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William R. Ware, PhD - Editor

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Type 2 diabetes is highly prevalent and most individuals either just diagnosed or with existing disease are medicated, first with one drug, and then frequently with polypharmacy. That complications are associated with elevated blood glucose appears well established. However, blood glucose, whether measured fasting, after a glucose challenge, or by the blood marker of average levels (HbA1c), is also a biomarker like blood pressure and serum cholesterol. Not only is reducing certain elevated, risk associated biomarkers viewed as beneficial, but in the last decade it became popular to set targets, in some cases, rather arbitrarily, and engage in intensive drug therapy to achieve these targets. In this issue, after briefly reviewing the studies that revealed no impact on diabetic complications with intensive glucose lowering as compared to the less aggressive approach, we examine how well the less aggressive approach really works with emphasis on metformin, the first line drug used when someone is diagnosed with diabetes. Readers will perhaps be surprised or even shocked at what recent studies have revealed. Also discussed is a recent trial, concerned with lifestyle modification to prevent complications of diabetes, which was halted because of futility.

Blood pressure is another marker which some would view as having rather arbitrary thresholds for the diagnosis of various levels of hypertension. A recent study found no benefit from drug treatment of mild hypertension on the prevalence of serious acute events traditionally associated with this disorder.

Finally, readers may recall that in the June 2012 issue, the hypothesis was discussed which held that methanol (methyl alcohol, wood alcohol) when ingested is converted into formaldehyde, an exceedingly active, toxic and mutagenic chemical. Sources of methanol include canned goods, smoked meat and fish, and an artificial sweetener in common use. It is thus interesting that a study from Harvard just published found that high vs. low consumption of aspartame-sweetened soda was associated with an increase in the risk of non-Hodgkin lymphoma and multiple myeloma. The article even cites the paper in "Medical Hypotheses" by Woodrow Monte connecting aspartame with a number of chronic diseases. Monte's new book was the inspiration for the June IHN commentary.

***Recommended for holiday reading**: "Over-diagnosed. Making people sick in the pursuit of health", by three physicians, H. Gilbert Welch, L. M. Schwartz and S. Woloshin. They are professors at the Dartmouth Institute for Health Policy and Clinical Practice. Beacon Press, 2011. This book discusses a number of issues that have come up in recent IHN newsletters that relate to screening, thresholds for declaring diagnosis, guidelines prepared by potentially biased experts, etc.*

And finally, 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 a Happy Holiday Season and good health in the year ahead,

William R. Ware, PhD, Editor

Highlights

PROBLEM WITH DRUG INTERVENTIONS TO CONTROL HYPERGLYCEMIA IN TYPE 2 DIABETICS

Historically, regulatory approval of drugs for type 2 diabetics primarily required only evidence that they lowered blood sugar. No attention was paid to increased risks, especially cardiovascular. However, over the past decade there have been a number of incidents where the use of approved drugs resulted in an increase of acute and fatal cardiovascular events, a famous case being the insulin sensitizer rosiglitazone (Avandia), which made history when the maker paid a record $3 billion in civil and criminal penalties, related in part to concealing safety data. Finally, in 2008 the FDA has endorsed the requirement that pre-approval and post approval trials must meet certain standards associated with ruling out cardiovascular side effects.[1] In this context the following recent study is of interest.

The sulfonylurea class of diabetes drugs has been around for a long time. Back in 1961 the question was already being asked: do sulfonylureas increase adverse cardiovascular events? The importance of this question is underscored by prevalence of its use. Figures from 2007 indicate that 10.1 million Americans (approximately 34% of patients treated for diabetes) used a sulfonylurea as part of their regime. A retrospective cohort study (observational data) has just reported which examined the risk of acute heart attack, stroke or death (composite outcome) among users of either metformin (a very common glucose control drug) or a sulfonylurea class drug.[2] The study linked U.S. National Veterans Health Administration databases and Medicare files. There were 155,015 individuals in the metformin group, 98,655 in the sulfonylurea group.

It was found that the use of sulfonylureas increased the incidence of the composite outcome by a factor of 2.2 per 1000 person years use with a 95% confidence interval of 1.4 to 3.0. This was equivalent to a 21% increase in hospitalization associated with the composite endpoint events. The comparison was with metformin. Other downsides associated with sulfonylureas compared to metformin include increases in weight and lipid levels and greater risk of acute low blood sugar, but both drugs provide similar blood glucose control. This is not good news for the millions of sulfonylurea users worldwide.

