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This issue departs from the normal format to devote the entire issue to the presentation of a discussion of a theory of the diseases of civilization which confront all of us, young and old. These include Alzheimer's disease, multiple sclerosis, heart disease, cancer, diabetes, lupus, rheumatoid arthritis, birth defects and autism. Mainstream medical science would no doubt ridicule the notion that there is a common thread running through all of these disorders, and it is no doubt true that most are multifactorial in terms of primary causes.

However, this does not eliminate the possibility of one important causative factor common to all; it is just that this strikes one as not terribly likely. Nevertheless, anyone looking at the broad picture must deal with what appears to be a rapidly changing and recently accelerating incidence of these diseases over the past century. Broad-based explanations frequently offered lack detailed biological and mechanistic justification and are made complex by many potential confounders. It is not terribly informative to point to lifestyle and environment when incidence goes from virtual non-existence a century ago to epidemic rates today. Details and mechanisms are needed at the primary causative level that are consistent with the underlying pathophysiology and not falsified by simple observations, as turned out to be the case when LDL was thought to drive atherosclerosis.

In physics the Holy Grail is the unified theory of everything, or at least the basic but extraordinarily complex features of our microscopic and macroscopic world, including, ideally, the whole universe. Such a dream is no doubt unrealistic in the world of chronic disease and the diseases which appear to be associated with our "advancing" civilization, especially when the goal is elucidating primary causes. A hypothesis approaching a unified theory of the diseases of civilization has recently been proposed by Professor Woodrow Monte, Emeritus Professor of Nutrition, at Arizona State University. This hypothesis was put forward in 2010 in the journal "Medical Hypotheses" and then in vastly greater detail in 2012 in a 236-page book fully documented with 745 citations. The title is "While Science Sleeps, a Sweetener Kills". This title is somewhat misleading since, while the sweetener aspartame (NutraSweet) is a major factor, this book is about the simple alcohol methanol and how over the past two centuries our exposure to it has continuously increased, recently dramatically. The theory is based on the havoc that methanol causes in the human body and how it is plausible that it is one of the primary causative factors, through a metabolite, of the diseases of civilization.

The reader is encouraged not to dismiss this as absurd or just another idea like the many which are advanced and then disappear. Methanol is a much more prevalent substance in our food and beverages and, in some cases, in what we inhale. Its toxicity is vastly underappreciated. It is a unique toxin in that animal studies do not reveal the magnitude of this toxicity. There are compelling financial reasons for the food industry to suppress any hint of toxicity. The localized damage its first metabolite is capable of inflicting is even less appreciated. Yet chronic exposure is very common, even among those who do not consume methanol via beverages sweetened with aspartame, since avoiding this synthetic chemical is hard to do even if diet drinks are shunned, given it has become ubiquitous in processed foods. The fundamental science involved in Professor Monte's hypothesis should be considered with an open mind. It is hoped that readers will find this story fascinating.

If you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at <http://www.yourhealthbase.com/vitamins.htm>.

Wishing you and your family good health,

William R. Ware, PhD, Editor

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THE HIDDEN DANGER IN OUR MIDST AND HOW IT KILLS US

Methanol is a highly toxic simple alcohol. One or two teaspoons of this volatile liquid are sufficient to kill the average-weight adult. If poisoned, those who survive suffer a number of serious symptoms including permanent or temporary blindness, blurred vision, loss of color vision, vertigo, unsteady gait, dizziness, spasticity, seizures, and optical neuropathy, and this is not the complete list. Therefore, most would consider this chemical as something obviously to be avoided and wonder why it is the topic of this issue of *International Health News*. People do not knowingly expose themselves to highly toxic substances. The answer is that most are unaware of the fact that methanol exposure at sub-fatal levels is very common and the toxicity ignored or the evidence suppressed. The most common sources are found in the beverage and canned food isles of the supermarket and on the shelves of tobacco vendors. The fact that almost no one makes the association with these products and methanol is an indication of skillful marketing. Furthermore, the serious and prevalent health issues which we will discuss are in fact related only indirectly to methanol since they appear to arise from a metabolite, formaldehyde, which is even more poisonous than methanol. We will start with one of the major sources of dietary methanol.

The artificial sweetener aspartame (*NutraSweet*[®]) was approved for human consumption by the U.S. FDA on July 24, 1981, in spite of objections arising out of internal scientific reviews and from outside experts, and approved as a carbonated beverage sweetener in 1984. Of particular concern was the apparent connection with cancer which turned up in animal studies. This chemical food additive has subsequently been the subject of constant controversy, legal challenges, books condemning it, and sensational success in marketing worldwide, especially in diet drinks and in making low-fat and diet foods more palatable. Due to significant efforts by the manufacturer over the years, aspartame is generally regarded as safe, an assertion based on animal studies. However, after ingestion, aspartame yields two amino acid molecules and one molecule of methanol. For animals, methanol is not particularly toxic, but this is most certainly not the case for humans and thus the concern among some scientists regarding this now common food and beverage additive.

Recently a comprehensive review of this subject by a respected food and nutrition scientist, Professor (Emeritus) Woodrow C. Monte of Arizona State University, has appeared.¹ The provocative title is *While Science Sleeps a Sweetener Kills* and it also available as an e-book (see Amazon.com for either). The 745 references are available separately from this 215-page review and can be found on the book's website. While it would normally have been appropriate for your editor to simply prepare a book review for what he regards as a highly significant publication, the importance of the overall message and the associated details seem to merit a detailed discussion. Monte's book and references provide the scientific documentation for the major issues that will be raised. A summary of the Professor Monte's views also appeared in 2010 in the journal *Medical Hypotheses*² where methanol was described in the title of the paper as a chemical "Trojan horse." What

Monte has devised is a theory regarding what he regards as a major concern associated with the diseases common to our advancing civilization. It is a fascinating story.

