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This issue begins with a brief discussion of the alleged misdeeds of the pharmaceutical industry which impact the confidence one can place in evidence-based medicine. Information is drawn from both major peer-reviewed journals and, as well, respected newspapers which report on evidence presented in court cases. This discussion could have been easily doubled in size given the flood of reports regarding this subject.

Recent results concerning the risk of coronary heart disease are discussed. Included is new information of the meaning of a zero calcium score, the importance of glycated haemoglobin in developing a true picture of risk, and the interesting role that angiotensin receptor blockers (hypertension medication) may play in arresting or reversing atherosclerosis.

A very recent study of the relationship between vitamin C supplementation and cataracts is reviewed which causes one to wonder about the utility of the peer-review process. In this study, a method of analysis was selected which masked what appears to be a null effect, and this alternative analysis is not even mentioned in the paper even though it can be argued that it has greater validity than the one used.

Several news briefs are presented which include an update on some interesting vitamin D research, and a brief commentary on the FDA attack on POM, the maker of a popular brand of pomegranate juice.

Finally, a Research Report is included in this issue which discusses the popular mainstream treatment for acid reflux and heartburn, the proton pump inhibitor. An attempt is made to present the case for the possibility that this approach represents such a radical intervention into the normal functioning of the stomach and gut that it should be viewed with considerable scepticism. It appears that something most learned in high school, and most doctors relearned in medical school, i.e. that the health and functioning of our digestive system depends on a high level of stomach acidity and that this is fundamental to our nutritional biochemistry and wellbeing, is in fact being ignored in order to treat symptoms of what is now commonly termed a disease. Furthermore, the possibility that low not high stomach acidity could be among the primary causes of digestive problems appears now to be almost completely ignored.

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 and well-being,

William R. Ware, PhD, Editor

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A BETRAYAL OF TRUST

The recent flurry of reports of what some would call misconduct by the pharmaceutical and medical device industry seems unprecedented. This adds to material presented in earlier issues concerning the ethics and operating principles of Big Pharma and the medical device makers. When drug companies

are dragged into court, a lot of material they would rather keep secret ends up in the public domain. It is regrettable that all of this leaves one with little confidence in an industry that so strongly impacts the lives of millions of individuals. The following is not a complete list.

- A U.S. Senate investigation has found that the medical device maker Medtronic paid almost \$800,000 in consulting fees over three years to a researcher who falsified data in a study of one of the company's products. The study published in the *British Journal of Bone and Joint Surgery* was subsequently withdrawn by the journal (New York Times November 11, 2009).
- Information revealed in court documents in the public domain suggests that clinical trials funded by Pfizer and Warner-Lambert's subsidiary, Parke-Davis, of off-label indications for the epilepsy drug Neurontin (gabapentin, used off-label for prophylaxis against migraine and treatment of bipolar disorders and neuropathic pain) were never reported. These revelations were presented in a recent paper in the *New England Journal of Medicine*¹ wherein the authors comment that the reporting practices observed in their analysis did not meet ethical standards for clinical research or maintain the integrity of scientific knowledge.
- Serious concerns about the evidence base for the anti-viral drug Tamiflu, a drug much in the news lately, has been raised both in the lay literature and, more importantly, in the *British Medical Journal (BMJ)*. In 2006 the highly respected Cochrane Collaboration, an organization of sterling reputation in the field of meta-analysis associated with important clinical questions, published a paper suggesting Tamiflu (a neuraminidase inhibitor made by the firm Roche) "worked." When they subsequently re-examined the studies previously used, which were supplied by the drug company, they found discrepancies and only two of the ten studies on which they based their assessment had actually ended up being published in medical journals. What followed could be material for staging a typical theatrical farce. The essence of what went on is described by Brownlee and Lenzer in an article in the *Atlantic* (December 10) which is available online. The Cochrane investigators had great trouble getting complete trial data from either the company or the authors in the case of published material. They were told some of the data had been lost, was not available, "we will get back to you," "I never worked on that study," etc. In the *Atlantic* article

part of what went on was aptly described as "the dog ate my homework." The data the Cochrane researchers finally got their hands on, while incomplete, included two studies by the company that showed the drug was ineffective, but they were never published.

A vastly more complete and shocking version of this story is available in a set of papers, letters, commentary, etc in the *BMJ* (too many to cite). There is even a report from an employee of a medical writing firm who told the *BMJ* that he and colleagues had been hired by Roche to ghost-write studies stressing key messages outlined by the company. The final conclusions of the latest Cochrane Collaboration study² are as follows; (a) neuraminidase inhibitors have *modest* effectiveness against influenza in otherwise healthy individuals (adults); (b) post-exposure, this class of drug is not effective except against a small component of those with influenza-like illness where the influenza was laboratory confirmed; (c) neuraminidase inhibitors *might be regarded as optional* for reducing symptoms of seasonal influenza *but paucity of good data has undermined previous findings for Tamiflu's prevention of complications from influenza* (italics added).

This is the drug that nations all over the world have paid billions of dollars to stockpile. Even the FDA package insert for this drug has little good to say about it.

- Publications resulting from mining for information in documents obtained from drug companies in the process of court proceedings continue unabated. The November 23 issue of the *Archives of Internal Medicine* contains a meta-analysis of unpublished studies by Merck concerning adverse effects associated with the drug Vioxx. This study demonstrates that Merck had data demonstrating a trend toward increased cardiovascular risk associated with this drug as early as December 2000, with statistically significant conclusions available by June 2001, which were 3 ½ years before the drug was withdrawn for these reasons. In an accompanying editorial, Woloshin and Schwartz³ comment "Had the message—that Vioxx was no more effective than other NSAIDs, had a GI safety advantage only for people at especially high risk for bleeding, and tripled the chance of myocardial infarction compared with naproxen (Aleve)—been effectively delivered, Vioxx sales

likely would have plummeted. Instead, they increased.” This report adds to an earlier revelation based on court documents in a class action suit in Australia (*The Australian*, April 1, 2009). Emails revealed that the company prepared a hit list of doctors and researchers who were making statements that Merck did not like regarding Vioxx. The emails suggested such tactics as “neutralize” and “discredit” and the use of threats regarding funding to institutions and interference with academic appointments. Some merely call this playing hard-ball.

- A study in the December 23 *JAMA* reported that premarket approval of cardiovascular devices by the FDA is frequently based on studies that lack adequate strength and in addition may be prone to bias. Fifty-one of 78 premarket approvals were based on a single study and in many studies, discrepancies were found between the number of patients enrolled and the number used in the analysis.⁴
- The U.S. Justice Department has filed a suit against Johnson & Johnson alleging that kickbacks totalling tens of millions of dollars were used to increase its sales of drugs to nursing homes. One of the drugs was an antipsychotic drug that is used as a “chemical restraint.” In a news release by the Justice

Department, it was stated that kickbacks such as those alleged distort the judgments of health care professionals and put profits ahead of sound medical treatment” (*The Washington Post*, January 16, 2010).

Some would call the problems discussed above systemic, and lament that there is not much that can be done, given the structure of the industry, direct-to consumer-advertising, the key role of drug reps or the drug companies themselves in “continuing medical education,” the necessity of drug company support of clinical studies and the manner of operation of the so-called regulatory bodies. The price of getting caught is frequently small compared to profits. It is a cost of doing business and appears to be “business as usual” in the industry. The bottom line appears to be that the lifeblood of mainstream medicine involves pharmaceuticals and that this will continue to be the case for the foreseeable future, and while the ethics of a company should raise questions about the validity of the hype; the implications regarding so-called evidence based medicine appear to be ignored. Yet one cannot have evidence which includes fraudulent and dishonest science since it is not evidence at all and only leads away from the truth.