To gain perspective in this important area, the drug approach to type 2 diabetes, consider the following studies that have looked at intensive vs. standard glucose lowering and as well, how well metformin alone really works. The results may come as a surprise.

In 2008 two papers were simultaneously published in the *New England Journal of Medicine* which certainly got considerable attention, and not just among those involved in the treatment of diabetes. The ACCORD study randomized 10,251 patients with type 2 diabetes to receive intensive therapy targeted at getting HbA1c down from a median level of 8.1% to below 6.0%, generally considered normal. The control received standard therapy targeting a level of 7.0% to 7.9%. As compared with standard therapy, the use of intensive therapy for 3.5 years increased mortality and did not significantly reduce major cardiovascular events and in fact identified previously unrecognized potential for harm.[3]

The ADVANCE study randomized 11,140 type 2 diabetics to either standard glucose control using mostly oral glycemic drugs and an intensive intervention group using mostly one drug, a modified release sulfonylurea called Gliclazide, which at baseline was used by only 7.6%, but this increased to over 90% by the end of the trial. Use of insulin was also increased as part of the intensive program. There were 19 primary and secondary endpoints. Only combined major macrovascular and microvascular events were found have reduced risk, and the reduction was small (10%) and was due mostly to a reduction in new or worsening nephropathy (kidney problems). Thus for 18 out of 19 endpoints there was no significant benefit. A 10% effect is viewed by some as a small or clinically insignificant effect. The absolute benefit of the intensive intervention on new or worsening nephropathy was 1.1%, which is equivalent to needing to treat 91 patients to achieve one benefit over the duration of the trial which had a median follow-up of 5 years.[4]

The ACCORD study was more compelling than ADVANCE because it did not emphasize one drug but intensified current therapy with variations and also increased the use of insulin. In both ADVANCE and ACCORD, at the end of the study the HbA1C levels in the intensive treatment groups and the control groups were 6.4-6.4% and 7.5% respectively, thus approximately meeting the goal of examining the impact of achieving significant reductions in average circulating glucose. While there is good evidence that elevated HbA1c is a surrogate marker for the risk of events used as endpoints in these two studies, the results called into question the notion that benefit would derive from lowering the marker. Nevertheless, this is a fundamental assumption associated with the medical treatment of diabetes.

From 2009 to 2011 three meta-analyses were published which examined studies targeted at the same question as ACCORD and ADVANCE.

- Turnbull *et al* concluded that more intensive glucose lowering modestly reduced major macrovascular events and increased hypoglycaemia in persons with type 2 diabetes. Four major studies were examined which all had found no significant effect for this endpoint but when combined produced a small but statistically significant effect of 9% reduction. They also found a 15% reduction in heart attacks, mostly driven by the ACCORD result. If one looks at the ACCORD results, the absolute reduction in fatal and non-fatal heart attacks was 0.8%, or 125 parsons needed to undergo the intervention to prevent one such event over 3.5 years. For all-cause mortality, cardiovascular death or non-cardiovascular death, the meta-analysis found no significant benefit from aggressive glucose lowering.[5]
- Hemmingsen *et al* concluded from a meta-analysis of 14 studies that for patients with type 2 diabetes, intensive glycemic control does not seem to reduce all-cause mortality and that data from randomized clinical trials remain insufficient to prove or refute an association with cardiovascular complications or retinopathy. For non-fatal heart attack, 8 studies yielded an absolutes risk reduction of 0.24% or the need to treat over 400 individuals to prevent one event over approximately 6 years (range 4.5-10 years).[6] Comparison was with standard glucose control.
- Boussageon *et al* examined 13 studies. For all-cause mortality and death from cardiovascular causes, all heart attacks, all strokes, non-fatal strokes, combined macrovascular events and heart failure, microvascular events (retinopathy and need for photocoagulation, blindness or visual deterioration, new or worsening neuropathy, new renal failure, peripheral vascular events, and amputation), no significant benefits of intensive treatment vs. standard treatment were found. A small effect was found for worsening microalbuminuria (kidney function) based on 9 studies, 8 of which were insignificant.[7] As Turnbull and Zoungas comment concerning this study, for non-fatal heart attack, while a 15 % relative risk reduction was found over 5 years 117-150 patients would need to be treated to avoid one fatal heart attack. They also call attention to the result of the meta-analysis which found that one severe episode of hypoglycaemia would occur for every 15-52 patients treated.[8]

These results all apply to a comparison between standard care and intensive blood glucose lowering. Standard care generally aims at glucose control down to a level manifest by an HbA1c of 7% to 7.5%. Untreated type 2 diabetics can have values considerably higher. Thus the obvious question, since the

American Diabetes Association (ADA) lists metformin as the first-line of standard care after diagnosis of type 2 diabetes, to what extent does it reduce the cardiovascular and other vascular complications of diabetes, the most important reason for lowering elevated blood glucose. Put directly, the question is, does it work? Silly question? It has been use for decades for just that purpose. Read on.