The position taken by the Professor Monte is strongly anti-aspartame but is in fact based entirely on the toxicity and pathophysiological impact of the methanol component which is released upon ingestion into the stomach and gut and reaches the circulation. Methanol is also called methyl alcohol or wood alcohol and is the smallest alcohol known to organic chemistry (CH_3OH). Beverage alcohol, i.e. ethanol, incidentally is $\text{CH}_3\text{CH}_2\text{OH}$. Both are very small by protein standards and cross the blood brain barrier easily. In addition, smoking results in the inhalation of significant amounts of methanol which ends up in the circulation.

Monte's thesis^{1,2} can be summarized as follows. For a detailed documentation, which would generate too many citations for this newsletter, the reader is referred to Monte's book and its online references. However, throughout the review, a few key references will be provided, some of which are not in Monte's book.

- The advent of significant chronic human methanol exposure closely and temporally correlates with the population incidence and increases of diseases of civilization (DOC) such as cancer, heart disease, multiple sclerosis, Alzheimer's disease, lupus, autism, and rheumatoid arthritis. Sharp increases in incidence correlate with the introduction and ramping up of consumption of aspartame which has offered the opportunity for very high intakes of methanol previously unknown to humans. One liter of an aspartame-sweetened drink represents, in terms of methanol, 1 to 5% of the lethal or potentially harmful dose depending on body weight and based on numbers given by Monte on pages 23 and 58 of his book, taking into account the possibility of low body weight of young individuals who are among the most frequent consumers and the variation of aspartame in widely-consumed, sweetened drinks. There are also significant associations related to work and environmental exposure.
- As mentioned above, consumption of aspartame, which is made up of two

amino acids and methanol, is equivalent through the break-up of the molecule to consuming methanol. Since aspartame is consumed in large quantities, this makes aspartame the most important dietary source of this alcohol today. Other dietary sources include tomatoes and tomato products, black currants, home and commercially canned foods (canning releases methanol) and wood-smoked meats and fish. Heating wood releases methanol—thus the name wood alcohol. Aside from sweetened beverages, aspartame is also present in a wide variety of prepared foods and candy and sugar-free chewing gum. Liquors and schnapps made from over-ripe or rotten fruit can contain up to 4-5% methanol as well as ethanol and the methanol can remain in the body for some time after the ethanol has been metabolized. Tobacco smoking is the only other non-industrial or work-related source of heavy exposure to this alcohol. A pack of cigarettes is equivalent to a liter of diet soda in terms of methanol exposure.

- Humans are unique among animals, including primates, in that the liver enzyme *catalase* is a mutant and does not metabolize methanol, thus allowing significant first-pass concentrations to appear in the circulation. Animals on the other hand have a catalase which efficiently metabolizes methanol in the liver. This takes place in a special structure inside the cell called a peroxisome. The formaldehyde that results from the catalase-assisted metabolism of methanol in animals is produced in close proximity to enzymes that further metabolize it to produce energy and yielding carbon dioxide and water. Methanol thus has low toxicity to animals. The very high toxicity to humans is mostly due to its remote metabolism to produce formaldehyde, frequently far removed from enzymes that can further metabolize formaldehyde to yield harmless products. For animals such as rats, dogs, rabbits and monkeys, the minimal lethal dose of methanol is between 6 and 9 grams per kg of body weight, whereas for man it is about 0.09 grams per kg of body weight. Thus 6 grams is sufficient to kill a 70 kg male. Furthermore, it is easy to prove that

methanol is safe if one relies only on animal studies because of the huge difference in toxicity. Extensive use has been made of this fact by the sweetener industry to back claims that aspartame is safe for human consumption, now a widely accepted conclusion in spite of the above facts.

- Accidental human methanol poisoning makes it clear that this alcohol is highly toxic. These tragic events have provided considerable information concerning the symptoms, pathological presentation at autopsy and the mechanism of acute methanol poisoning. Before methanol toxicity was appreciated, methanol was for a short period used with disastrous results as an ethanol substitute in fruit and seasoning extracts. Pure methanol is however available in large quantities in hardware and building supply stores for use as a solvent. While labelled as a poison, it is doubtful that the general public realizes just how toxic it is.
- Circulating methanol will eventually encounter the enzyme *alcohol dehydrogenase* (ADH), which will convert methanol into formaldehyde. Formaldehyde is highly reactive and will rapidly find a nearby partner with which to react, for example LDL, or DNA or RNA or a protein such as myelin basic protein or tau protein in the brain. The enzyme that converts formaldehyde to formic acid, a rather innocuous molecule, is frequently not in the vicinity.
- ADH is localized in such places as the brain vasculature, arteries, spinal cord, breast tissue, etc, and thus the new molecules formed by reaction with formaldehyde are also localized. But the enzyme is absent in most tissues. For example, in the brain it is localized in the circulation system and not in the brain tissue itself.
- The new molecules resulting from the conversion of methanol to formaldehyde and its subsequent reaction are in many cases recognized by the immune system and macrophages mount an attack. This can lead to inflammation and the destruction of critical tissue. Thus a protein which has reacted with formaldehyde is a candidate for elimination. If it serves a vital function, this function will be impaired. Toxicity of

formaldehyde leading to multiple sclerosis (MS) or Alzheimer's disease has been associated with such reactions. Toxicity of formaldehyde in the arterial wall followed by an immune reaction leading to foam cells has been associated with atherosclerosis.

