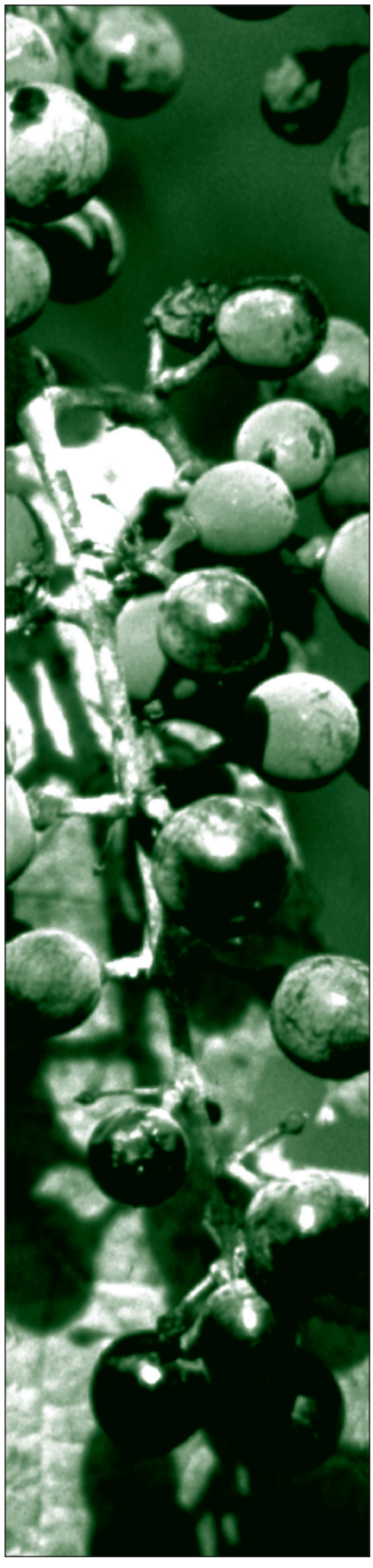
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Wine and Health

Introduction

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. Excessive 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). Because the problems associated with alcoholism (Abrams *et al.*, 1987; Schmitz and Gray, 1998), and the cerebral chemical changes associated with addiction (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 (250–300 ml/day – about one-third of a 750-ml bottle) has distinct health benefits. Multiple epidemiological studies suggest that daily, moderate, alcohol consumption (Thun *et al*., 1997; Doll *et al*., 2005), and especially wine (Grønbæk *et al*., 2000; Renaud *et al*., 2004) is associated with a reduction in all-cause mortality. This is expressed in a U-shaped curve, with increased 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 reduces the frequency of certain cancers and several other diseases. These epidemiological correlations are being supported by *in vivo* studies that provide molecular explanations for these associations. The principal element missing in confirming a causal relationship involves detailed information on the dynamics of absorption, metabolism, and elimination of the proposed active ingredients.

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 are less likely to show those alcohol-related problems that have given alcohol a bad reputation (Smart and Walsh, 1999). In addition, wine has a higher social image than other alcoholic beverages (Klein and Pittman, 1990).

The use of wine as a medicine, or as a carrier for medications, has a long history. It goes back at least to the ancient Egyptians (Lucia, 1963). Ancient Greek and Roman society used wine extensively in 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 evil. Alcoholism is now appropriately viewed as a genuine disease, possessing a complex etiology (Nurnberger and Bierut, 2007), with both genetic and environmental aspects. Thus, the social climate is changing, and the legitimate use of wine in medicine and health is being investigated seriously.

Nevertheless, it is unlikely that doctors will soon be prescribing wine for its health benefits. Too often, people have a difficulty recognizing the limits of rational use. Even dietary flavonoid supplements (one of the benefits of wine consumption) may be detrimental if taken in excess (Skibola and Smith, 2003).

Metabolism of Alcohol

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, including humans.

In humans, ethanol enters the bloodstream either via the consumption of beverages containing alcohol, 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 flow. Most of the blood supply from the digestive tract passes through the liver before dispersing to the rest of the body.

The liver metabolizes about 95% of alcohol in the plasma, at about 15 ml/h. The rest of the alcohol 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, 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. The acetic acid may be released into the blood or converted to acetyl CoA. From this point, metabolism may flow along any of the standard biochemical pathways (Fig. 7.15).

As noted, 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 that oxidizes ethanol slowly, whereas *ADH1B*3* encodes for a highly active version (about 30 times more efficient) (Thomasson *et al*., 1995). These allelic variants are common among African Americans. Fast and slow acting isozymes of ADH1C are common in Europeans. Rapid alcohol oxidation may donate a degree of protection against alcoholism, by quickly converting ethanol to acetaldehyde. Such individuals tend to drink less and show more rapid and marked negative consequences to alcohol consumption than do those metabolizing alcohol more slowly (Wall *et al*., 2005). However, this probably reduces some of the health benefits of ethanol consumption. The effect of mutants of mitochondrial acetaldehyde dehydrogenase gene (*ALDH2*) is discussed below.

