beverages can suppress digestive juice flow, the release of bile, and induce stomach spasms. Wine also aids digestion indirectly by inactivating gastrointestinal pathogens.

Despite the general beneficial effects of moderate amounts of alcohol on digestion, the phenolic content of red wine may counter some of these effects. For example, tannins and phenolic acids can interfere with the action of certain digestive enzymes, notably α-amylase, lipase and trypsin (Rohn *et al.*, 2002; Gu *et al.*, 2011). Digestion may be further slowed by phenolics polymerizing with food proteins. These effects may be mollified by the presence of ionic carbohydrates commonly found in food (Gonçalves *et al.*, 2011), as well as by salivary proteins. Both monomers and proanthocyanidins bind with basic, proline-rich, and histatin proteins in the saliva. Their bonding is reversible, depending on equilibrium conditions. They can become irreversible, though, in the presence of metal ions, upon oxidation, or with pH changes (Luck *et al.*, 1994). Normally, these insoluble saliva/tannin complexes remain stable in the stomach and upper alimentary tract (Lu and Bennick, 1998). Thus, the potential of tannins to inactivate digestive enzymes or disrupt mineral uptake can be reduced. Degradation of these complexes, and their moieties, subsequently occurs in the colon. In contrast, pepsin-activated protein breakdown is activated by monomeric phenolics, such as quercetin, resveratrol, catechin, and epigallocatechin gallate (Tagliazucchi *et al.*, 2005). Clearly the issue is complex and much more needs to be known. Not only are the effects potentially different in the stomach and small and large intestines, but, also, phenolic chemistry changes during passage through the digestive tract.

Another potential influence of the phenolic content is a decrease in iron and copper absorption in the

intestinal tract (Cook *et al.*, 1995). Although this may be undesirable, limiting the bioavailability of iron has the potential benefit of reducing the formation of toxic lipid hydroperoxides during digestion. The antioxidant effect of polyphenolics also applies to peroxide generation in the stomach (Kanner and Lapidot, 2001; Kanner *et al.*, 2012).

The activation of gastric juice release not only aids food digestion, but also inactivates enzymes involved in ulceration. Even more significant may be the antibiotic action of wine constituents against *Helicobacter pylori* (Fugelsang and Muller, 1996). *H. pylori* is often considered the primary causal agent of stomach ulceration. Thus, moderate wine consumption may have a prophylactic effect in limiting ulcer initiation (Brenner *et al.*, 1997). The bacterium has also been implicated in gastritis, vitamin B_{12} malabsorption, and gastric adenocarcinoma. However, chronic secretion of gastric juice can produce irritation that may provoke ulceration, heartburn, and favor the development of adenocarcinomas in the lower esophagus.

Wine may further aid human sustenance by increasing nutrient uptake. Congeners in wine combine with metallic ions, vitamins, and fatty acids, facilitating their transport across the intestinal wall.

Consuming wine with food slows the rate of alcohol uptake in the blood (Fig. 12.1). In the absence of food, about 80% of the alcohol is absorbed through the intestinal wall. This proportion increases when jointly consumed with food, but it is spread over a much longer period. This results primarily by food retarding gastric emptying. Consequently, alcohol transfer into the intestines is delayed. This gives the liver more time to metabolize the ethanol being absorbed, lowering the maximal blood alcohol levels reached. However, taking sparkling wine on an empty stomach increases short-term alcohol uptake by about 35% (Ridout *et al.*, 2003). Because the same wine, with its carbon dioxide removed, did not have the same influence, it is suspected that carbon dioxide was the active ingredient. It has occasionally been proposed that carbon dioxide relaxes the pyloric sphincter, allowing earlier transfer of fluids from the stomach into the duodenum, and thereby its absorption into the blood.

The rate of alcohol metabolism differs considerably among individuals, with rates commonly varying between 90 and 130 mg/kg/h. A person's hormonal and nutritional state also affects their ethanol metabolic rate.

Finally, wine can also have a beneficial cultural/psychologic effect on food intake and digestion. The association of wine with refined eating promotes slower food consumption, permitting biofeedback mechanisms to regulate food intake. In addition, wine consumption can promote a more relaxed lifestyle, something increasingly valuable in our overly compulsive society. Whether this explains the reported improved appetite of many elderly and anorectic patients, when wine is taken with the meal, is unknown.

Phenolic Bioavailability

Most investigations on the health benefits of moderate wine consumption have involved phenolics. However, to fully evaluate their effects, it will be necessary to understand the dynamics of phenolic uptake, concentration, metabolism, and elimination. Such data are just now starting to become available. Thus, while absorption via the intestinal system is required for activity (except locally), it alone does not imply bioavailability at the cellular level.

In absolute terms, the proportion of flavonoids derived from wine is relatively small – estimated to be about 4 mg/day/person in the United States (Chun *et al.*, 2007). This compares with about 200 mg/day from all sources. This value would increase to about 37 mg flavan-3-ols and 47 mg procyanidin dimers, based on 180 mL of red wine per day (Forester and Waterhouse, 2009). This is near the upper limit of what is typically considered moderate wine consumption.

In the mouth, mid-sized flavonoid polymers often bind to salivary proteins, forming stable complexes (De Freitas and Mateus, 2003; Pizarro and Lissi, 2003). This significantly limits their uptake in the stomach and small intestine. Passage through the stomach does not modify the majority of wine phenolics. Amongst flavonoids, anthocyanins appear to be those that most quickly traverse the stomach and pass into the blood (Passamonti *et al.*, 2003). They are also effectively translocated across the wall of the small intestine (Talavéra *et al.*, 2005). Phenolic acids, such as caffeic acid (Simonetti *et al.*, 2001), and resveratrol (Soleas *et al.*, 2001) also readily pass into the plasma via the intestinal tract. In contrast, flavonoid polymers tend to remain in the intestine, until degraded to phenolic acids and aldehydes by bacteria in the colon (large intestine) (Aura, 2008; Fig. 12.3). Also metabolized in the colon are any anthocyanins or catechins monomers that have not already been absorbed and/or microbially degraded. For example, gallotannins are microbially converted to urolithins (Truchado *et al.*, 2012b). Although these by-products have little antioxidant action, they do have anticancer effects and can have beneficial effects on intestinal inflammatory disease (Giménez-Bastida *et al.*, 2012). This may be a consequence of tannin metabolites enhancing the growth of *Bifidobacterium* and *Lactobacillus* spp., or attachment, similar to that of flavan-3-ols (Bustos *et al.*, 2012).

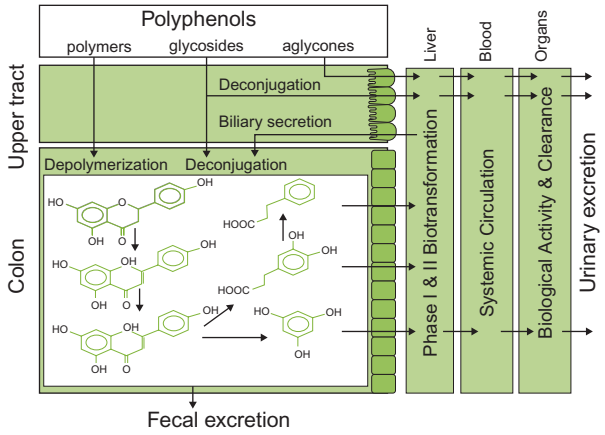

Figure 12.3 Schematic depiction of metabolic fate of dietary polyphenols in the human–microbial superorganism. Within the colonic compartment, the microbial bioconversion pathways of naringenin are depicted. Within the host, dietary polyphenols and their microbial bioconversion products successively undergo liver phase I and II metabolism, absorption in the systemic circulation, interaction with organs, and excretion in the urine. (From van Duynhoven *et al.*, 2011, reproduced by permission.)

Depending on the specific compound, variable amounts are absorbed into the blood via the colon (Ward *et al.*, 2004).

Studies on the bioavailability of phenolics, once they enter the bloodstream, are still preliminary (Williamson and Manach, 2005). Although many simple flavonoids may be quickly absorbed into the plasma, most appear to be rapidly conjugated, that is, methylated, sulfated, transformed to glucuronides, or otherwise metabolized (see Williams *et al.*, 2004; Forester and Waterhouse, 2009). Hydroxycinnamic acids are also rapidly absorbed and metabolized into glucuronide and sulfate conjugates (Nardini *et al.*, 2009). This both reduces their toxicity (potential carcinogenicity) as well as facilitates their excretion by the kidneys. However, the latter reduces their potential beneficial effects. Small amounts of tartaric acid esters of cinnamic acids are also found in the plasma. These transformations could significantly affect their antioxidant and other attributes, as well as their ability to move into tissue cells and their surrounding fluids.