DOES A ZERO (NORMAL) CALCIUM SCORE MEAN ONE CAN FORGET ABOUT CORONARY HEART DISEASE?

A paper by Min *et al*⁵ addressing this question which was just published in the *Journal of the American College of Cardiology* has the amusing subtitle “What Is the Warranty Period for Remaining Normal?” The extent of atherosclerosis is frequently judged by a so-called coronary artery calcium scan (CAC) using electron beam computed tomography (EBCT). A zero score (no calcified plaque detected) has been found to carry a very low risk of subsequent adverse coronary events, whereas elevated scores and especially high scores are associated with much increased risk. This subject has been discussed in a number of contexts in recent issues of *IHN*.

Min *et al* examined the progression of the CAC in 422 individuals with baseline zero calcium score undergoing annual EBCT scanning over a 5 year period. The results were compared with 621 individuals with baseline CAC > 0. For those initially with a zero score, a score > 0 was found in 0.5,

1.2%, 5.7%, 6.2% and 11.6% after 1,2,3,4 and 5 years follow-up. Among those who developed a CAC > 0 over the total period (106 subjects) age, smoking, diabetes and hypertension were found to be associated with the risk of developing a positive score. It is interesting to note that dyslipidemia, defined as a total cholesterol > 200 mg/dL, was not a significant risk factor and was not even included in the multivariable analysis. Diabetes carried a 140% risk increase from CAC = 0, and for smoking it was 68%. Unfortunately, the distribution of calcium scores among those who developed signs of atherosclerosis during the follow-up were not given, and thus it is difficult to judge the clinical significance of the observed incidence. It would have been interesting to know how many had a CAC of < 5 or < 10, etc. For individuals with baseline CAC >0, 80% experienced progression. In a multivariable analysis, only baseline CAC was independently associated with increased hazard of progression. Cholesterol > 200 mg/dL showed a

non-significant 19% *protective* effect in the univariate analysis (HR = 0.81, 95% confidence interval 0.65-1.01, p = 0.064). In the text hyperlipidemia was listed as a risk factor for progression without mentioning that it may decrease the risk.

For the CAC = 0 group, approximately one-half had hypertension, and nearly two-thirds had dyslipidemia and overall, 92% had ≥ 1 CHD risk factor with a mean of 2.1. All subjects with dyslipidemia were taking statins. The authors conclude that the CAC = 0 score provides a significant 4-year "warranty period." Once the CAC score is > 0 , the magnitude of the score becomes a "robust" predictor of CAC progression. Furthermore, they provide strong evidence that annual calcium scans are unnecessary for anyone with a zero score, and that a 4-5 year interval appears reasonable.

The risk of CHD can be assessed by looking at actual events (unstable angina, heart attack, perceived need for vascular intervention such as a stent or bypass surgery), or it can be assessed in terms of the existence of atherosclerosis and increases in risk can be related to increases in plaque burden. When this latter approach is taken, it is interesting that cholesterol is a non-issue. This is consistent with a large number of imaging and autopsy studies which found that LDL or total cholesterol was not related to plaque burden or progression, and in fact, lowering LDL with statins had no impact on either.⁶ This inability of statins to influence atherosclerosis prevents one from arguing that in the study of Min *et al* the failure of dyslipidemia to appear as a significant risk factor for incidence or progression was due to the fact that it was "treated" dyslipidemia.

The connection with diabetes is interesting in that it was a factor for incidence for those with CAC = 0 at baseline but not progression in those with CAC > 0 . Nevertheless, it appears to eventually be associated with adverse CHD events and ranks with existing CHD as an event risk factor. The diagnosis of diabetes involves a rather arbitrary threshold involving fasting glucose, a glucose tolerance test, or the value of glycated hemoglobin. But diabetes is

in fact a multifactorial disease involving metabolic dysfunction and inflammation. The study of Min *et al* underscores the importance of recognizing the prediabetic state at an early stage and attempting to reverse it.

In an accompanying editorial, H. S. Hecht points out that the overtreatment of and unnecessary diagnostic procedures associated with CHD are common in individuals who are at low risk by virtue of their calcium score (< 100).⁷ He reminds readers that in a study of individuals in the Framingham intermediate risk category, 63% were downgraded to low risk based on CAC scores. He points out that the cost of overtreatment in low-risk asymptomatic populations is high, and views a CAC = 0 as "priceless."

It appears that there is movement toward a consensus that a calcium scan should be a part of the health status evaluation of a significant fraction of the adult population. It is clear from the study of Min *et al* that even if the result is normal, a repeat every 5 years is not unreasonable. There will be a vocal group pointing out the perceived dangers of the associated radiation, but the reader is referred to the November 2008 issue of IHN where a Research Review on radiation and cancer for what is hoped is a more realistic view – www.yourhealthbase.com/archives/ihn192bt.pdf. If a significant CAC is observed, there are really no evidence-based interventions. However, avoiding diabetes, dealing with any symptoms of prediabetes with diet and exercise, making certain regarding an optimum vitamin D status, making use of the Omega-3 Index as a guide to long-chain omega-3 fatty acid intake and correcting high triglycerides and low HDL cholesterol with diet could be very important. Hypertension is the only consistently observed risk factor for the progression of coronary atherosclerosis as measured by the calcium score, but there is little evidence that lowering blood pressure will slow or reverse coronary atherosclerosis. However, see the study discussed below. Ideally, of course, blood pressure should be reduced and controlled without recourse to prescription drugs but again, a convincing evidence-base appears lacking.

ANGIOTENSIN BLOCKERS AND PROGRESSION OF ATHEROSCLEROSIS

In the last newsletter a study was reviewed that suggested that angiotensin receptor blockers

(ARBs) used to treat hypertension also had significant beneficial effects on patients with pre-

existing Alzheimer's disease. Now a study has appeared which indicates a beneficial effect of this drug on the progression of coronary atherosclerosis as measured by intravascular ultrasound (IVUS) identified accumulation and swelling in artery walls.⁸ Repeated use of his technique provides a measure of the change in the percent atheroma (plaque) volume and the total atheroma volume. The study was prospective, randomized and multicenter and all subjects had stable angina and coronary artery disease. When the subjects underwent percutaneous coronary intervention for culprit lesions, IVUS was also performed in their non-culprit vessels (< 50% blockage). Patients were then randomly assigned to an ARB (olmesartan) or treated with a combination of beta-blockers, calcium channel blockers, diuretics, nitrates, glyemic control agents and/or statins at the physician's discretion, thus serving as a control. A second IVUS was performed at a 14-month follow-up. Patient characteristics and blood pressure control were identical between the two groups. But the follow-up IVUS showed significantly decreased total atheroma volume and percent atheroma volume (5.4% vs. 0.6% and 3.1 vs. 0.7% respectively) for the comparison between the control vs. olmesartan. The authors suggest that this ARB has merit for patients with stable angina in that it appears to lower the rate of coronary atheroma progression.