- If DNA reacts with formaldehyde it can be methylated and the resultant mutation can then go on to trigger cancer. The ability of formaldehyde to methylate DNA has been demonstrated, with the formaldehyde traceable to methanol with radioactive tracer techniques. Because of the presence of ADH, breast tissue is particularly susceptible to the action of formaldehyde and the affected tissue can become a precursor for breast cancer.
- The fetus is in general highly susceptible due to the rapid and complex developmental processes, and formaldehyde can induce birth defects and premature delivery. Undesirable neonatal exposure can be through mother's milk or even aspartame-sweetened baby food sources.
- The enzyme ADH has a 16:1 preference for oxidizing ethanol over methanol and thus when both are present, ethanol offers significant competitive protection as long as it is present. Small amounts of alcohol are made in the colon by fermentation and enter the circulation. These low levels of alcohol are enough to hinder conversion in the liver of methanol to formaldehyde and then mostly on to formic acid through the action of another enzyme. This allows some of the ingested methanol to circulate. As Monte points out, only two things can happen to the circulating methanol. It is converted to formaldehyde when it encounters an ADH enzyme, or it is eventually eliminated through the urine, sweat or respiration. Alcohol in the circulation gives this elimination process time to take place and intentionally consumed alcohol further shifts the metabolism-elimination in favour of elimination. High levels of methanol intake however, can overwhelm the alcohol protective mechanism.
- Ethanol is the only emergency treatment for methanol poisoning, and serious cases are maintained in a state of total inebriation for several days in order to limit toxicity and allow the non-reactive

elimination can take place. More importantly, this action of alcohol provides an attractive explanation for the famous but mysterious U-shaped curve associated with the risk vs. benefit of beverage alcohol in not only heart disease but other diseases of civilization which Monte associates with methanol intake and formaldehyde production.

- Formaldehyde when administered by itself orally, by inhalation or by injection is highly toxic and carcinogenic. However, its extreme reactivity limits its range from the point of entry. It is the localization of formaldehyde via its production from methanol in specific sites in the human body through the action of the enzyme ADH that is central to the argument concerning the danger of formaldehyde in connection with the diseases of civilization. Formaldehyde is too reactive to survive in the circulation, but this is not true for methanol.
- Women have a reduced ability to detoxify methanol in their guts. They are also the prime target for advertising of diet soda and low-fat aspartame containing foods.
- Some of the diseases of civilization (DOC) have in common the characteristic that the proposed causative problems, such a plaque in the brain or arteries, tau protein tangles, or myelin protein destruction, all occur very close to the vascular sources containing ADH. These DOC also show the classical U-shaped risk-benefit association with beverage alcohol intake with significant protection at low to moderate levels of consumption. These diseases are also consistently associated with smoking, a major source of methanol for humans. This can hardly have occurred by chance and points to methanol as a major common factor in the etiology of these diseases.
- The sharp increase in the incidence of the DOC correlates with the introduction and

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) results from the progressive deterioration of the myelin protective sheath surrounding the axons in the brain. Myelin is made up mainly of myelin basic protein (MBP). According to the hypothesis of Monte, formaldehyde from methanol reacts with MBP to form an altered

then the increasing production of aspartame.

The above represents what appears to be a very serious indictment of inhaled and ingested methanol. Because the critical enzyme ADH is localized rather than evenly distributed throughout the human body, the possibility of localized damage, mutations and disease initiation must be taken very seriously. Controlled human experiments are clearly unethical. Accidental methanol poisoning episodes, however, are very informative in revealing a number of symptoms as well as the pathological manifestations seen at autopsy. However, an uncontrolled human experiment with high doses of methanol, in many cases on a continuous basis for years, has been ongoing since 1981 when aspartame was introduced, an additive that has had great appeal to populations who were becoming weight and diet conscious or turned with increasing frequency to artificially-sweetened beverages simply to quench thirst and provide pleasure. Countries such as Japan, where exposure to dietary methanol was historically negligible, now has a chemical plant devoted to the production of aspartame to meet domestic and regional demand. The introduction of aspartame may be historically one of the most flagrant examples of human experiments on an uninformed and unsuspecting population. Some would argue that GMO foods trump this. But the basic science of the toxicity and dangers related to the methanol are much better understood than those for GMO foods, and as the 745 references in Monte's book attest, there is a lot of research out there to look at.

There are a number of points in this brief summary that need amplification and clarification. The discussion will be organized by disorder.

protein which then stimulates macrophages to destroy it. As the destruction proceeds, this ultimately distorts nerve cell communication leading to a large number of neurological symptoms well known to sufferers of the disease. Conventional wisdom regards MS as an autoimmune disease, but this view has

been a dead-end with no cure and only palliative drugs of marginal or debatable effectiveness. The incidence of MS has increased dramatically over the past three decades.