Most of these metabolites still retain one or more reducing phenolic group, and, thus, may still possess antioxidant properties. Nevertheless, there is growing evidence that phenolic metabolites act primarily as signaling molecules, notably in oxygen-stress-related pathways (Williams *et al.*, 2004). Correspondingly, smaller amounts of active ingredients are needed for activation than for direct antioxidant reactions. This might explain the discrepancy between the low levels of free phenolics in the plasma and their apparent effects. An example may be the increased activity and gene expression of antioxidant genes in erythrocytes after red wine consumption (Fernández-Pachón *et al.*, 2009). Even survival of most of these metabolites in the plasma is comparatively short (a few hours). Their breakdown products rapidly appear in urine shortly after plasma uptake. Future studies are needed to investigate the antioxidant efficacy of phenolic metabolites and their conjugated complexes at concentrations found in the plasma. Their efficacy at binding to, and translocation into tissue cells needs to be known.

Admittedly, these investigations are complicated by the immense diversity of grape and wine phenolics, which is augmented by their subsequent metabolism via the intestinal flora and enzymes in the plasma and tissue cells. In addition, there are ethical issues in dealing with human subjects. People also differ markedly in their metabolic and colonic microbial diversity. Consequently, most studies involve tissue cultures or animal models.

The presence of phenolics in the plasma permits their likely uptake into most body tissues. This generality does not necessarily apply to the brain. Except where there are specific transport proteins, most compounds above a molecular weight of 500 Da are excluded by the blood–brain barrier. This barrier consists of tight connections between the endothelial lining of cerebral capillaries. This prevents the diffusion of molecules between vascular endothelial cells, as is typical elsewhere in the body. However, with anthocyanins (Passamonti *et al.*, 2005) and simple flavonols (Youdim *et al.*, 2004), access to the brain apparently can occur within minutes of consumption. Initial animal studies suggest rates of uptake in the brain at about 10% that of the blood (Wu *et al.*, 2012).

Antimicrobial Effects

The prophylactic action of wine against gastrointestinal diseases has been known for millennia, long before their microbial origins were even suspected. This action is complex and not well understood.

The antimicrobial effect of alcohol was discovered in the late 1800s. Nevertheless, alcohol is not particularly antimicrobial, certainly at the concentrations found in wine (its sterilant action is optimal at about 70%). Thus, the antibiotic action of wine results primarily from other constituents, probably its phenolic content. Modification of anthocyanins during fermentation increases their toxicity to viruses, protozoans, and bacteria. Other phenolic compounds, typical of red wines, are also bacteriostatic and fungistatic. For example, *p*-coumaric acid is particularly active against

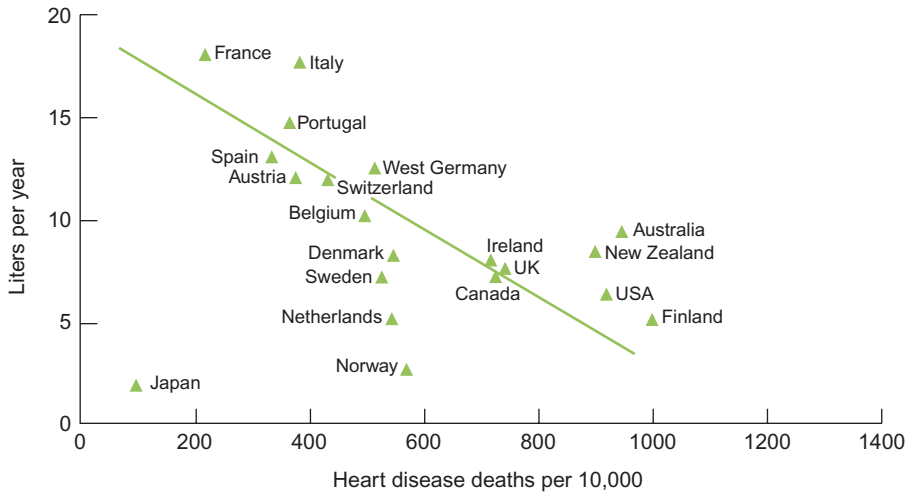

Figure 12.4 Relationship of per capita alcohol consumption with 1972 heart disease death rates in men aged 55–64 in 20 countries. (From La Porte *et al.*, 1980, reproduced by permission.)

gram-positive bacteria, such as *Staphylococcus* and *Streptococcus*; whereas other phenols inhibit Gram-negative bacteria, such as *Escherichia*, *Shigella*, *Proteus*, and *Vibrio* (Masquelier, 1988). The latter cause serious forms of diarrhea and dysentery. Phenolics may also be inhibitory to intestinal pathogens such as *Clostridium difficile*, *C. perfringens*, and *Bacteroides* (Lee *et al.*, 2006). Despite wine being more effective than mildly antimicrobial agents, such as bismuth salicylate (Weisse *et al.*, 1995), full action may take several hours (Møretrø and Daeschel, 2004; Dolara *et al.*, 2005).

An indirect effect, limiting intestinal problems (and improving digestion), may be illustrated by the action of the colon flora on anthocyanin structure. It favors the growth of *Bifidobacterium* spp. and *Lactobacillus-Enterococcus* spp. (Hidalgo *et al.*, 2012). These have been associated with a healthy gut microflora (Hord, 2008). There is also considerable variation in the effects of different flavanols and procyanidins, both promoting and inhibiting the adhesion of probiotic lactobacilli to the intestinal wall, depending on their metabolic modification during passage through the intestinal tract (Bustos *et al.*, 2012).

In most instances, the mechanism by which phenolics have their action is unknown. However, in the case of quercetin, the effect may be partially attributed to its inhibition of DNA gyrase, whereas with epigallocatechin, disruption of cell membrane function appears central to its antibiotic action. Alternative methods of action may involve suppression of cell adherence and colony formation on the gut lining (Selma *et al.*, 2012; Truchado *et al.*, 2012a). Adherence is often a prerequisite for the cascade of events leading to disease development. Low pH and the presence of various organic acids appear to accentuate the antimicrobial action of both wine phenolics and ethanol. Organic acids may themselves be antimicrobial, as is the case with *Bacillus cereus* (Vaz *et al.*, 2012).

Wine is also active against several viruses, including the herpes simplex virus, poliovirus, hepatitis A virus, as well as rhinoviruses and coronaviruses. The effect on the latter two groups appears reflected in the reduced incidence of the common cold in moderate alcohol consumers (Cohen *et al.*, 1993), particularly those drinking red wines (Takkouche *et al.*, 2002). If you have to gargle, port is certainly one of the more pleasant options available.

Cardiovascular Disease

The most clearly established benefit of moderate alcohol consumption, notably wine, relates to a nearly 30–35% reduction in death rate due to cardiovascular disease (Klatsky *et al.*, 1974, 2003; Renaud and de Lorgeril, 1992; Figure 12.4). Alcohol consumption is also correlated with a decrease in the likelihood of intermittent claudication (pain or cramping in the calf of the leg). Claudication is a common indicator of peripheral arterial disease. Recent studies have confirmed that incidental factors, such as gender, race, lifestyle, educational level, etc. do not affect these results (see Mukamal *et al.*, 2006). Studies have also demonstrated that daily consumption of alcohol significantly reduces the incidence of other forms of cardiovascular disease, such as hypertension (Keil *et al.*, 1998), heart

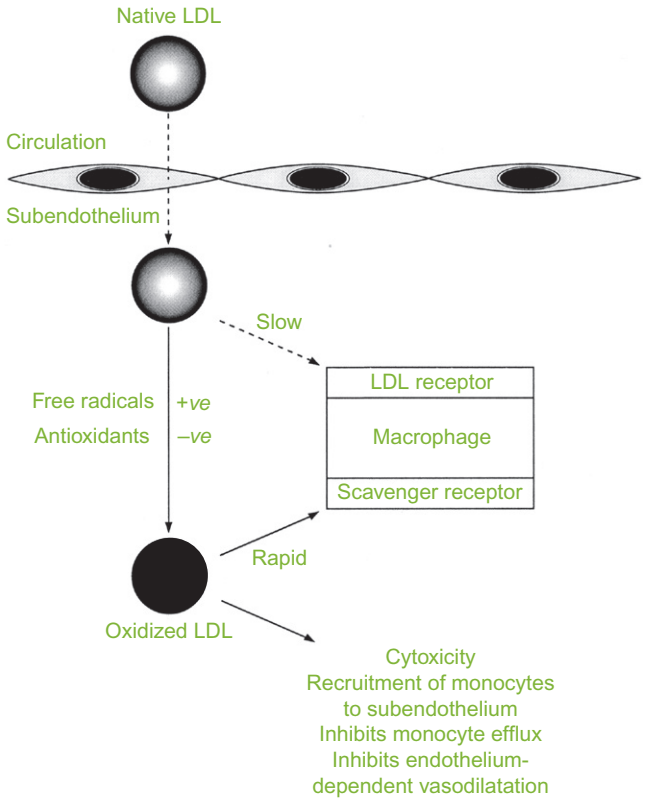

Figure 12.5 The oxidative-modification hypothesis of arteriosclerosis. (From Maxwell, 1997, reproduced by permission.)

attack (Gaziano *et al.*, 1999), stroke (Truelsen *et al.*, 1998; Hillbom, 1999), and peripheral arterial disease (Camargo *et al.*, 1997). Those who consume wine moderately live, on average, 2.5–3.5 years longer than teetotalers, and considerably longer than heavy drinkers. The prime area of contention is the degree to which these benefits accrue from the effects of ethanol vs. phenolic and/or other constituents (Rimm *et al.*, 1996).