A second metabolic routing of ethanol metabolism occurs only when the blood alcohol concentration is

high. It entails an inducible pathway involving microsomal cytochrome P4502E1. It 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 (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 by alcohol dehydrogenase.

The metabolism of ethanol to acetate (acetic acid) has the advantage that tissue cells can regulate its transport. This is not true for ethanol, which can diffuse freely across cellular membranes. Control of transport is central to proper cellular function.

Physiological Actions

The ability of ethanol to displace water, and its unregulated passage cross cell membranes, explains much of alcohol's cytoplasmic toxicity. In addition, its oxidation to acetaldehyde is more rapid than the subsequent 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. Differentiating between the 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 higher brain function. This is most noticeable in enhanced sociability – by blocking social inhibitions. For others, it quickly induces drowsiness (Stone, 1980). This probably explains why taking a small amount of wine (90–180 ml) before bed often helps people, notably the elderly, suffering from insomnia (Kastenbaum, 1982). Half a glass of wine provides the benefits of sleep induction, without causing 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 diuretic effect frequently 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 often associated with excessive alcohol intake.

In addition to the direct effects of ethanol, the accumulation of acetaldehyde may have several undesirable consequences. It may be involved in much of the chronic damage associated with alcoholism. At low rates of alcohol intake, acetaldehyde metabolism is sufficiently rapid to limit its accumulation and liberation from the liver. At higher concentrations, acetaldehyde rapidly consumes glutathione reserves in the liver – an crucial 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 generate 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 their rigidity. By limiting their ability to squeeze through the narrowest capillaries, oxygen supply to tissue cells may be restricted. This could participate in suppressed brain function. Nerve cells show only respiratory (oxygen-dependent) metabolism. It is estimated that the brain consumes up to 20% of the blood's oxygen supply.

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

Food Value

Wine's major nutritional value comes from the rapidly metabolized, caloric value of its ethanol content. Alcohol does not need to be digested, and can be absorbed directly through the intestinal wall. In rural viticultural areas, wine historically functioned as a major source of metabolic energy for the adult population. Wine in those regions was a food.

Wine contains small quantities of several vitamins, notably the 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. The phenolic (Hyde and Pangborn, 1978) and alcohol (Martin and Pangborn, 1971) contents of wine activate the release of saliva. In addition, wine promotes the release of gastrin as well as gastric juices. Succinic acid is the principal wine ingredient activating the release of gastric juices (Teyssen *et al*., 1999). 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. It also promotes inactivation of pathogenic food contaminants. 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 the release of bile in the intestines. Wine acids and aromatics also induce 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.

Despite the general beneficial effects of alcohol on digestion, the phenolic content of red wine may retard digestion. For example, tannins and phenolic acids interfere with the action of certain digestive enzymes, such as α-amylase, lipase and trypsin (Rohn *et al*., 2002). Digestion may be further delayed by polymerization between tannins and food proteins. Although potentially delaying digestion in the small intestine, it continues in the colon. In contrast, some phenolics, such as quercetin, resveratrol, catechin, and epigallocatechin gallate, promote pepsin-activated protein breakdown (Tagliazucchi *et al*., 2005).

The phenolic content of wine also decreases the intestinal absorption of iron and copper. Although this may be undesirable by limiting the bioavailability of iron under deficiency conditions, it has the benefit of reducing the formation of toxic lipid hydroperoxides during digestion in the intestines. The antioxidant effect of polyphenolics also applies to hydroperoxide generated in the stomach (Kanner and Lapidot, 2001).

Wine also has a cultural/psychologic effect on digestion. The association of wine with refined eating promotes slower food consumption, permitting biofeedback mechanisms to induce satiety and 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 improved appetite of many elderly and anorectic patients when wine is taken with the meal is unknown.

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 on *Helicobacterium pylori* (Fugelsang and Muller, 1996). *H. pylori* is considered the primary cause of stomach ulceration. Moderate wine consumption appears have a prophylactic effect limiting ulcer initiation (Brenner *et al*., 1997). The bacterium is also implicated in gastritis, vitamin B_{12} malabsorption, and gastric adenocarcinoma.