An accompanying editorial points out that, although several biologically plausible characteristics of coronary plaque have been proposed which might be associated with adverse coronary events, there

are no studies addressing this issue. Thus studies are needed using ARBs as an intervention with adverse events such as heart attack or sudden cardiac death as endpoints.⁹ if carried out, the results would be of considerable interest. The impact of ARBs on the incidence and progression of coronary plaque measured in asymptomatic individuals would also be of great interest. In the meantime, benefits that accrue to those on ARBs for hypertension. Since hypertension is widespread and its treatment of considerable benefit to Big Pharma, there may indeed be studies of ARBs in the context of CHD in the near future. Also, the extent and progression of coronary calcium is an attractive endpoint since it produces results in a few years without involving huge numbers of asymptomatic individuals required for intervention studies with adverse event endpoints. Thus studies involving ARBs and EBCT, which is non-invasive, with the incidence and/or progression of coronary calcification in healthy individuals as an endpoint would be of great interest. Stay tuned!

This paper and the IHN Research Report concerning Alzheimer's disease (see www.yourhealthbase.com/Alzheimer's_Prevention.htm) remind one of the paper by Law and Wald¹⁰ also discussed previously which took the position, based on a perhaps unrealistically huge meta-analysis, that the practice of measuring blood pressure be abandoned and that everyone should be on anti-hypertensive drugs. It appears that if one accepts this radical view, then the drug of choice should be an ARB!

DO VITAMIN C SUPPLEMENTS PUT ONE AT RISK FOR CATARACTS?

In a paper just published in the *American Journal of Clinical Nutrition* it is concluded that supplementation in the range of 1g/d puts one at a 25% increased risk of cataracts.¹¹ Millions take vitamin C supplements at this dose level and higher levels are not uncommon. In a prospective study the authors obtained baseline data and then followed up for on average about 8 years. The endpoints concerned cataracts in their various clinical manifestations. At baseline the researchers gathered information about all the confounding factors they could think of and they also collected data on supplement use. However, the intake of vitamin C for those on only C as a supplement was derived from some earlier studies of how much people generally took if they supplemented with C, i.e. about 1000 mg/day. For some obscure reason,

they did not ask the C supplement users how much they took, or if they did it was not reported.

When the study was over they had at least two choices as to how to do the calculations. One would be to look at the incidence in the group that took vitamin C (5%) as a single supplement as compared to the rest of the cohort. Those taking C alone took quite a bit (about 1g/d) if one can believe their indirect way of estimating intake, the rest of the cohort had a very small intake which was about 60 mg/d for the fraction that took a multivitamin (only 9%) and about 100 mg/d for the total cohort from food. Thus the suggested reference group would include those who used no supplements and those who used supplements including a multivitamin, but not those who took only vitamin C supplements.

This directly compares those on high dose vitamin C to those on low dose or no vitamin C. They elected not to do this but instead use as a reference for relative risk the 41% of the total cohort that did not use any supplements at all and compared this to the 5% that took only Vitamin C. There are many differences in this group compared to the total cohort minus the C supplement users which are difficult to incorporate in correcting for confounding, and this introduces the possibility of bias specifically associated with the use of this group as a reference in epidemiologic calculations.

If one does the simple epidemiology 101 calculation based on the comparison of the C supplement users vs. the remaining cohort, the incidence of cataracts was 117.6 per 1000 in the no vitamin C group and 116.7 per 1000 in the vitamin C group. Thus there is no significant difference. With numbers so close there is no need to discuss the calculation of the relative risk *reduction* (not increase) associated with C supplementation or the number need to treat with C to *prevent* one cataract (actually it is about 1100), but this is statistically and clinically meaningless). This result might be changed during multivariate analysis, but examination of their multivariate analysis when using only individuals who took no supplements as a reference suggests that more extensive statistical analysis is not needed, would move results closer to the null and would not create a statistically significant result, much less a clinically significant result. This simple calculation and result is consistent with the picture the authors paint in the discussion section, paragraph 3, where they provide evidence that earlier studies are highly variable and inconsistent and show benefit, harm or nothing at all for vitamin C supplementation in this context. When there is such a wide range of study results, it

generally means that there is no effect at all, and it is suggested that in the study being discussed, this is also the case.

The same calculation based on their reference population but without age adjustment or multivariate analysis produces a relative risk increase that is similar to the reported age-adjusted value of 27%, so even the crude risk calculation given above must be quite close to what they would get had they used the total cohort minus those taking only C supplements as a reference. It would appear that the non-users of any supplements are different than the group that simply did not supplement with C. From the data provided, 45% of the total cohort were taking supplements other than vitamin C or a multivitamin.

It is possible that both a refined version of the above calculation and the suggested multivariate calculation were actually done and did not produce pleasing results. Papers with null results which confirm a number of earlier studies do not make the evening news. So the statistical game is played to get a result that is useful to the authors, but one that may be totally incorrect.

The bottom line is what some medical scientists have been saying for decades—you have to look at the methods section and very carefully examine the tables and the associated assumptions. Since this is not practical for most individuals practicing in the medical field, researchers have a big advantage and they can say just about anything they want, use any spin they want and get away with it. The restricted reference group is not even mentioned in the abstract. As critics have also been pointing out for decades, the peer-review process for journal articles does not work very well.

THE OBESITY PARADOX

Obesity is a well established and major risk factor for hypertension, heart failure and coronary heart disease. However, paradoxically, overweight or obese patients with hypertension, heart failure, coronary heart disease and peripheral artery diseases appear to have a more favourable short- and long-term prognosis, especially when measured by mortality. This more favourable prognosis among the overweight and obese is also seen in end-stage renal disease and dialysis, advanced cancers, chronic obstructive lung disease and rheumatoid arthritis.¹² Recognition of this phenomenon goes

back some time but recently most of the research has focused on cardiovascular disease. It has been suggested that studies of this paradox are confounded by what is called cachexia, which is a wasting syndrome caused by disease which causes weakness, loss of weight, fat and muscle, and increases the risk of mortality. However, recent studies do not seem to support this as the explanation.

A recent study has examined this paradox in the context of so-called purposeful weight loss during

cardiac rehabilitation and an exercise training program.¹³ Mean age of the cohort was about 68 years with 23% of the cohort female. When separated into just two groups, low BMI was about 23, high about 30, and for fat, low body fat was about 24% and high body fat about 30%. Overall mortality among 529 coronary patients according to BMI was: <25, 13%, 25-30, 4.2%, 30-35, 4.8% and > 35, 1.8%. Those with low body fat had a mortality of 10.6% whereas for high body fat, it was 3.8%. While these were significant differences, there was no significant difference between mortality among

those who had a low weight loss vs. a high weight loss during the intervention program, although the high weight loss resulted in a measurable benefit in terms of 3-year mortality (5.1% vs. 3.1%). The authors comment that this latter result was consistent with the observation from the Mayo Clinic where better event-free survival was associated with weight loss. This paradox merely illustrates the great complexity of human biochemistry and disease and underscores the arrogance associated with ignoring this fact or assuming that it is adequately understood.