Atherosclerosis is the principal cause of most cardiovascular disease (Libby, 2001). It apparently results from chronic injury to the arteries (Fig. 12.5). Although associated with several independent factors, most damage appears to be a consequence of lipid oxidation – in a special subgroup of cholesterol-apoproteins complexes, the low-density lipoproteins (LDLs). Because of the hydrophobic nature of cholesterol and triglycerides, their transfer in the plasma requires a special transport vehicle. As illustrated in Fig. 12.6, lipoprotein complexes consist of an outer membrane of phospholipids, in which apoproteins and free cholesterol occur. They enclose a hydrophobic core possessing numerous triglycerides and cholesteryl esters. The specific apoproteins in the complex regulate the metabolism of the associated lipids.

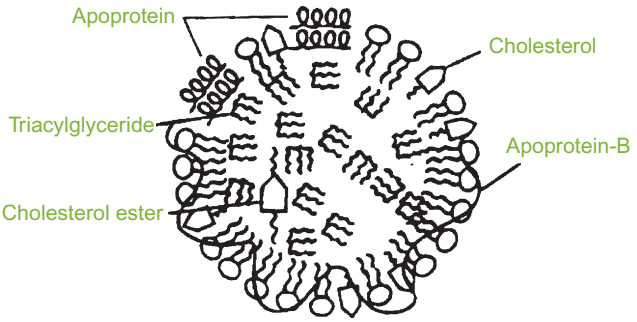

Figure 12.6 General structure of a triglyceride-rich lipoprotein. (From Walzem and Hansen, 1996, reproduced by permission.)

Normally, LDLs function in supplying cholesterol for cellular membrane repair and the synthesis of steroids. However, in high concentrations, they may accumulate in the artery wall. If they remain there for an extended period, their lipid content tends to become oxidized. In an oxidized state, lipids are cytotoxic and indirectly irritate the artery wall. As a consequence, special adhesion proteins attach to the artery wall. Monocytes and helper T-cells of the immune system bond to these proteins. In addition, affected endothelial cells may secrete compounds, such as endothelin-1. Endothelin-1 activates the migration of monocytes and T-cells into the artery wall. Procyanidins, principally found in red wines, are particularly effective in suppressing the production of endothelin-1 (Corder *et al.*, 2001). In the layer just underneath the endothelial lining (intima), accumulated monocytes mature into macrophages. Both macrophages and T-cells may release a range of cytokines that further activate the immune system, involving localized inflammation. Activated macrophages tend to engulf oxidized LDLs. However, as the LDLs are not degraded, their progressive accumulation gives the macrophage the appearance of being full of bubbles. This has given rise to the term foam cells. They are the first clear evidence of the beginning of localized arterial swelling (plaques). Occasionally plaques bulge into the vessel. More frequently, they initially enlarge outward into the surrounding tissue. Action of immune cells in the plaque also induces migration of smooth muscle cells from the artery wall into the intima. Here they proliferate and produce collagen, forming a fibrous cap over the plaque. Additional LDLs slowly collect, provoking further rounds of inflammation and plaque enlargement. These accretions may develop their own vasculature, becoming fibrous and inelastic. As the plaques enlarge, they may produce irregular protrusions into and block the artery lumen.

Even without restricting blood flow, plaques set the stage for platelet aggregation, clot formation (thrombus) and the blockage that can precipitate a heart attack or stroke. In the later phases of plaque formation, unknown factors enhance inflammatory changes in the plaque. These disrupt the integrity of the cap. For example, collagenases secreted by macrophages inhibit collagen synthesis by smooth muscle cells. Sudden rupture of a plaque permits blood infiltration into the plaque. Because plaques contain potent blood clotting factors, thrombus development is almost instantaneous. It is currently thought that plaque rupture is the principal factor inducting thrombus formation, and precipitating a heart attack, stroke, or other cardiovascular trauma.

If risk factors of atherosclerosis, such as smoking, high blood pressure, high dietary sources of cholesterol, and possibly infection by pathogens such as *Chlamydia pneumoniae* and cytomegalovirus (CMV) are eliminated, atherosclerosis appears to be at least partially reversible. Part of the reversal process involves the action of high-density lipoproteins (HDLs). Of the two principal forms, ethanol augments the presence of HDL_3, whereas exercise increases the level of HDL_2. The effect of ethanol on HDL concentration appears to be independent of beverage type (van der Gaag *et al.*, 2001). Either form of HDL favors the removal of cholesterol from the arteries, transferring it to the liver for metabolism. HDLs also appear to interfere with LDL oxidation. Because the HDL/LDL ratio affects the degree and rate of cholesterol turnover, the slower the rate, the greater the likelihood of oxidation (Walzem *et al.*, 1995) and eventual plaque formation.

The beneficial effect of moderate alcohol consumption on the HDL/LDL ratio is now relatively clearly established. Less well understood is its effect in lowering the concentration of C-reactive protein (CRP) (Levitan *et al.*, 2005). CRP is an indicator of inflammation. Its level usually rises in correlation with the risk of atherosclerosis.

Moderate alcohol consumption also reduces the incidence of another risk factor for cardiovascular disease – type 2 diabetes. Chronically high values of circulatory glucose, associated with type 2 diabetes, appear to generate high plasma triglyceride and LDL levels. The beneficial effects of alcohol on glucose and insulin metabolism appear not to occur if intake is not coincident with meal consumption (Augustin *et al.*, 2004). Phytoestrogens, such as resveratrol, have a similar effect in reducing triglyceride and LDL contents in the circulatory system (see Bisson *et al.*, 1995).

Another of alcohol's beneficial influences involves disruption of events leading to clot formation. Platelets are less 'sticky' in the presence of alcohol, thus, less likely to aggregate, limiting clot formation. Alcohol also increases the level of prostacyclin (interferes with clotting) and raises the level of plasminogen activator (a clot-dissolving enzyme).

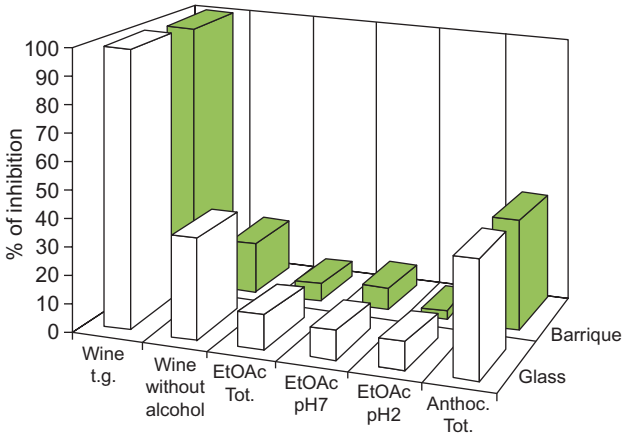

Figure 12.7 Inactivation of platelet aggregation induced by several red wine fractions (barrel- or bottle-aged, their dealcoholized versions, total ethanol extracts (EtOAc) and ethanol extracts at pHs 7 and 2, and anthocyanin extracts from the wines. (From Baldi *et al.*, 1997, reproduced by permission.)

Clots, adhering or becoming stuck to the roughened surfaces of narrowed atherosclerotic vessels, may block blood flow. The oxygen deficiency and cell death that result are central to the damage caused by a heart attack or stroke. Thus, it is not surprising that inhibitors of platelet aggregation reduce the frequency of these cardiovascular crises and their sequelae. It is the rationale for recommending the daily consumption of acetylsalicylic acid (ASA) (an inhibitor of platelet aggregation). Ethanol (Renaud and Ruf, 1996), as well as wine phenolics, such as resveratrol and anthocyanins, have similar effects (Fig. 12.7).

An additional example of the importance of ethanol in cardiovascular disease is the correlation between alcohol dehydrogenase (*ADH*) genotype and the incidence of myocardial infarction. Individuals homozygous for *ADH1C*2* (slow metabolizers of ethanol) are significantly less likely to have a heart attack than heterozygous individuals, and even less likely than homozygous individuals for *ADH1C*1* (fast metabolizers of ethanol) (Hines *et al.*, 2001).

Individually, many phenolics, such as resveratrol, catechin, epicatechin, and quercetin have inhibitory effects on platelet aggregation (Keli *et al.*, 1994). In a recent *in vitro* study, though, monomeric or low-molecular-weight flavonoids and hydroxycinnamic acids enhanced platelet aggregation and LDL oxidation, with only large polymers being inhibitory (Shanmuganayagam *et al.*, 2012). In another investigation, the combined effect of several

phenolics was superior to single compounds (Wallerath *et al.*, 2005). The action partially results from the enhanced synthesis and release of nitric oxide by endothelial cells. This has been found to occur at resveratrol concentrations associated with moderate wine consumption (Gresele *et al.*, 2008). Chlorogenic acid also appears to activate nitric oxide production (Mubarak *et al.*, 2012). Nitric oxide induces vasodilation (by relaxing vascular smooth muscle), reduces blood pressure, and limits platelet adhesion to blood vessel endothelia. Indicative of the complexities of such interactions is the observation that flavonoids may also inactivate nitric oxide (Verhagen *et al.*, 1997). In addition, nitric oxide, notably as peroxynitrile, oxidizes LDLs. Clearly, much more still needs to be known before a clear picture emerges.