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

Finally, consuming wine with food slows the rate of alcohol uptake in the blood (Fig. 12.1). In the absence of food, about 80% of alcohol absorption occurs through the intestinal wall. This value increases in the presence of food. By retarding gastric emptying, food consumption slows the transfer of alcohol into the intestine. This extends the period over which the liver can metabolize ethanol. The result is a reduction in the maximal alcohol content reached in the blood. However, taking sparkling wine on an empty stomach increases short-term alcohol uptake by about 35% (Ridout *et al*., 2003). Although the cause of the difference is unknown, it is suspected that carbon dioxide relaxes the pyloric sphincter,

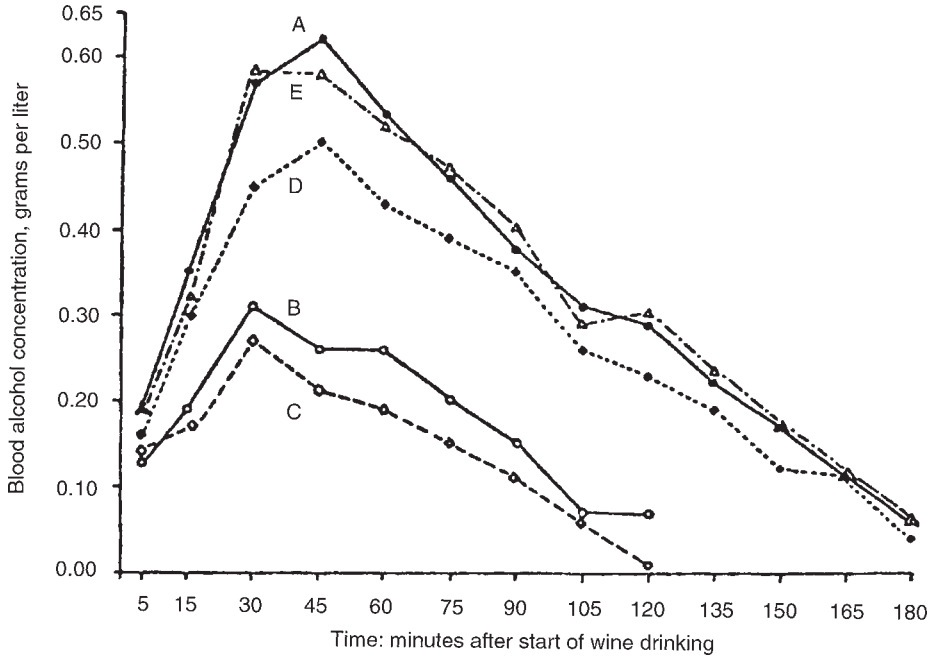

Figure 12.1 Blood alcohol concentrations after wine drinking in a single dose. A, fasting; B, during a meal; C, 2 hours after a meal; D, 4 hours after a meal; E, 6 hours after a meal. (From Serianni *et al.*, 1953, reproduced by permission)

allowing earlier transfer of fluids from the stomach into the duodenum.

The rate of alcohol metabolism differs considerably among individuals, with rates commonly varying between 90 and 130 mg/kg/h. The hormonal and nutritional state of the individual can affect the rate of ethanol metabolism.

Phenolic Bioavailability

To fully understand the significance of wine phenolics to health, it will be necessary to know the dynamics of their uptake, concentration, metabolism, and elimination. Such data are just now starting to become available.

In the mouth, mid-sized flavonoid polymers often bond 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. Nevertheless, flavonoids such as anthocyanins 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, polymers tend to remain in the intestine until degraded by bacteria in the colon (Scalbert *et al.*, 2002). A small portion of their breakdown products, primarily phenolic acids, are subsequently absorbed into the blood via the colon (Ward *et al.*, 2004).

Studies on the bioavailability of flavonoids in the blood are in their infancy (Williamson and Manach, 2005). Although many flavonoids are quickly absorbed into the plasma, most appear to be rapidly conjugated – being methylated, sulfated, transformed to glucuronsides, or otherwise metabolized (see Williams *et al.*, 2004). These transformations could significantly affect their antioxidant and other properties, as well as their ability to move into tissues. Most of these metabolites still retain a reducing phenolic group, and, thus, may 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). Smaller amounts of chemical are needed for signaling reactions, than direct antioxidant effects. This might explain the discrepancy between the low levels of free phenolics in the plasma and their apparent effects in the body. Future studies will have to investigate the efficacy of phenolic metabolites and conjugated complexes, at concentrations found in the plasma. Their efficacy at binding to, or translocation into tissue cells, is little known. Survival of most of these constituents in the plasma is

comparatively short (a few hours). Breakdown products of phenolic metabolism rapidly appear in urine shortly after uptake in the plasma.

Presence in the plasma probably permits their diffusion into most body tissues. This does not 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 exists due to tight connections between the endothelial cells that makeup the lining of cerebral capillaries. This prevents the diffusion of molecules between vascular endothelial cells that is typical elsewhere in the body. However, with anthocyanins (Passamonti *et al*., 2005) and simple flavonols (Youdim *et al*., 2004), access to the brain occurs within minutes of consumption.

Antimicrobial Effects

The prophylactic action of wine against gastrointestinal infections has been known for millennia, long before the microbial nature of infectious diseases was suspected. This action is complex and not fully understood.