Metformin is the standard first line of treatment to which other drugs are added as needed. The second drug is typically a sulphonylurea. Boussageon *et* al[9] published a meta-analysis in 2012 which is thus of considerable interest since it examines a number of studies with clinical event endpoints where metformin was compared with diet, a placebo, usual non-drug care or insulin. Also included were treatment protocols where metformin plus a sulphonylurea were compared with sulphonylureas as sole treatment. In 13 randomized controlled trials, 9560 patients were given metformin and 3550 patients were given diet and exercise or a placebo. Metformin did not significantly affect all-cause mortality, cardiovascular mortality, all strokes, heart failure, peripheral vascular disease, amputations and microvascular complications. The authors conclude that although metformin is considered the gold standard, its benefit/risk ratio remains uncertain. This seems to be quite an understatement. As evidence of the inconclusive nature of the results, they point out that a 25% *reduction* or a 31% *increase* in all-cause mortality could not be excluded. For cardiovascular mortality, the numbers were 33% and 64%.

In connection with the meta-analysis of Boussageon *et al*[9] it is of interest to look at just the studies with a significant number of events that used metformin alone vs. either diet or usual non-drug care for the major endpoints of all-cause mortality, cardiovascular mortality and all heart attacks. Only two studies with longer than 12 months follow-up qualified, UKPDS 35[10] and Rachmani *et al*[11]. If one pools the results from these two studies and gives them equal weight, then as shown in the table below, for three endpoints there is no statistically significant benefit found according to your editor's calculations, since the confidence intervals all contained the null (no effect) result 1.00.

ENDPOINT	OR	95% CI
All Heart attacks	0.77	0.57—1.04
All-cause mortality	0.80	0.61—1.06
Cardiovascular mortality	0.79	0.58—1.10

These two studies together involved 537 subjects in the treated group and 609 in the control group. For the two studies selected for the above analysis, the other endpoints examined in Boussageon *et al* were found only in the UKPDS study. The number of events was small and the results all statistically insignificant.

The 2012 American Diabetes Association (ADA) Standards of Medical Care in Diabetes clearly indicate that metformin should be initiated as therapy for type 2 diabetes at the time of diagnosis. If the patient has markedly elevated blood glucose or HbA1c, then the advice is to consider insulin with or without additional agents. If metformin alone does not achieve or maintain satisfactory HbA1c levels over 3-6 months at maximal tolerated doses, the recommendation is to add a second oral agent.[12] This more intensive treatment is of course related to the subject of the several meta-analyses discussed above which find no benefit or in rare cases, a small positive benefit but unreasonable numbers needed to treat.

Thus the interesting conclusion appears to be that, not only does intensive glucose lowering not appear to offer benefit for type 2 diabetics, neither does following the ADA recommendations and use the gold standard – the well-known and very popular drug metformin, employed to achieve glucose control and lowering, plus additional drugs if needed. Even though the above protocol is widely viewed as evidence-based, this appears to be questionable on the basis of a number of clinical trials which find otherwise. Is it possible that, in terms of benefit for the variety of endpoints discussed, the wrong risk marker, i.e. high blood glucose, is being targeted? After all, it appears impossible with numerous randomized, controlled trials or their combination in meta-analyses to find any significant evidence of benefit except for one or two endpoints where the numbers needed to treat are so high

that the clinical significance is open to question. However, it appears well established that high circulating glucose or an elevated HbA1c is a risk factor, provided one does not attempt to demonstrate this by drug-induced lowering.

Drugs used to treat glycaemia and lower HbA1c fall into two major classes, insulin sensitizers and drugs that mimic the action of insulin. The above studies suggest that these interventions do not significantly impact the root causes of the macrovascular and microvascular complications of diabetes and therefore appear to be ineffective.