Supplemental to the effects on platelet aggregation, phenolic wine constituents can bind directly with LDLs (limiting their oxidation); indirectly reduce their macrophage-mediated oxidation; and preserve the action of paraoxonase (further protecting LDLs from oxidation) (Aviram and Fuhrman, 2002). Furthermore, red wine phenolics directly or indirectly limit the migration of smooth muscle cells into the intima of artery walls. These influences probably explain some of the added benefits of wine versus other alcoholic beverages in reducing the incidence and severity of cardiovascular disease. Although flavonoids tend to suppress inflammation, conflicting observations put the clinical significance of their anti-inflammatory action to atherosclerosis in question.

Red wines usually have been credited with superior health-related benefits than white wines, especially relative to cardiovascular disease. This presumably results from their higher flavonoid content (Tian *et al.*, 2011). This view is supported by studies where white wine has shown the same effects as red wine, when supplemented with grape polyphenolics (Fuhrman *et al.*, 2001). Nevertheless, prolonged skin contact, or choice of particular cultivars, can enhance the presence of phenolic acids in white wine. Common phenolics in white wine, such as caffeic and coumaric acids, as well as flavonols such as quercetin, are well-known potent antioxidants.

The low sodium content of wine is an incidental benefit. It may permit wine consumption by those on a low-sodium diet, for example those with high blood pressure or heart attack victims. The high potassium to sodium ratio of wine (20:1) is a further benefit.

Antioxidant Effects

The antioxidant action of wine phenolics not only appears to play an important role in limiting LDL peroxidation (Maxwell *et al.*, 1994; Rice-Evans *et al.*, 1996), an early stage in atherosclerosis, but also inhibits the action of lipoxygenases throughout the body. Phenolics can also directly scavenge free oxygen radicals, such as superoxide and hydroxyl radicals, as well as chelate iron and copper, limiting their involvement in radical formation (Morel *et al.*, 1994; Rice-Evans *et al.*, 1996). In addition, tannin subunits (catechins and epicatechins) appear to protect other cellular components from oxidation. Other well-known antioxidants in the human diet include vitamins E and C (tocopherol and ascorbic acid), β-carotene, and selenium.

One of the antioxidants relatively unique to wine is resveratrol. It is a phenolic (stilbene) compound produced in response to plant stresses, such as fungal attack. Other plants producing resveratrol include mulberries, blueberries, peas, and peanuts. It has greater antioxidant action than common dietary antioxidants, such as vitamin E and ascorbic acid (Frankel *et al.*, 1993). There is also direct evidence that resveratrol can enter the blood system at levels sufficient to suppress cyclooxygenase (COX) and 5-lipoxygenase pathways. These are involved in the synthesis of proinflammatory mediators (Bertelli, 1998). In addition, resveratrol can activate proteins involved in nerve cell differentiation, synaptic plasticity, and neuronal survival (Tredici *et al.*, 1999). All are crucial to learning and recovery from nerve damage.

Additional potent antioxidants in wine include flavonols, such as quercetin, and flavonoid tannin subunits (Miller and Rice-Evans, 1995). Flavonoids have been shown to possess various mechanisms of action, some directly quenching free radicals, others increasing the level of endogenous antioxidants such as glutathione, whereas others prevent the influx of calcium ions associated with oxidative stress (Ishige *et al.*, 2001). They may also be more effective antioxidants, as well as occurring at higher concentrations, than resveratrol. Their content depends partially on the duration of skin contact and the type of fining. PVPP (polyvinylpolypyrrolidone), for example, markedly reduces quercetin content (Fluss *et al.*, 1990).

Alternatively, de la Torre *et al.* (2006) have suggested that ethanol may directly activate biosynthesis of hydroxytyrosol in the body. Consumption of red wine, with a concentration of 0.35 mg hydroxytyrosol, increased the concentration of hydroxytyrosol in the blood more than administration of olive oil containing 1.7 mg hydroxytyrosol. Hydroxytyrosol is a well-known antioxidant phenolic found in olive oil.

Vision

Many of the beneficial influences of alcohol and wine consumption show a J-shaped curve (Fig. 12.2).

This also applies to its effect on age-related macular degeneration (Obisesan, 2003; Fraser-Bell *et al.*, 2006). The disease expresses itself as a progressive degeneration of the central region of the retina (macula), leading to blurred or distorted vision. It results as a consequence of local atherosclerosis that deprives the retina of oxygen and nutrients. It is the leading cause of blindness in adults over the age of 65. A similar relationship has been found for cataract development. In both conditions wine antioxidants are suspected to be the active protective agent. At higher rates of intake, ethanol promotes a pro-oxidant action that could negate the benefits of wine antioxidants.

Neurodegenerative Diseases

Alzheimer's is one of the most investigated of neurodegenerative diseases, affecting more than 15 million people worldwide. It is not surprising that researchers have investigated whether wine consumption affects the incidence of neurodegenerative diseases affected by oxidative stress, such as Alzheimer's (Barnham *et al.*, 2004). Flavonoids not only activate key respiratory enzymes in mitochondria (Schmitt-Schillig *et al.*, 2005), but also decrease the production of reactive oxygen species, by stimulating the production of catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase (Martín *et al.*, 2011). A pattern appears to apply here, as with so many other health-related benefits of wine and alcohol consumption – moderate intake is beneficial, whereas high consumption or abstinence is prejudicial.

Alzheimer's disease has been correlated with the accumulation of extracellular amyloid β-peptide (plaque), and the formation of intracellular neurofibrillar tangles containing tau-protein. The latter supports microtubule cytoplasmic structures. Many *in vitro* studies have shown that antioxidant compounds, such as vitamin E, protect neurons from β-amyloid accumulation. Tannins have also been shown to inhibit the formation of, and destabilize pre-existing β-amyloid fibrils (Ono *et al.*, 2008), whereas resveratrol promotes the degradation of amyloid β-peptides (Marambaud *et al.*, 2005). Wine consumption is also linked in epidemiological studies to a reduction in the incidence of Alzheimer's disease (Truelsen *et al.*, 2002; Letenneur, 2004; Luchsinger *et al.*, 2004). Even mild cognitive impairment, and the progression of idiopathic dementia may be reduced with moderate alcohol consumption (Solfrizzi *et al.*, 2007). Even grape juice has been found to be effective in this regard (Krikorian *et al.*, 2012). Like other health benefits, these finding may not, in and by themselves, justify wine consumption, but they are encouraging to those who choose wine as part of their preferred lifestyle.

Osteoporosis

Age-related bone mass loss affects both sexes, but is more frequent in postmenopausal women. Many risk factors, dietary influences, and hormonal supplements can affect its progress and severity. Of these factors, moderate alcohol consumption has been found to favor bone retention (Ganry *et al.*, 2000; Ilich *et al.*, 2002). Tucker *et al.* (2009) found data consistent with higher benefits from wine than other alcohol-containing beverages. The source of these benefits may be a combination of enhanced calcium uptake, associated with alcohol consumption (Ilich *et al.*, 2002), the phytoestrogen effects of phenolics, such as resveratrol and kaempferol, or other unsuspected influences.

Gout

In the 1800s, there were many reports linking gout with wine consumption, notably port. Gout is caused by the localized accumulation of uric acid crystals in the synovium of joints. Their presence stimulates the synthesis and release of humoral and cellular inflammatory mediators (Choi *et al.*, 2005). Gout is also associated with reduced excretion of uric acid in the kidneys. Mutations in the gene that encodes urease, the enzyme that metabolizes uric acid to allantoin (a soluble by-product), is often involved in gout.

Dietary predisposing factors for gout include red meat, seafood, and beer. This is presumably because purines, the principal source of uric acid, are found in higher concentrations in these products than many other foods or beverages. Alcohol consumption may occasionally aggravate gout by increasing lactic acid synthesis. It, in turn, favors uric acid reabsorption by the kidneys. Despite this, wine consumption appears not be associated with an increased risk for gout. In contrast, it seems to favor reduced serum urate levels (Choi and Curhan, 2004).

Medical historians suspect the nineteenth century gout–port association was connected with lead-induced kidney damage (Yu, 1983; Emsley, 1986/1987). Samples of port from the nineteenth century show high lead contents. Lead contamination probably came from the stills used in preparing the brandy added in port production. In addition, the former use of pewter and lead-glazed drinking cups, and prolonged storage of port in lead crystal decanters or stemware could have further augmented lead content (Falcone, 1991; Guadagnino *et al.*, 1998).