The antimicrobial effect of alcohol was discovered in the late 1800s. Nevertheless, alcohol is not particularly antimicrobial at the concentrations found in wine (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 commonly found in red wines are also bacteriostatic and fungistatic. For example, *p*-coumaric acid is particularly active against gram-positive bacteria, such as *Staphylococcus* and *Streptococcus*, whereas other phenols inhibit gram-negative bacteria, for example *Escherichia*, *Shigella*, *Proteus*, and *Vibrio* (Masquelier, 1988). The latter cause serious forms of diarrhea and dysentery. Despite wine being more effective than antimicrobial agents, such as bismuth salicylate (Weisse *et al*., 1995), full action may take several hours (Møretrø and Daeschel, 2004; Dolara *et al*., 2005). 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. The low pH and presence of various organic acids appear to accentuate the antimicrobial action of both wine phenolics and ethanol. It is not without good reason that Roman armies added wine or vinegar to their drinking water. Diarrhetic soldiers do not win wars.

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 12.2 provides an example of such results. Alcohol consumption also decreases 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 the results (for example, 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 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 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. 12.3). Although associated with several independent factors, most damage develops as a result of the oxidation of lipids in a special subgroup of cholesterol–apoproteins complexes, the low-density lipoproteins (LDLs). Because of the hydrophobic nature of cholesterol and triglycerides, their transfer via the blood requires a special transport vehicle. As illustrated in Fig. 12.4, 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.

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 form, lipids are cytotoxic and indirectly

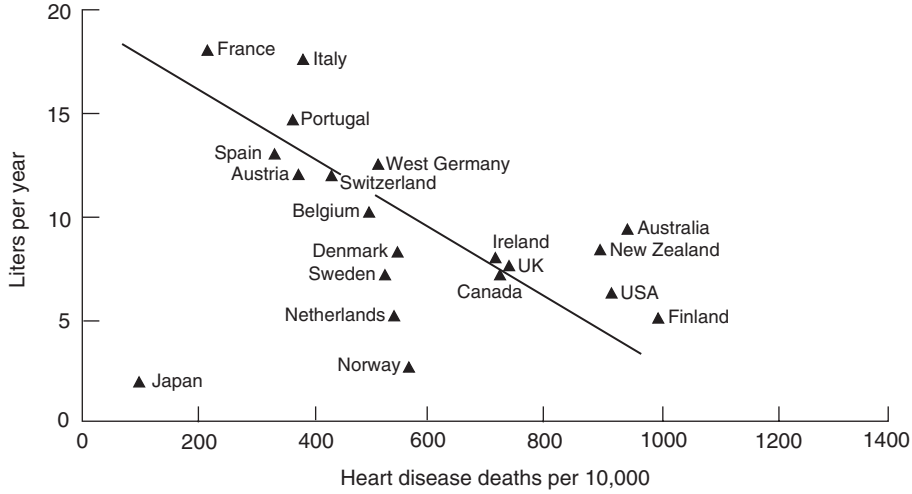

Figure 12.2 Relationship of per capita alcohol consumption with 1972 heart disease death rates in men aged 55–64 in 20 countries. (From La Porte *et al.*, 1980, reproduced by permission)

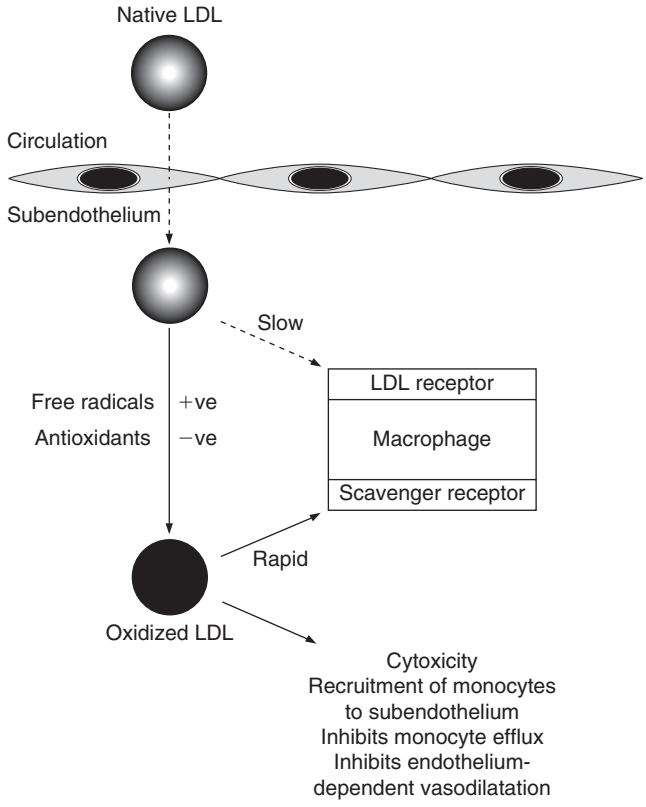

Figure 12.3 The oxidative-modification hypothesis of arteriosclerosis. (From Maxwell, 1997, reproduced by permission)