The association of MS with methanol is beautifully illustrated by the fact that it shares many of the symptomatic and pathological (autopsy) characteristics of either acute or chronic methanol poisoning. Monte lists and documents 20 symptoms and 13 autopsy findings methanol poisoning shares with MS (p71) The number is so high that that it is highly unlikely this occurs by chance. The changes seen in the brain are also highly unusual both in morphology and location. As regards location, MS is termed "perivascular" with much of the damage clustered in sites surrounding blood vessels and in particular small veins. In addition, there is evidence of damage to the blood vessels within the plaque. MS shares this characteristic with Alzheimer's disease. This is critical to the hypothesis since other than sites within the cerebral veins and arteries, the brain is completely free of ADH and methanol circulates freely throughout the brain when present in the circulation. The plaques of MS and the damage of Alzheimer's only occur at the precise areas where ADH converts methanol into formaldehyde. Monte cites evidence directly indicating the action of formaldehyde in modifying MBP in the pathogenesis of MS. Thus the pathophysiology looks like an autoimmune disease but in fact it is an immune reaction to the adduct of formaldehyde to MBP. The increase in the incidence of MS directly correlates with the increase in aspartame production as does MS mortality, but mortality has about a 10 year lag. Finally, it is highly significant that the only universally accepted causative agent for MS is cigarette smoking! But after decades of research, no one till now has connected the dots.

In countries where MS was rare before the introduction of aspartame, it is consistently found that there have been huge increases correlating temporally with the increased intake of this sweetener. For example, in Japan, MS was relatively rare, and then suddenly started to increase and has quadrupled in the past 30 years since the introduction of aspartame. As mentioned

above, to meet the aspartame demand, Japan now has a plant manufacturing this compound. The Shetland Islands have the highest incidence of MS in the world. Their diet is rich in smoked fish which they prepare over burning peat which has 3 times the methanol content of slow-burning wood, itself a good source of methanol. On the other hand, the Faroe Islands have a very low MS rate but they have held to the tradition of air-drying their fish and do not consume smoked food. Many other similar examples are discussed in Monte's book.

Industrial, workplace and environmental exposure have also been implicated in MS. Individuals living downwind from a plant in Wellington Colorado had high incidence of MS. They were exposed to very high levels of airborne methanol. Teachers repeatedly exposed to methanol while operating the classical Ditto machines (duplicating machines) also were found to have high incidence. Even exposure in a teacher's lounge where a heavily used machine was located was enough to produce enhanced prevalence. Both male and female teachers were affected.

Monte explores the history of MS as it relates to the etiology of this disorder. The first identifiable case was in 1822 and described as a rare disease of the rich in 1865. The incidence increased steadily until the early 1980s when it became an epidemic. The male/female ratio also changed from favoring males to females by 4 to 3 to the reverse with a ratio of 4 to 1 in favour of women. These observations are consistent with the advent of canning in the early 1800s which then increased in the later part of the 19th century and into the 20th century, increased smoking, the use of methanol as a stove fuel and cleaning fluid, its use as a solvent for glue in leather and shoe factories and as a solvent in printing and the famous Ditto machine. Over the years the popularity of canned fruit and vegetables increased dramatically and home canning became very popular. The big event in the early 1980s was a new source of methanol in the form of aspartame. Foods and beverages containing this additive became increasing popular and their consumption spread until it was worldwide. In the early history, men received greater exposure than women in the workplace and had higher MS

incidence. In addition, the exposure was via inhalation. When ingestion became another important form of exposure, another factor came into play. The enzyme ADH is much less prevalent in the female gut than in the male, and thus women got higher doses of methanol into the blood from ingested sources than men while men had more formaldehyde generated in the gut, but the gut response is robust enough that this did not result in serious gut pathology. Men, however, report more gastric discomfort associated with aspartame than do women. For men, workplace exposure declined over the decades. Now MS is well known to be predominantly prevalent in women and the methanol hypothesis provides a rationalization.

ALZHEIMER'S DISEASE (AD)

This disorder needs little introduction. Most readers know victims and have seen the impact on families and caregivers. Recent studies cited by Monte have provided a mechanism for AD being a disease caused in part by methanol. This mechanism focuses on the tau protein and how formaldehyde can react with it to first induce polymerization and then aggregation to produce the hallmark tangled plaques seen at autopsy. Like MS, the plaques are seen in close proximity to the cerebral vasculature where ADH resides.

Monte asserts that the association of smoking and Alzheimer's disease has been profoundly distorted by industry-supported studies. In

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

The sequence of events leading to atherosclerosis starts with a normal human artery, and ends up with calcified, non-calcified and mixed plaque, and obstructive atheroma containing a variety of substances, including cholesterol and evidence of extensive macrophage activity and phagocytosis. How this all happens is far from clear, in spite of the impression given by mainstream medicine that the standard model is satisfactory. Monte provides a model the central feature of which is the conversion of methanol to formaldehyde in the artery followed by a reaction between LDL and formaldehyde to generate an "oxidized LDL" which then triggers an attack (immune reaction) with inflammation, macrophage attack to destroy the oxidized LDL, formation of foam cells and more macrophages, etc.,

MS and beverage alcohol consumption has received little attention. A study in 1999 found alcohol consumption was associated with lower disability scores in patients with MS irrespective of the course of MS.³ A very recent study found a strong protective effect of moderate alcohol consumption and an increase in the time to severe disability (EDSS score 6) in relapsing MS.⁴ Moderate alcohol consumption was defined as from one drink weekly to up to two or more drinks daily. The authors point out that the accumulation of disability in relapsing MS could be explained by demyelination and axonal injury, the mechanism for the action of methanol induced formaldehyde damage in MS proposed by Monte for which alcohol is protective.

fact, these are responsible for the widespread belief that smoking is protective. According to a recent study from the University of California, San Francisco, when the analysis of cohort studies is carried out while controlling for industry affiliation, smoking increased the risk of AD by 45% to 72%, statistically significant.⁵ Like MS, in most studies AD exhibits a U-shaped risk-benefit curve in connection with alcohol consumption.⁶ Symptoms common to methanol poisoning are seen in AD. Since the introduction of aspartame, the incidence of and mortality associated with AD has dramatically increased.