Arthritis

A number of drugs used in treating arthritis have a tendency to irritate the lining of the stomach. This side-effect may be counteracted by the mildly acidic, dilute alcohol content of table wines. Other beneficial effects connected with moderate wine consumption may accrue from its mildly diuretic and muscle relaxant properties. The diuretic action of wine can help reduce water retention and minimize joint swelling. Wine can also directly reduce muscle spasms and the stiffness associated with arthritis. The anti-inflammatory influences of wine phenolics, notably resveratrol (Elmali *et al.*, 2007), may also play a role in diminishing the suffering associated with arthritis.

Diabetes

Wine consumption has been shown to attenuate insulin-resistance in type 2 diabetes (Dixon *et al.*, 2001; Napoli *et al.*, 2005). This may result from wine phenolics quenching oxygen radicals, thought to be pivotal in the damage associated with type 2 diabetes. Type 2 diabetes appears to result when body cells fail to respond properly to the presence of insulin. The incidence of metabolic syndrome is also lower in wine drinkers (Rosell *et al.*, 2003). These effects may be due to one or more of the following: the influences of alcohol on metabolism; the antidiabetic properties of the element vanadium (for which wine is a significant source) (Brichard and Henquin, 1995; Teissèdre *et al.*, 1996); the hypoglycemic and hypolipidemic effects of phenolics such as resveratrol (Su *et al.*, 2006); or through some effect on endothelial nitric oxidase synthase (Leighton *et al.*, 2006). It appears there may be considerable specificity. For example, in a comparison between malvidin- and delphinidin-3-*O*-glucosides, only the predominant anthocyanin in grapes (malvidin) seems to have a significant hypoglycemic effect (Lida *et al.*, 2012).

Relative to diabetes mellitus (type 1 diabetes), moderate consumption of dry wine was found to present no adverse effects on sugar control (Gin *et al.*, 1992; Bell, 1996).

Goitre

In an epidemiological study, Knudsen *et al.* (2001) found a strong link between alcohol consumption and a reduced prevalence of goitre and solitary thyroid nodules. The origin of this apparent protective effect is unknown.

Kidney Stones

Drinking water has long been associated with reducing the development of kidney stones. Increased urine production is thought to limit calcium oxalate crystallization. What is new is the observation that wine consumption further reduces the production of these painful and dangerous inclusions (Curhan, 2007).

Cancer

Moderate amounts of alcoholic beverage consumption have been correlated with a reduced incidence in some cancers (see Bianchini and Vainio, 2004), but increased the risk for others, notably those of the throat and gastrointestinal tract (Ebeler and Weber, 1996; Parry *et al.*, 2011).

In certain instances, these influences may derive from the effects on carcinogens, such as ethyl carbamate. At the concentrations typically found in table wine, though, ethanol diminishes the carcinogenicity of ethyl carbamate. Certain wine phenolics can be protective, whereas others mutagenic, especially at high concentrations. For example, quercetin can induce mutations in laboratory tissue cultures, but is a potent anticarcinogen in whole-animal studies (Fazal *et al.*, 1990). This apparent anomaly may result from differences in the concentrations of quercetin used, and/or the low levels of metal ions and free oxygen found in the body (vs. tissue culture). In addition, quercetin, along with several other phenolics that are potential carcinogens, lose this attribute when present as a glycoside. Most phenolics in the plasma occur in some conjugated state, not as free phenolics. In addition, phenolics may detoxify the small quantities of nitrites commonly found in food. However, in the presence of high nitrite concentrations (a preservative found in smoked and pickled foods), nitrites are converted into diazophenols (Weisburger, 1991). These appear to favor the development of oral and stomach cancers.

Several phenolics can limit or prevent cancer development through a diversity of effects, such as DNA repair, carcinogen detoxification, enhanced apoptosis (programmed cell death), disrupted cell division (Hou, 2003; Aggarwal *et al.*, 2004), or enhanced immunostimulation (Tong *et al.*, 2011). For example, resveratrol induces the redistribution of the Fas receptor. It is a cellular attachment site for TNF (tumor necrosis factor). Its action is part of a sequence that can lead to cancer cell apoptosis (Delmas *et al.*, 2003). Resveratrol is also well known as an inhibitor of angiogenesis – the production of new vasculature essential for most tumor growth. Other effects of resveratrol include inhibition

of cyclooxygenase-2 (Subbaramaiah *et al.*, 1998) and P450 1A1 (Chun *et al.*, 1999). Cyclooxygenase-2 is thought to be involved in carcinogenesis, whereas P450 1A1is an important hydroxylase. It can convert several environmental toxicants and procarcinogens into active carcinogens.

Flavones and flavonols strongly restrict the action of common dietary carcinogens, notably heterocyclic amines (Kanazawa *et al.*, 1998). It is estimated that these compounds, produced during cooking, are consumed at a rate of approximately 0.4–16 μg per day (Wakabayashi *et al.*, 1992). The antiallergic and anti-inflammatory properties of flavonoid phenolics probably also contribute to the anticancer aspects of these flavonoids (see Middleton, 1998).

The major exception to the general benefit of moderate wine consumption may be breast cancer (Viel *et al.*, 1997). The correlation is more evident in those with the ADH1C*1 (fast metabolizers of ethanol to acetaldehyde, a known carcinogen) (Terry *et al.*, 2006). However, findings from the long-duration Framingham Study indicate no relationship between moderate alcohol consumption and the incidence of breast cancer (Zhang *et al.*, 1999). Ethanol, although not itself a carcinogen, can enhance the transforming effect of some carcinogens.

Another example of a negative effect of wine consumption, at least in excess of moderate intake, is to increase the incidence of mouth and throat cancers (Barra *et al.*, 1990).

Allergies and Hypersensitivity

Alcoholic beverages may induce a wide diversity of allergic and allergy-like reactions. In sensitive individuals, these may express as rhinitis, itching, facial swelling, headache, cough, or asthma. Occasionally, ethanol plays a role in these responses, for example the flushing reaction of many Asians. Nevertheless, sulfur dioxide is potentially the most significant wine irritant. Figure 12.8 illustrates the range of sulfur dioxide contents potentially found in Californian wine. A small proportion of wine-sensitive asthmatics may experience bronchial constriction on exposure to sulfite (Dahl *et al.*, 1986). In a study by Vally and Thompson (2001), wine containing 300 ppm sulfite induced a rapid drop in forced expiratory volume, reaching a maximal decline within about 5 min. Recovery took between 15 and 60 min. The same individuals did not respond to wine containing 20, 75, or 150 ppm sulfite. Why sensitive asthmatics episodically react to wines with low SO_2 contents may be related to changes in the state of their asthma control. Surprisingly, red wines appear to provoke more asthma problems than white wines, even though red wines typically have lower sulfur dioxide contents than white wines.

The rapidity of the reaction to sulfite suggests some malfunction in the amount of glutathione in lung tissue, or the activity of glutathione *S*-transferase in reducing sulfite to glutathione *S*-sulfonate. Normally, sulfite is rapidly converted to sulfate by sulfite oxidase

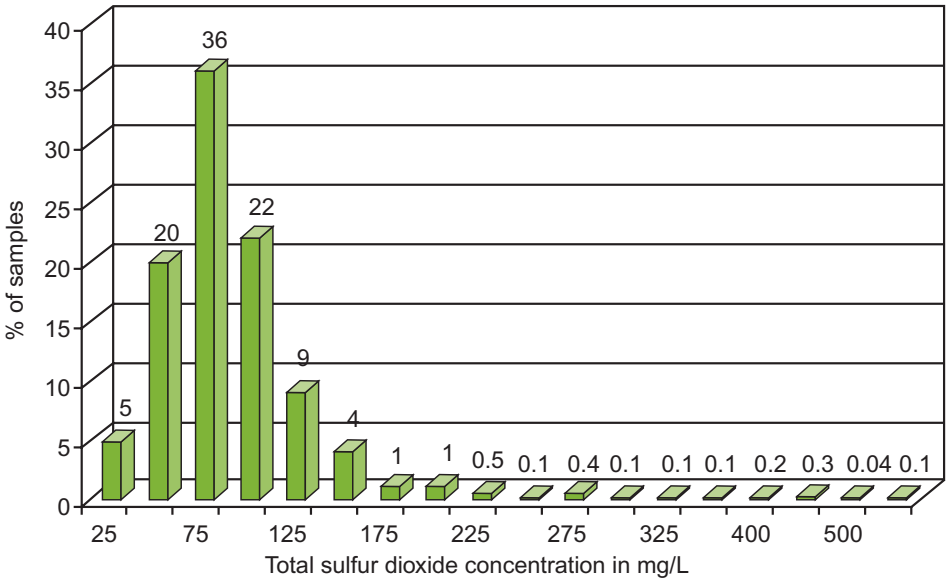

Figure 12.8 Total SO_2 concentration for Californian wines (mg/L). (Reprinted from Peterson, G.F., *et al.*, 2000, permission conveyed through Copyright Clearance Center.)

in the blood. However, low levels of this enzyme could permit sulfite to persist, provoking a heightened response in hypersensitive individuals.