Today there are cries (from the wilderness) for a return to traditional approach of treating type 2 diabetes and the adoption of carbohydrate restriction in the context of diabetes prevention and therapy.[13-17] The success achieved by Richard K. Bernstein using carbohydrate restriction and carefully selected carbohydrates matched to the individual's metabolism is now documented in several editions of his book *Dr. Bernstein's Diabetes Solution*.[18] The HbA1c levels he achieves are vastly better than anything conventional medicine appears able to achieve, and this is accomplished with diet. Drugs or insulin are used only when absolutely necessary. Taken together, the relevant medical literature and the evidence in Bernstein's book should give cause for reflection among diabetologists.

It seems important, however, to emphasize that there do not appear to be any studies that provide satisfactory evidence for the efficacy of *dietary* glucose-lowering in type 2 diabetics on the complications of this disease. However, it can be argued that this approach appears to alter the metabolism naturally in the direction and approaching that of a non-diabetic. The required studies may never be done.

DIABETES TRIAL HALTED BECAUSE OF FUTILITY

In mid-October, 2012 it was announced (see theheart.org, October 19) that the Action for Health Diabetes (Look AHEAD) trial was halted after 6 years follow-up because there was no difference in the rates of non-fatal heart attack or stroke, death, or hospitalization for angina among type 2 diabetes patients randomized to an "intensive" lifestyle intervention and those randomized to the control arm consisting of education alone. The only published data is from two papers, one reporting one year results and baseline data, the other four-year data.[19,20] The intervention group was assigned a calorie goal based on initial weight (1200-1800 calories), less than 30% calories from fat (< 10% from saturated fat), and a minimum of 15% total calories from protein. Exercise was set at 175 minutes per week with such activities as brisk walking. All subjects were diabetic with baseline HbA1c of about 7.3%, fasting blood glucose of 152 mg/dL, and BMI 36, i.e. obese. Most subjects were heavily medicated at baseline with 86% on diabetic medication, 73% on blood pressure medication, and 49% taking lipid-lowering drugs. At year 4, the comparative medication usage numbers were 91%, 81% and 90%, respectively. Thus in this study, meaningful changes in cardiovascular markers were sought in the face of increasing use of medication. In all the data presented, only confounding by medication of the LDL cholesterol levels was addressed in the statistical analysis. The authors claim that otherwise this was not an issue but no data were presented. The absence of clinical benefit in terms of event endpoints at year 6 of course suggests the intervention was useless.

If one assumes 25% fat, 20% protein then the suggested diet was high carbohydrate and low in fat, a diet commonly viewed by mainstream medicine and nutritionists as ideal for diabetics. A detailed report was presented at the end of 4 years based on changes in cardiovascular risk markers. The data are typical of this type of study. At year one, there are fairly large changes (up for fitness and HDL, down for weight, HbA1c, blood pressure, triglycerides, and LDL), and large differences between the control and intervention groups. The changes in some of the markers from baseline to year four were as follows: BMI, 36 to 34, HbA1c 7.5% to 7%, Systolic blood

pressure, 128 to 124, and triglycerides 183 to 163. These numbers are taken from graphs. The authors tabulated data is averaged over 4 years, which magnified the differences and down-played the convergence. No year 6 biomarker data are as yet available, but it seems unlikely that the differences between the two groups diverged.

Thus it should come as no surprise that this study provided null results for acute event endpoints at year six. It should probably have been stopped at year four when it became apparent that the differences in the control and intervention groups were converging to clinically insignificant differences. Even if this had not happened, it seems likely on the basis of a considerable recent literature, some of which has been discussed above, that targeting risk factors is not working. Yet consider editorial comment on the year four results: "These findings are exciting and provide solid evidence of sustained benefit of simple interventions such as TLC (therapeutic lifestyle changes), on multiple important cardiovascular risk factors in type 2 diabetes."[21]

NO BENEFIT FROM DRUGS IN MILD HYPERTENSION

Observational or follow-up studies have traditionally provided information on risk factors and their association with chronic disease. It is then assumed that if steps are taken to change the level of the risk factor in a favourable direction, benefit in terms of reduced risk of the endpoints in question will occur. Examples of commonly assessed markers include fasting blood glucose, blood pressure and the various forms of cholesterol. For each, the pharmaceutical industry has interventions which bring about the desired changes. Naturally, the industry has a very strong and vested interest in the levels triggering pharmaceutical intervention, and they appear well represented among the groups of experts who create guidelines judging by the conflict of interest disclosures in the medical literature.