GLYCATED HEMOGLOBIN AND CARDIOVASCULAR RISK

There are several indicators that permit the evaluation of an individual's carbohydrate metabolism. These include fasting blood glucose, the now unpopular two-hour glucose tolerance test and the blood level of glycated hemoglobin (HbA1C). The last provides an average measure of blood glucose levels over a period of a two to three months and averages the metabolic response to dietary glucose including post-meal spikes. It has a low intra-individual variability, particularly in persons without diabetes and does not require fasting for a meaningful determination. While fasting glucose and if indicated, a glucose tolerance test, have historically been the approach to diagnosing diabetes, the new 2010 guidelines from the American Diabetes Association include HbA1C \geq 6.5%. Rather than being mainly a tool for monitoring glucose control in diabetics, it now ranks as a diagnostic criterion for diabetes with fasting blood glucose \geq 126 mg/dl (7.0 mmol/L), a 2-hour blood glucose level of \geq 200 mg/dL (11.1 mmol/L) during the glucose tolerance test, or a random blood glucose of \geq 200 mg/dL in a patient with classic symptoms of hyperglycemia or a hyperglycemic crisis.¹⁴

Since the presence of diabetes enhances the risk of cardiovascular disease (CVD), one might also expect a connection between CVD risk and HbA1C, even in the absence of diabetes. A study reported in the March 4th issue of the *New England Journal of Medicine* provides dramatic evidence supporting this conjecture.¹⁵ This was a prospective cohort study involving over 11,000 non-diabetic participants without a history of cardiovascular disease with a median follow-up time of about 14 years. A number of participant characteristics were available at baseline including HbA1C and fasting glucose. The number developing diabetes, coronary

heart disease (CHD) and stroke (non-bleeding) were determined over the follow-up period. Compared to a baseline HbA1C of 5.0% to 5.5% (reference), those with levels 5.5% to less than 6%, 6.0% to less than 6.5% and greater than 6.5% increased risk of CHD of 23%, 78% and 95%. Interestingly, the risk for a diagnosis of diabetes for these same HbA1C levels were about 2 fold, 4.5 fold and 16.5 fold compared to those with levels in the reference range. These estimates of risk were adjusted for a number of confounders and were all statistically significant. HbA1C was a stronger predictor of risk of CVD or death from any cause than fasting glucose.

In the discussion section of the paper, the authors make a number of points. Over 2.4 million people in the U.S. who are not diagnosed with diabetes have HbA1C higher than 6.5% and 7 million have a value higher than 6% or higher. This study found that those with HbA1C \geq 6% were a high risk for the development of not only diabetes but also CVD even after adjusting for confounding factors, and that this was independent of baseline fasting glucose. Furthermore, elevated glycated hemoglobin as a marker for CVD in this non-diabetic population remained associated with both CVD and any-cause mortality independent of fasting glucose. Thus this study reinforces the view that HbA1C should have a prominent place in diabetes diagnosis and that it is a significant marker for the risk of CVD. It follows that it should be monitored to detect early elevation and progression and steps taken to return it to \leq 5.5%. Indeed, it can be argued HbA1c should be a standard test requested during any physical exam and appears more informative than the commonly requested fasting or casual blood glucose test. As discussed in the Research Review on diabetes diagnosis (see

www.yourhealthbase.com/diagnosis_of_diabetes.htm) and frequently in this newsletter, one approach to reducing HbA1c is through diet and exercise,

especially carbohydrate restriction and muscle building exercise.

NEWS BRIEFS

STATINS AND HDL CHOLESTEROL

In the context of primary prevention of cardiovascular disease, the focus has been on LDL and LDL targets as achieved by statins. As readers of this Newsletter know, this view is becoming more and more controversial. At the recent American Heart Association 2009 Scientific Sessions held in November 2009, Dr. Richard Karas and coworkers presented results of a new meta-analysis which highlights the fact that statins do not eliminate the risk of low HDL levels. In 20 randomized clinical trials, the median baseline HDL levels were 45 mg/dL vs. 48 mg/dL after statin intervention. i.e. a rather small change.

Finding a drug that elevates HDL is of great interest to the pharmaceutical industry, but thus far, there has been no success, only disaster. Two studies are underway that combine statins and niacin in patients either with elevated triglycerides and low HDL or patients with existing vascular disease. Readers of this newsletter are probably aware of the impact of diet on HDL levels with the low-fat diet high in refined carbohydrates producing low levels. Your editor has an acquaintance with severe angina who reduced his HDL to below 30 mg/dL, a highly unsatisfactory level, with a high-carb diet involving almost no fat and his triglycerides were also very high. Thus he increased his risk of an adverse CHD event while thinking he was involved in a beneficial intervention. Furthermore, replacing carbohydrate with any type of fat increases HDL levels and the effect on both HDL levels and the beneficial subtype of HDL is greater for saturated fat compared to unsaturated fat.¹⁶ Mainstream medicine is no doubt still a long way from suggesting increasing saturated fat, given that it has been demonized for several decades. Also, low HDL results from long term consumption of a raw food diet.¹⁷ For additional information on low HDL, the related metabolic syndrome and the dyslipidemia characterized by high triglycerides and low HDL, see the Research Report on carbohydrate restriction in the September 2009 issue – www.yourhealthbase.com/archives/ihn200sq.pdf

VITAMIN D AND RISK OF COLORECTAL CANCER

A very large and interesting case-control study has just been reported in the *British Medical Journal* (BMJ) which examined the association between vitamin D status and the risk of colorectal cancer as well as colon and rectal cancer separately.¹⁸ More than 52000 individuals from 10 western European countries were involved. Vitamin D status was obtained from blood samples by measuring 25-hydroxyvitamin D (25(OH)D). Extensive corrections were employed for confounding and in addition, the interaction with both calcium and preformed vitamin A (retinol) were examined. When the range for 25(OH)D of ≥ 50 to <75 nmol/L (third quintile) was used as a reference, the results for the next and the highest quintile (≥ 100 nmol/L) adjusted for confounders but not for calcium and vitamin A showed a risk reductions in the range of 20-30% for CRC, colon and rectal cancer, but the results did not manage to achieve statistical significance. However, when the adjusted results were stratified by calcium intake, for 25(OH)D levels > 75 nmol/L a statistically significant risk reduction was found and for dietary intakes of calcium ≥ 1114 mg/d, reached a statistically significant 28% reduction. Also, similar stratification against retinol intake revealed that the risk reduction disappeared at intakes \geq approximately 1000 microg/day of retinol. This is equivalent to about 3300 IU pre-formed vitamin A.

In the February 2010 issue of *The Vitamin D Newsletter*, the editor, Dr. John Cannell, M.D., discusses these results in some detail. He cites a paper based on the Nurses' Health Study¹⁹ which found vitamin A completely thwarted the beneficial effects of vitamin D, a result completely consistent with the study in the BMJ. He goes on to discuss earlier studies where a U-shaped curve was obtained for risk reduction of various cancers associated with 25(OH)D levels. These studies were done before there was much awareness of vitamin D, multivitamin supplements contained insignificant amounts and supplementing with vitamin D alone was unusual. Yet these studies found some individuals with 25(OH)D levels that were quite high and thus hard to explain given the latitudes involved. The simple answer he suggests is that it came from cod liver oil, which was a very popular supplement. However, this fish oil also contains high levels of retinol which would have been sufficient to negate the beneficial effects of the vitamin D. Thus the U-shaped results where a high vitamin D status failed to protect,

but the effect was seen at lower levels where there was reduced interference from vitamin A. Cannell also comments that some multivitamin producers are now cutting back on the vitamin A content of their products. Also, for beta-carotene, which is also used in some preparations instead of preformed vitamin A, the equivalence to retinol is low enough that there should be no concern. This newsletter is available free from www.vitamindcouncil.org.