until plaque is built-up. The standard model visualizes all the action taking place by molecular penetration of the inner lining of the artery, the endothelium. This offers no problem to the methanol-formaldehyde mechanism since methanol would penetrate the endothelium easily being a really tiny molecule, and the artery contains the required enzyme ADH to convert it to formaldehyde. But there are many obscure details in both the standard model and that of Monte. Ravnskov and McCully⁷ have proposed a model where all but monocytes enter the interior of the artery via the arterial microcirculation system called the *vasa vasorum* and that the trigger for macrophage activity and inflammation is an interaction involving LDL with microbial components, i.e. an infection-based model. Subsequent LDL aggregation, a well-

established aspect of LDL participation in the immune reactions, is postulated to block the microcirculation resulting in low oxygen levels, cell death and in some cases rupture to produce a myocardial infarct. This new theory can be modified by simply replacing chemicals derived from microbial activity with LDL that has reacted with formaldehyde and which is now well established as an activator and target for macrophage activity. The location of the ADH in arteries causes all the action to take place there, in keeping with the characteristics of a methanol-related disorder. Also, smoking is one of the most important risk factors for cardiovascular disease and, as mentioned above, the association can be attributed to inhaled methanol which goes directly into the circulation.

The alcohol U-shaped risk-benefit phenomenon is probably best known for

DIABETES

Diabetes comes in two types, 1 and 2. The former is most common in juveniles whereas type 2 is mostly an adult disorder, although the type 2 disease is now becoming more common in younger individuals. The risk of type 2 diabetes is strongly associated with smoking. In addition, associated with the risk of developing type 2 diabetes is the famous U-shaped curve for alcohol consumption with moderate consumption associated with about a 30% decrease in risk, and long term alcohol use appears to be associated with improved glycemic control in type 2 diabetes.¹⁰ Monte points out that the consumption of at least one 12 ounce can of diet soda a day for 4 years was found to be associated with a statistically

CANCER

The case for the connection between methanol and cancer presented and documented by Professor Monte is as follows. The main obstacle faced by the G.D. Searle company when they tried to get FDA approval of aspartame was evidence of its ability to induce cancer in laboratory animals. Nevertheless, it was approved for human consumption. Now consistent with the rest of the world, the U.S. has finally declared formaldehyde a known human carcinogen. In fact, it has been classed as a Group I carcinogen by the International Agency for Research in Cancer. *No known safe level of exposure exists.* It is a dangerous carcinogen

cardiovascular disease. Furthermore, chronic alcoholics who are drunk most of the time turn out at autopsy to consistently have pristine arteries. In addition, Monte points out that the arterial plaque seen in atherosclerosis looks in some respects like that seen in MS and AD in the brain. In fact, the hypothesis that AD has a vascular origin and is related to vascular disease in the brain is an ongoing subject for debate.

If the methanol-formaldehyde mechanism is important in atherosclerosis, one might expect moderate alcohol consumption to impact the incidence and progression of coronary artery plaque, a prerequisite precursor. The evidence, however, is inconsistent at this point.^{8,9} Part of the problem may be statistical adjustment for smoking since smoking and alcohol consumption are strongly correlated.

significant 67% increase in the risk of developing type 2 diabetes. The insulin-producing beta cells in the pancreas are located in regions of unusually high concentration of ADH. The adolescent and young adult population are targets for aggressive marketing of diet drinks and aspartame-sweetened foods. Smoking is also popular. Monte provides the example that the incidence of diabetes increased by 1000% between 1982 and 1995 in the greater Cincinnati area with females having twice the incidence of males and being diagnosed a year earlier. Mainstream medicine points to obesity and lack of exercise. Perhaps they miss the main culprit!

and mutagen. Furthermore, through the use of radioactive tracer methods, formaldehyde-modified proteins and DNA have been unequivocally associated with methanol. Since methanol is vastly less toxic to animals because they have a catalase which efficiently protects them from the carcinogenic effects of methanol-generated formaldehyde, finding cancer in aspartame-fed animals should rise to grave concerns for humans who are vastly more sensitive to its toxic action.

It is well known that certain types of DNA methylation and inappropriate chromosomal cross-linking play a major role in

carcinogenesis. Both can be produced by formaldehyde. Some call formaldehyde a *methylation machine*. Over 60 methylation defects of DNA from human cancer cells have been identified. Formaldehyde can be produced in close proximity to chromosomes. Monte shows the strong correlation between a number of cancers and the increase in aspartame consumption after 1981. Smoking is also a risk factor for various cancers, consistent with the methanol theory. It is estimated that smoking is a causative factor for 30% of all cancer mortality.¹¹

Monte also discusses the connection between methanol and breast cancer. Women have a reduced ability to detoxify methanol in their guts. Laboratory animals fed even low levels of aspartame develop mammary cancers. Occupational exposure of teachers to methanol from Ditto machines has been associated with increased breast cancer incidence. In addition, the breast tissue levels of ADH are significant but vary and those with high levels are more prone to develop breast cancer. Also, the cells that produce milk contain high concentrations of ADH and mammary epithelial cells have no way to protect themselves from formaldehyde since they contain no *aldehyde dehydrogenase* enzyme which could convert formaldehyde to non-carcinogenic formic acid. Smoking appears to increase the risk of breast cancer, but the association is complicated by genetic factors, whether it is initiated at a very young age, whether it starts before a first full-term pregnancy, and in addition, there is the possibility that some carcinogens in tobacco

AUTOIMMUNE DISEASES

It may surprise some readers to learn that formaldehyde plays a critical role in the preparation of vaccines and is used to transform the bacteria or viruses into a form that is much more active for the formation of antibodies. The procedure is tricky and involves control of concentration and time of exposure. The point is that formaldehyde can also accomplish a similar effect at ADH locations by acting on suitable molecules.