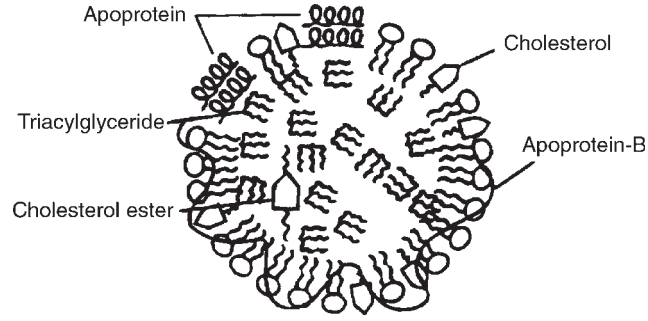

Figure 12.4 General structure of a triglyceride-rich lipoprotein. (From Walzem and Hansen, 1996, reproduced by permission)

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), monocytes mature into macrophages. Both macrophages and T-cells may release 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 enlarge inward, but more frequently they bulge 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 enlargement of the plaque. 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 the 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. Either form tends to remove cholesterol from the arteries, transferring it to the liver for metabolism. HDLs also appear to interfere with LDL oxidation. The effect of ethanol on HDL concentration appears to be independent of beverage type (van der Gaag *et al*., 2001). The slower the rate of LDL turnover, the greater the likelihood of oxidation (Walzem *et al*., 1995).

The beneficial effect of moderate alcohol consumption on the HDL/LDL ratio is now 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.

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

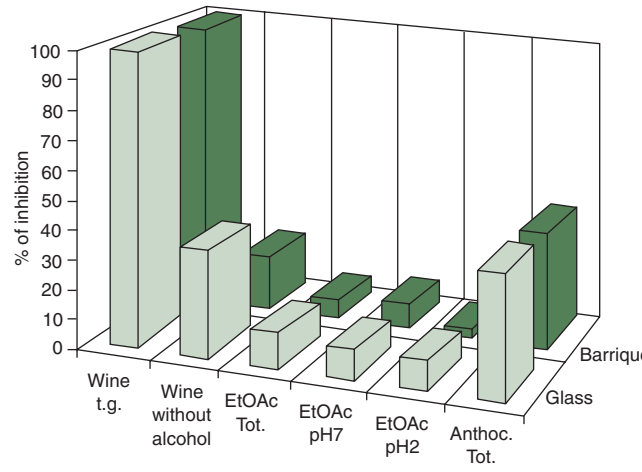

Figure 12.5 In activation of platelet aggregation induced by several red wine fractions (barrel- or bottle-aged, their dealcoholized versions, and total ethanol at pH 7 and 2) and anthocyanin extracts from the wines. (From Baldi *et al*., 1997, reproduced by permission)

to aggregate to form a clot. Alcohol also increases the level of prostacyclin (interferes with clotting) and raises the level of plasminogen activator (a clot-dissolving enzyme). 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. 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. 12.5).

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. Those 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). Nevertheless, the combined effect of several phenolics is superior to single compounds (Wallerath *et al*., 2005). The action partially results from the enhanced synthesis and release of nitric oxide by endothelial cells. Nitric oxide induces vasodilation (by relaxing vascular smooth muscle), 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.

In addition to effects on platelet aggregation, phenolic wine constituents bind directly with LDLs (limiting their oxidation), indirectly reduce macrophage-mediated oxidation of LDLs, and preserve the action of paraoxonase (further protecting LDLs from oxidation) (Aviram and Fuhrman, 2002). Furthermore, red wine phenolics 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 benefits to white wines, relative to cardiovascular disease. This probably results from their higher flavonoid concentration. This view is supported from 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 wines. 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 heart attack victims. The high potassium to sodium ratio of wine (20 : 1) is a further benefit.

Antioxidant Effects

Wine phenolics are not only important antioxidants in wine preservation, but also play a role as antioxidants in the human body. By limiting LDL peroxidation (Maxwell *et al.*, 1994; Rice-Evans *et al.*, 1996), they restrict one of the critical early stages of atherosclerosis. This probably results from the inhibition of lipoxygenases, as well as the scavenging of free oxygen radicals, such as superoxide and hydroxyl radicals, and by chelating iron and copper (involved 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 antioxidants of importance in the human diet are vitamins E and C (tocopherol and ascorbic acid), β-carotene, and selenium. The occurrence of tocopherol in the precursor of LDLs may provide a natural, but short-term, protection from oxidation.