VITAMIN D AND NON-MELANOMA SKIN CANCER

The incidence of non-melanoma skin cancer (NMSC) is frequently used in studies as a surrogate for sun exposure and thus vitamin D status. NMSC affects close to a million Americans annually and rarely metastasizes. This non-life threatening cancer is partly caused by sunlight exposure, is relatively easily treated, and nevertheless is the main reason for the current widespread custom of sun avoidance. In a study just published in the journal *Cancer Causes Control*²⁰ the interesting results were that (a) high vitamin D status as measured by 25(OH)D is strongly and inversely related to the risk of NMSC and (b) the incidence of NMSC is a poor surrogate for sun exposure or adequate vitamin D status. The study involved elderly men, and for those in the highest quintile of 25(OH)D (> 30 ng/mL) there was a 47% lower odds of NMSC than for those in the lowest quintile, and these results achieved statistical significance. These results are obviously ironic, especially when one considers the multitude of health benefits associated with high 25(OH)D levels, especially with regard to cancer and heart disease, both of which, it can be argued, present a somewhat higher level of danger than NMSC.

THE BUGS APPEAR TO BE WINNING

It has gotten to the point where writing about drug-resistant bacteria seems like walking down the street carrying a placard saying the world is about to end, or at any rate, the world we have come to know where infectious diseases have been tamed by antibiotics. An article in the journal *Infection Control and Hospital Epidemiology* reports a surge in drug-resistant strains of *Acinetobacter* which causes severe pneumonia and bloodstream infections in U.S. hospitals.²¹ Not only have intensive care and other patients been affected, but *Acinetobacter* infections are now being seen in soldiers returning from the war in Iraq. These strains are resistant to a last-line antibiotic treatment (imipenem) reserved for drug-resistant bacterial infections. Over the past 7 years there has been a three-fold increase in the proportion of cases resistant to this antibiotic. This bacterium joins the list headed by *methicillin-resistant Staphylococcus Aureus*. One wonders who will ultimately win given that the pipeline for new antibiotics targeted on this problem is not exactly budging at the seams. In addition, it appears that the overuse of antibiotics under many clinical settings continues unabated.

FDA ATTACKS THE COMPANY MARKETING POM WONDERFUL, A POPULAR SOURCE OF POMEGRANATE JUICE

In a recent letter to the company POM Wonderful, the U.S. food and Drug Administration (FDA) has declared²² that the POM Wonderful pomegranate juice is an unproven drug and demanded that the company stop providing health information relating to this produce on their website. This alleged violation of U.S. federal law revolves not around claims made on the bottle but rather the fact that the bottle label contains the company website and on this website the company discusses reports in the peer-reviewed medical literature concerning studies showing benefits of pomegranate juice in the context of atherosclerosis, blood flow/pressure, prostate cancer and erectile dysfunction. The FDA cites four journal references on the website as evidence of the product's intended use which they claim is equivalent to using the juice as an unapproved drug. The mere act of citing medical journal articles that are in the public domain constitutes advertising that turns a fruit juice available in most supermarkets into a drug. Their letter also makes it clear that personal testimonials are not allowed. What ever happened to free speech? They go on to say that,

"Your POM Wonderful 100% Pomegranate Juice and POMx products are offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layperson can use these drugs safely for their intended purposes. Thus, your products are misbranded under section 502(f)(1) of the Act, in that the labeling for these drugs fails to bear adequate directions for use [21 U.S.C. 352(f)(1)]."

The philosophy evident in this paragraph speaks for itself. One would think that the FDA would also forbid authors of journal articles to disclose commercial sources of the products they are using in studies, as was the case with POM juice in the prostate cancer studies, since when they report beneficial results they are also promoting “unproven drugs” that the general public can purchase without prescription. The letter ends with the standard threats such as “product seizure and/or injunction” if the violations of the law outlined in great detail in their letter are not at once addressed. There is a certain irony in the fact that the letter originated in the FDA Center for Food Safety and Applied Nutrition. This episode reminds one of similar attacks on cherry and walnut producers, as well as Alice in Wonderland. The letter is available on the internet.²²

Readers of this newsletter, especially those who read the Prostate Monitor section which appears every other month, are already familiar with some of the research regarding pomegranate juice and prostate cancer. In fact, one can find at least 30 scientific articles on the anticancer potential of this juice.

Erratum: Issue #205, March 2010, p. 3, second paragraph, should read **1300 mg/d of EPA and 860 mg/d of DHA**

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RESEARCH REPORT

HEARTBURN, ACID REFLUX THE LONG-TERM RISKS OF PROTON PUMP INHIBITORS

INTRODUCTION

So-called acid reflux is a widespread problem. Check out the space allotted to antacids in the drugstore. Early in December 2009, the *Canadian Institute for Health Information* released a report indicating that the use of prescription anti-gastroesophageal reflux drugs, i.e. proton pump inhibitors (PPIs) had increased by 60% between 2001-2002 and 2007-2008 based on drug claims by Canadians over 65 in six provinces. In 2007-2008 over 20% of seniors filled prescriptions for PPI drugs. It was also found that PPIs were being used for longer periods of time. The study was based on public insurance data for seniors filling prescriptions for PPI drugs (e.g. Nexium, Prilosec, Prevacid, Protonix). And this does not include over-the-counter PPIs such as Prilosec OTC. This number is not surprising. Gastroesophageal reflux disease (GERD) is one of the most common diseases in the Western world with 44% reported to have symptoms once a month and 20% once a week and 10% daily.¹ Mainstream medicine's answer to most problems is a prescription, and GERD is no exception. Some would debate the label "disease."

GERD occurs when stomach fluid is not held back by the sphincter (valve) between the stomach and the esophagus. The acidic liquid serves as a potent irritant to the lower end of the esophagus with associated inflammation, pain, and potential long-term tissue damage and even cancer. The discomfort is commonly described as heartburn. Reflux that reaches the throat can irritate or damage the larynx and vocal cords. The discomfort can be severe enough for sufferers to actively seek help through over-the-counter remedies such as antacids, coating agents or H2-receptor antagonists (e.g. Zantac) and many turn to their physicians who potentially have a number of recommendations, one of which is a prescription PPI drug which changes the stomach pH (the chemist's measure of acidity, 7 being neutral) from 1-2 to 4-6 by inhibiting hydrochloric acid secretion. Non-drug interventions include weight reduction if overweight, avoidance of certain acidic foods, coffee, tea, alcohol and carbonated drinks, eating smaller meals more frequently, not eating at least 3-4 hours before bedtime and elevating the head of the bed by 6 or so inches. Other recommendations include exercise, not smoking, sleeping on the left side and avoiding excessive intake of non-steroidal anti-inflammatory drugs such as ibuprofen.² The extent to which these non-drug recommendations are evidence-based is beyond the

scope of this discussion. One wonders how often patients are told to try these before a prescription for a PPI is written, or if patients even give them a chance. Judging from the amazing number of people worldwide taking PPIs, the answer is probably not very often.

The mechanism involved in GERD is complex but centers on the esophageal sphincter. The sphincter is normally opened by the act of swallowing and otherwise is normally closed. If the sphincter operates only weakly or opens when it should not, acidic fluid can get into the esophagus and cause irritation, inflammation, cellular transformations, etc. A distended stomach full of food can also cause the sphincter to malfunction as can a hiatal hernia, which is a hernia that forms between the sphincter and the stomach. The hernia can trap acidic fluid and inject it when the valve opens. It is thought that most gastric reflux occurs after eating when the stomach is full and is partly due to transient opening of the valve due to a distended stomach.