THE BEVERAGE ALCOHOL (ETHANOL) CONNECTION

Central to the methanol hypothesis is the protective effect of moderate alcohol consumption on the prevalence or mortality associated with the diseases implicated. Since

smoke may be particularly active.¹² The apparent importance of passive smoke exposure among younger, primarily premenopausal women who have never smoked is also important and suggests other important carcinogens aside from formaldehyde.¹³ Alcohol is also a well-established positive risk factor and not well studied as a protective agent among smokers. One study of smoking associated risk for breast cancer did find a suggestion of a protective effects of alcohol among smokers who started as teenagers.¹⁴

The highest concentration of ADH is in the liver and this would lead one to expect that that the methanol-formaldehyde-cancer mechanism should operate efficiently there. But the liver contains large quantities of the enzyme that further metabolize formaldehyde and thus offers protection. Nevertheless, liver cancer tripled in the years since the introduction of aspartame. Furthermore, a recent study found current smoking strongly increased the risk of liver cancer and in the study population almost half of all liver cancers were attributable to smoking. What is particularly interesting about this study is that the researchers also looked at the impact of alcohol consumption and found that as compared to low or no intake, moderate intake was highly protective.¹⁵ These results are obviously completely consistent with the methanol hypothesis and suggest that high levels of methanol allow enough formaldehyde to react with liver tissue rather than with *aldehyde dehydrogenase* enzyme, and this is associated with liver cancer.

Monte develops a theory that both rheumatoid arthritis and lupus are triggered by formaldehyde derived from methanol. Aside from the activating effect of formaldehyde in the preparation of vaccines, the three critical aspects of this theory are location, a U-shaped curve for alcohol's beneficial action, and fact that cigarette smoking is a strong risk factor for both disorders. Readers can find the details and documentation in Monte's book.

these diseases together constitute the majority of reported causes of death, it is of interest that meta-analyses involving a large number of studies and over a million subjects found

the U-shaped curve for *total* mortality.¹⁶ Maximum relative risk reductions are typically about 20% and cross the relative risk line of 1.0 at about 4 drinks per day for men and 2-3 for women. Given that a significant percentage of the total mortality is associated with DOC, the implication is an alcohol-associated mechanism that is not disease-specific but cause-specific, and a contributing factor in a significant number of these diseases. This is consistent with the methanol hypothesis of the DOC.

For ethanol to be protective in the context of this discussion, it must be present to compete with methanol for the action of the *alcohol dehydrogenase* enzyme which facilitates the conversion of methanol or ethanol to either formaldehyde or acetaldehyde, respectively. Thus the protective action of one or two drinks a day should not offer 24-hour protection and yet generates a U-shaped curve indicating protection for the endpoint in question. However, for most individuals the beverage alcohol is added to small amounts produced in the colon, and thus the ingested alcohol adds, in many cases quite considerably, to the smaller protective effect of the endogenous

BUT IT IS MOSTLY CIRCUMSTANTIAL EVIDENCE

Of course. Involving *post hoc, ergo propter hoc arguments*, yes indeed. To properly examine the aspartame connection with various disorders, it would be necessary to mount a large human study over say 10-20 years (clinical manifestations can take that long) where subjects are randomized to several different daily doses of this sweetener or a sweet placebo (Incidentally a serious obstacle) and disease incidence monitored. Who would sponsor such a study? Who would want to participate? Unbiased information on which informed consent might be based would scare most potential participants. However, this is an approved food additive regarded worldwide as completely safe by all the authorities charged with protecting humans from dangerous food additives. Tens of thousands of pounds are produced annually. Its toxicity is for all but the critics a non-issue. Such a study would be viewed by the experts as really dumb. However, an uncontrolled study has been ongoing since 1981 without informed consent. The problem is collecting data when whole populations are involved, and organizations that collect population

ethanol. Very high, continuous circulating ethanol, as is present in chronic drunks actually appears to yield amazingly pristine arteries at autopsy, completely free of atherosclerosis, even in older, unhealthy and malnourished individuals. On the other hand, as mentioned above, studies of the impact of alcohol consumption on coronary artery plaque as measured by coronary calcium have been inconsistent. The reasons are not clear but may depend in part on the manner and extent to which adjustment for smoking was carried out during the statistical analysis, since smoking is for some the main source of methanol. This is an interesting and challenging area for future research.

A simple solution to the problem hypothesized above is not to smoke or consume aspartame or methanol-containing beverages or artificially-sweetened foods, and to minimize the consumption of canned foods, tomatoes, smoked fish and meat. Long lists of processed foods containing aspartame are available on the internet. Then enjoy a glass or two of wine with dinner in keeping with the Mediterranean and some other cultures.

disease data and associated biomarkers and other relevant data obviously do not ask about aspartame consumption. Why should they?

It is noteworthy how smoking is a constant thread running through the above anecdotal evidence. It is odd that cigarette smoke would have one or more general pathogens such that one would see this association in a variety of diseases, and for cancer, an association not strongly dependent on the site. On the other hand, methanol is not a carcinogen but generates mutations and other adverse effects via a metabolite at diverse locations depending on where the ADH enzyme resides. The hypothesis of Monte seems considerably strengthened by the both the frequent positive association with smoking and negative association with alcohol, a connected pair, that is hard to explain by any other mechanism than what he proposes when one considers the range and diversity of disorders implicated.