Targets for risk markers thus become very important since they influence the dose and number of drugs ultimately prescribed as the physician works with the patient to achieve the perceived benefit associated with having, for example, blood pressure, LDL cholesterol and fasting blood glucose "at target." This in fact has become a cornerstone of mainstream medicine's approach to preventive medicine. The use of drugs is of course totally realistic given the well documented difficulty patients have with adherence to lifestyle changes including diet. In fact, the latest development being promoted is the polypill, one version of which contains a cholesterol lowering drug and three different blood pressure medications.

It is thus of interest to examine a recent analysis from the Cochrane organization, famous for excellent meta-analyses related to important health issues.[22] The question addressed was the benefit of drug treatment for mild hypertension, defined as 140-159/90-99 mm Hg. Patients with mild hypertension are very frequently treated with blood pressure lowering drugs. The question examined was the impact of this intervention on actual events. The intervention was supposed to reduce risk. It may surprise readers to learn that they found, even after contacting some of the researchers for additional data, that there were only 4 randomized, controlled trials specifically looking at primary prevention in patients with mild hypertension that met their criteria for acceptability for pooling in a meta-analysis. One was done in the early 1990s and the others in the late 1970s. The included studies involved 8912 patients with mild hypertension treated for 4 to 5 years. It was found that drug treatment did not significantly reduce total mortality, coronary heart disease or stroke, and they were not referring to clinically significant, simply statistical significant. The authors commented that mild hypertensives probably represent about half of the hypertensive patients treated and this intervention was viewed as supported by gold-standard evidence. They viewed this analysis as indicating that this was in fact not true and recommend that patients be advised to adopt the DASH diet and engage in more adequate exercise instead of pills.

Critics were quick to point out what they viewed as limitations in this study (Heart.org, August 15, 2012). The main problem was that the event numbers were small for mortality, 77 in the treatment arm, 90 in the placebo group. There were only 10 strokes in the treatment group, 20 in the controls. Also, the endpoint of the progression of hypertension in was not examined. Thus the study of necessity lacked desirable power to find significant answers, and thus the call for larger studies of this important subgroup of hypertensive patients. These criticisms actually provide an additional argument for the assertion that the use of medication to treat mild hypertension is not evidence-based.

In a paper titled *The Failure of Risk Factor Treatment for Primary Prevention of Chronic Disease*, Mark Hyman, M.D. points outs that four recent large trials targeting blood pressure, lipids and glucose, while effective in lowering the risk factors, did not show benefit in reducing nonfatal heart attack, nonfatal stroke, or death from cardiovascular disease.[23] Another example involves reducing the marker homocysteine which also failed to yield benefit in terms of events. It seems that there is a fundamental flaw in the argument that even though the level of a risk factor suggests increased probability of certain major events, raising or lowering the level in a theoretically beneficial direction does not necessarily in fact produce the expected benefit. Yet this is central to the approach of mainstream medicine and their partners the pharmaceutical industry. It is also a key component in the development of new drugs. Lower beta-amyloid and Alzheimer's patients will benefit—not so. Perhaps the picture which emerges is not surprising. The approach involves treating surrogate markers rather than causes. As discussed above, the glucose-lowering drug metformin, the officially agreed upon first treatment for type 2 diabetes, indeed accomplishes this but has no impact on all-cause mortality, cardiovascular mortality heart attacks, strokes, peripheral vascular disease, leg amputation or microvascular complications in type 2 diabetics. This is the conclusion based on a meta-analysis of 13 randomized controlled trials involving over 13000 patients.[9] But avoiding these complications was why patients were taking this drug and why it is one of the most popular drugs for glucose control. Evidentially, treatment accomplished lowering a marker but did not address the fundamental causes of these complications.

The real issue here is the basic philosophy concerning risk factors. They are also surrogate markers. It is tacitly assumed that if a risk factor is too low or two high, fixing this will reduce the risk in question. While this is nice in theory, there are enough examples where this is not true to raise concerns about the dominant place this notion holds, not only in mainstream medicine but also in how it influences the behavior of drug companies. These companies have a strong vested interest in targets that will prompt the greatest use of their drugs when in many cases the targets are not evidence based. Targets for LDL cholesterol provide a recently discussed example where it was pointed out that there is no scientific basis to support treating to guideline LDL targets, and the safety of doing this has never been proven,[24] Furthermore, the focus on risk factors and the emphasis on treating them in terms of primary prevention has provided a serious distraction for the real challenge, getting at causes and dealing with them effectively, not putting people on pill for life that, when to describe the real benefit as modest is a gross exaggeration. That is not prevention, it is simply a manifestation of desperation in that no one has come up with something better that gets past the regulators and makes money for the drug industry.