Untreated GERD can cause formation of scar tissue which if severe can result in swallowing difficulty. Cellular changes caused by the irritation can progress to esophageal cancer, a precursor of which is called Barrett's esophagus. Thus GERD is a potentially serious problem. It is important to recognize that the "disease" ranges from mild to serious, and at the mild end the symptoms may have little clinical relevance. Our human biochemistry is such that stomach acid (hydrochloric acid) is an essential component in a complex digestive process that takes place in the stomach and intestine. It can be argued on general principles that significantly reducing or virtually eliminating stomach acid is such a profound change in the normal stomach milieu and in a major digestive pathway that is not a brilliant idea except over the short term, and that long-term adverse effects should not come as a surprise and need to be balanced against therapeutic benefits which must relate to serious consequences of failure to treat properly.

It appears that prescription PPIs are now being used as first-line treatment for GERD. PPIs are the most potent medications available to reduce gastric acid secretion and are now among the most widely prescribed drugs worldwide. Based on short-term side effects, they appear to be regarded as very safe. However, concerns over long-term safety of PPIs have been continually raised over more than a decade. Also, a number of studies have found that acid-suppressive medications are being inappropriately prescribed in many of the populations studied.

SERIOUS PPI SIDE EFFECTS

There have been several recent reviews of the adverse side effects of long-term use of PPIs.^{3,4} These include

- *Infections.* These include *Clostridium difficile* colitis, bacterial gastroenteritis and colonization of the stomach lining by *H. pylori*. The risk of *C. difficile* is particularly acute in the hospital setting but is starting to be seen outside in the communities. Bacteria infecting the intestine normally must pass through the stomach if the inoculation is via ingestion and low pH presents a critical barrier. *H. pylori* is famous for its connection with stomach and duodenal ulcers. Other infections with elevated risks include salmonella, campylobacter and pneumonia. In all cases there is evidence but of variable strength. A single dose of most PPIs does not maintain the gastric pH > 4 for 24 hours and thus each day there is a period when higher acidity toxic to bacteria can be present. But the elevated risk of *H. pylori* overgrowth suggests that the acid suppression in this case is sufficient to cause real risk.^{4,7} The association with respiratory infections in general is suggestive but weak.⁸ Two doses a day of a PPI, which is not uncommon, can effectively eliminate the protection from infection provided by normal (high) stomach acidity for 24 hours.
- *Hip fracture risk.* Targownik has recently summarized population-based case-control studies, including a large study reported at the 2009 Digestive Disease Week meeting. The duration of PPI use in these the studies was "within a year" to at least 7 years. Odds ratios were almost all significant and those that were ranged from 30% to 350% increase for the risk of hip fracture associated with the use of PPIs. While this represents significant risk, the mechanism is unknown and may be more complex than simply low calcium absorption in the stomach due to acidity.⁹ These observational studies do not prove causality but are suggestive and should motivate concern, especially for those taking PPIs without meeting the normal indications, i.e. those subjected to overtreatment.
- *Magnesium deficiency, also called hypomagnesemia.* This has not been systematically studied. However, recently there have been seven case reports of individuals with very low magnesium levels which resolved after withdrawal of a PPI. The latest was reported in 2009 by Kuipers *et al*¹⁰ who also reviewed earlier reports. The connection with PPI use was reinforced by the recurrence of

hypomagnesemia after re-challenge with the PPI. The authors discuss possible mechanisms but are unable to draw significant conclusions. They do point out that PPIs also impact the intestinal acid concentration and that PPI users have more alkaline intestinal milieu. Hypomagnesemia can cause weakness, muscle cramps, cardiac arrhythmia, tremors, confusion, hallucinations, epileptic fits, and hypertension and this is not the complete list.

- *Gastric cancer.* There have been very few significant studies of the potential connection between PPI use and stomach cancer. In one study which involved 8 years follow-up of over 500,000 patients, non-users of PPIs had a gastric cancer rate of 0.01% whereas for users it was 0.16%.¹¹ The most recent study appears to be Poulsen *et al.*¹² In this paper the authors comment that for patients with *H. pylori* stomach infection, long-term PPI use has been associated with an increase of atrophic gastritis, a process of chronic inflammation of the stomach leading to loss of gastric glandular cells and their eventual replacement by intestinal and fibrous tissues. This sequence is regarded as a precursor of stomach cancer. Poulsen *et al* found that only when the number of prescriptions exceeded 15 (21% of the active users of PPIs in the study) was there a significant increase in gastric cancer with approximately a doubling of the relative risk of incidence. A recent review¹³ suggest that the evidence is strong enough so that *H. pylori* eradication is indicated for infected individuals who are candidates for long-term PPI use, but the suggestion is not accompanied by a discussion of preventing recurrence while on a PPI. It is interesting in this context that *H. pylori* can survive a pH levels between 4 and 8 but only replicate when the pH is between 6 and 8; however, there are regions of the gastric system where this is not relevant.¹³

ALCOHOL YIELDS A CARCINOGEN IN THE LOW-ACID STOMACH

While this is a side effect of PPIs it seems to deserve its own section. Many microbes, including those that normally reside in the mouth, can not live at normal stomach pH with pH lower than about 4 being fatal. On the other hand when the pH is above 5 bacterial proliferation is expected. In an interesting study, Väkeväinen *et al*^{14,15} examined the gastric pH and bacterial content in the stomachs of eight volunteers, starting with baseline measurements and then inhibiting stomach acid production for seven days with the PPI lansoprazole (Prevacid) twice daily. Thus each subject served as its own control. The researchers were investigating the production of acetaldehyde, a potential carcinogen, from bacterial action on alcohol in the stomach. Subjects drank alcohol diluted with water to correspond to normal drinks. Then their gastric juices were obtained. The first stage was before the PPI treatment and the average stomach pH was 1.3. Very low levels of acetaldehyde were found and attributed to that generated in the saliva during the ingestion of the alcoholic drink. After the PPI treatment, the mean pH of the gastric juices was 6.1 (almost neutral as compared to strongly acid) and there was a huge increase in acetaldehyde and now a large number of different bacteria were found living in the stomach. Most of these bacteria were demonstrated to have the capability to produce acetaldehyde from alcohol. Not only does this illustrate the role of a strongly acidic stomach as a bacterial shield, but once this shield is broken, bacterial colonization which produced acetaldehyde from alcohol was observed. Acetaldehyde is a known local carcinogen and a well-known risk factor for upper digestive tract cancers at the concentrations found in this study. It was already known that strains of *Candida albicans* from the oral cavity have the capacity to generate acetaldehyde. Furthermore, excessive alcohol consumption is a well-known risk factor for upper digestive tract cancers, although confounding by the use of PPIs was probably not considered. This study provides a possible mechanism since alcohol per se is not carcinogenic. Finally, atrophic gastritis which leads to low stomach acidity and reduced pepsin production is a known risk factor for stomach cancer and can be caused by a persistent bacterial invasion of the stomach. The authors discuss other evidence addressing the biologic plausibility of the acetaldehyde-stomach acid-cancer connection.