The main thrust of this discussion, which is based almost entirely on Professor Monet's book, is simple prevention by avoidance, not

treatment of the DOC. It may be possible to arrest progression of the diseases implicated by avoiding methanol, which in fact is really easy to do once the sources are recognized (brand names *NutraSweet*, *Equal*, *Canderel*, *Spoonful*, *Benevia*, *NutraTaste*), but cures are for the most part not in sight for the DOC and mainstream medicine is concerned with palliation, control and treating symptoms. In general, interventions that cause regression are only modestly beneficial, if at all. Visit a nursing home to see the evidence of limited success firsthand.

Obviously the minimum safe level of chronic methanol exposure for humans is unknown. The strong possibility is that the initial historic increase in disease-causing exposure was through the methanol in canned fruits and vegetables, smoked foods and tobacco. This suggests that the minimum dangerous chronic exposure level might be quite low, which makes the huge added exposure in the aspartame era of even greater concern.

There are of course other factors driving the DOC. We now live in an environment where exposure to a vast array of toxic, carcinogenic, mutagenic and hormone-mimicking chemicals

is the norm. Some find they cannot live in a new house they just had built! Toxic chemicals are ubiquitous, the basis of huge industries, and studies examining their impact on human health is neither fashionable nor easily funded, for very good reasons. The relative importance of even the most important toxins will probably never be sorted out.

The above discussion has been limited to the methanol component of aspartame and thus ignores health issues potentially associated with one of the two amino acid components. That is a separate story which includes the impact on the brain of aspartic acid, an excitotoxin, which along with glutamate found in many processed foods and as a common additive in Chinese cooking (MSG) can have disastrous health consequences. MSG masquerades under a variety of different names in order that it cannot be easily identified on processed food labels.

An important omission from the above discussion involves the association of the methanol-formaldehyde process with birth defects and autism. This subject will be explored in a future issue of *International Health News*.

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The Prostate Monitor

Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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6th YEAR



This issue discusses the strong negative recommendation of the latest U.S. Preventive Services Task Force regarding prostate cancer screening. This recommendation has received considerable coverage in the TV and print media. The Task Force recommendation is, in general, consistent with that made by the American Cancer Society, the European Association of Urology and the American Urological Association. These organizations urge caution and informed or shared decision making. Given the complexity of the issue and the credentials of those on each side of the debate, this appears to be simply a fantasy.

Wishing you good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at

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The U.S. Preventive Services Task Force has published its official and latest position on PSA screening in the *Annals of Internal Medicine*, July 17 issue, and the publication plus two commentaries are available free.¹⁻³ Google the journal name or use PubMed. The Task Force reviewed new evidence of the benefits and harms of PSA screening with emphasis mainly on two recent studies that appeared after their 2008 recommendations.

The Task force recommends against PSA screening for men of any age in the U.S. population but points out that this does not apply to surveillance after diagnosis or treatment, pointing out that this was outside the scope of the review, which is rather obvious. PSA screening was regarded as having a moderate to high certainty of producing no net benefit or that the harm outweighed the benefit. The rating given was the lowest in their scheme except for issues where there is insufficient evidence to even make a recommendation.

Simultaneously the journal published two short articles, one pro and one con regarding the Task Force position. The critical article had nine authors including some of the most well-known and respected names in prostate urology.³ Their criticism was based on the assertion that the Task Force overlooked or misinterpreted significant methodological flaws in the two trials upon which they principally relied. The points were as follows:

- The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) had a greater than 50% contamination rate by non-protocol PSA measurements in the control Group.
- PLCO pre-screened 40% of the participants prior to the trial.
- Two-thirds of the patients with abnormal screening tests did not have a prompt biopsy.

These flaws, according to the authors, impair the claim that this was a true screening trial. The cumulative incidence rate for prostate cancer mortality did not differ significantly in the screened vs. control groups and the incidence of prostate cancer was only slightly higher in the screened group. However, the critics could find much less ammunition in the European Randomized Study of Screening for Prostate Cancer (ERSPC). In fact the following were in their favour:

- After a median of 11 years follow-up, the cumulative incidence of prostate cancer was 8.2% in the screened group and 4.8% in the control group.
- Prostate cancer mortality was reduced by 21% in the screened group and 29% in the control group after adjustment for noncompliance.
- The ERSPC trial had only a 15 % contamination and a subgroup corrected for failure to follow the screening protocol and contamination gave a 31% reduction in the probability of prostate cancer-specific mortality.

The main flaw in this second study appears to be its duration. The critics took the position that both trials were too short to provide answers to the proposed issue, given the natural history of prostate cancer.

The Task Force concluded that the decrease in prostate cancer-specific mortality amounted to few lives saved and this benefit did not outweigh the harms of screening and diagnosis (false positives with their associated anxiety and biopsy complications and harms related to the treatment of screen-detected cancer). The Task Force acknowledged the strong evidence that treatment of localized prostate cancer reduced mortality compared to observation alone and that surgery and radiation therapy showed an approximate 35% decrease in mortality. However, the Task Force took the position that perioperative events, incontinence, erectile dysfunction as complications to surgery and bowel problems associated with radiation therapy must be weighed against benefits of treatment.

The critics of the Task Force recommendations made the following additional points:

- Diagnostic procedures and related complications occur in unscreened populations as well, and at a later stage in cancer discovery.
- The Task Force focused on mortality and thus ignored the substantial problems associated with living with advanced cancer.
- The Task Force failed to give adequate consideration to high risk populations such as men with family history of prostate cancer or men of African descent.
- The Task Force ignored the epidemiologic data that showed a 40% decrease in prostate cancer mortality and a 75% decrease in presentation with advanced disease since PSA testing began in the early 1990s.
- The Task force did not qualify its recommendations by age, which is not realistic since someone over 75 will most probably die of other causes before developing metastatic prostate cancer and younger men should benefit from screening and early detection of curable cancer.