At greater risk are individuals afflicted with a rare, autosomal, genetic disease, caused by a deficiency in sulfite oxidase (Shih *et al.*, 1977; Crawhall, 1985). Affected individuals must live on a very restricted diet, low in sulfur-containing proteins. It is estimated that the synthesis of sulfite, associated with normal food metabolism, generates approximately 2.4 g sulfite/day. The sulfites in wine contribute only marginally to this amount. Because of the gravity of sulfite oxidase deficiency, most affected individuals die before reaching adulthood.

A separate, allergy-like reaction, provokes rapid facial and neck flushing (cutaneous erythema). It develops shortly after alcohol consumption. Other symptoms often include peripheral vasodilation, elevated heart rate, nausea, abdominal discomfort, and broncho-constriction. The syndrome is associated with a malfunctional form of mitochondrial acetaldehyde dehydrogenase (ALDH2*2) (Enomoto *et al.*, 1991), and is particularly pronounced in the absence of at least one functional allele). ALDH2 is the principal enzyme oxidizing acetaldehyde to acetic acid. It is estimated that up to 50% of eastern Asians express this allergic-like reaction on alcohol consumption. It has been suggested that the *ALDH2* mutant, frequently found in eastern Asians, may reflect an evolutionary selective adaptation to the endemic occurrence of hepatitis B in the region (Lin and Cheng, 2002). The resulting avoidance of alcohol would avert any synergism between alcohol and hepatitis B-induced liver damage. A malfunctional alcohol dehydrogenase allele (*ADH2*) is also suspected to play a contributing role in flushing reactions (Eriksson *et al.*, 2001).

Elevated levels of acetaldehyde are thought to cause flushing by activating the localized release of histamine from mast cells. Histamine induces vasodilation and an associated influx of blood that appears as a reddening of the associated tissue. The connection between acetaldehyde and histamine is supported by the action of antihistamines in reducing the reaction, if taken in advance of an alcohol challenge (Miller *et al.*, 1988). An alternative proposal is that this flushing reaction results from a direct, cutaneous, alcohol-induced vasodilation. The phenomenon tends to be suppressed by acetylsalicylic acid (aspirin), if taken before an alcohol challenge (Truitt *et al.*, 1987). Facial flushing, concomitant with alcohol consumption, but devoid of other symptoms, is occasionally experienced by Caucasians. Whether this is related to an ALDH malfunction is unclear.

The onset of a similar collection of unpleasant symptoms, associated with the abnormal accumulation of plasma acetaldehyde, is often used in the treatment of alcoholism. Disulfiram (Antabuse) is a potent inhibitor of ALDH.

The histamine content of wine has frequently been thought to contribute to the severity of various allergy-like reactions. However, wine is low in histamine content. Figure 12.9 illustrates the range found in some wines. Thus, it seems unlikely that wine is a major

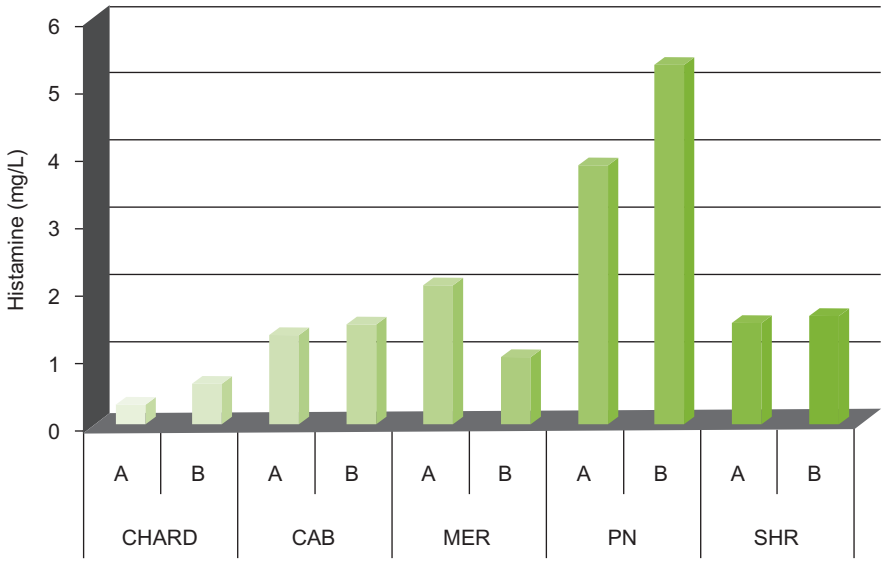

Figure 12.9 Comparison of mean histamine concentration in red and white Australian wines during a 27-year period. CHARD – Chardonnay, CAB – Cabernet Sauvignon, MER – Merlot, PN – Pinot noir, SHR – Shiraz; A – 1982–1990, B – 2003–2009 vintage sampling period. (From Bartowsky and Stockley, 2010, reproduced by permission.)

source of histamine-based problems. Other common foods are much higher in histamine content, for example cheeses. Nonetheless, wine could provoke increased sensitivity. This may explain the benefit of antihistamines in diminishing the rhinitis occasionally associated with wine consumption (Andersson *et al.*, 2003). In addition, antihistamines counteract the broncho constriction in individuals showing histamine intolerance. Histamine intolerance presumably relates to reduced activity of diamine oxidase (Wantke *et al.*, 1996).

Idiopathic allergic and other immune hypersensitive responses to wine are difficult to predict or diagnose. Reactions may include the induction of headaches, nausea, vomiting, general malaise, or a combination of these. In a few instances, IgE-related anaphylaxis reactions have been reported to grape PR proteins (endochitinase and thaumatin) (Pastorello *et al.*, 2003). The effects may involve urticaria/angioedema (red patches or wheals on the skin/swelling), and occasionally shock. Residual amounts of fining agents, such as egg whites, have also been implicated in some allergic reactions (Marinkovich, 1982). In a double-blind, placebo-controlled trial, wines fined with egg white, isinglass, or non-grape derived tannins presented 'an extremely low risk of anaphylaxis' to egg-, fish-, or peanut-allergic consumers (Rolland *et al.*, 2006). In an ELISA study, only egg white and lysozyme could be detected in wine samples (Weber *et al.*, 2007). Nevertheless, with more than 1000 compounds potentially occurring in wine, it is not surprising that some individuals may occasionally show some form of adverse reaction to specific wines or wine types.

In addition to physiological reactions to wine constituents, there is a wide range of equally important psychological responses (Rozin and Tuorila, 1993), both positive and negative. Traumatic memories, associated with the first exposure to, or excessive consumption of, a particular beverage can create an association that lasts a lifetime. Other people have come to associate certain products with social groups, lifestyles, or behaviors. Such attitudes can make the beverage either unacceptable, or desirable, as the case may be.

Headaches

People occasionally avoid wine because it induces headaches. Regrettably, the wine/headache connection has been little studied. Central to any progress, though, is effective differentiation of the multiplicity of headache syndromes relative to their distinctive etiologies.

One of the most severe headache syndromes, potentially associated with wine consumption, is the migraine. Migraines appear to be induced by a wide range of environmental stimuli, possibly because migraines themselves have a complex etiology. The dilation of cerebral blood vessels, partially as a result of histamine release, appears to be a common element in many headache syndromes. Migraines may be one of them, although current thought suggests a neurological rather than a vascular origin. When red vs. white wines were discovered to contain higher concentrations of biogenic amines, such as histamine and tyramine, there was the initial assumption that they were the culprits. However, it was later realized that the normal levels of histamine in red wines are below those that generally trigger a migraine. In addition, double-blind studies have seemingly exonerated histamine in most red-wine-induced migraine headaches (Masyczek and Ough, 1983). Nevertheless, alcohol can suppress the action of diamine oxidase, an important enzyme in the small intestine that inactivates histamine, and other biogenic amines (Jarisch and Wantke, 1996). Thus, in individuals with histamine intolerance, sufficient histamine may enter the blood system to provoke a vascular headache or unrelated allergy-like symptoms. However, this view does not correlate with the observation that spirits and sparkling wine are more frequently associated with migraine attacks than table wines (white or red) or beer (Nicolodi and Sicuteri, 1999). Both spirits and sparkling wines are low in histamine content. However, both are more likely to be taken alone, possibly on an empty stomach, leading to more rapid and higher spikes in blood alcohol content.