ALTERNATIVE INTERVENTIONS

Aside from the non-drug interventions outlined above, a dietary supplementation program for patients with GERD was described recently by Ricardo de Souza Pereira.¹⁶ This was a single blind randomized intervention trial where a PPI (omeprazole) was compared with a mixture of supplements (melatonin, 6 mg; tryptophane, 200 mg; vitamin B12, 50 microg; methionine, 100 mg; B6, 25 mg; betaine, 100 mg; and folic acid, 10 mg, all per day). The first phase covered 40 days. Patients randomized to receive the set of supplements (176) all reported complete regression of symptoms after 40 days and the only side effect was sleepiness. Of those randomized to the PPI drug treatment (175), 115 reported regression. During a second phase of the study, those in the drug group who reported residual GERD symptoms were given the supplements for 40 days and reported that all symptoms disappeared. About 30% of patients did not notice the recurrence of GERD but the rest required

continued treatment with the supplements and Pereira found that melatonin alone was not effective (personal communication). The author suggests that the action of melatonin may be associated with its ability to inhibit nitric oxide biosynthesis and thus impact the sphincter relaxation associated with GERD symptoms. While there is reason for concern over the high dose of folic acid employed, this amount of folic acid used may not be necessary.

A case history of a GERD patient was presented by Melvyn Werbach the same year and using a similar protocol.¹ It was found that treatment with a PPI failed to produce permanent relief after it was discontinued in each of three 20-day trials. When the PPI was used along with a supplement set which included melatonin, vitamins and amino acids, the PPI could be withdrawn after 40 days without a return of symptoms. When the supplements were withdrawn, symptoms returned unless 3 mg of melatonin per day was maintained. This is inconsistent with the experience of Pereira. Werbach also discusses other potential mechanisms whereby melatonin might influence GERD. These include antioxidant effects and stimulation of the immune system.

HIGH STOMACH ACIDITY VS. LOW STOMACH ACIDITY

It is interesting that both supplement programs used in the above studies included betaine hydrochloride, an over-the-counter supplement which is commonly used to raise, not lower stomach acid levels and is employed when a deficiency of acid is interfering with digestion and in fact also causing heartburn. This is sufficiently counterintuitive that one does not often see it recommended though your editor has seen it highly recommended by practicing physicians in some of the newsletters to which he subscribes. But it is worth recalling that in normal healthy individuals, eating stimulates the secretion of hydrochloric acid in amounts required for digestion, and hydrochloric acid is what a chemist calls a strong acid (completely dissociated in water) and these normal healthy individuals do not have GERD! This is the way our digestive biochemistry works when it is in tune with our genetic blueprint, which goes back at least to the Stone Age. A very acid stomach is completely natural and in addition, essential. This is probably even taught in high school!

A frequent suggestion seen on the internet and in the literature is to use betaine hydrochloride as a tool for differential diagnosis. If the symptoms of acid reflux disappear with betaine hydrochloride plus pepsin in a dose-dependent fashion, then the acid reflux problem probably can not be solved by inhibiting acid secretion with a PPI since in fact the problem is not enough acid. Some physicians "titrate" the betaine hydrochloride until it produces acid reflux, and then back off the dose to see if the problem is solved. This approach appears to have some merit since it prevents the recommendation of a therapy that goes in the wrong direction, i.e. decreasing rather than increasing stomach acid. This will probably never be a popular approach since it has two problems: (a) it is counterintuitive and (b) betaine is not a prescription drug and the patient has to be sent to a health food store. Incidentally, Dr. Natasha Campbell-McBride reports in her book *Gut and Psychology Syndrome* that she has great success with betaine hydrochloride with pepsin in both children and adults with low stomach acid which she finds normally accompanies a dysfunctional gut. Betaine is not without its risks, can be dangerous if one has an ulcer and probably should only be used after consultation with a physician. Knowledge of the actual state of acidity in the stomach would be very helpful. A 24-hour stomach acid measurement technique is available which uses a pill that transmits data to an external radio receiver. Low stomach acid frequently accompanies aging. But stomach acid is not a simple matter like the acid concentration in a laboratory bottle. It varies with the location in the stomach, the proximity to the walls, the stage in the fasting, eating, digesting and emptying cycle, etc. There are remarkable local variations in particular near the exit from the esophagus which are being explored.¹⁷

ARTIFICIALLY ELEVATED STOMACH pH AND THE DIGESTIVE SYSTEM

Thus we come to an interesting question. Given that PPI use is widespread and there appears to be a trend toward long-term use, even for reflux problems that are minor, is establishing an abnormal and very much less acidic stomach environment, at least over most of the day, a good idea? In an editorial, McColl and Gillen from the University of Glasgow comment that treating GERD with profound acid inhibition will never be ideal because acid secretion is not the primary underlying defect and patients with reflux disease generally have normal acid secretion.¹⁸ They take the position that it is never ideal to treat one abnormality by creating another and that the real target should be the dysfunction of the gastroesophageal barrier. There are other questions such as do PPIs really reduce the risk of esophageal cancer and the incidence and frequency of serious esophageal reflux incidents? Also, what about the fact that low and high stomach acidity can produce some of the same symptoms that lead to a prescription for PPI. Shouldn't this problem in differential diagnosis be addressed first? Let's first

examine the problem of the stomach and its normal high level of acidity. If instead the acidity is low, i.e. a higher pH, what are the consequences regarding digestion in the stomach and intestines?

The stomach is normally highly acidic. When a meal is ingested, the pH goes up due to the diluting and buffering and neutralizing action of the food. This triggers hydrochloric acid secretion which rapidly drops the pH back down toward the pre-meal level. The enzyme pepsin is also secreted into the stomach. These two chemicals facilitate the break-up of proteins, which are made up of amino acids, into smaller amino acid chains called peptides, along with some single amino acids. If the stomach lacks acid, this preliminary digestion of protein will be inhibited. When the stomach is functioning properly, these peptides, free amino acids along with the rest of the contents of the meal are passed along to the duodenum and then into the small intestine. During this transit, if the acidity is too low, the mechanism that generates intestinal digestive enzymes and injects bile will fail to trigger or operate properly, setting up the scene for digestive dysfunction in the intestine where fats, carbohydrates, proteins and peptides are broken down and as well, micronutrients such as minerals and vitamins are absorbed and vitamins even synthesized. Partially digested proteins can be passed through the intestinal wall in a dysfunctional intestinal system and trigger allergies and autoimmune reactions. Some are neurologically active molecules which end up in the brain and can act as opiates. Maldigested carbohydrates are consumed by abnormal bacteria in the gut, encouraging their growth and continued colonization. When the intestinal system is dysfunctional, fats are not properly digested if at all and vitamin and mineral metabolism also becomes dysfunctional. Thus stomach acid is a central and critical actor in the whole digestive process.

The high stomach acidity also provides a shield for bacterial invasion, preventing colonization in the stomach and severely limiting bacterial passage into the intestine. Elevated stomach pH removes this barrier and allows bacterial overgrowth in the stomach and the colonization by undesirable bacteria in the intestines. Stomach bacterial overgrowth can disrupt the acid and enzyme biochemistry and lay the groundwork for gastritis and stomach cancer. In the intestine, overgrowth of unfriendly bacteria can cause major dysfunction of the gut which in turn allows undesirable molecules to pass through the walls of the intestine, interferes with digestion, and alters immunity.

We evolved to have a digestive system which accommodates a very low pH in the stomach, uses acidity as part of a complex signalling system, and has a valve at the lower end of the esophagus which prevents this acid stomach fluid from irritating the lining of this tube or getting back to the throat. Acid reflux, irritation of the esophagus, Barrett's esophagus syndrome, and esophageal cancer are abnormal. Given this simplified view, one can ask, does it make sense if the stomach acid is causing pain or irritation in the esophagus, to profoundly change the pH of a complex system which has evolved over eons. Generally when one messes around with complex human biochemical systems to change one critical aspect or treat a symptom, the end result is not good because in fact a cascade of events ensues. The fact that most prescription drugs have lists of side effects that are very long illustrates this. The PPI is no different, as is indicated by the side effects discussed above.