The viewpoint favouring the Task Force recommendation emphasized the standard arguments against screening that have been discussed repeatedly in *The Prostate Monitor*.² The author pointed out that most Americans have been taught for decades to fear all cancer and the best approach is early detection and aggressive treatment. This was termed blind faith with little appreciation of the harms of screening. He also raised the point that overdiagnosis makes screening seem to save lives when it does not. Overdiagnosis includes cases never destined to result in prostate cancer-specific mortality. He quotes the famous statement of Whitmore, "If a cure is necessary, is it possible, and if a cure is possible, is it necessary."

While the Task force recommendation will probably have a large impact on Medicare coverage or that of third-party insurers, the critics believe that elimination of reimbursement would take us back to an era when prostate cancer was often discovered at an advanced and incurable stage. However, the author of the defence of the recommendation tells us that we must heed science and those who continue to advocate PSA screening exhibit blind faith in early detection. However, the real reason for the above debate is really very simple. The PSA test is really rather lousy with nothing validated or approved that can immediately replace it. Is it back to the old digital rectal exam, a screening test that also has many problems, does not provide as solution to the above issues, and is actually in many practices part of prostate cancer screening anyway.

Everyone involved in the ongoing debate, it can be safely assumed, agrees that guidance must come from evidence-based recommendations and that everything must be "scientific." Disagreement is in the details and the above debate solves nothing nor does it resolve the basic issues. But there is a more fundamental problem associated with evidence-based medicine.

It is not evidence-based medicine, it is probability-based medicine, rather like the sophisticated probability methods used by some players of blackjack which worked well enough that they caused significant problems in casinos. Nevertheless, we are talking about merely a shift of the odds slightly more in the favour of the player. Probability-based medicine is also population-based medicine. It averages over large populations to come up with recommendations to be applied to an individual. It also deals with improved odds, many of which are quite small but attract attention because they are "statistically significant." It brings medicine to the point where the patient-physician interaction can almost entirely be handled by a computer with the input of the appropriate data and test results. Those who are pushing for a more personalized form of medicine are really talking about genetics, not listening to patients during office visits much longer than now common.

It also appears that in medicine, the word science is somewhat abused, unless one regards those devising a blackjack systems as using science, which is of course debatable. The phrase *it has been*

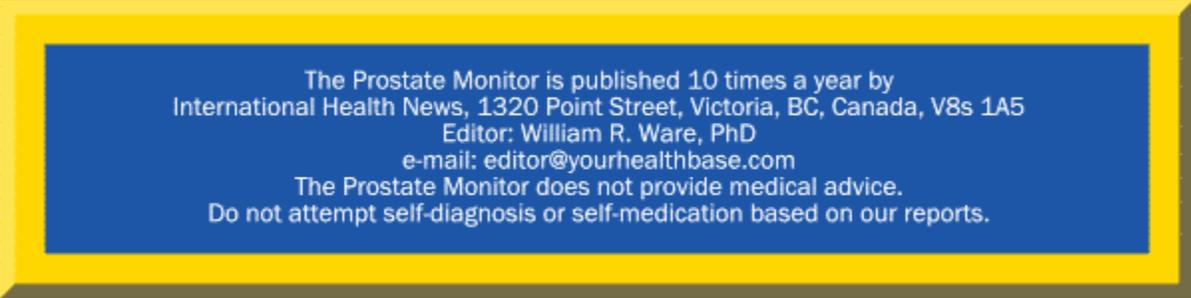
scientifically demonstrated needs to be taken with a considerable dose of salt. Probability-based medicine is all about statistics. Studies need, indeed require experts in biostatistics. They are able to offer up to the researchers a wide variety of presentations of their results, each with its own spin. After the dress rehearsals and revisions, the final production is presented to the audience in the form of a paper, supplementary data rarely viewed, and tables that many physicians cannot fully understand. How many physicians know how to calculate the odds ratio from the coefficients of a logistic regression analysis? How many know that the reciprocal of the *absolute* risk reduction yields the number needed to treat? How many appreciate the powerful deceptive force of the relative risk reduction number?

The classic example is the statin drug. While not applicable to the issue of prostate cancer, it is now quoted frequently in books by famous physicians who are starting to question the system (e.g. *The Creative Destruction of Medicine*, by Eric Topol). Take this statin drug and it will reduce your chances of a heart attack by 20% (or even more, depending on the study being promoted) you are told. Do this for the rest of your life, even if now you are totally asymptomatic, and even at what probability-based medicine considers to be a low risk. An alternative but equivalent statement based on the same data is simply that if you take this drug for at least 5 years, you have about a 1 in a 100 probability of it being beneficial (one patient benefits, 99 do not) and the risks are unknown because of suppression of data, conflicts of interest, totally inefficient adverse event reporting and recording, and advice and guidelines bearing the stamp of approval of high-profile professional societies or government agencies that are in fact drafted by individuals with close ties to the companies that sell the drugs.

The prostate screening problem is slightly different but still critically dependent on statistics, cut-offs, and arbitrary thresholds. The reader is referred to the April issue of *The Prostate Monitor* for a detailed example of what is really probability-based medicine, not evidence-based medicine, where the issue involved was the merit of the new prostate cancer marker PCA-3.

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