Patients are clearly being misled by being told of the benefits of reducing risk markers. Even when there is evidence of benefit, in primary prevention of an acute complication it is not uncommon that the number of individuals that must be treated to prevent one acute event is 50 to 100 or even more. Being told that one has an elevated risk marker but don't worry, we can treat this, is simply not enough. The patients perception will be significantly altered if told they may be among the unlucky 99 out of every 100 treated who achieve no benefit, and thus question or even disparage the term "treated." They may also be alarmed if they know that no studies exist that directly apply to them that demonstrate the prevention of acute events about which they are concerned and may become confused about all the hype concerning evidence-based medicine. The blood pressure study discussed above is a good example.

POTENTIAL DANGERS OF ASPARTAME. AN UPDATE

The June 2012 issue of IHN was entirely devoted to the hypothesis that methanol when converted to formaldehyde in humans has the potential to cause a number of chronic diseases. The major source of methanol is smoking, canned foods, smoked fish and meat and finally, the artificial sweetener aspartame. A paper just published in the *American Journal of Clinical Nutrition* relates to this subject.[25] The lead author is from Harvard medical school and one of the authors is the famous nutritional epidemiologist from Harvard, Dr. Walter W. Willett. The study reported involved two large databases, the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). At issue was the question is the consumption of aspartame-containing soda associated with so-called hematopoietic cancers (blood cell cancers)? The comparison was with sugar-sweetened soda. The incentives for this study were indications in the literature that aspartame might be carcinogenic in animals, and the fact that aspartame breaks down to yield methanol which is converted to formaldehyde, which the authors point out is a documented human carcinogen.

Dietary intake, which included detailed information about soda consumption, was assessed as part of the 1984 questionnaire in the NHS and again in 1986 in both the NHS and HPFS cohorts in 1986. Diet was subsequently reassessed every four years. The data allowed the determination of aspartame intake and allowed the analysis of association with non-Hodgkin lymphoma, multiple myeloma and leukemia.

Results of statistical significance after adjustments for 14 confounding factors were as follows: When < 1 serving/week of diet soda was compared to ≥ 1 serving/day, for men it was found that the increase risk of non-Hodgkin lymphoma was 31%, multiple myeloma 102%, and for the pooled results for men and women, the adjusted result was 42%. When the fifth quintile of aspartame consumption was compared with the lowest quintile, (zero mg/day), the increased risk of non-Hodgkin lymphoma was 64% and for multiple myeloma 236%.

The results for sugar sweetened soda indicated an increased risk for men of 66% for non-Hodgkin lymphoma and a 39% increase in leukemia for women.

The authors suggest the strong gender dependence in the diet soda results may be due to differences in the activity of the enzyme alcohol dehydrogenase (ADH) that converts methanol to formaldehyde since it is considerably higher in men. In this study the researchers also examined the association between alcohol consumption and the cancer risk in men and found men who consumed the least amount of alcohol had the highest risk. Alcohol (ethanol) is a strong competitive inhibitor of the action of the enzyme ADH and thus allows methanol to be eliminated via urine breath and sweat without being converted into formaldehyde.

They do not emphasize the importance of this observation independent of the gender difference since a protective effect of alcohol consumption points directly to aspartame as a potential causative agent. The suggestion that formaldehyde derived from aspartame plays a significant role in the incidence of a variety of cancers is supported by the finding of a J or U shaped relationship in some studies of alcohol consumption and the incidence of bladder cancer, colorectal cancer, pancreatic cancer, lung cancer and brain cancer. It is remarkable seeing this effect in diverse cancers unless there is a common factor that plays a role in causation. This will be discussed in a future issue of IHN.

The positive results for sugar-sweetened soda obviously confuse the issue and the authors suggest an alternative hypothesis where some factor or factors common to both sodas contribute to the risk. But the study revealed that there was no association with sugar itself whereas in the case of the diet soda, a direct and strong association was obtained for the aspartame. If some unknown factor in both types of soda were acting, this is would also leave unexplained the strong association between aspartame intake and multiple myeloma since no effect of sugar sweetened soda was found for this cancer.

The cancers in question involve blood cells and if formaldehyde is the carcinogenic agent, it must reach these cells prior to reacting elsewhere. Dr. Woodrow Monte (personal communication) explains this by pointing out that men process a large amount of methanol in their stomach and gut ADH sites and the massive circulation to the gut epithelial would guarantee formaldehyde leakage directly into the circulation where it could then react with blood cells. This helps explain the greater impact of aspartame on men in this study.

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