One of the antioxidants relatively unique to wine is resveratrol. It is a phenolic (stilbene) compound produced in response to fungal attack or other stresses. Other plants producing resveratrol include mulberries, blueberries, peas, and peanuts. It has greater antioxidant action than 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 activates proteins involved in nerve cell differentiation, synaptic plasticity (important in learning), and neuronal survival (Tredici *et al.*, 1999).

Additional potent antioxidants in wine are 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. For example, PVPP (polyvinylpolypyrrolidone) markedly reduces quercetin content (Fluss *et al.*, 1990).

Alternately, de la Torre *et al.* (2006) have suggested that ethanol itself may modify human metabolism, increasing the synthesis of hydroxytyrosol. The latter is a well-known antioxidant phenolic found in olive oil. 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, at a concentration of 1.7 mg hydroxytyrosol.

Vision

Many of the beneficial influences of alcohol and wine consumption show a U-shaped curve. This also applies to its effect on age-related macular degeneration (Obisesan *et al.*, 1998; Fraser-Bell *et al.*, 2006). The disease expresses itself as a progressive degeneration of the central region of the retina (macula) that leads 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 situations, wine antioxidants are suspected to be the active protective agent. At higher rates of intake, ethanol promotes a prooxidant action that could negate the benefits of wine antioxidants.

Neurodegenerative Diseases

Alzheimer's is one of the most investigated of neurodegenerative diseases, affecting approximately 15 million people worldwide. It is not surprising that researchers have investigated whether wine consumption reduces the incidence of neurodegenerative diseases affected by oxidative stress (Barnham *et al.*, 2004). A pattern appears to apply here, as with so many other health-related benefits of wine and alcohol consumption. Moderate intake is beneficial, whereas heavier consumption or abstinence is prejudicial.

Alzheimer's disease is associated 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. Tannic acid has also been shown to inhibit the formation of, and destabilize preexisting β-amyloid fibrils (Ono *et al.*, 2004), 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). Like other health benefits, these finding may not, in themselves, justify wine consumption, but they are encouraging to those who choose wine as part of their preferred lifestyle.

Osteoporosis

Age-related loss in bone mass affects both sexes, but is particularly prominent in postmenopausal women. Many risk factors, dietary influences, and hormonal supplements can affect its occurrence and severity. Of these factors, moderate alcohol consumption has been found to favor bone retention (Ganry *et al.*, 2000; Ilich *et al.*, 2002). These studies did not separate between various alcoholic beverages, thus, whether bone retention is due to enhanced calcium uptake associated with alcohol consumption (Ilich *et al.*, 2002), the phytoestrogen effects of phenolics, such as resveratrol, or some other influence is unknown.

Gout

In the 1800s, there were many reports linking gout with wine consumption, especially 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 often 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 include red meat, seafood, and beer – presumably due to the increased availability of purines, the principal source of uric acid. 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 has not been found to be associated with an increased risk for gout (Choi *et al.*, 2004).

Medical historians suspect the gout–port connection in the nineteenth century was associated 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 its uptake from stills, used in making 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, could have further augmented the lead content (Falcone, 1991).

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 antiinflammatory influences of wine phenolics, notably resveratrol, 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 (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 do not respond properly to the presence of insulin. Moderate alcohol consumption is also associated with reduced incidence of this form of diabetes

(Dixon *et al.*, 2001). The incidence of metabolic syndrome X 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 (of which wine is a significant source) (Brichard and Henquin, 1995; Teissèdre *et al*, 1996); the hypoglycemic and hypolipidemic effects of phenolics like resveratrol (Su *et al.*, 2006); or through some effect on endothelial nitric oxidase synthase (Leighton *et al.*, 2006). Moderate consumption of dry wine has no adverse effect on sugar control in diabetic patients (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. This effect may result from some unknown protective effect of ethanol.

Kidney Stones

Drinking water has long been associated with reducing the development of kidney stones. Increased urine production helps prevent the crystallization of calcium oxalate in the kidneys. What is new is the observation that wine consumption further reduces the production of these painful and dangerous inclusions (Curhan *et al.*, 1998).

Cancer

The consumption of moderate amounts of wine has not been shown to increase the incidence of most cancers. In contrast, increased consumption tends to increase the risk of certain cancers (see Ebeler and Weber, 1996).

In certain instances, these influences may derive from indirect effects on carcinogens, such as ethyl carbamate. At the concentrations typically found in table wine, though, ethanol diminishes the carcinogenesis of ethyl carbamate. Certain wine phenolics can be protective, whereas others can be mutagenic, especially at high concentrations. For example, quercetin can induce mutations in laboratory tissue culture, 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 the low level of metal ions and free oxygen found in the body (vs. tissue culture). 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 can induce 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), and disrupted cell division (Hou, 2003; Aggarwal *et al.*, 2004). For example, resveratrol induces the redistribution of the Fas receptor. It is a site for the attachment of TNF (tumor necrosis factor) in colon cancer. Its action is part of a sequence that leads to the death of the affected cancer cells (Delmas *et al.*, 2003). Resveratrol is also well known as an inhibitor of angiogenesis – the production of new vasculature essential for 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 1A1 is an important hydroxylase. It can convert several environmental toxicants and procarcinogens into active carcinogens.