HOW WELL DO PPIs WORK?

PPIs are presumably taken for two reasons. One is to eliminate the pain and discomfort of acid reflux, i.e. heartburn relief, prevent stricture formation in the esophagus, promote healing of an inflamed esophagus and esophageal ulcers and stomach ulcers, and finally, serve a prophylactic in the context of heavy and prolonged use of non-steroidal anti-inflammatory agents. In addition, they are used to prevent the progression of Barrett's esophagus to adenocarcinoma of the esophagus and precursor cellular changes.

Failure of GERD patients to respond to the standard once-a-day PPI dose is common and the typical response is to increase the dose to twice daily. This appears to improve outcome although there do not appear to be relevant data actually proving this.¹⁹ Two doses a day extend the acid suppression to practically the entire 24 hour period. For individuals with Barrett's esophagus with so-called macroscopic markers of advanced disease such as strictures, ulcers and nodules, the use of PPIs may reduce the prevalence of these markers. It has been argued that PPI use prior to visual examination (endoscopy) is indicated because the benefit associated with PPI use outweighs the importance of loss of information. Long-term PPI use has been shown to decrease the progression of Barrett's esophagus to dysplasia and cancer.²⁰

But according to critics, PPIs are being prescribed to some individuals who in fact may not have indications justifying this intervention. Also, for this group as well as anyone taking this class of drug, the so-called rebound effect may be significant. In short, when PPI therapy is stopped, there is enhanced acid secretion and this has been observed even in healthy individuals. Thus stopping PPI-use is inducing the symptoms for which it is used therapeutically. Furthermore, this rebound effect makes short-term therapy problematic since patients will want to return to treatment when their symptoms reappear with a vengeance. The stage is set for long-term use.

WHY IS GERD SO COMMON AND INCREASING IN PREVALENCE?

Finally, there is the interesting question as to why GERD is so common. In fact, the sales of PPIs are second only in the US to lipid-lowering drugs. The paradox is that the underlying cause may be related to too little, not too much stomach acid. Dr. Natasha Campbell-McBride in her book *Gut and Psychology Syndrome* (Ch. 4) points out that in her clinical experience people with abnormal gut flora (bacteria) almost without exception have low stomach acid production. Normal acid secretion is strongly inhibited by toxins produced by *Candida*, *Clostridia* and other pathogens. Thus digestive dysfunction in the stomach appears closely related to gut health, and gut health in many individuals is severely compromised by repeated assaults from toxins and antibiotics. Overuse and inappropriate use of antibiotics is widely recognized in a number of contexts as is the end result whereby friendly and essential gut flora are killed off, but this practice appears to continue unabated. Unfriendly bacterial overgrowth is fed in part by high sugar and high carbohydrate diets. It is reasonable to suspect that most individuals do not attempt to rectify the harm done to their gut flora by repeated antibiotic use, or if they do, they use ineffective methods such as yogurt containing insufficient if any bacteria or the wrong strains. A dysfunctional gut impacts the biochemistry involved in signalling and generating stomach acid and stomach digestive enzyme generation, so many individuals with a dysfunctional gut have impaired digestion. This then causes the initial digestive process in the stomach to also be dysfunctional. A stomach that is distended can cause the sphincter to malfunction, and although the acidity of the reflux fluid is lower if low stomach acid is a problem, it is still high enough to be very irritating to the esophageal tissue. Given the predilection to overeat and to eat so rapidly that the brain does not have a chance to tell one that the stomach is full would appear to be a lifestyle component that aggravates GERD.

Thus the counterintuitive treatment of acid reflux with betaine hydrochloride, ideally combined with the stomach digestive enzyme pepsin which is involved in protein digestion, and why betaine was included in the supplemental protocols described above. Incidentally, so-called supplemental *digestive enzymes* are generally formulated to contain only enzymes that act in on intestinal digestion and thus do not directly improve the digestion process in the stomach.

Furthermore, according to Dr. Campbell-McBride, when stomach acid is low, the acidity of the food and fluid entering the duodenum on its way to the small intestine fails to provide the appropriate pH-dependent signals that regulate the intestinal pH and intestinal digestive enzymes and bile supply, with the result that the dysfunctional digestion that started in the stomach now continues in the intestine. As she points out, this can have severe nutritional and neurological consequences. It is interesting in this connection that three of the major side effects of PPIs are abdominal pain, diarrhea and constipation, all suggestive of gut dysfunction.

The PPI drugs treat the problem of GERD by getting rid of the irritant, namely the stomach acid, but this does not address the real cause of the problem and in the process profoundly alters the entire digestive system in a manner which can only be described as adverse. The popularity of this class of drug is well established, and perhaps even demonizes stomach acid. This would appear to lead in just the opposite direction from a sensible approach, and result in highly abnormal side effects such as bacterial overgrowth in the main part of the stomach as well as other side effects described above.

ACID CONTROL ALTERNATIVES

Over-the-counter antacids such as Tums are the traditional approach to self-treatment of acid reflux and can be effective in treating occasional episodes. Those antacids which simply temporarily neutralize stomach acid are fundamentally distinct from agents which interact with acid secretion. There is also the class of drug called histamine (H₂) receptor antagonists (H₂RAs) which reduce acid production in the stomach. Readers will recognize such common brands as Pepcid AC, Tagamet and Zantac. These are also used for self-treatment but have largely been replaced, at least in the clinical setting, by the PPIs which are viewed as being more effective. In some jurisdictions, PPIs are also available over the counter which can lead to elective long-term use.

The essential point appears to be the distinction between long-term use and occasional use, and it is the use of H2RAs or PPIs over the long term which represents the most drastic disturbance of the entire digestive system and processes, opens the system to unwanted invasion from unfriendly pathogens and can lead to total system dysfunction.

Finally, diet should be considered when attempting to reduce or eliminate acid reflux. The WebMD website www.webmd.com/heartburn-gerd provides a discussion of the common offenders. Included are citrus fruits such as oranges and grapefruit or their juices, tomatoes, garlic, onions, spicy foods and pepper, peppermint, cheese, nuts, avocados, alcohol, caffeine, chocolate and carbonated beverages. A common recommendation is to keep a food log and note the personal culprits and avoid them. However, heartburn induced by a large meal or by reclining after a large meal can be independent of specific food triggers.

CONCLUSIONS

Medical mythology seems to thrive on demonizing, with fat, cholesterol and now stomach acid. Those who think stomach acid is bad because it causes esophageal cancer and therefore should be eliminated, ideally completely, need to consider what is normal in the digestive system and why all normal stomachs are highly acidic. Unfortunately, PPIs might be viewed as the poster child for a philosophy that neglects primary causes and concentrates on symptoms. Symptoms disappear and everyone is happy, but perhaps only temporarily! It seems Big Pharma is almost always happy! However, root causes have not been addressed. It is also not surprising that when therapy causes such a fundamental alteration of an essential biological system, driving it to an extreme of abnormality, serious side effects emerge. But it must be emphasized that there are genuine medical situations where PPIs are indeed indicated at least in the short term and should not be rejected.

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