Although the biogenic amine content of wine appears to be insufficient to cause migraines in most individuals, the phenolic content of wine might explain why red wines are more frequently associated with a variety of headache sequelae than white wines. On average, red wines contain about 1200 mg/liter phenolics, vs. 200 mg/liter for white wines. Some, but not all, phenolics suppress the action of platelet phenolsulfotransferase (PST) (Jones *et al.*, 1995; Yeh and Yen, 2003). It is an important detoxifier of phenolics and amines. Distinct isozymic versions, PST-M and PST-P, preferentially catalyze the sulfation (detoxification) of various endogenous and xenobiotic biogenic amines and phenolics. Individuals having low levels of platelet-bound PST-P are apparently more susceptible to migraine headaches (Alam *et al.*, 1997). Small phenolic compounds can prolong the action of potent hormones and nerve transmitters, such as histamine, serotonin, dopamine, adrenalin, and noradrenaline. Biogenic amines activate the liberation of 5-hydroxytryptamine (5-HT, serotonin), an important brain neurotransmitter. It also promotes platelet aggregation and blood vessel dilation. An increase in intercranial pressure may be involved in the perception of pain in a migraine attack

(Pattichis *et al.*, 1995). Nonetheless, most research suggests alternate associations between histamine and migraines. People prone to migraine headaches may also show abnormal and cyclical patterns in platelet sensitivity to 5-HT release (Jones *et al.*, 1982; Peatfield *et al.*, 1995). This may explain why wine consumption is not consistently linked to migraine induction.

In the treatment of the possibly, closely related cluster-headache syndrome, small doses of lithium have been suggested as preventive (Steiner *et al.*, 1997). Because some red wines have a higher than average lithium content, the possibility exists that they might limit the development of, rather than induce, this type of headache.

Another recognized headache syndrome is the red wine headache (Kaufman, 1986). It may develop within minutes of consuming red wine and is often dose-related. The headache reaches its first peak within approximately 2 hours, tends to fade, but returns roughly 8 hours later, in a more intense form. The headache seems related to the release of type E prostaglandins, important chemicals involved in dilating blood vessels. If this association is correct, the inhibition of prostaglandin synthesis by acetylsalicylic acid, acetaminophen, or ibuprofen could explain why they can prevent headache development, when taken prior to wine consumption (Kaufman, 1992).

A distinct wine-related headache has been dubbed the red head (Goldberg, 1981). It develops within an hour of waking, after drinking no more than two glasses of red wine the previous evening. The headache, associated with nausea, is particularly severe when reclining. Although the headache is somewhat relieved by standing, it itself exacerbates the nausea. The headache usually lasts a few hours before dissipating. A similar phenomenon has been reported with some white wines, or mixtures of white wine, taken alone or with coffee or chocolates. Its chemical cause is unknown (Kaufman, 1986).

In most instances, headaches associated with wine consumption are assumed to be induced by tannins. However, they are poorly absorbed in the upper digestive tract. In contrast, monomeric phenolics, such as caffeic acid and catechins are readily absorbed, potentially inciting headaches. This may explain why aged red wines (in which most tannins occur as large polymers) tend to be less associated with headache induction than their younger versions. A classic example is the ease with which the youngest of all red wines, Beaujolais nouveau, produces headaches in those prone to their occurrence. Large tannin polymers remain largely unmodified until entering the colon, where bacteria metabolize them to low-molecular-weight phenolics (Déprez *et al.*, 2000). Because this can take up to 2 days, they presumably are not (or not recognized to be) involved in wine-induced headache initiation.

Depending on phenolic metabolism in the plasma, phenolics may be detoxified (*o*-methylated or sulfated), or made more 'toxic' (oxidized to *o*-quinones). *O*-quinones can inhibit the action of the catechol-*O*-methyltransferase (COMT). By so doing, the breakdown of the neurotransmitter dopamine is retarded, and the availability of μ-opinoid (painkilling) receptors is restricted. Consequently, the perception of pain, associated with cerebral blood vessel dilation, may be exacerbated. Trigeminal nerves in the meninges, structures that cover the brain and its outer blood vessels, can transmit pain signals that connect to the sensory cortex.

Resveratrol, a phenolic found in higher concentration in red than white wines, inhibits the expression of cyclooxygenases. These are involved in the synthesis of prostaglandins (Jang and Pezzuto, 1998), dilators of cerebral blood vessels. This is another example of where some wine phenolics may counter, rather than induce headache development. In contrast, ethanol tends to elevate the concentration of prostaglandins (Parantainen, 1983).

The ability of some yeast strains to produce prostaglandins (Botha *et al.*, 1992) introduces the intriguing possibility that they may occur as wine constituents. If produced in sufficient quantity, yeast-derived prostaglandins could be another, or supplemental agent, involved in headache development. Yeast-derived prostaglandins could also theoretically provoke inflammatory lung problems such as asthma.

Although red wines are generally more associated with headache production than white wine, some headaches are exclusively associated with white table wines. Its characteristics and etiology are even less well understood than those evoked by red wines. In some individuals, this situation may be associated with a sensitivity to sulfites, which are generally found in higher concentrations in white than red wines, especially when young.

One of the most recognized alcohol-related headache phenomena is that associated with binge drinking – the hangover (veisalgia) (Wiese *et al.*, 2000). Although not consistently associated with a headache, it is frequently part of the sequelae. Hangovers are characterized by tremulousness, palpitations, tachycardia, sweating, loss of appetite, anxiety, nausea, and possibly vomiting and amnesia. When accompanied with a headache, it possesses symptoms similar to a migraine. The headache is global, but frequently concentrated anteriorly, and associated with heavy, pulse-synchronous throbbing. It usually starts a few (>3) hours after the cessation of drinking, when the blood alcohol level is declining

and other hangover symptoms have already developed (Sjaastad and Bakketeig, 2004). Duration is seldom more than 12 hours.

Despite its all-too-frequent occurrence, the causal mechanism(s) remains unclear. Various compounds have been implicated, notably ethanol (and its primary breakdown products, acetaldehyde and acetic acid), methanol (through its metabolic by-products, formaldehyde and formic acid), and various congeners. None of these has been adequately established as individually or collectively being the principal causal agent(s), but undoubtedly are involved.

Despite the absence of clear causal relationships, ethanol is typically viewed as the principal perpetrator. This view is supported by the physiologic effect of ethanol on the pituitary gland. Ethanol limits production of the hormone vasopressin. The result is a reduction in water reabsorption by the kidneys (increased urination), resulting in partial tissue dehydration. Contraction of the membranes covering the brain (the meninges) could pull on fibers attaching the outer most layer (dura mater) to the skull, causing pain sensors to discharge. Alternatively, the diuretic effect of ethanol could result in electrolytic imbalance. The resultant disruption of normal nerve and muscle function could theoretically induce symptoms such as headache, nausea, and fatigue. Ethanol can also induce the breakdown of glycogen in the liver. The resulting influx of glucose, on being eliminated in the urine, could produce hypoglycemia and a feeling of weakness. Finally, the breakdown of ethanol, via the hepatic microsomal pathway, increases the release of free radicals in the blood, causing cellular damage and a diverse range of metabolic disruptions. An old Spanish proverb notes that:

Wine hath drowned more men than the sea.

Because glutathione is important in the inactivation of free radicals, taking an amino acid supplement, *N*-acetyl-cysteine (NAC), has been suggested as a partial remedy. NAC is rich in cysteine, an amino acid that forms the core of glutathione. In addition, glutathione facilitates the conversion of acetaldehyde to acetic acid and subsequent metabolism, as well as binding with acetaldehyde. Acetaldehyde can disrupt membrane function (partially by interfering with the action of cytochrome P-450 oxidase), and consequently cerebral neurotransmitter action. This is presumably the rationale for commercial products such as Hangover Helper™ and Rebound™. They are designed to counter the effects of acetaldehyde.

In addition, congeners (such as fusel alcohols and methanol) may exacerbate the effects of ethanol and acetaldehyde. The methanol content of wine is typically low, and its metabolism slow. Eventually, though, it is converted by ADH to formaldehyde, and subsequently formic acid. Its potential for concentration in distilled beverages might enhance methanol's involvement in hangovers associated with these beverages. The product Chaser™ has been developed as a means of limiting the uptake of such congeners. Its formulation, a combination of activated calcium carbonate and vegetable carbon, is thought to bind congeners in the stomach, preventing their uptake by the blood.

Hangovers have also been associated with deregulation of cytokine pathways (Kim *et al.*, 2003), as well as increased levels of C-reactive protein in the plasma (Wiese *et al.*, 2004).

Some purported remedies, such as artichoke extract, have not stood up to rigorous clinical testing (Pittler *et al.*, 2003), but others, such as an extract from *Opuntia fiscus-indica* (Prickly Pear), apparently reduce the severity of some hangover symptoms (Wiese *et al.*, 2004). It is thought to work as an inflammatory mediator. Pyritinol (a vitamin B_6 derivative) has also been reported to reduce some hangover symptoms (Khan *et al.*, 1973).

Regrettably, for suffers, there is no known universally effective treatment for a hangover. Although time is the only sure cure, avoidance of overindulgence is the only assured prophylactic.

Taking wine with meals is probably the best known and reliable preventative, combined with limited consumption. Food delays the movement of alcohol into the intestinal tract. Because uptake is slowed, there is more chance that absorption may match the body's ability to metabolize ethanol. In addition, delayed transfer to the intestinal tract could slow the uptake of phenolic compounds, and other potential provocateurs, diminishing their maximal concentration in the blood.