Flavones and flavonols strongly restrict the action of the common dietary carcinogens, 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 antiinflammatory 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 against cancer may be breast cancer (Viel *et al.*, 1997). This 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). High rates of wine consumption have been linked with an increased incidence of mouth and throat cancers (Barra *et al.*, 1990). Ethanol itself is not carcinogenic, but can enhance the transforming effect of some carcinogens.

Allergies and Hypersensitivity

Alcoholic beverages may induce a wide diversity of allergic and allergic-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. 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 tend to provoke more asthma problems than white wines, even though red wines typically have lower sulfur dioxide contents than white wines.

The speed of the reaction to sulfite suggests some malfunction in the amount of glutathione in lung tissue, or the activity of glutathione *S*-transferase reducing sulfite to glutathione *S*-sulfonate. Normally, sulfite is rapidly converted to sulfate by sulfite oxidase in the blood. However, low levels of this enzyme could permit sulfite to persist, provoking a heightened response in hypersensitive individuals.

At potentially 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 people die before reaching adulthood.

An intriguing allergy-like reaction is a rapid facial and neck flushing (cutaneous erythema) shortly after alcohol consumption. Other symptoms often include peripheral vasodilation, elevated heart rate, nausea, abdominal discomfort, and broncho-constriction. This reaction is found in up to 50% of eastern Asians. The syndrome is associated with a malfunctional form of mitochondrial acetaldehyde dehydrogenase (ALDH2) (Enomoto *et al.*, 1991). This is the principal enzyme oxidizing acetaldehyde to acetic acid. A malfunctional alcohol dehydrogenase allele (ADH1B) may also play a contributing role in the flushing reaction (Takeshita *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 the 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 this flushing, if taken in advance of an alcohol challenge (Miller *et al.*, 1988).

Antihistamines can also diminish the rhinitis that may be associated with the consumption of red wine (Andersson *et al.*, 2003). In addition, antihistamines counteract the bronchoconstriction in individuals showing histamine intolerance. Histamine intolerance presumably relates to reduced activity of diamine oxidase (Wantke *et al.*, 1996).

It has been suggested that the *ALDH2* mutant in eastern Asians noted above may reflect an evolutionary selective adaptation to the endemic occurrence of hepatitis B in that region of Asia (Lin and Cheng, 2002). The resulting avoidance of alcohol would avert any synergism with hepatitis B-induced liver damage. 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.

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. However, this possibility is supported by its suppression by acetylsalicylic acid (aspirin), if taken before an alcohol challenge (Truitt *et al.*, 1987). An alternative proposal is that the flushing results from a direct, cutaneous, alcohol-induced vasodilation.

Idiosyncratic 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 reactions may involve urticaria/angiodema (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). However, 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 800 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 unacceptable.

Headaches

People occasionally avoid wine consumption because it induces headaches. This situation has regrettably seen little study. Central to progress is effective differentiation of the multiplicity of headache phenomena and their specific etiologies.

One of the most severe headache syndromes potentially associated with wine consumption is the **migraine**. Migraines may be induced by a wide range of environmental stimuli, possibly because migraines are themselves a complex of etiologically distinct events. The dilation of blood vessels in the brain, as a result of histamine release, can be the common element in many instances of headache development. 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 found in red wines are below those that generally trigger a migraine. In addition, double-blind studies have seemingly exonerated histamine in red-wine-induced migraine headaches (Masyczek and Ough, 1983). Nevertheless, alcohol can suppress the action of diamine oxidase, an important enzyme of 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. However, this view does not correlate with the observation that spirits and sparkling wine were more frequently associated with migraine attacks than other alcoholic beverages (Nicolodi and Sicuteri, 1999). Both spirits and sparkling wines are low in histamine content.

Although the biogenic amine content of wine appears to be insufficient to cause migraines in most individuals, the phenolic content of wine can induce headaches. Correspondingly, red wines are more frequently associated with headache production than white wines. On average red wines contain about 1200 mg/liter vs. 200 mg/liter for whites. Some phenolics suppress the action of platelet phenolsulfotransferase (PST) (Jones *et al*., 1995). Individuals having low levels of platelet-bound PST are apparently more susceptible to migraine headaches (Alam *et al*., 1997). Suppression of PST results in reduced sulfation (detoxification) of a variety of endogenous and xenobiotic ("foreign") compounds, including biogenic amines and phenolics. Without inactivation, biogenic amines can activate the liberation of 5-hydroxytryptamine (5-HT, or serotonin), an important neurotransmitter in the brain. 5-HT also promotes platelet aggregation and the dilation of small blood vessels in the brain. The pressure so created can cause intercranial pain, and the instigation of a migraine (Pattichis *et al*., 1995). People prone to migraine headaches also may show abnormal and cyclical patterns in platelet sensitivity to 5-HT release (Jones *et al*., 1982; Peatfield *et al*., 1995). This may be involved in why wine consumption is not consistently linked to headache induction. Small phenolic components in wine also prolong the action of potent hormones and nerve transmitters, such as histamine, serotonin, dopamine, adrenalin and noradrenaline. These could affect headache severity and other allergic reactions.

In the treatment of the possibly closely related **cluster-headache syndrome**, small doses of lithium may be preventive (Steiner *et al*., 1997). Because some red wines have higher than average lithium contents, they may prevent, 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 and ibuprofen could explain how these medications 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 is associated with nausea. The headache is particularly severe when reclining. Although the headache is relieved somewhat by standing, this 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, tannins (polyphenolics) are poorly absorbed in the digestive tract. In contrast, their monomers are readily absorbed. 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 counterparts. 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 two days, they cannot be involved in headache induction. However, headache induction may result from monomeric phenolics, such as caffeic acid and catechins. Depending on their 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 enzyme catechol-*O*-methyltransferase (COMT). By so doing, the neurotransmitter dopamine is not broken down, and the availability of μ-opinoid (painkilling) receptors is restricted. Consequently, the perception of pain associated with cerebral blood vessel dilation may be enhanced.

Resveratrol, a phenolic found in higher concentration in red than white wines, inhibits the expression of cyclooxygenases. Cyclooxygenase is 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 prostaglandins may occur as constituents in wine. 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 wines 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 an accompanying phenomenon. A hangover is characterized with tremulousness, palpitations, tachycardia, sweating, loss of appetite, anxiety, nausea, and possibly vomiting and amnesia. When a headache accompanies the hangover, it possesses symptoms similar to a migraine. The headache is global, more frequently located 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) remain 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).

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 membrane covering the brain (the dura) could pull on fibers attaching the dura to the skull, causing pain sensors to discharge. Alternately, 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 is eliminated in the urine, producing 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 symptoms. It is said that:

Wine hath drowned more men than the sea.

Because glutathione is very 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 its subsequent metabolism, as well as binding irreversibly with acetaldehyde.

The accumulation of acetaldehyde has also been proposed as a major activator of hangover initiation. For example, acetaldehyde can disrupt membrane function (partially by interfering with the action of cytochrome P-450 oxidase), and consequently cerebral neurotransmitter action. Commercial products such as Hangover Helper™ and Rebound™ have been developed to counter the effects of acetaldehyde. In addition, congeners (such as fusel alcohols and methanol) may exacerbate the effects of ethanol and acetaldehyde. Although the methanol content of wine is particularly low, its metabolism by ADH to formaldehyde, and subsequently

formic acid, could be a significant factor with distilled beverages. The product Chaser™ has been developed as a means of limiting the uptake of such congeners. Its formulation of activated calcium carbonate and vegetable carbon is thought to bind congeners in the stomach, preventing their uptake in the blood.

Hangovers are also associated with disregulation 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 trial (Pittler *et al*., 2003), but others, such as an extract of *Opuntia fiscus-indica* (Prickly Pear), apparently reduces 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, there is no known universally effective treatment for a hangover. Although time is the only sure cure, avoidance is preferable.

Taking wine with meals is probably the best-known and reliable preventive, combined with limited consumption. Food delays the movement of alcohol into the intestinal tract, where some 80% of the alcohol is absorbed. Because the uptake is slowed, absorption more evenly matches the body's ability to metabolize alcohol. It also delays the uptake of phenolic compounds and diminishes their maximum 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*., 2006). 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 a pH of 5.7. This is typically not a problem for the consumer who takes wine with meals. Food and saliva secretion limit, if not prevent, demineralization of tooth enamel.

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 the enamel.

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 also tended to be heavy smokers, use illicit drugs, consume large amounts of coffee, have poor nutrition, or show 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. 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 now generally recommended that pregnant women, or women wishing to become pregnant, refrain from alcohol consumption during this period. Whether total abstinence is fully warranted is unknown, but erring on the side of caution is certainly judicious.

Contraindications

The most important contraindication relates to those with a past history of alcohol abuse. For the majority of the adult population (except pregnant women), moderate wine consumption appears to have considerable 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 the inflammation and slow the natural 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 *Helicobacterium 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 individual prone to this problem.

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. 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 before surgery. This avoids increasing the incidence of 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 simultaneous consumption 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, it induces a very unnerving reaction. This 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, consumption of alcohol 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 their potential applicability under conditions of moderate consumption 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. Details can be found in Adams (1995), Fraser (1997), and Weathermon and Crabb (1999).

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