Dental Erosion

Wine tasting is not normally considered hazardous to one's health. However, recent studies have found that dental erosion can be a risk (Mok *et al.*, 2001; Mandel, 2005; Chikte *et al.*, 2005). Damage results from the frequent and extended exposure to wine acids. Removal of calcium softens the enamel, which becomes susceptible to erosion by masticatory forces and tooth brushing. Demineralization commences at about pH 5.7. Dental erosion is not a problem for the typical consumer, who takes wine with meals. Food and saliva secretion limit, if not prevent, demineralization of tooth enamel. However, after many years, professional wine tasters may experience tooth disfiguration, affecting both tooth shape and size. Cupping, a depression in the enamel, exposing dentine at the tip of molar cusps, is a frequent clinical sign. Erosion can also contribute to severe root abrasion at the gum line. Protection is

partially achieved by rinsing the mouth with an alkaline mouthwash after tasting, application of a fluoride gel (such as APF), and refraining from tooth brushing for at least one hour after tasting. The delay permits minerals in the saliva to rebind with enamel. For more protective protocols see Ranjitkar *et al.* (2012).

In contrast to this risk factor, consuming red wine may have some direct oral benefits. Proanthocyanidins in wine can limit the adherence and biofilm-forming activity of caries-inducing *Streptococcus mutans* (Daglia *et al.*, 2010). Gibbons (2013) provides a fascinating insight into the association of this bacterium with changes in human diet which resulted from a switch from a hunter-gather to an agriculture lifestyle. Mark Twain also made pronouncements about dental health, which might be equally applied to wine:

> *"I always take it (Scotch whiskey) at night as a preventive of toothache. I have never had the toothache; and what is more, I never intend to have it," from* Europe and Elsewhere

Fetal Alcohol Syndrome

Fetal alcohol syndrome (FAS) refers to a set of phenomena including suppressed growth, mild mental retardation, and subtle facial abnormalities (Wattendorf and Muenke, 2005). It was first described in 1973, and appeared most markedly in the children of alcoholic mothers. They tended also to be heavy smokers, users of illicit drugs, consumers of large amounts of coffee, had poor nutrition, or showed a combination of these (see Scholten, 1982; Whitten, 1996). It is suspected that alcohol is the principal cause, although the concentration and timing associated with FAS are still uncertain. Acetaldehyde accumulation may also be involved, as well as other environmental factors.

In addition, even more subtle effects have now been detected, giving rise to the acronym FASD (fetal alcohol spectrum disorders). Because the consequences may be lifelong, it is generally recommended that pregnant women, or women wishing to become pregnant, refrain from alcohol consumption during this period. Whether total abstinence is warranted is unknown, but erring on the side of caution is judicious. Individual sensitivity to FASD expression is unknown in advance. This also applies to breastfeeding; it too could detrimentally affect infant development.

Toxins

The presence of toxins in wine is seldom mentioned, outside academic circles, presumably because of their minimal presence. The only mycotoxin for which there may be regular analysis is ochratoxin A (O'Brien and Dietrich, 2005; Varga and Kozakiewicz, 2006). Other potential mycotoxins that could occur in wine include isofumigaclavine, festuclavine, roquefortine, all produced by *Penicillium* spp. (Moller *et al.*, 1997); fumonisins by *Aspergillus niger* (Mogensen *et al.*, 2010), and trichothecenes by *Trichothecium roseum* (Schwenk *et al.*, 1989). Because these fungi are secondary saprophytes, they typically occur only on rotted grapes (thankfully, not those noble-rotted). Although the exclusion of all rotted grapes is essentially impossible, their inclusion is limited as much as feasibly possible. Otherwise, the sensory quality of the wine is likely to be debased.

Pesticide residues are other potential toxins that could be present in wine. Their levels are usually below those known to be toxic to humans, due to: regulations limiting their use and last application prior to harvesting; precipitation or metabolism during winemaking; or loss and degradation during maturation. In addition, most importing countries possess regulations on permissible levels and systems to check for compliance.

Methanol is present, but in amounts insufficient to have any known negative consequences. The same also appears to be true for diacetyl and other potentially toxic compounds. In concentrations well above those found in wine, diacetyl can form covalent adducts with guanosine, uncoil DNA, and induce apoptosis (More *et al.*, 2012).

It may initially be disconcerting to think of trace amounts of toxins in wine, but this situation applies to all food, water, and air. Xenobiotics are an inescapable aspect of life, both modern and ancient. Their universal presence in the natural environment presumably provided the selective pressures that favored the evolution of organs, such as the liver and kidney, and the presence of multiple detoxifying enzyme systems in animals. Thankfully, our bodies inactivate most xenobiotics rapidly and effectively, without our conscious knowledge. In addition, governmental agencies set regulations and assess compliance to limit the better-known toxicants to well below known safe limits. As long as exposure to toxicants is kept to a bare minimum, consumers can basically forget they exist. Overreaction to one source of toxicant can give rise to a unjustified faith that none is present.

Contraindications

The most important wine contraindication relates to those with a past history of alcohol abuse. For the majority of adults (except pregnant women), moderate wine consumption appears to have significant health benefits.

Nevertheless, there are several situations in which wine consumption, even in moderate amounts, can complicate or diminish the effectiveness of disease treatment.

1. The acidic nature of wine can aggravate inflammation and slow the healing of ulcers in the mouth, throat, stomach, and intestinal tract. Other constituents in wine may also be detrimental in this regard. Thus, all beverages containing alcohol are usually contraindicated in cases of gastritis, gastric cancer, and bleeding in the upper digestive tract. Nevertheless, the prophylactic action of red wine against *Helicobacter pylori*, and the suppression of histamine production by the gastric mucosa (Masquelier, 1986) may require a reconsideration of the old prohibition in mild cases. In the presence of pancreatitis, alcohol is absolutely contraindicated.
2. Wine, along with other alcoholic beverages, may provoke gastroesophageal (acid) reflux in individuals prone to this syndrome.
3. In liver disease, the consumption of wine is normally contraindicated. The presence of alcohol puts additional stress on an already weakened vital organ. Chronic alcohol abuse can lead to cirrhosis of the liver.
4. In acute kidney infection, wine should be avoided. The consumption of alcohol increases the burden on an organ essential to eliminating toxic metabolic wastes.
5. In prostatitis or genitourinary infections, the consumption of alcohol can complicate matters. The diuretic action of wine may increase the frequency of urination or, conversely, it may induce highly painful urinary retention.
6. In epilepsy, the consumption of even moderate amounts of wine may increase the frequency of seizures.
7. Consumption should be strictly limited in most situations of hypertension, hemorrhagic stroke, or atrial fibrillation.
8. In patients about to undergo surgery, the effect of alcohol on reducing platelet aggregation is undesirable. Thus, it is recommended that patients terminate any alcohol (as well as aspirin) consumption well before surgery. This avoids increasing any tendency to enhance intra- and postoperative bleeding (Wolfort *et al.*, 1996).

The consumption of alcohol is also ill advised when eating certain mushrooms. The most well-known example is the antabuse reaction associated with consumption of alcohol with *Coprinus atramentarius* (Inky Cap). Another mushroom generating the same response is *Boletus luridus* (Budmiger and Kocher, 1982). The antabuse reaction derives its name from the trade name of disulfiram, a medication used in the treatment of alcoholism. It functions as an inhibitor of acetaldehyde dehydrogenase. Even when small amounts of alcohol are consumed, along with disulfiram, a very unnerving reaction follows. These may include flushing, sweating, weakness, vertigo, blurred vision, difficulty breathing, nausea, chest pain, palpitation, and tachycardia. In severe cases, the reaction can provoke acute congestive heart failure, convulsion, and death. Simultaneous consumption of alcoholic beverages while using certain drugs (e.g., cephalosporins, griseofulvin, chloramphenicol, sulfonylurea, metronidazole) can produce similar symptoms in sensitive individuals.

Wine and Medications

In addition to the antabuse reaction just noted, simultaneous consumption of alcohol with certain medications can generate various unpleasant to dangerous reactions. Regrettably, most of the literature relating to alcohol–drug interactions comes from studies on alcoholics or binge drinkers. This limits the potential applicability of the data from such studies to conditions of moderate consumption and when taken with meals. Nevertheless, even small amounts of alcohol may cause loss of muscle control in people taking tricyclic antidepressants. In addition, red wines can reduce the effectiveness of MAO (monoamine oxidase) inhibitors, used in controlling hypertension. The long-term use of acetaminophen can enhance alcohol-induced kidney damage.

Other contraindications involve the intensification of the effects of barbiturates and narcotics. In combination with certain antidiabetic agents, such as tolbutamide and chlorpropamide, alcohol can cause dizziness, hot flushes, and nausea. Mild reactions may occur with a wide range of other medications, such as sulfanilamide, isoniazid, and aminopyrine. Additional details may be found in Adams (1995), Fraser (1997), and Weathermon and Crabb (1999).

In conclusion, it seems best to let Samuel Clemens' wisdom, relative to health and aging, have the last word:

> *"The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd druther not."* Mark Twain *in* Following the Equator.

Suggested Reading

Wine and Food

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